

Ex. 1



5 People >

Text Message
Thu, Sep 17, 10:00 AM

Olivia Ray-Owner

Hey ladies....please let me know status of dana/jen valo/jill/becca and when they are able to start QC'ing.

10:00 AM

And what william said about houston.

10:00 AM

AND....what jen vasilio said about pt safety

10:01 AM

Last thing....even tho we are canceling Saturday clinics, please urge both sites to still come in so we can try and have everything cleaned up sooner rather than later. Pretend the FDA will be walking in Monday morning. If not tomorrow.

10:03 AM

We can have bfast and lunch available, etc.

10:04 AM

Jen Vasilio safety concerns:

- 30 min post vaccine observation time is frequently <30 min
- visits conducted OOW
- HIPAA violations
- source documentation not consistent with protocol required procedure

10:20 AM



Text Message





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Olivia Ray-Owner

Who has been doing less than 30? Same ppl? Everyone? And can we get the specific items in source that aren't matching?

10:22 AM

Also...fuller and koch. How did they react?

10:22 AM

I think we can all certainly dive into QCing, but I would like us to create a solid monitoring plan, but this is going to require a bit of thought. I'd like to work on this with as a team; Marnie, William, Kandy, etc.

I don't think it is as simple as pulling a chart and looking for missing check boxes or missing initial in a header/footer which I have been seeing a lot of when I have QC'd the QC'er.

10:29 AM

We need to be able to reconcile time of IP prep and admin, for example. This cannot be done by everyone that is QC'ing to ensure we do maintain the blind. This is one reason I think we need to carefully consider what it is we are looking at especially if we are approaching this from the perspective of an FDA auditor, which I 100% think we should be.

I also do not know what Dr. F and Dr. K think. I would have liked the opportunity



Text Message





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I also do not know what Dr. F and Dr. K think. I would have liked the opportunity to discuss this with them individually and I still would. I have spent the last hour talking to my staff, ensuring the pause in enrollment is not a BAD thing, trying to calm everyone down. As soon as our call ended, the word was out and rumors started like wildfire.

10:34 AM

Olivia Ray-Owner

Can you check to see if Marnie has gotten to fuller yet? If not, whoever can get to him right away, should do so. We have a little more time with Koch since he's not onsite today and seem to almost suggest it.

10:36 AM

Mercedes Livingston-Chief Operating Officer

Brook- do you want me to call Koch? I don't mind.

10:37 AM

Kristi Raney

Liked "I think we can all certainly dive into QCing, but I would like us to create a solid monitoring plan, but this is going to require a bit of thought. I'd like to work on this with as a team; Marnie, William, Kandy, etc.

I don't think it is as simple as pulling a chart and looking for missing check boxes or missing initial in a header/footer which I have been seeing a lot of when I have QC'd the QC'er.

10:39 AM



Text Message





5 People >

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10:39 AM

We need to be able to reconcile time of IP prep and admin, for example. This cannot be done by everyone that is QC'ing to ensure we do maintain the blind. This is one reason I think we need to carefully consider what it is we are looking at especially if we are approaching this from the perspective of an FDA auditor, which I 100% think we should be. "

I agree with all said here

10:39 AM

I think that was Brook

10:39 AM

And everything said is exactly right. Exactly how we need to be thinking

10:39 AM

Sure, I can check and I can speak to Koch. I have already reached out to him. I also want to be clear on the reason behind the pause. I'm okay with telling our patients we are waiting on supplies, I guess, but would rather have put a different reason behind it; like we are very close to meeting our enrollment expectations/numbers study wide and have to momentarily pause to look at that or something similar?? To me saying that we ran out of supplies or IMP may give the impression that we aren't or Pfizer is not prepared.

10:42 AM



Text Message





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Olivia Ray-Owner

Kristi, are you ok with that? If so, I'll have chrystal change the tune

10:43 AM

Mercedes Livingston-Chief Operating Officer

I don't see a problem with what we have said. If pts question that, we just say there is a lot of interest in this trial which is fantastic and it's just taking time to have supplies sent to us.

10:44 AM

Kristi Raney

Wait. Who said anything about running out of supplies??

10:49 AM

Olivia Ray-Owner

If arturo questions us on why we are stopping enrollment:

[9/17, 10:27 AM] Kristi Raney: So I feel like we need to say we met our committed number and with the V2 and v3 on top Of each other, we are at a good place with our resources to support what we have.

10:49 AM

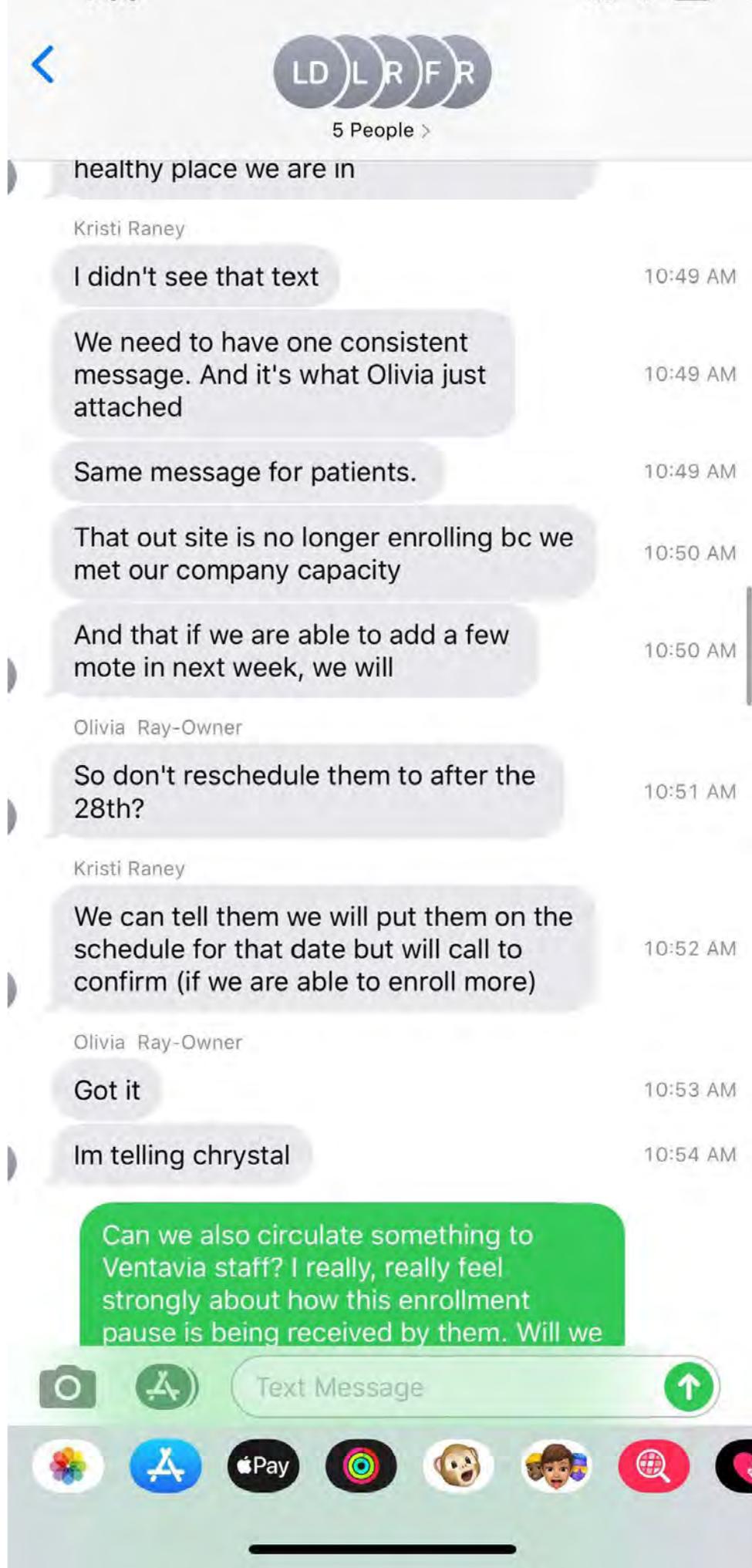
[9/17, 10:27 AM] Kristi Raney: And make it like it's no big deal

[9/17, 10:28 AM] Kristi Raney: I wouldn't say one negative thing. I would keep it that we are in a perfect place. We are being responsible by considering we have a certain bandwidth and these visits on top each other has hit our bandwidth. And we want to maintain the



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have corrective actions and findings that come from our internal QC? maybe, probably, yes, but Ventavia should be proud of the efforts/teamwork and let's focus on more training, putting more thorough policies and procedures in place, and get ready for Novavax and other studies in our pipeline!

10:56 AM

Olivia Ray-Owner

Yes, I'm good with that

10:58 AM

Marnie Fisher (personal cell) - Director Of Operations

All, this is Marnie and my personal phone so I'm just catching up- not sure who all is on this but agree that we need to get on the same page as to what we need to QC and what actions we need to take right now, since we're in a time crunch for clean-up. I think it would be good to come up with a list of the major findings and then decide a consistent action plan for each time and then we get moving on it.

11:07 AM

I'm waiting to talk to Dr Fuller yes

11:08 AM

Dr Fuller is aware 👍

11:17 AM

Kristi Raney

Want me to send an email to Ventavia about the pause or does someone else want to take that?

11:33 AM

I don't care...I know we are all

11:33 AM



Text Message





5 People >

I don't care...I know we are all scrambling a bit.

11:33 AM

Mer or Marnie...it can come from one of y'all or I can send

11:34 AM

Thu, Sep 17, 1:16 PM

Mercedes Livingston-Chief Operating Officer

Marnie/Kandy/Brook- I just updated Visit 2 source and emailed it out based off a clarification letter that came out this morning. Please make sure your sites are using it starting now.

1:16 PM

Lovica "Kandy" Downs (personal cell) - Regional Director

Hey Kristi
So word of mouth beat us all for getting the word to sites.
But I need approval for Houston halt.

1:30 PM

Mercedes
Ok about source

1:31 PM

Kristi Raney

You said they didn't need to be put on hold? What happened?

1:32 PM

Lovica "Kandy" Downs (personal cell) - Regional Director

Talked with William. And his has.concerns. and feels would be good.

1:33 PM

Sorry just talked this out.

1:33 PM

Arlington handled this morning with

1:35 PM



Text Message





5 People >

Arlington handled this morning with send email

1:35 PM

Olivia Ray-Owner

What concerns?

1:39 PM

Marnie Fisher (personal cell) - Director Of Operations

William will directly message you all right now.

1:59 PM

Actually he's going to call Mercedes for ease.

1:59 PM

Olivia Ray-Owner

Can someone send William's cell?

2:03 PM

Marnie Fisher (personal cell) - Director Of Operations

[972-977-7856](tel:972-977-7856)

2:08 PM

Olivia Ray-Owner

Kandy: please have HOU cancel tomorrow and beyond. Reschedule 28th and after. Have christine talk to Dr. Tran: we are pausing bc we are at capacity and don't want to overdue it. Plus, arturo coming out next week, so want to get everything QC'd before his visit. I will resend texts from earlier about handling the pts.

2:19 PM

That out site is no longer enrolling bc we met our company capacity

And that if we are able to add a few mote in next week, we will

2:19 PM



Text Message





5 People >

That out site is no longer enrolling bc we met our company capacity

And that if we are able to add a few mote in next week, we will

2:19 PM

We can tell them we will put them on the schedule for that date but will call to confirm (if we are able to enroll more)

If arturo questions us on why we are stopping enrollment:

[9/17, 10:27 AM] Kristi Raney: So I feel like we need to say we met our committed number and with the V2 and v3 on top Of each other, we are at a good place with our resources to support what we have.

2:19 PM

[9/17, 10:27 AM] Kristi Raney: And make it like it's no big deal

[9/17, 10:28 AM] Kristi Raney: I wouldn't say one negative thing. I would keep it that we are in a perfect place. We are being responsible by considering we have a certain bandwidth and these visits on top each other has hit our bandwidth. And we want to maintain the healthy place we are in

Lovica "Kandy" Downs (personal cell) - Regional Director

Will do right now

2:20 PM

Olivia Ray-Owner



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Mercedes Livingston-Chief Operating Officer

Marnie- have you confirmed Jennifer will be in FW tomorrow to QC?

2:49 PM

Olivia Ray-Owner

Their

2:49 PM

Lovica "Kandy" Downs (personal cell) - Regional Director

In office

2:53 PM

On office

2:54 PM

Olivia Ray-Owner

Yes, but all charts need to be QC'd after each station

2:54 PM

Kristi Raney

Don't cancel anyone on their way...that might piss then off and they can call the news, etc

2:54 PM

Mercedes Livingston-Chief Operating Officer

Yes, I meant if they were scheduled far enough out cancel but if they are there then see them.

2:56 PM

Lovica "Kandy" Downs (personal cell) - Regional Director

Not cancelling. All there being seen

2:56 PM

Marnie Fisher (personal cell) - Director Of Operations

Jennifer Valo is out tomorrow but will start QCing first thing Monday

3:18 PM



Text Message



Ex. 2

Brook Jackson

From: Brook Jackson
Sent: Wednesday, September 23, 2020 2:41 AM
To: Olivia Ray
Cc: Marnie Fisher; Kristi Raney; Kandy Downs; William Jones; Mercedes Livingston
Subject: RE: Daily QC Goals - Per Site

All,

It's very late and I am meeting some of my team at 6a to go over the QC plan since they weren't available due to the clinic schedule. I will have more solid numbers tomorrow; I appreciate your patience.

I do not anticipate that Ft. Worth is 100% finished with QC by Friday, unfortunately. Here is what I am facing:

CC is not accurately capturing our visit window.

Vaccine delays being captured incorrectly in CC. – Mercedes aware and working to correct, but I need to find a way to run a report in cc to find all of these subjects...should be pretty easy.

Enrolled # in EDC does not equal # in CC.

I was QCing a chart that has not been entered into EDC and is 21 days old.

We have close to 100 queries; oldest is 28 days.

Subject visits are being scheduled with zero process in place. This is why we have 11 subjects scheduled from 9-930, for example.

We have missing charts.

We have visits that are out of window that no one is aware because the previous visit is just simply not being looked at.

We have missing laboratory specimens that site/sponsor is aware of.

I might be in a little bit of shock.

Brook

From: Brook Jackson
Sent: Wednesday, September 23, 2020 12:07 AM
To: Olivia Ray <oliviaray@ventaviaresearch.com>
Cc: Marnie Fisher <mfisher@ventaviaresearch.com>; Kristi Raney <kristiraney@ventaviaresearch.com>; Kandy Downs <kdowns@ventaviaresearch.com>; William Jones <wjones@ventaviaresearch.com>; Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>
Subject: Re: Daily QC Goals - Per Site

Hi everyone,

I am just leaving clinic and will get my proposal outlined and sent when I get home.

Brook

On Sep 22, 2020, at 4:59 PM, Olivia Ray <oliviaray@ventaviaresearch.com> wrote:

So WEA has 2 follow up visits on Thursday. Is the newhire in WEA able to see those on her own yet? I am thinking we could ask Kati to work in Keller that day seeing patients, so Angi could QC another 20 or 30 charts.

Olivia Ray

<image002.png>

Managing Member, Executive Director

Ventavia Research Group, LLC

1307 8th Avenue Suite 202

Fort Worth, TX 76014

t: 817-348-0228

m: 214-394-0772

e: oliviaray@ventaviaresearch.com

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www.ventaviaresearch.com

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From: Marnie Fisher <mfisher@ventaviaresearch.com>

Sent: Tuesday, September 22, 2020 4:52 PM

To: Kristi Raney <kristiraney@ventaviaresearch.com>; Kandy Downs <kdowns@ventaviaresearch.com>; Brook Jackson <bjackson@ventaviaresearch.com>; William Jones <wjones@ventaviaresearch.com>

Cc: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>; Olivia Ray <oliviaray@ventaviaresearch.com>; Marnie Fisher <mfisher@ventaviaresearch.com>

Subject: RE: Daily QC Goals - Per Site

Here's my proposal for Keller based on what was done last week:

Week of 9/14/20	Charts Completed	# QC'ers	QC'ers
Mon	21	2	Anne, Becca
Tues	42	2	Anne, Becca, Marnie (minimal)
Wed	35	2	Anne, Becca
Thurs	41	2	Anne, Becca
Fri	32	3	Anne, Dana, Jill

171

Week of 9/21/20	Charts Completed	# QC'ers	QC'ers

Mon	15	2	Anne, Becca
Tues	20	3	Anne, Becca, Jill, Marnie (minimal)
Wed	100	5	Anne, Becca, Jill, Marnie, Katie, Angi
Thurs	60	3	Anne, Jill, Marnie (busy clinic- 30pts)
Fri	80	3.5	Anne, Jill, Marnie, Katie 1/2 (busy clinic- 20 pts)

275

TOTAL: 446 (number is over due to the repeat QC'ing with the checklist)

Regards,
Marnie

From: Kristi Raney <kristiraney@ventaviaresearch.com>

Sent: Tuesday, September 22, 2020 2:13 PM

To: Kandy Downs <kdowns@ventaviaresearch.com>; Brook Jackson <bjackson@ventaviaresearch.com>; Marnie Fisher <mfisher@ventaviaresearch.com>; William Jones <wjones@ventaviaresearch.com>

Cc: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>; Olivia Ray <oliviaray@ventaviaresearch.com>

Subject: Daily QC Goals - Per Site

Hello Ventavia Leaders!

I'm sending this email for Mercedes (she is driving and wanted to get this out).

Can each site please map out your sites plan/goal for knocking out QCing and send with your summary for today?

Let me give an example:

- If FW had **300 charts**
- **4 QC'ers** (freshly trained with all the new bells/whistles)
- **QC 30 charts/day** per QC'er

Wed: 30 (charts per person) * 4 (QC'ers) = 120 QC'ed charts

Thurs: 30 * 3 (if we are down a QC'er) = 90

Fri: 30 * 3 = 90

TOTAL = 300

So all charts would be QC'ed by EOB Friday with this example.

We need this back so we can tell the recruiters when they can start scheduling patients for next week. I think most of the sites will be ready to go my Monday (hopefully sooner), but we need this before we can really make that educated guess.

Mer is calling Arturo shortly to see where Pfizer currently sits with enrollmen (current enrollment number).

Thanks, all!!

Kristi

Kristi Raney

Managing Member, Executive Director

Ventavia Research Group

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<http://www.platinum-research.net/>

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Ex. 3

file 1

Berg & Androphy

November 23, 2020

Transcript by TransPerfect

WILLIAM JONES: Repeated system failures. And so those things that we needed to have in place, or establish different systems.

MARNIE: Do you mind to [INDISCERNIBLE] I'm sorry, just because I don't want us to all be here so late. It's 6:00.

WILLIAM JONES: Oh yeah.

MARNIE: Because I want this discussion. That's what I'm saying. But, maybe I can explain it a little bit differently. I guess, so now the concern is, I assumed the photos were on your work phone. But then it dawned on me, I don't think you had it. But then I guess that – now we're looking at maybe a breach of confidentiality, if that's got, if that has sponsor information on those photos. You've deleted the photos. Had they gone anywhere else –

BROOK JACKSON: I haven't showed –

MARNIE: Have you sent them to anyone besides me?

BROOK JACKSON: No, I have not.

MARNIE: Okay. Next question is, anyway, so, I guess let me explain. So we'll figure out the unblinded piece. We've got two on the unblinded log. I think – I feel like I'm okay because I –

WILLIAM JONES: Can you catch me up real quick? Because since I'm being looped in real quick. There were pictures? There were –

MARNIE: Yeah, sorry. You probably didn't –

WILLIAM JONES: Right. Uh huh.

MARNIE: [INDISCERNIBLE] didn't tell you all this.

WILLIAM JONES: I'm [INDISCERNIBLE] about the presentation and stuff, and making sure everybody gets [INDISCERNIBLE].

MARNIE: Right, so, Brook walked up into the – was here late, and went into the lab. We call it the lab, where they store the drug and mix it.

WILLIAM JONES: Okay.

MARNIE: She found an open tote that had all of the blinded drug exposed – the boxes were in this carton and it has information on there. No, I didn't look closely at the photos. I saw the photos, like when she showed me on her phone, like from a distance. I saw that yes, it was obvious, there were tons of boxes in there. And obviously it had information on it. But then she also showed me, which is a concern, and we're gonna address, is there were exposed, used

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Berg & Androphy
November 23, 2020
Transcript by TransPerfect

needles that were thrown into the biohazard bags, versus the sharps containers. And so that's why we're trying to figure out the unblinded issue, how to handle like me –

BROOK JACKSON: I didn't even look at that piece. I –

MARNIE: What's that? The details?

BROOK JACKSON: Right, right. I didn't...

MARNIE: And that's okay. Like I said, and I didn't even look –

BROOK JACKSON: But to question –

MARNIE: You sent me the photos and I didn't look at them.

BROOK JACKSON: But to question my intent of taking the pictures is offensive.

MARNIE: No, it's not –

BROOK JACKSON: It is to me.

MARNIE: No, well let me tell you why. I mean, I don't want to speak for you, I don't want to just assume that my assumption – because I'm thinking you're trying to have proof. You've got proof, and so if we do a write up –

BROOK JACKSON: Right.

MARNIE: But I guess that's where I'm confused.

BROOK JACKSON: No! I mean, I wouldn't –

MARNIE: We've got proof to show, "Hey, you know, look, we found this."

BROOK JACKSON: Right, right.

MARNIE: And so there's no – that was my – but I didn't want to assume that. Is that right? I mean, it's – because, and the reason I ask is because I know you didn't want to give them a written warning for it. But then, I guess, why did we have pictures of it? If you didn't want to do a warning? You know, a write up for them? That's what I'm trying to – me personally – I'm trying to understand. My thinking was, is because we're gonna be counseling them –

BROOK JACKSON: Because the event hadn't even happened yet.

MARNIE: Which event? The –

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Transcript by TransPerfect

BROOK JACKSON: The situation with Candy. I took the pictures days before that happened.

MARNIE: Oh, I see what you're saying. With the intention – hold on – with the intention to write them up, right? At that time?

BROOK JACKSON: I didn't know who did it, Marnie!

MARNIE: Okay. Okay –

BROOK JACKSON: This was a Thursday night!

MARNIE: Let me ask you this. To write up anyone that had left them out, is that –

BROOK JACKSON: No! Not necessarily. I mean, not necessarily. I took the pictures to show that this is what I found.

MARNIE: It's a prop.

BROOK JACKSON: Period.

MARNIE: Okay. Okay, it's okay – I'm not –

BROOK JACKSON: It's not okay. It's not o-kay!

MARNIE: I'm trying to explain to you, Brook, it's – and you know how, with management, I can't just assume – I need to hear from you so I can address it and we can move forward.

BROOK JACKSON: Any concern that I've had, I've shared with you. I've taken it to you. I've looped in our leaders. And I'm just –

MARNIE: Well, and I hate it, I feel like...

BROOK JACKSON: No, I think that you're part of it, to be honest, Marnie. Because if you guys do not grasp the severity of what we're doing, then you're part of it.

MARNIE: No, we do grasp severity. I mean –

BROOK JACKSON: So why are you – why am I continually questioned about why I'm the one saying this?

MARNIE: No, no, no, that's not what we're questioning. I'm saying of all the –

[00:05:00]

file 1

Berg & Androphy

November 23, 2020

Transcript by TransPerfect

again, and maybe I'm not explaining myself well – is to me, like, and I saw your email where you listed up something, right, and that's fine.

BROOK JACKSON: Which email are you talking about?

MARNIE: When you listed out the concerns that you're saying. You told me you sent that to me, like listing – because I asked you, "List out the items that you're talking about that are warning letter." Like, but I mean specifically, like, "We've got, say for example, there's four patients that had lab samples missing. Here's where I found this. This is where I recognize that this occurred –

WILLIAM JONES: You want an itemized list.

MARNIE: I want to see like, truly, like proof of it. Not that I'm not believing you, but I need to see it and see what are we doing next. And I guess that's the next question, is, and this is part of where I guess the confusion is of not – you're telling it, but what are we doing to fix it? When you're recognizing it – because at your level you should be able to see it, and I know you can, because I've heard from you.

BROOK JACKSON: Marnie, Marnie, since I started here, with you, and William, you've been witness to this, I've given you face to face, in the email, I've copied you, I've let Mercedes know –

MARNIE: You've given me specific patient information.

BROOK JACKSON: Listen, it's not just patients that create concerns for –

MARNIE: I know, I know.

BROOK JACKSON: Okay? So, when we have written documented procedures, that we're not following as a company, it's as big a concern as any of the others that I've brought to your attention.

MARNIE: I know. But again, you can say that, but I need specific information.

BROOK JACKSON: I've given – I'm going –

MARNIE: You haven't!

BROOK JACKSON: Marnie, I have given you –

MARNIE: You haven't given me a specific SOP that we're not following. Now COVID, you said the COVID – but again, you're telling me the entire document. Like when you say "COVID plan" I mean, which part of it are you concerned about? Are you saying –

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BROOK JACKSON: I've told you that too. Like we're supposed to be wearing these with this on top. It's supposed to be documented three times a day that we're doing these –

MARNIE: Okay, yes, you did. And I remember this.

BROOK JACKSON: Okay, so this is why I'm so confused!

MARNIE: Okay, okay. But, what have you done now? Once you've identified it, what have you done? Are you putting something in action? Because that's what we need for the RDs, when you recognize –

BROOK JACKSON: Yes, I'm doing what you told me to do and adding it to a list.

MARNIE: No, that's –

BROOK JACKSON: Yes, that's what you've told me to do.

MARNIE: Okay, yes, I understand that. But what I'm saying is, that's in terms of get it down on paper, and let's sit down and go over every item that you have a concern about. But at the same time when you're at the site, and you're identifying problems, like, your experience, like, I'm expecting you, when you identify it, that you go address it and start working on it right then.

BROOK JACKSON: For example, like the biohazard, I addressed it and took care of it immediately. I've talked about these things to you guys over and over and over again.

MARNIE: Okay, good. Okay –

BROOK JACKSON: Now, you know, procedural things and documentation and our SOPs, I can only point out to you what I see. It's not up to me to change those. I brought them to your attention when I first started and you told me to put it on a list. I think you might have been present for one of those conversations. We talked about...

MARNIE: Yes, yes – [INDISCERNIBLE]

BROOK JACKSON: Putting things on a list.

MARNIE: I know. I'm saying – [OVERLAY]

BROOK JACKSON: Keller, Fort Worth, Houston. I'm talking about – I haven't seen Houston, but I can imagine, if it's like this, if anything –

MARNIE: Okay, to back up, yes, Keller. Because that moment I told you, and both of you, I said hey, because we were talking a lot. We were there to QC that day.

BROOK JACKSON: Uh huh.

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MARNIE: And I told both of you, and William, correct me if I'm wrong, but I said, "Look, I get it. I understand." We are all in the same situation right now and we all have a great amount of experience, knowledge, expertise, and we have all these ideas, and there's so much going on, but right that second, like, we couldn't get to that right now. And that's what I meant. There is so much that we need to work on, that's what I said, "Keep making a list of those items, just like I do." I'm always keeping a list of the things that I know need, that we've gotta work on. But we can't do it all at the same time. We can't stop –

BROOK JACKSON: I disagree.

MARNIE: You know what I'm saying? Like, we can't stop –

BROOK JACKSON: I disagree.

MARNIE: Okay, well – and that's okay.

BROOK JACKSON: I've told you, I've sent you an email –

MARNIE: In that moment, like our action was to QC that day. That was our action.

BROOK JACKSON: But you're telling me, if we're finding stuff, we have to stop and address that now.

MARNIE: Yes.

BROOK JACKSON: And then in the same breath you're telling me we can't do everything right now. What if everything we're finding are things that we need to do right now? And they are!

MARNIE: Okay, then that's what I mean, like then we need to prioritize.

BROOK JACKSON: That's exactly why I sent you a text message the other day, Marnie, and I said, "I'm having a hard time..."

MARNIE: Yes.

BROOK JACKSON: "Trying to prioritize what you..."

MARNIE: But okay, so that [INDISCERNIBLE]

[00:10:00]

BROOK JACKSON: And you didn't answer. You didn't answer me.

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MARNIE: No, because it talked to you, Brook. I talked to you. I said, "Look."

BROOK JACKSON: You...

MARNIE: And I told you several times, I said, and I told Candy the same thing, "Look, right now..." You said "in general", you didn't say, "I have a hard time prioritizing warning letter actions." You said, "I'm having a hard time prioritizing." I get it. And I told you, "I do too." But right now, what I told you is...

BROOK JACKSON: Focus on the task list is what you told me.

MARNIE: I said, "The priority," I said, "we've got our calls in the morning." I said, "Prioritize the task list. But at the same time, get at the site and start tackling the site." That's all –

BROOK JACKSON: Okay, we talked and then the [PH] Jaylin situation happened.

MARNIE: Okay.

BROOK JACKSON: And you said, "Go take care of that. And then we'll hook back up."

MARNIE: Yes.

BROOK JACKSON: And the last time that we hooked up was when we started talking about documenting this.

MARNIE: Okay. But that's because both of you, or both you and I both, have been stretched thin this week.

BROOK JACKSON: I know! And there's – Marnie, I get it.

MARNIE: Wait, let me group us back in. I know, there's so much to talk about. But, let me bring up one more thing. Because another item that got brought to my attention today was some source documents that were from Burleson that –

BROOK JACKSON: I don't know anything about that.

MARNIE: Someone, I guess you had your laptop bag over here. And someone saw yellow pages that looked like source. And I don't think they realized it was your bag. I don't know what they thought it was, to be honest. But they grabbed them, and it was a stack of papers. I honestly don't know how much. But it was a Burleson patient, I think that Mercedes screened. And it was a copy of it.

BROOK JACKSON: I don't even know what you're talking about. I haven't even been to Burleson.

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MARNIE: Well, I know, and that's why –

BROOK JACKSON: I have no idea – I have no idea what you're talking about.

MARNIE: I had no idea when they told me – the only thing I can – the only thing I can imagine is Alma works in Burleson and she's been at Fort Worth for a while. But going back and forth. So the only thing I can think of is she printed something and –

BROOK JACKSON: I mean, I would tell you. I have no idea.

MARNIE: So does that ring a bell?

BROOK JACKSON: Not at all!

MARNIE: Did you have any Burleson –

BROOK JACKSON: Not that I know of.

MARNIE: Screenings or –

BROOK JACKSON: Not that I know of.

MARNIE: Okay. And I don't know what your –

BROOK JACKSON: I mean, what if I did? I mean – I really don't know –

MARNIE: That's what I was gonna ask, if you –

BROOK JACKSON: What you're talking about. I would –

MARNIE: Well, that's where I was going. It seemed weird, because what I was gonna ask you is why, I guess, why did you have them? And what for? Is there something concerning or –

BROOK JACKSON: Well, where are they? Let's look at it and we can talk about what's concerning and what's not.

MARNIE: I don't know.

BROOK JACKSON: I don't know what you're talking about.

MARNIE: Okay. Well, that's why I wanted to ask you, because the last thing, that's one thing I tell everyone, I'm never gonna accuse anyone of anything.

BROOK JACKSON: Accuse me of what? I'm a regional director. I have access to everything here. I mean –

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MARNIE: Well, you don't have access to Burluson's source documents though. Like you wouldn't have access.

BROOK JACKSON: I don't even know where to pull those from, Marnie. I don't even know.

MARNIE: Okay, well, that's why I'm asking you, because it was found in your bag. Someone said it was your bag that was over there, where you were sitting yesterday, your laptop bag.

BROOK JACKSON: What color was it?

MARNIE: I don't know. I don't know, I'm sorry.

BROOK JACKSON: Well, I'm sorry you're having to question me about this kind of stuff but I really, like, I mean, this is just ridiculous.

MARNIE: Okay. I mean, for one, I'm asking because if there's a concern –

BROOK JACKSON: I would have brought it.

MARNIE: Okay. Okay. And I mean, I guess, um, we'll talk more about unblinded, like what to do. Just again, I feel like I didn't – like you sent me the photos, thank you, and I didn't pull them up. Now granted, that's – whether [INDISCERNIBLE] or not, so I might have to [INDISCERNIBLE]

BROOK JACKSON: Should I not have taken the pictures?

MARNIE: The problem is is the breach of confidentiality and it was on your personal phone. Because there's sponsor information on those boxes. And, but my thinking was you did it because, again, because it's proof that, okay, this is a problem.

BROOK JACKSON: I mean, that's it.

MARNIE: And this is something that we've got to address.

BROOK JACKSON: That's it. The only reason I stayed up there that night is because I stayed later with Mercedes, and we were talking about the biohazard situation in Keller, and she was like, "I've been upstairs before. We do ours by weight. And I've been upstairs before, where they're throwing away urine specimens and there's things..."

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MARNIE: And it was on a personal [INDISCERNIBLE]. Because there's sponsor information in those boxes. And – but my thinking was you did it because, again –

BROOK JACKSON: The reason...

MARNIE: It's proof that, okay, this is a problem.

BROOK JACKSON: I mean, that's it.

MARNIE: And this is something that we've got to address.

BROOK JACKSON: That's it. The only reason I stayed up there that night is because I stayed later with Mercedes, and we were talking about the biohazard situation in Keller, and she was like, "I've been upstairs before. We do ours by weight. And I've been upstairs before, where they're throwing away urine specimens and there's things in the biohazard that don't need to be there." So that's why I checked that area.

WILLIAM JONES: Did you [INDISCERNIBLE]

BROOK JACKSON: Yeah, yeah. It's weight based.

MARNIE: Yeah, and I'm glad you did it.

BROOK JACKSON: Well, I'm not.

MARNIE: Yeah, and I'm sorry that you're upset and I'm sorry that there's –

BROOK JACKSON: I'm not upset, but I feel like I'm being targeted and I would you know, because –

MARNIE: Okay, I'm sorry you feel targeted.

BROOK JACKSON: Because I brought up my concern.

MARNIE: Yeah, and please don't think that.

BROOK JACKSON: How can I not, Marnie?

MARNIE: I can't control how you think. I'm just telling you, I'm telling you honestly, don't think that. Because, again, this is all about –

BROOK JACKSON: So it's just a coincidence that all of a sudden I have papers I shouldn't have, um, asking about what my intent is, you know, I took your advice and talked to Mercedes and felt like that went well, but –

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MARNIE: Yeah, and why don't we just end the evening. It's late, and let's regroup tomorrow. And I want to go over – bring your binder, bring your binder with, you said you flagged your concerns, and that's what – I want, I need to see exactly what you're talking about. So then I can address it. Because if you just say, "concerns about processes," "concerns about we're not following COVID," like, and you did give me details about COVID, I remember our discussion, and that's something I need to pull that up, we need to look at. But again, that would be something I would, when you're here in the morning, get with Jen and start getting that in place. If they're not following that policy, we're not all following that policy, then we've got to get on it. I mean, myself included.

BROOK JACKSON: I agree. But can I please remind everybody that this is day 13 for me?

MARNIE: Yes, and please don't feel like the pressure –

BROOK JACKSON: How can I...

MARNIE: Like I told William, I told both of you, I get it. Like I said before, we're all coming from such great experience, we have so many ideas, and I'm in the same boat. I can't even be in my role right now because we're all being pulled to so many different areas. And I appreciate it, because you're diving into QC and you can't get to Regulatory.

WILLIAM JONES: Right.

MARNIE: You're coming in and you're trying to learn Ventavia and new space, and I get it. And we're dealing with a potential audit. So, we appreciate you, Brook. I hate that you feel like this and I can't control how you feel, but I say, let's regroup tomorrow and just spend time – I'll spend the time. Let's sit down and go over –

BROOK JACKSON: I'm just 100% super, super disappointed in this company. In the way that I've been treated for the last –

MARNIE: Treated by who?

BROOK JACKSON: By you.

MARNIE: By me?

BROOK JACKSON: Uh huh.

MARNIE: What have I done, exactly?

BROOK JACKSON: Well, I just feel like I've shared, I told you I feel like I can come to you and talk to you about my concerns. And you like agree with them.

MARNIE: I do, I agree with a lot of concerns.

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BROOK JACKSON: Okay, so why am I being questioned about what I'm bringing to the attention? Why – you are questioning me! You questioned my intent about bringing something to everybody's attention.

MARNIE: Brook, I'm not – I'm not – I do, I agree with a lot of your concerns, and I've told you that.

WILLIAM JONES: Can I ask something real quick?

BROOK JACKSON: Sure.

WILLIAM JONES: Okay. So, and this is just me trying to be – sometimes I can be a robot, so forgive me for that ahead of time. I understand and I've heard you bring concerns. One of the things, like from a data capture portion – and I know y'all know this, but just being real objective – if we know that we have 50 of these bad documentation practices on informed consent, for example, if we know that we have 50, by going through and QCing every chart, when we put forth a plan, a new process or whatever, that 50, by the end of the next week, should maybe be 5. By the end of two weeks should be none existing.

[00:05:00]

But right now, what I'm seeing, objectively, we haven't even finished quantifying the number of errors and categorizing the number of what types of errors we're seeing because in my mind, it looks like it's something new every day. It's something new, I mean, we thought it was documentation and people scratching out stuff. Oh, but it's documentation, people scratching off and initialing way over here on the right, on Thursday. Next Tuesday, after QCing 500 more charts, it feels like, then it's not only that and them initially way over to the east, or yeah, it's them also snaking everything. And it's not just in one site, it's also in Houston and it's also – and we need to talk about that, and we need to compile all of that. And we don't have the numbers, the numbers of staff, and we don't have the numbers of incident. We don't have an incident rate. And I feel like what we're asking for is something that really is called an incident rate. And we're using different terms. And we're trying to categorize it.

MARNIE: I'm probably – I'm obviously not explaining myself.

WILLIAM JONES: That's how it appears in my mind. So when we actually do put forth a plan, a process, which I know that you know how to do, and I know you know how to fix it, but if we start fixing it before we have the final numbers, we really don't know the impact of the change. We really don't know. We know it's a clean up on our file. We know that. And we know that it's significant. It is. There's – we're gonna get some kind of letter of information at least, when the FDA gets here. Know it.

BROOK JACKSON: Okay.

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MARNIE: Does that make more sense? I'm obviously not explaining myself well. I'm trying to find –

WILLIAM JONES: But that's what I'm hearing. What I'm hearing is, is that she's providing information but the numbers is what they're really getting at –

MARNIE: It's not the specifics, is what I'm trying to get to. That's why the tracker I thought was so important, because we can plug that information in there, and then filter it so we can see, "Okay, all these findings..."

BROOK JACKSON: Yeah, but now we stopped that because it was like, "Okay, we just need to get these out of the charts." So then, my spreadsheet changed from tracking to checking off that those things were done, that they were scanned, and to EDC, EDC has been updated.

MARNIE: Right.

WILLIAM JONES: So, this is what – and see, this is my fault then. I own this part. This is where my communication or lack thereof comes in. Because once I finish [PH] locking this out, on Fridays I've dedicated for communication and data. Just dumping everything into the tracking system. I didn't expect the travel for Houston. I didn't expect to find what I found in Houston and to have to do an immediate training in Houston. But it has always been my plan and intent to put everybody's data into the Excel spreadsheet. And remember, because I know I said I was gonna do that, I just haven't even gotten to that yet.

BROOK JACKSON: That's everybody's – that's everybody's excuse. And I hate that because I feel like that has like a bad connotation behind it.

WILLIAM JONES: No.

BROOK JACKSON: But it's everybody's reason.

WILLIAM JONES: Yeah.

BROOK JACKSON: And their understanding.

WILLIAM JONES: I have put forth effort towards doing that, especially for tomorrow, and I'm moving more of that out so that I can make progress.

BROOK JACKSON: So, finally, I was given – things were taken off of my plate that were taking, like, a long time. So really today was – has been the only like real day that I've had to –

MARNIE: Like, I saw you diving in the charts. Yeah.

BROOK JACKSON: I mean, I did 16 – I mean, I am QCing. But it's like here and there.

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MARNIE: And we saw you, no, we see it.

WILLIAM JONES: 16 is impressive.

MARNIE: No, I see it. And again, I'm – I guess the reason I am, I'm talking to you now because I've got to talk about all of these things and you're with me, and that's why I'm bringing all of them up now. But –

BROOK JACKSON: But if you – if you guys don't see what I'm seeing. If like, get on Google. Google "Warning Letters." Google them.

WILLIAM JONES: Yeah. Yeah.

MARNIE: No, I know what you're saying. I do. Again –

BROOK JACKSON: And when I'm on our calls, and I hear that, I know from Christie and Olivia that they knew, that they pushed you hard, and we didn't have the infrastructure to protect our patients, that's a problem. And if you think that I am not loyal or that I have some ill intent, I've only been here for 13 days. Imagine how some of these other people feel that feel overwhelmed and overworked and you know, cry every day. If they're ever questioned, do you think they're gonna have –

[00:10:03]

like, Ventavia at the top? No, they're just gonna let it go. If they're ever asked a question where they could potentially like maybe you know, go one direction, you know, and protect [INDISCERNIBLE] them or they could go completely the other and not.

MARNIE: Well, first, I don't think you have ill intent.

BROOK JACKSON: I don't!

MARNIE: I can't speak for everyone.

BROOK JACKSON: I'm not that kind of person.

MARNIE: I don't think anyone thinks you have ill intent. I can tell you that. And second –

BROOK JACKSON: Somebody does. Because the question was asked. What my intent was.

MARNIE: Well, and maybe that was my poor choice of words, and I apologize. It's – for me, as a manager, I want to make sure I'm understanding everybody's intentions, for whatever they do. Whether it's taking photos, I apologize if it sounded the way it did. And I apologize. I just – that's why I started off with, "I feel like I know the answer, because I just, you know, it seems obvious to me, but I need to know your opinion." It's just what I value – that's how I evaluate.

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BROOK JACKSON: I haven't been afraid to give my opinion to anybody and I never will.

MARNIE: No, and I appreciate it. But let me back up, because I want to make sure I say – I don't think you have ill intent. I don't think anyone thinks that. But Christie and Olivia also do not – they have patient safety as number one.

BROOK JACKSON: No, they don't.

MARNIE: I do believe that.

BROOK JACKSON: I do not. Because I have heard them on the phone say that they knew that we did not have the patient room, we did not have the staff, we did not have the things in place that were needed to make sure that we did this. I've heard them say that.

MARNIE: Okay, I haven't heard that, to the description of what you're saying. I'm saying, we have recognized that yes, we are busy, we have a – it's so fast moving, we've been enrolling so many patients, we've got a new space that we're gonna be looking at that's gonna be so much better. We do have a space issue. But they would never put patient safety at risk. I can guarantee that. I feel very confident in that. [INDISCERNIBLE] your opinion –

BROOK JACKSON: Well, putting patients in the hallway, Marnie, without supervision.

MARNIE: Well, okay, so again, and that's another issue is, I would say, again, and I know –

BROOK JACKSON: What am I doing to –

MARNIE: I know you've been stretched thin, but no, my statement would be, okay, I never understood that they weren't checking on patients and I never understood that they were talking to patients about PHI in the hall. Now, I would never imagine they would do that. Now that you're bringing it to the attention, we've got to fix it. So that's what I mean by when you're at the site, go ahead and knock that out. And keep a list, because – and that's why I keep saying, "Keep a list." Because there's so many things we need to work on. That's the only reason why I say that. Not to put off like, "Oh, just add it to a list." That's not what I mean. I mean, track the concerns that you're seeing, because we can't get to all of them and that's why I'm saying it, Brook. I can't – we can't expect you to fix everything. Just like we can't expect –

BROOK JACKSON: You're asking me to though. Because it's everything –

MARNIE: I know. No. What I'm asking is, the items that you truly feel like are warning letter, and I feel like you're very experienced to know, then let's tackle those.

BROOK JACKSON: But that's what I'm saying, that I don't think that everyone quite understands that it's not just one particular thing. It –

MARNIE: What would you suggest we do then? And that's what my question is –

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BROOK JACKSON: Part of it we're doing.

MARNIE: Okay, so do you feel like, do you feel that way? Like, are you more comfortable with what we're doing is going to correct those major concerns that you have?

BROOK JACKSON: I think we're working towards that, yes. Yes.

MARNIE: Okay, well that makes me feel better. And I will relay that back too, because again, any time anyone says "Warning Letter" "shutdown" people freak.

BROOK JACKSON: Okay.

MARNIE: And for valid reasons. I mean, it is – and again, I'm not saying I'm – I don't blame you.

BROOK JACKSON: I hope that no matter what comes from me, or William, or whatever, however this came about, I hope it's eye opening, because on your call – your last training call, your question was you wanted anybody to feel like they could welcome their family member in here for participation in one of our studies and could you feel comfortable doing that right now? Would you? I wouldn't. No.

WILLIAM JONES: I thought you were asking me – I remember, yes, when I asked the question.

BROOK JACKSON: You asked that question, yeah, and I think it's a great question. That's a great question, that stops and makes you think. Like, would you let – would you? I would if I was a coordinator and I could make sure that doctor [PH] Guk stayed where he was supposed to, you know?

[00:15:01]

Because it's not the vaccine that concerns me, it's our process, etc. But I mean, I've been open, I've been honest. You know –

MARNIE: Yeah, and we appreciate that.

BROOK JACKSON: And I think if y'all spend some time, you know, looking at – and you've gone through audits, you've gone through audits.

MARNIE: Uh huh.

BROOK JACKSON: You've been a part of these. But there have been warning letters, and it's not just they come in and you know, a 483 is issued. There is like a process. There's interviews, it's so cool. And I can't – like eventually, like, this is what I want to do in my career. And then they take that information – the investigator like takes that information back and then they have

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that investigator's boss review those findings and from those come warning letters. So it's not like they just immediately come in and you get a warning letter. So, it's a progressive thing. So, I think that's – I think that's been misunderstood by some, and shutdown has been misunderstood by some. So, again, it's not that I said those were gonna happen right away, but you know, there could be, like, that progression of things happening. And, it's not just one thing that could justify their recommendation. It could be that we ...

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BROOK JACKSON: And then they take that – the investigator like takes that information back and then they have that investigator’s boss review those findings and from those come warning letters. So it’s not like they just immediately come in and you get a warning letter. So, it’s a progressive thing. So, I think that’s – I think that’s been misunderstood by some, and shutdown has been misunderstood by some. So, again, it’s not that I said those were gonna happen right away, but you know, there could be, like, that progression of things happening. And, it’s not just one thing that could justify their recommendation. It could be that we have all the [PH] Capas that we have, that you know –

WILLIAM JONES: A lot of note to files.

BROOK JACKSON: A lot of note to files.

MARNIE: I know, I know. That’s why –

BROOK JACKSON: We have an emergency response protocol that we’re not following. It says in that protocol that we have an epi dose range on everybody’s chart. That’s not there. They’re gonna look at – and especially –

MARNIE: And I saw that you emailed Mercedes, right, about that. I just saw that – I didn’t see that before.

BROOK JACKSON: Especially –

MARNIE: You sent it yesterday, I think.

BROOK JACKSON: Uh huh. Yeah.

MARNIE: Okay, so this is what I’m talking about. This is what helps.

BROOK JACKSON: Okay, so you haven’t checked your emails.

MARNIE: I know. I know. I’m behind on email, I will say. But I do – I get – this is what need.

BROOK JACKSON: I have 39, just like that.

MARNIE: Okay.

BROOK JACKSON: I have 39 drafts, just like that, that I haven’t been able to send!

MARNIE: Oh, drafts, I’m sorry, I was thinking, okay – then I need to – okay. Well, can you send them? I mean, can you print it so we can – again, I guess the way I look at it is I’m wanting to see, okay, when I say, “Listen up, emergency response email” – that’s one piece. COVID, that’s another one. Missed, you know, lab samples. You know, how many? There’s five patients? That’s what I’m saying, like, and then we can priori -

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BROOK JACKSON: And it's just like everybody's running around like chickens with their heads cut off and you know –

WILLIAM JONES: If I can jump in real quick, I think one of the things, look, how do you prioritize when there's a lot of dysfunction?

MARNIE: Right.

WILLIAM JONES: And here's the thing. If there was a list of all of these urgent things, because what I had – the only things that I could see – I don't look at the clinical contents. I don't have...

MARNIE: Correct.

WILLIAM JONES: I mean, I'm over the QC patients. So, you see – you have a different aspect than I do.

BROOK JACKSON: I don't mean to interrupt you, but when I was talking about wrong drug, there are patients that were randomized to the wrong strata.

MARNIE: Like, can you point them out, in terms of PC?

BROOK JACKSON: I need to find them, okay?

MARNIE: Okay, and that's what I'm getting at.

BROOK JACKSON: That's what I'm looking for.

MARNIE: So we can look at them?

BROOK JACKSON: These are just situations that I know have happened, because of what I've looked at in EDC.

MARNIE: Oh, okay.

BROOK JACKSON: But I just haven't had a – that's what I told you [INDISCERNIBLE] and I were doing tonight is looking through that.

MARNIE: Okay.

BROOK JACKSON: EDC, and so I can make –

MARNIE: [INDISCERNIBLE] you're looking for those details, but that's fine.

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BROOK JACKSON: Marnie, we don't talk that – I don't have access to you that much and I just, I'm trying.

MARNIE: Okay, and I know you are. I know. And I'm sorry I – I can't –

BROOK JACKSON: I just –

MARNIE: Tell you enough how sorry I am that you're taking it in this way.

BROOK JACKSON: Well, I'm an expert, okay. Do I make mistakes? Yes. But I've been doing this for a very long time and I'm responsible and I'm trustworthy and for all of those attributes, to be questioned, it just is – makes me very upset.

MARNIE: But then again, it's not being questioned.

BROOK JACKSON: You did – you did question my intent.

MARNIE: Remember, I told you –

BROOK JACKSON: And why I haven't – why I haven't brought these things to your attention.

MARNIE: No, no –

BROOK JACKSON: They're very important.

MARNIE: I'm not saying you haven't brought. You've told, we've talked about concerns. I'm saying details. Again, like identifying, when you say those stratifications, which patients? So we can grab them and fix it. That's what I hear you saying.

BROOK JACKSON: I hear you –

MARNIE: Because we need to fix it. If it's a warning level potential, in your opinion, my point is, grab those patients and let's fix it.

[00:05:00]

And then the next one, whatever the next big item. If it's the missing lab samples, or the COVID plan, let's grab that. Let's look at it and let's implement fixes, that's what I mean. Is those specifics. Because I don't know how to help you until I know the details. And I know you're experienced to know exactly what to do and that's why I said, "Come off the calls, that's fine –

BROOK JACKSON: Okay, we had an action plan.

MARNIE: Yes.

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BROOK JACKSON: We've had an action plan, and that was starting today I knew that I was gonna be here late, working, so I started later and then I sat on the phone with Mercedes for an hour on the side of the highway, so we could work out that detail. And then I stopped by Walmart because they felt like they wanted that table, and I was like, "I need to get this for them." And bought the snacks, so everybody could do their training and not have to leave for lunch and have Uber, you know, Eats coming and – I'm trying.

MARNIE: I know you are. And thank you for doing that. Because I know they really appreciated that. Truly. Okay, let's – are we finished here? Are you good? For now? It's late. We can regroup tomorrow?

WILLIAM JONES: I appreciate your efforts. And I appreciate you sharing. And what I'm hearing, I honestly, I think that there is a communication thing that's there, that honestly, is part of teams forming, storming, norming and performing. I remember – yeah, you remember that?

MARNIE: I know.

WILLIAM JONES: So, and I mean, I know Brook you know this too. It's just we're still forming. I celebrate my third week tomorrow – being here – so I got you by a few days. A few. And when I tell you I can identify with a lot of the stressors, what really needs to happen I heard here, and she's kind of giving you a prioritization list. Anything with patient information, or patient safety as a primary concern. That's what you need to – let's drop everything and focus there first. That's what I'm hearing you say.

MARNIE: Yes, please, yes. Because I trust your opinion. I do trust your opinion of your concerns. And it's hard for me when I don't have the details, because I don't – I don't know what to do – how to help you. I know you know how to fix it, with your experience. So when you tell me that, and that's where the confusion, I think, again, when we're not handling that instead of everything else, that's where the confusion comes in.

BROOK JACKSON: It's just a – it's just, there's just a lot of contradicting statements that you're making and –

MARNIE: Right now?

BROOK JACKSON: Uh huh. Yeah.

MARNIE: Like what? For example, just so I know.

BROOK JACKSON: You know, if I find a problem, fix it, or bring it to someone's attention. I feel like I've brought them to your attention, multiple times, Marnie. I've talked to Candy about them –

MARNIE: Okay, I feel like you're back into the – but that's what I'm saying. You're telling me a generalized statement of certain problems. You see what I'm saying? Like, the dosing piece.

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You never gave me details of what you were talking about. So all I know to tell you is go find it. I've asked you several times to go locate which patients you're talking about in terms of how these major findings – we're already working on the other, you know, overall. Because there's all the issues. But in terms – that's why I'm saying, you stop what you're doing, and focus on what is immediate –

BROOK JACKSON: I needed to know where to prioritize my time. And we talked about that.

MARNIE: Right. And then we did that today.

BROOK JACKSON: And then yesterday we implemented a plan for me to dive in here and –

MARNIE: Yes.

BROOK JACKSON: And get that information to you.

MARNIE: Yes.

BROOK JACKSON: And that's what I'm doing.

MARNIE: Okay, perfect. I feel like now we're on the same track, right? I think we did it. Don't be on the calls, don't worry about the daily –

BROOK JACKSON: I wasn't on the call.

MARNIE: I know, I'm just recapping. That was the plan. Because I see it and I understand it, and I know when I was trying to dive into Ft. Worth, the only – there were so many things, I felt like what you probably feel like. It's hard to even –

BROOK JACKSON: I don't think so.

MARNIE: Well, and I don't mean it in terms of that, I mean in terms of understanding, "Okay, there's this huge list of things and I don't even know where to begin. Because there are so many priorities.

[00:10:01]

There are so many tasks and responsibilities." That's why I said, do what – I wanted you to do what I was trying to do, that I couldn't, is dive into Ft. Worth, don't worry about the email, the calls. I will keep you posted about anything on our calls or ask questions, like I did earlier to get feedback about whatever is needed. You focus on the site. But – the priority is those emergent findings that you're seeing. I need you to focus on – not just me, we need you to focus and use your expertise and knowledge, address those patient findings that you're speaking of. And I'll handle emergency response, COVID, I'll start looking at that. And the hard part too is because I've been pulled to Keller and I apologize. That's – again – the situation of –

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BROOK JACKSON: I understand. I get it.

MARNIE: You need to dive into QCs, so I don't want you to feel neglected in any way.

BROOK JACKSON: I understand, but I don't –

MARNIE: Good. I think moving forward let's regroup tomorrow, stick with the plan, don't worry about the call. Don't worry about email right now unless, if there's something urgent I'll let you know. Or any of us, I'll just tell everyone – I mean, I already did pretty much, on our call this morning.

BROOK JACKSON: [INDISCERNIBLE]

MARNIE: We can get you quickly if we need to.

BROOK JACKSON: Do you feel like that leadership knew about this before, like I said anything on that – on our call that morning?

MARNIE: You mean about what? The –

BROOK JACKSON: Like, findings and just any, like, that this was – like any of this, to this magnitude was going on? You know?

MARNIE: And that's what I want you to realize, is you're new, I don't think you realize how valuable you are so far, because you just came in and had –

WILLIAM JONES: Fresh eyes. You found so much!

MARNIE: The confidence to speak up and they listen to you.

BROOK JACKSON: And I didn't just take – I didn't just take –

MARNIE: They listen to you and they took action. So I hope you realize that –

BROOK JACKSON: But I went to – I went to Candy especially and asked her, like, “Do you – are you seeing what I'm seeing?” “Yeah. Yeah, we've brought this up before.” And I just – you know? Why hasn't she been writing this down for you guys?

MARNIE: I mean, she'll you know, she'll write down concerns, and again –

BROOK JACKSON: She's been monitoring the blinded stuff.

MARNIE: Yeah, and whenever she has concerns, she brings them up, we address them, but no, the magnitude, no. And I think you're coming in at just the right time because we need your

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expertise at this current time, because I think, like I said, it's changed a lot, even since I started to really dive into Fort Worth, since you started, because that was before COVID really hit. And – actually, it was at the beginning of it. And so, people weren't to the level of stress that they are that you're seeing now. Because not only – and you have to remember, well, you may not know...

BROOK JACKSON: And this isn't just like – this isn't just me like – like I feel like you have this gift with people, calming them down, talking to them from like an HR perspective.

MARNIE: I don't feel like it right now.

BROOK JACKSON: Well, it's because my integrity is being questioned, but the [PH] Burleson's, I mean, all this stuff just coming up here at once. I don't – that's just not me.

MARNIE: Okay.

BROOK JACKSON: But I went to my counterpart Candy and asked her the same question, "Are you concerned?" And she said, "Yeah." So, are you interviewing her?

MARNIE: I will. Uh huh. And I've talked to her, but yeah, I mean, I will. I'll –

BROOK JACKSON: Has she addressed the immediate things? Like, I just want to – it's – I just keep treeing to remind myself, "God Brook, you're only here, you've only been here 13 days." And I don't have access to systems and you know, I got locked out here the other night because I didn't have key fob and sat in the parking lot, then I stayed here till 12:30 and I worked till 3:00 when I got home and I just, that's just me though. You will always get 110%.

MARNIE: Yeah.

BROOK JACKSON: Even today. After – after you made me feel this way.

MARNIE: Well, again, I apologize. I would never want you to feel your integrity –
[OVERLAY]

BROOK JACKSON: And I think this is coming, it's coming from, it's not just coming from you. I really don't feel like that. I feel like some of it's – I mean, I don't know where it's coming from. But I took your advice and I talked to Mercedes today and I felt like we were at this different spot, and then I get a text message when I'm –

[00:15:00]

I just feel like – I feel like I'm being targeted because I said something.

MARNIE: No.

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BROOK JACKSON: I really absolutely do.

MARNIE: Well, again, I'm sorry that it came across that way. I think we're just – we're handling –

BROOK JACKSON: You don't even know the half of it.

MARNIE: We're handling – and again, I guess, don't feel singled out. We're just [OVERLAY]

BROOK JACKSON: I feel targeted. I really do.

MARNIE: ... everyone, Brook, but well, but it's not a target.

BROOK JACKSON: I said something and now like –

MARNIE: We just need to understand it. And I think that's the problem, is until we can really see it, which I think we are, you're giving more detail, I'm seeing it more. Like I told you, I see it now that we're talking about it.

BROOK JACKSON: It's not that I have not been trying to give you details, it's like I haven't been able to dive in. I can give you these –

MARNIE: Okay.

BROOK JACKSON: You know, things that have been shared with me and you know, I don't have access. So I have to sit over the shoulder of somebody and then that's dependent on how many patients they're seeing a day. So I could give you a million reasons why, but at the end of the day, they're just excuses and until ...

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MARNIE: Yes, I know. I get it, I get it. Trust me. That I get so much. That's what I'm trying to tell you is, and I told leadership this morning, it's the same way I felt – I could not really do – I couldn't even get my hands, I couldn't get my hands wrapped around even what was going on at Fort Worth, even just being at the site every day, until I – unless I let go of everything. And I think you need to do that. And we support it. Completely support it. And I just lost my train of thought, where I was going.

BROOK JACKSON: You were telling leadership...

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MARNIE: Yeah, just the same thing that, you know, I feel like you're in the same boat that I felt, where it's almost like I couldn't even explain. Kind of like you're saying, like right now. I couldn't really give the details, because there was just so much, I couldn't even explain it. And I couldn't wrap my brain around things. So, I know what you're feeling in that regard, and so that's why I'm saying, dive into the site, keep doing what you're doing. Prioritize right now those major findings that we can tackle and fix. Oh, I know where I was going. And now –

BROOK JACKSON: I don't even know, like, where they are. Where – like, I mean, the like charts are –

WILLIAM JONES: Here's the thing. I don't know if y'all ever – maybe y'all probably heard this one. *Five Dysfunctions of a Team*, by Patrick Lencioni – we have to pick something. Because if it's all important then none of it is important. You have to pick something.

MARNIE: Yeah.

WILLIAM JONES: What I hear from you and the passion that I'm hearing when you're talking about this stuff is stuff centered around patient – immediate patient safety.

BROOK JACKSON: Which they already know, William.

WILLIAM JONES: Yeah, but as far as the granularity, but details and [INDISCERNIBLE] –

MARNIE: Yeah, that's the piece that.

WILLIAM JONES: That's you.

BROOK JACKSON: Okay, if we're gonna talk about just the safety, the safety of the patient component, they know that they don't have the rooms to manage the number of patients that their recruitment goals that they're putting for these sites.

MARNIE: That's –

WILLIAM JONES: So what would be your recommendation? As the expert?

BROOK JACKSON: As the expert – you just –

MARNIE: Hold that thought. And, what are you seeing that has led to that's a safety issue –

WILLIAM JONES: The causality.

MARNIE: That you've seen, that's gonna be a warning letter? That's what I mean. That detail. So we can target –

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BROOK JACKSON: But nobody would ever know if we were putting patients in the hallway and they weren't being monitored. But –

MARNIE: But they are, they are being checked on. See that's what I mean, like, they are.

BROOK JACKSON: Marnie, no, they're not.

MARNIE: They are! Because I see them out there. When I'm coming and going, I'm seeing people out there all the time. They are but, now, do we have it documented? That's where I would say, "Okay..." That's what I mean by go find – okay, that's a concern. Are we documenting it? Is it clear? So we can speak to that. But anyway, I'm going to have to get going. I'm sorry.

BROOK JACKSON: You can go, yeah.

MARNIE: I mean, I don't want to stop y'all, but –

WILLIAM JONES: [INDISCERNIBLE]

MARNIE: What I was getting at is now we know why you don't have access, is because of the employee forms. So I sent the email to Katie –

BROOK JACKSON: Access?

MARNIE: To like the – all the systems, to getting your key, getting your fob. I sent that to Katie, copied you, so you have them and I told you she's probably going to [INDISCERNIBLE]

BROOK JACKSON: Oh was it – I mean I guess I was procrastinating – not because I didn't want to because I just was trying to do other things. And I'm like okay, it's a –

MARNIE: Well, I sent her an email, to leadership to let them know that I didn't realize either. I don't know where that [INDISCERNIBLE] – that must have been a misunderstanding.

[00:05:00]

I think you said you didn't get...

WILLIAM JONES: I didn't. Yeah.

MARNIE: I don't –

BROOK JACKSON: And then I didn't sign my forms because I had questions about them. Because they're processes that we're not following and I wasn't comfortable doing that.

MARNIE: Well, and that's what I want to talk about. That's what I want – if you bring your binder, where you flagged that. Let's go over it. Because you know, like I told you, the Ops

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manual is being revised, you might know there's things in there that we – that are not, you know, that need to be revised. But I would – I do want your feedback on that. So we can fix it.

WILLIAM JONES: See, I don't – I'm sorry. I just – hey, I'm a single dad. I have to rush home and get my kids and stuff, so.

MARNIE: I know, I know, I'm sorry. And I do too. I just realized that –

WILLIAM JONES: And they are texting me like crazy. But here's the thing. I don't want to – I don't want to see anything less than authentic in a teammate. So Brook, I mean, if you wanna talk about it, I got about an hour and a half drive home.

BROOK JACKSON: We've talked about it.

MARNIE: Do you really – you have an hour and a half?

WILLIAM JONES: Yeah.

BROOK JACKSON: We've talked about it.

WILLIAM JONES: Yeah.

MARNIE: Okay.

WILLIAM JONES: Goodness.

MARNIE: Sorry, I don't mean to rush off. I just didn't realize how late it was and I thought, "Oh my gosh, I'm supposed to get home." So – let's –

BROOK JACKSON: If anybody ever questions something that they are going in my bag to look for, please bring it to my attention.

MARNIE: Going into what?

BROOK JACKSON: If somebody's going through my stuff and they see something that they have a question about, please address it. Please ask that person to bring it to my attention.

MARNIE: Oh, of course, well, I don't know – I need to get more detail, but I don't think they realized it was your bag until after. Until – because you were the only one sitting there.

BROOK JACKSON: No I wasn't. Mercedes was been here, Dana's been there. [INDISCERNIBLE] has been there. William's been in here, you've been in here. What do you mean they didn't realize it was my bag?

MARNIE: I mean, I'm saying I don't think they knew who's bag it was that –

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BROOK JACKSON: Then how did they realize that it was mine then? How did it come up?

MARNIE: Can I give you – can I find out for you? I don't want to misspeak.

BROOK JACKSON: I don't wanna know. I just – please relay the message. If they know it's mine, and there's a question about what's in my bag, bring it to my attention.

MARNIE: Okay.

BROOK JACKSON: [INDISCERNIBLE] because –

MARNIE: And I think, I mean, someone confirmed it was your bag, but I can't. I'm just relaying. And that's why – that's why I'm asking you. Because it was confirmed it was your bag.

BROOK JACKSON: Well, you know, I get my stuff and I'm upstairs and I grab my stuff and I come back down here, so I just –

MARNIE: I know, and you could have grabbed something off the copier. It's okay. It's just, again, it's just trying to understand. And the reason for that is because we've had – I'm not saying that you're taking charts, but we've had missing charts. We've had you know, we've had occurrences like this before that people don't realize that they grabbed other documents from other sites. I mean... I could – you know, again, I can get more detail. I just was told it was – the person didn't know it was your bag.

BROOK JACKSON: I don't want any more details. I really don't think I can handle it.

MARNIE: Okay, so, are you gonna go home and –

BROOK JACKSON: Yeah, I'm gonna go home.

MARNIE: Okay, all right. Well, I'll touch base with you in the morning. Okay? Thank you again for all this stuff.

BROOK JACKSON: You're welcome.

MARNIE: I appreciate you bringing all that. And I know they really appreciate it, I can tell you that. Okay, William, thank you. And we'll figure out unblinding tomorrow. That's obviously, if that's okay.

WILLIAM JONES: Sure.

MARNIE: I feel like I'm okay to stay blinded, but I mean, if y'all feel like I need to –

WILLIAM JONES: Have you deleted everything? Have you –

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MARNIE: Yeah, she said she deleted it. I didn't ever open her – but she sent me the photos, but since I'd already –

BROOK JACKSON: You asked me to.

MARNIE: What?

BROOK JACKSON: You asked me to.

MARNIE: What?

BROOK JACKSON: To send you the pictures.

MARNIE: No, I know. I'm saying, yes, no, that was appropriate. I'm saying I didn't actually pull them up – I didn't look at them when she sent them to me, for that reason.

WILLIAM JONES: Okay.

MARNIE: But, I saw on her phone, when she showed me enough to see that yes, there is Neils in there, it had an open [INDISCERNIBLE] drug. Now, I didn't visually see the numbers, like what they were, but I could tell that there were identifiers on them. So, I think that's why we were questioning like if I should maybe –

BROOK JACKSON: I mean, y'all are like splitting hairs. Because if you really, like, wanna talk about who's –

MARNIE: About what, I'm sorry?

BROOK JACKSON: I'll put it –

WILLIAM JONES: Blinded and everything?

BROOK JACKSON: I'll put it on my list.

MARNIE: Y'all have a great night and thank you so much.

WILLIAM JONES: Thanks Marnie. You have a good evening too.

MARNIE: Do you all mind [INDISCERNIBLE]

Ex. 4

<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES Food and Drug Administration</p> <p>INVESTIGATIONAL NEW DRUG APPLICATION (IND) <i>(Title 21, Code of Federal Regulations (CFR) Part 312)</i></p>	<p>Form Approved: OMB No. 0910-0014 Expiration Date: March 31, 2022 <i>See PRA Statement on page 3.</i></p> <p>NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)</p>
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1. Name of Sponsor	2. Date of Submission (mm/dd/yyyy)
--------------------	------------------------------------

3. Sponsor Address	4. Telephone Number (Include country code if applicable and area code)
Address 1 (Street address, P.O. box, company name c/o)	6A. IND Number (If previously assigned)
Address 2 (Apartment, suite, unit, building, floor, etc.)	
City	State/Province/Region
Country	ZIP or Postal Code
5. Name of Drug (Include all available names: Trade, Generic, Chemical, or Code)	
Continuation Page for #5	

7A. (Proposed) Indication for Use	Is this indication for a rare disease (prevalence <200,000 in U.S.)? <input type="checkbox"/> Yes <input type="checkbox"/> No	
	Does this product have an FDA Orphan Designation for this indication? <input type="checkbox"/> Yes <input type="checkbox"/> No	If yes, provide the Orphan Designation number for this indication: <input style="width: 100px;" type="text"/>
		Continuation Page for #7

7B. SNOMED CT Indication Disease Term (Use continuation page for each additional indication and respective coded disease term)

8. Phase of Clinical Investigation to be conducted Phase 1 Phase 2 Phase 3 Other (Specify): _____

9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314), Drug Master Files (21 CFR Part 314.420), and Biologics License Applications (21 CFR Part 601) referred to in this application.

10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..	Serial Number _____
--	------------------------

11. This submission contains the following (Select all that apply)

<input type="checkbox"/> Initial Investigational New Drug Application (IND)	<input type="checkbox"/> Response to Clinical Hold	<input type="checkbox"/> Response To FDA Request For Information
<input type="checkbox"/> Request For Reactivation Or Reinstatement	<input type="checkbox"/> Annual Report	<input type="checkbox"/> General Correspondence
<input type="checkbox"/> Development Safety Update Report (DSUR)	<input type="checkbox"/> Other (Specify): _____	

Protocol Amendment	Information Amendment	Request for	IND Safety Report
<input type="checkbox"/> New Protocol	<input type="checkbox"/> Chemistry/Microbiology	<input type="checkbox"/> Meeting	<input type="checkbox"/> Initial Written Report
<input type="checkbox"/> Change in Protocol	<input type="checkbox"/> Pharmacology/Toxicology	<input type="checkbox"/> Proprietary Name Review	<input type="checkbox"/> Follow-up to a Written Report
<input type="checkbox"/> New Investigator	<input type="checkbox"/> Clinical/Safety	<input type="checkbox"/> Special Protocol Assessment	
<input type="checkbox"/> PMR/PMC Protocol	<input type="checkbox"/> Statistics	<input type="checkbox"/> Formal Dispute Resolution	
<input type="checkbox"/> Human Factors Protocol	<input type="checkbox"/> Clinical Pharmacology		

12. For Originals, is the product a combination product (21 CFR 3.2(e))? <input type="checkbox"/> Yes <input type="checkbox"/> No	Combination Product Type (See instructions)	Request for Designation (RFD) Number
---	---	--------------------------------------

13. Select the following only if applicable. (Justification statement must be submitted with application for any items selected below. Refer to the cited CFR section for further information.)

<input type="checkbox"/> Emergency Research Exception From Informed Consent Requirements, 21 CFR 312.23 (f)		<input type="checkbox"/> Individual Patient, Non-Emergency 21 CFR 312.310
<input type="checkbox"/> Charge Request, 21 CFR 312.8		<input type="checkbox"/> Intermediate Size Patient Population, 21 CFR 312.315
		<input type="checkbox"/> Individual Patient, Emergency 21 CFR 312.310(d)
		<input type="checkbox"/> Treatment IND or Protocol, 21 CFR 312.320

Expanded Access Use, 21 CFR 312.300

For FDA Use Only		
CBER/DCC Receipt Stamp	DDR Receipt Stamp	Division Assignment
		IND Number Assigned

14. Contents of Application – This application contains the following items <i>(Select all that apply)</i>			
<input type="checkbox"/> 1. Form FDA 1571 (21 CFR 312.23(a)(1)) <input type="checkbox"/> 2. Table of Contents (21 CFR 312.23(a)(2)) <input type="checkbox"/> 3. Introductory statement (21 CFR 312.23(a)(3)) <input type="checkbox"/> 4. General Investigational plan (21 CFR 312.23(a)(3)) <input type="checkbox"/> 5. Investigator’s brochure (21 CFR 312.23(a)(5)) <input type="checkbox"/> 6. Protocol (21 CFR 312.23(a)(6)) <ul style="list-style-type: none"> <input type="checkbox"/> a. Study protocol (21 CFR 312.23(a)(6)) <input type="checkbox"/> b. Investigator data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572 <input type="checkbox"/> c. Facilities data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572 	6. Protocol (Continued) <ul style="list-style-type: none"> <input type="checkbox"/> d. Institutional Review Board data (21 CFR 312.23(a)(6)(iii)(b)) or completed Form FDA 1572 <input type="checkbox"/> 7. Chemistry, manufacturing, and control data (21 CFR 312.23(a)(7)) <ul style="list-style-type: none"> <input type="checkbox"/> Environmental assessment or claim for exclusion (21 CFR 312.23(a)(7)(iv)(e)) <input type="checkbox"/> 8. Pharmacology and toxicology data (21 CFR 312.23(a)(8)) <input type="checkbox"/> 9. Previous human experience (21 CFR 312.23(a)(9)) <input type="checkbox"/> 10. Additional information (21 CFR 312.23(a)(10)) <input type="checkbox"/> 11. Biosimilar User Fee Cover Sheet (Form FDA 3792) <input type="checkbox"/> 12. Clinical Trials Certification of Compliance (Form FDA 3674)		
15. Is any part of the clinical study to be conducted by a contract research organization? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, will any sponsor obligations be transferred to the contract research organization? <input type="checkbox"/> Yes <input type="checkbox"/> No If Yes, provide a statement containing the name and address of the contract research organization, identification of the clinical study, and a listing of the obligations transferred <i>(use continuation page)</i> .			
Continuation Page for #15			
16. Name and Title of the person responsible for monitoring the conduct and progress of the clinical investigations			
17. Name and Title of the person responsible for review and evaluation of information relevant to the safety of the drug			
<p>I agree not to begin clinical investigations until 30 days after FDA’s receipt of the IND unless I receive earlier notification by FDA that the studies may begin. I also agree not to begin or continue clinical investigations covered by the IND if those studies are placed on clinical hold or financial hold. I agree that an Institutional Review Board (IRB) that complies with the requirements set forth in 21 CFR Part 56 will be responsible for initial and continuing review and approval of each of the studies in the proposed clinical investigation. I agree to conduct the investigation in accordance with all other applicable regulatory requirements.</p>			
18. Name of Sponsor or Sponsor’s Authorized Representative			
19. Telephone Number <i>(Include country code if applicable and area code)</i>		20. Facsimile (FAX) Number <i>(Include country code if applicable and area code)</i>	
21. Address		22. Email Address	
Address 1 <i>(Street address, P.O. box, company name c/o)</i>		23. Date of Sponsor’s Signature <i>(mm/dd/yyyy)</i>	
Address 2 <i>(Apartment, suite, unit, building, floor, etc.)</i>			
City	State/Province/Region		
Country	ZIP or Postal Code		
24. Name of Countersigner			
25. Address of Countersigner		26. Email Address	
Address 1 <i>(Street address, P.O. box, company name c/o)</i>		WARNING : A willfully false statement is a criminal offense (U.S.C. Title 18, Sec. 1001).	
Address 2 <i>(Apartment, suite, unit, building, floor, etc.)</i>			
City	State/Province/Region		
Country United States of America	ZIP or Postal Code		
27. Signature of Sponsor or Sponsor’s Authorized Representative		28. Signature of Countersigner	
<input type="text"/> Sign		<input type="text"/> Sign	

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Office of Operations
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Please do NOT send your completed form to this PRA Staff email address.

Ex. 5

<p>DEPARTMENT OF HEALTH AND HUMAN SERVICES FOOD AND DRUG ADMINISTRATION</p> <p>STATEMENT OF INVESTIGATOR (TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312) (See instructions on reverse side.)</p>	Form Approved: OMB No. 0910-0014 Expiration Date: March 31, 2022 See OMB Statement on Reverse. NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).
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1. NAME AND ADDRESS OF INVESTIGATOR			
Name of Clinical Investigator			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED (Select one of the following.)	
<input type="checkbox"/> Curriculum Vitae	<input type="checkbox"/> Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED			CONTINUATION PAGE for Item 3
Name of Medical School, Hospital, or Other Research Facility			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY			CONTINUATION PAGE for Item 4
Name of Clinical Laboratory Facility			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

5. NAME AND ADDRESS OF THE INSTITUTIONAL REVIEW BOARD (IRB) THAT IS RESPONSIBLE FOR REVIEW AND APPROVAL OF THE STUDY(IES)			CONTINUATION PAGE for Item 5
Name of IRB			
Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

6. NAMES OF SUBINVESTIGATORS (If not applicable, enter "None")			
CONTINUATION PAGE – for Item 6			

7. NAME AND CODE NUMBER, IF ANY, OF THE PROTOCOL(S) IN THE IND FOR THE STUDY(IES) TO BE CONDUCTED BY THE INVESTIGATOR			

8. PROVIDE THE FOLLOWING CLINICAL PROTOCOL INFORMATION. (Select **one** of the following.)

- For Phase 1 investigations, a general outline of the planned investigation including the estimated duration of the study and the maximum number of subjects that will be involved.
- For Phase 2 or 3 investigations, an outline of the study protocol including an approximation of the number of subjects to be treated with the drug and the number to be employed as controls, if any; the clinical uses to be investigated; characteristics of subjects by age, sex, and condition; the kind of clinical observations and laboratory tests to be conducted; the estimated duration of the study; and copies or a description of case report forms to be used.

9. COMMITMENTS

I agree to conduct the study(ies) in accordance with the relevant, current protocol(s) and will only make changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

I agree to personally conduct or supervise the described investigation(s).

I agree to inform any patients, or any persons used as controls, that the drugs are being used for investigational purposes and I will ensure that the requirements relating to obtaining informed consent in 21 CFR Part 50 and institutional review board (IRB) review and approval in 21 CFR Part 56 are met.

I agree to report to the sponsor adverse experiences that occur in the course of the investigation(s) in accordance with 21 CFR 312.64. I have read and understand the information in the investigator's brochure, including the potential risks and side effects of the drug.

I agree to ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

I agree to maintain adequate and accurate records in accordance with 21 CFR 312.62 and to make those records available for inspection in accordance with 21 CFR 312.68.

I will ensure that an IRB that complies with the requirements of 21 CFR Part 56 will be responsible for the initial and continuing review and approval of the clinical investigation. I also agree to promptly report to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others. Additionally, I will not make any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

I agree to comply with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements in 21 CFR Part 312.

**INSTRUCTIONS FOR COMPLETING FORM FDA 1572
STATEMENT OF INVESTIGATOR**

1. Complete all sections. Provide a separate page if additional space is needed.
2. Provide curriculum vitae or other statement of qualifications as described in Section 2.
3. Provide protocol outline as described in Section 8.
4. Sign and date below.
5. FORWARD THE COMPLETED FORM AND OTHER DOCUMENTS BEING PROVIDED TO THE SPONSOR. The sponsor will incorporate this information along with other technical data into an Investigational New Drug Application (IND). INVESTIGATORS SHOULD NOT SEND THIS FORM DIRECTLY TO THE FOOD AND DRUG ADMINISTRATION.

10. DATE (mm/dd/yyyy)

11. SIGNATURE OF INVESTIGATOR

Sign

(WARNING: A willfully false statement is a criminal offense. U.S.C. Title 18, Sec. 1001.)

The information below applies only to requirements of the Paperwork Reduction Act of 1995.

The burden time for this collection of information is estimated to average 100 hours per response, including the time to review instructions, search existing data sources, gather and maintain the data needed and complete and review the collection of information. Send comments regarding this burden estimate or any other aspect of this information collection, including suggestions for reducing this burden to the address to the right:

Department of Health and Human Services
Food and Drug Administration
Office of Operations
Paperwork Reduction Act (PRA) Staff
PRASStaff@fda.hhs.gov

"An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB number."

DO NOT SEND YOUR COMPLETED FORM TO THIS PRA STAFF EMAIL ADDRESS.

Ex. 6

Investigational Product Manual

Protocol Number C4591001

IND: 19736

EudraCT Number: 2020-002641-42

Phase 2/3

**A PHASE 1/2/3 PLACEBO-CONTROLLED,
RANDOMIZED, OBSERVER-BLIND, DOSE-FINDING
STUDY TO EVALUATE THE SAFETY, TOLERABILITY,
IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2-
RNA VACCINE CANDIDATES AGAINST COVID-19 IN
HEALTHY ADULTS**

ATTENTION: The active supplies are shipped and stored at ultra-cold temperatures of -80 to -60°C (-112 to -76 °F). See section 5.2 of this manual for ultra-cold handling requirements before unpacking



Worldwide Research & Development

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Quality Assurance Approver

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Revision History

Version	Version Date	Summary of changes
1.0	30JUN2020	Not applicable – first version
2.0	21JUL2020	<p>Cover page:</p> <ul style="list-style-type: none"> Update Protocol name to name in Protocol Amendment 4, 30 June 2020. <p>Approvals</p> <ul style="list-style-type: none"> Revised name of Supply Chain lead approver <p>Source Documents</p> <ul style="list-style-type: none"> Update protocol to C4591001 Clinical Protocol Amendment 4, 30 Jun 2020 Update Impala Quick Reference Guide to V4 05 Jul 2020 <p>Acronyms/Terms/Definitions</p> <ul style="list-style-type: none"> Updated acronyms to add ISF and SSID <p>Section 3 Investigational Product and Study Overview</p> <ul style="list-style-type: none"> Update Figure 1 Schema to align with Protocol Amendment 4 Update label and product pictures to those that potentially will be used to support Stage 2/3 <p>Section 3.2 Ancillary Items Required for Investigational Product</p> <ul style="list-style-type: none"> Update text to provide guidance that Sponsor will provide 0.9% sodium chloride for use as diluent at clinical sites. Revised the recommended needles for dose preparation to 21 Gauge 1 inch or 1.5 inches in length Added a statement to ensure that the participant specific blinded label is not only blinded to the product name, but also to the dose and final injection volume. <p>Section 4 Interactive Response Technology</p> <p>Added a description of the available 3-page laminated tool that may be used as a reference when performing the randomization and drug assignment functions in IMPALA.</p>

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Version	Version Date	Summary of changes
2.0	21 JUL 2020	<p>Section 5.2 Product Receipt</p> <ul style="list-style-type: none"> • Removed reference to Mylar pouch. • Added, “In circumstances where a transfer of IP inventory from one clinical site to another clinical site is required, shipping conditions will be different. Detailed instructions on how to proceed will be sent to both donating and receiving sites, as needed.” • Remove these sentences since they do not apply to this study. “Impala (IRT) is able to accept both a missing or damaged temperature monitor entry, In these cases the kits are quarantined in the system until it can be determined if an excursion has taken place.” • Replace text “and sending both pages to the email address indicated on that page” with “sign, date, and file in the Investigator Site File (ISF), <p>Section 8.1 Drug Dispensing per Visit</p> <ul style="list-style-type: none"> • Added colored label descriptions for the BNT162 Vaccine Vials <p>Section 8.3 General Preparation Guidelines</p> <ul style="list-style-type: none"> • Added a statement to remind sites that dose preparation must occur in an area that is isolated from blinded site personnel and the participants to maintain the study blind <p>Section 8.6 Preparation and Administration of IP</p> <ul style="list-style-type: none"> • Added a few statements to the list of Key Points <ul style="list-style-type: none"> ○ Reminder to ensure dose preparation occurs in an isolated area ○ Preparation of the 10 mcg dose using the 0.3 mL/vial configuration required the use of an ISO5 environment or better • Added colored label descriptions to the IP descriptions in the supplies table • Revised the preparation needle recommendations to 21 G 1 inch or 1.5 inches in length

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<p>2.0</p>	<p>21 JUL 2020</p>	<p>Section 5.2 Product Receipt</p> <ul style="list-style-type: none"> Removed reference to Mylar pouch. Added, “In circumstances where a transfer of IP inventory from one clinical site to another clinical site is required, shipping conditions will be different. Detailed instructions on how to proceed will be sent to both donating and receiving sites, as needed.” Remove these sentences since they do not apply to this study. “Impala (IRT) is able to accept both a missing or damaged temperature monitor entry, In these cases the kits are quarantined in the system until it can be determined if an excursion has taken place.” Replace text “and sending both pages to the email address indicated on that page” with “sign, date, and file in the Investigator Site File (ISF), <p>Section 8.1 Drug Dispensing per Visit</p> <ul style="list-style-type: none"> Added colored label descriptions for the BNT162 Vaccine Vials <p>Section 8.3 General Preparation Guidelines</p> <ul style="list-style-type: none"> Added a statement to remind sites that dose preparation must occur in an area that is isolated from blinded site personnel and the participants to maintain the study blind <p>Section 8.6 Preparation and Administration of IP</p> <ul style="list-style-type: none"> Added a few statements to the list of Key Points <ul style="list-style-type: none"> Reminder to ensure dose preparation occurs in an isolated area Preparation of the 10 mcg dose using the 0.3 mL/vial configuration required the use of an ISO5 environment or better Added colored label descriptions to the IP descriptions in the supplies table Revised the preparation needle recommendations to 21 G 1 inch or 1.5 inches in length Added a statement to ensure that the participant specific blinded label is not only blinded to the product name, but also to the dose and final injection volume.
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Version	Version Date	Summary of changes
2.0	21 JUL 2020	<p>Section 8.6.1 Preparation of BNT162 Vaccine 10 mcg, Using Syringe to Syringe Dilution</p> <ul style="list-style-type: none"> Added a statement to ensure the blinded participant specific label is not only blinded to the product name, but also to the dose and final injection volume. Provided instructions to add the SSID of each participant who is dosed from the same vial on a single preparation record <p>Section 8.6.2 Preparation of BNT162 Vaccine 20 mcg and 30 mcg with the 0.3 mL/vial Using Syringe to Syringe Dilution</p> <ul style="list-style-type: none"> Revised the title to reflect that the instructions in this section are for preparation of the 20 mcg and 30 mcg doses with the 0.3 mL/vial configuration using in-vail dilution Added a statement to ensure the blinded participant specific label is not only blinded to the product name, but also to the dose and final injection volume. Provided instructions to add the SSID of each participant who is dosed from the same vial on a single preparation record <p>Section 8.6.3 Preparation of Placebo for BNT162 Vaccine (0.9% Sodium Chloride, USP)</p> <ul style="list-style-type: none"> Added a statement to ensure the blinded participant specific label is not only blinded to the product name, but also to the final injection volume. <p>Section 9 Investigational Product Accountability</p> <ul style="list-style-type: none"> Added a statement to inform sites that prepopulated IPALs will be provided for the active vaccine candidates, placebo, and the diluent.

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<p>3.0</p>	<p>29 July 2020</p>	<p>Revision History of Previous Version</p> <ul style="list-style-type: none"> Revision history in previous version (21JUL2020) mentioned an increase in thaw time, but was not made within the body of the document until now. <p>Cover page:</p> <ul style="list-style-type: none"> Updated Protocol name to name in Protocol Amendment 5, 24 July 2020. <p>Approvals</p> <ul style="list-style-type: none"> Revised name of Study Manager approver <p>Source Documents</p> <ul style="list-style-type: none"> Updated to Protocol Amendment 5 Updated to reflect new version of the Impala Quick Reference Guide to V5.0 24Jul 2020. Updated to reflect new version of the Dosage and Administration Instructions to V5.0, 28 July 2020. <p>Acronyms/Terms/Definitions</p> <ul style="list-style-type: none"> Updated BNT to single candidate Updated acronyms to add LNP – Lipid nanoparticle and VE – Vaccine Efficacy <p>Section 3 Investigational Product and Study Overview</p> <ul style="list-style-type: none"> Updated text to align with Protocol Amendment 5 Updated Figure 1 Schema to align with Protocol Amendment 5 Updated label and product pictures to those that will be used to support Stage 2/3 <p>Section 3.1 Pfizer Supplied Investigational Products</p> <ul style="list-style-type: none"> Updated table to remove BNT162b1 candidate and add BNT162b2 0.2 ml presentation Updated product pictures to remove BNT162b1 candidate and add BNT162b2, 0.2 ml presentation <p>Section 3.2 Pfizer Ancillary Items Required for Investigational Product</p> <ul style="list-style-type: none"> Updated table to remove BNT162b1 candidate and add BNT162b2 0.2 ml presentation Updated product pictures to remove BNT162b1 candidate and add BNT162b2 0.2 ml presentation. Added a note to indicate the rationale for why the <i>Participant Specific Blinding Labels</i> do not reflect the single BNT162b2 candidate, blinded dose, and final injection. The sponsor-provided <i>Participant Specific</i>
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<p>3.0</p>	<p>29 July 2020</p>	<p><i>Blinding Labels</i> were created in advance of the Phase 2/3 start. Therefore, the labels provided to the site and the images throughout the IP Manual do not reflect “BNT162b2 Vaccine 30 mcg or Placebo” or the final injection volume of 0.3 mL.</p> <p>Section 5.2 Product Receipt</p> <ul style="list-style-type: none"> Removed references to the BNT162b1 candidate and added the BNT162b2 0.2 mL/vial presentation. <p>Section 5.2.1 Temperature Excursions During Shipment</p> <ul style="list-style-type: none"> Created this section to describe process to manage temperature excursion for site shipments. <p>Section 6.1 Storage and Temperature Monitoring of Investigational Product at a Clinical Site</p> <ul style="list-style-type: none"> Updated description from BNT162b1 candidate to BNT162b2, 0.2 mL/vial presentation <p>Section 6.2 Temperature Excursions During Site Storage</p> <ul style="list-style-type: none"> Renamed this section Edited text for clarity Removed reference to BNT162b1 Highlighted <i>Almac Clinical Services Site Temperature Excursion Form</i> <p>Section 8: Dosage and Administration Instructions</p> <ul style="list-style-type: none"> Added “b2” to the BNT162 Vaccine descriptions as it is the candidate/construct that has been identified to be evaluated in Phase 2/3. Added the BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial) configuration <p>Section 8.1: Drug Dispensing per Visit</p> <ul style="list-style-type: none"> Removed the BNT162b1 candidate vial and added the BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial) configuration to the dispensing table along with its corresponding colored label description Removed the 60 day window for Vaccination #2 <p>Section 8.3: General Preparation Guidelines</p>
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<p>3.0</p>	<p>29 July 2020</p>	<ul style="list-style-type: none"> • Removed any text referencing the syringe to syringe dilution method as only the in-vial dilution method will be used for dose preparation in Phase 2/3. • Revised the in-use stability for doses that are prepared outside of an ISO5 environment, such as a tabletop or countertop, from 1 hour to 6 hours. <p>Section 8.4 In-Use Shelf Life and Storage Requirements for BNT162b2 Vaccine and Placebo Vials</p> <ul style="list-style-type: none"> • Increased the thaw time of the frozen BNT162b2 Vaccine vials from approximately 20 minutes to 30 minutes <p>Section 8.5 In-Use Shelf Life and Storage of Prepared Active and Placebo Dosing Solutions</p> <ul style="list-style-type: none"> • Removed any references to diluted solutions using the syringe to syringe method • Revised the in-use period of all diluted active and placebo solutions to reflect 6 hours, regardless of the preparation occurring within or outside of an ISO5 environment or better <p>Section 8.6 Preparation and Administration of IP</p> <ul style="list-style-type: none"> • Revised section description to indicate the information will cover dose preparation and administration instructions for the BNT162b2 30 mcg vaccine or Placebo. • Revised the list of videos in Firecrest to reflect the availability of the Dose Preparation and Administration of the BNT162b2 30 mcg or Placebo Dose Using the In-Vial Dilution Method • Edited the list of Key Points: <ul style="list-style-type: none"> ○ Listed the two BNT162b2 vial configurations and their corresponding fill volumes. The 0.3 mL/vial configuration has a 0.5 mL fill volume, while the 0.2 mL/vial has a 0.2 mL fill volume. ○ Removed any references to the BNT162b1 construct, syringe to syringe dilution method, as well as the 10 mcg and 20 mcg dose levels ○ Removed the requirement for a hood/biosafety cabinet as the 10 mcg dose has been removed. The use of a hood/biosafety cabinet is recommended and should be used if sites have access to an ISO5 environment or better. If a hood/biosafety cabinet is not available, sites may
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<p style="text-align: center;">3.0</p>	<p style="text-align: center;">29 July 2020</p>	<p>prepare the IP on a tabletop or countertop in an isolated area where there are no blinded site staff or participants.</p> <ul style="list-style-type: none"> ○ Added a reminder to allow refrigerated dosing solutions to reach room temperature prior to administration to prevent discomfort from injection of a cold solution and to maintain the study blind since the placebo is a room temperature solution. ○ Added a clarification regarding the ~30-minute wait time, which is only when the first prepared dose is for placebo in order to prevent any potential unblinding. ● Revised the table of supplies that are required for dose preparation <ul style="list-style-type: none"> ○ Removed the BNT162b1 vial and added the BNT 162b2 Vaccine 0.2 mL/vial configuration ○ Removed the 10 mL syringe and the fluid dispensing connector since the 10 mcg dose will not be prepared <p>Section 8.6.1 Preparation of BNT162b2 Vaccine (Active) 30 mcg Using the BNT162b2 Vaccine Concentrate for Solution for Injection (0.3 mL/vial)</p> <ul style="list-style-type: none"> ● Revised the title of this section as the preparation instructions for the 10 mcg dose level using the syringe to syringe dilution method was removed and replaced with the 30 mcg dose in-vial dilution instructions. ● Revised the preparation instructions to dilute the 0.5 mL fill volume in the vial with 2 mL of 0.9% Sodium Chloride to prepare a final diluted dosing solution of 2.5 mL. ● Revised the sufficient excess volume to withdraw from 0.4 mL to 0.35 mL to ensure each prepared 30 mcg dose has a final injection volume of 0.3 mL. This will allow for up to 5 doses to be prepared from the diluted dosing solution. ● Added a statement to allow for the use of a tabletop or countertop for dose preparation and removed any references to the 1 hour limited in-use stability. All IP regardless of the environment in which it was prepared has a 6 hour in-use stability. ● Removed any references to the 20 mcg dose preparation instructions
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<p>3.0</p>	<p>29 July 2020</p>	<ul style="list-style-type: none"> Revised the preparation steps to reflect increase in vial thaw time from approximately 20 to 30 minutes Revised the number of inversions for mixing the thawed vial and the diluted dosing solution from 5 to 10 inversions. <p>Section 8.6.2 Preparation of BNT162b2 Vaccine (Active) 30 mcg Using the BNT162b2 Vaccine Concentrate for Solution for Injection (0.2 mL/vial)</p> <ul style="list-style-type: none"> Revised the title of this section as it reflects the addition of the 30 mcg dose preparation instructions using the in-vial dilution method with the active 0.2 mL/vial configuration <p>Section 8.6.3 Preparation of Placebo for BNT162b2 Vaccine (0.9% Sodium Chloride, USP)</p> <ul style="list-style-type: none"> Added a statement to indicate prepared syringes should be kept refrigerated (2 to 8 °C) if not used immediately. Dosing syringes and diluted solutions that are refrigerated should be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution in the syringe is not cold to the touch. Revised the in-use stability for doses that are prepared outside of an ISO5 environment, from 1 hour to 6 hours. All IP regardless of the environment in which it was prepared has a 6 hour in-use stability. Added a clarification regarding the ~30-minute wait time, which is only when the first prepared dose is for placebo in order to prevent any potential unblinding. <p>Section 8.6.4 Administration of IP</p> <ul style="list-style-type: none"> Added a statement to ensure the equivalent final injection volume prepared is based on the active vial configuration used in dose preparation. Added a table (step 2) describing the recommended excess and final injection volume for the 30 mcg dose that is prepared with the 0.2 mL/vial configuration <p>Section 9 Investigational Product Accountability</p> <ul style="list-style-type: none"> Added a reminder that the empty, flattened cartons that are kept for accountability cannot be destroyed until after the unblinded CRA has performed his/her reconciliation. Destruction of these cartons shall be
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<p>3.0</p>	<p>29 July 2020</p>	<p>documented in the Pfizer Investigational Product Accountability Log or equivalent document along with the initials of the unblinded staff member performing the destruction.</p> <p>Appendices</p> <ul style="list-style-type: none"> • Revised existing <i>Preparation Records</i> <ul style="list-style-type: none"> ○ Replaced Appendices 2, 2A, and 3 with updated versions from Almac. ○ Replaced Appendix 5, which was initially a Preparation Record for the 10 mcg dose using the syringe to syringe dilution method. It has been replaced with the Preparation Record for in-vial dilution using the 0.3 mL/vial configuration. Additional edits made to the Preparation Record include the following: <ul style="list-style-type: none"> ▪ Removed any references to the BNT162b1 and 20 mcg dose level have been removed. The document now reflects preparation of the 30 mcg dose only. ▪ Revised the preparation instructions to dilute the 0.5 mL fill volume in the vial with 2 mL of 0.9% Sodium Chloride to prepare a final diluted dosing solution of 2.5 mL. ▪ Revised the sufficient excess volume to withdraw from 0.4 mL to 0.35 mL to ensure each prepared 30 mcg dose has a final injection volume of 0.3 mL. This will allow for up to 5 doses to be prepared from the diluted dosing solution. ○ Replaced Appendix 6 with new Preparation Record for preparing the 30 mcg dose with the 0.2 mL/vial configuration using in-vial dilution. ○ Revised the number of inversions on all BNT162b2 (active) Preparation Records from 5 to 10 inversions when mixing the thawed vial and the diluted dosing solutions. ○ Increased active BNT162b2 frozen vial thaw time from approximately 20 to 30 minutes. ○ Revised Appendix 7 (Preparation Record for Placebo) to remove the 10 mcg and 20 mcg doses. In addition, the Preparation Record now reflects the equivalent final injection volume that
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Version	Version Date	Summary of changes
		is prepared using the BNT162b2 0.2 mL/vial configuration
4.0	28 AUG 2020	<p>Approvers</p> <ul style="list-style-type: none"> Update Quality Assurance Approver <p>Acronyms/Terms/Definitions</p> <ul style="list-style-type: none"> Added Rest of world (ROW) <p>Section 3.1 Pfizer Supplied Investigational Product</p> <ul style="list-style-type: none"> Added new IP presentation image with purple cap Changed picture of placebo to labeled example. Added to Note to explain the differences in the single panel and booklet labels and in which countries they will or may be used. This information added for both active and placebo Updated pictures of examples of supply to include booklet labels for active and placebo. Updated label and product pictures to those that are in use or will be available including booklet labeled supply. Revised product descriptions to include colors of vial caps and noted that the IP containing vials are equivalent to each other. Added a summary table of packaging configurations to differentiate between active, placebo, and diluent supplies provided in the USA and rest of world (ROW) Added a statement instructing sites to track the lot number and manufacturer when utilizing the site's own supply. Added a description of diluent supplies that are provided in bulk supply (Argentina, Brazil and USA) or as individually labeled clinical supplies ROW (e.g. Germany and Turkey) <p>Section 3.2 Ancillary Items Required for Investigational Product</p> <ul style="list-style-type: none"> Added pictures of bulk and booklet labeled diluent. Updated text to describe provision of diluent and labeling. Updated text to include countries where the different presentations will be used. Revised table of ancillary supplies to remove the 10 mL syringes and fluid dispensing connectors which are no longer needed in dose preparation the previous Participant Specific Blinded Label with the new light green labels which reflect the BNT162b2 30 mcg or placebo dose level. The previous Participant Specific Blinded Label has been replaced with the new light green labels which reflect the BNT162b2 30 mcg or placebo dose level. Revised product descriptions to include colors of vial caps

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Version	Version Date	Summary of changes
		<ul style="list-style-type: none"> • Added a summary table of packaging configurations to differentiate between active, placebo, and diluent supplies provided in the USA and rest of world (ROW) • Added a statement instructing sites to track the lot number and manufacturer when utilizing the site’s own supply. • Added a description of diluent supplies that are provided in bulk supply (Argentina, Brazil and USA) or as individually labeled clinical supplies ROW (e.g. Germany and Turkey) <p>Section 4 Interactive Response Technology</p> <ul style="list-style-type: none"> • Updated text to indicate IRT functions that are performed by blinded and unblinded site personnel • Described laminated tool to support site staff completion of IRT actions • Added reminders to perform the review subject information function at both Vaccination #1 and #2 visits. • Added details to locate Quick Reference Guide. <p>Section 5.1 Product Ordering</p> <ul style="list-style-type: none"> • Text to describe provision and resupply of diluent by Sponsor • Updated Shipping Timelines to include special arrangements for Friday or Monday deliveries. <p>Section 5.2 Product Receipt</p> <ul style="list-style-type: none"> • Added diluent to the list of supplies that need to be acknowledged in the IRT • Replaced ‘Placebo’ with ‘Placebo and Diluent” since receipt process is the same. • Added guidance to download Temperature Monitor Data to Almac TempEZ and evaluate any temperature excursions before completing receipt into IRT system. <p>Section 5.2.1 Temperature Excursions During Shipment</p> <ul style="list-style-type: none"> • Added guidance to contact uCRA for replacement shipment if supplies deemed unacceptable for use. <p>Section 5.3 Lost, Damaged, or Incomplete Shipments</p> <ul style="list-style-type: none"> • Added request for sites to provide photographs of damaged supply to uCRA. <p>Section 5.4 Inventory Management</p> <ul style="list-style-type: none"> • Update number of cartons for BNT162b2 from 10 to 30 to 10 to 100 and for placebo from 10-30 to 20 to 200. • Update to carton dimensions for BNT162b2 from 2 x 2 x 3 inches to 1.4 x 1.4 x 2.3 inches and added mm equivalent measure for both vaccine and placebo cartons • Included dimensions for the packaged diluent vial. <p>Section 6 Storage, Handling, and Temperature Monitoring of IP and Diluent at Clinical Site</p> <ul style="list-style-type: none"> • Added diluent to section header

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Version	Version Date	Summary of changes
		<p>Section 6.1 Storage and Temperature Monitoring of Investigational Product at a Clinical Site</p> <ul style="list-style-type: none"> Added diluent to the list of temperature monitored supplies <p>Section 6.2 Temperature Excursions During Site Storage</p> <ul style="list-style-type: none"> Added text to inform sites that the temperature excursion form is available at the Almac TempEZ Connect website Replaced 'Placebo' with 'Placebo and Diluent' Update guidance for the placebo (0.9 % Sodium Chloride Injection, USP) to increase range from 15 to 25 °C to 15° to 30 °C (59° to 86 °F) based on definition of USP controlled room temperature. <p>Section 8. Dosage and Administration Instructions</p> <ul style="list-style-type: none"> Added clarifying statement regarding IP handling activities that are performed by the unblinded site personnel <p>Section 8.1 Drug Dispensing per Visit</p> <ul style="list-style-type: none"> Revised the vials dispensing table to reflect the use of white single panel and booklet labels. <p>Section 8.2 Investigational Product Dispensing Pilot using Impala Kit Verify Mobile Application</p> <ul style="list-style-type: none"> Added text to indicate the Kit Verify mobile app is available in the USA only. Also, reminded the user that the mobile app can only be used with new vials that are dispensed by the IRT. The mobile app cannot be used to verify container numbers of subsequent doses that are prepared from a previous assigned kit/container number. Added text to remind the user that Kit Verify does not support dose preparation activities and therefore, cannot be used to replace the verification step on dose preparation records. <p>Section 8.4 In-Use Shelf Life and Storage Requirements for BNT162b2 Vaccine and Placebo Vials</p> <ul style="list-style-type: none"> Included vial configurations Revised the number of inversions required after thawing from 5 to 10 in order to mix the concentrate thoroughly <p>Section 8.6 Preparation and Administration of IP</p> <ul style="list-style-type: none"> Key points to note section updated to include “Read the product description on the label to confirm the contents of the vial prior to dose preparation”. Revised the supplies table to reflect the availability of white carton labels on the 0.2 mL/vial supplies Replaced the previous Participant Specific Blinded Label with the new light green labels which reflect the BNT162b2 30 mcg or placebo dose level.

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Version	Version Date	Summary of changes
		<ul style="list-style-type: none"> • Recommended expiry times to assist sites with maintaining the study blind. <p>Section 8.6.2. Preparation of BNT162b2 Vaccine (Active) 30 mcg Using the BNT162b2 Vaccine Concentrate for Solution for Injection (0.2 mL/vial) Configuration</p> <ul style="list-style-type: none"> • Revised Step 1 to reflect the availability of white carton labels on the 0.2 mL/vial supplies • Revised Step 3 to indicate the use of a 1 mL syringe during dilution of the 0.2 mL/vial configuration. • Revised Step 9 to replace the previous Participant Specific Blinded Label with the new light green labels which reflect the BNT162b2 30 mcg or placebo dose level. <p>Section 8.6.3. Preparation of Placebo for BNT162b2 Vaccine (0.9% Sodium Chloride, USP)</p> <ul style="list-style-type: none"> • Revised Step 6 to replace the previous Participant Specific Blinded Label with the new light green labels which reflect the BNT162b2 30 mcg or placebo dose level. <p>Appendix 5: Preparation Record for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.3 mL/vial) Using In-Vial Dilution for Intramuscular Injection</p> <ul style="list-style-type: none"> • Revised the qualifications of the unblinded site staff who are performing dose preparation and completing the verification to be consistent with the protocol. • Added the countries who are using the 0.3 mL/vial supplies that have a yellow carton label • Added a statement to remind the reader not to share the date and start time of dose preparation as it is potentially unblinding • Revised the Preparation Record to allow for unblinded site staff to document and verify preparation steps followed for each syringe • Added page numbers on Preparation Record and corrected date format <p>Appendix 6: Preparation Record for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.2 mL/vial) Using In-Vial Dilution for Intramuscular Injection</p> <ul style="list-style-type: none"> • Revised the qualifications of the unblinded site staff who are performing dose preparation and completing the verification to be consistent with the protocol. • Added the countries who are using the 0.2 mL/vial supplies that have a blue or white carton label • Added a statement to remind the reader not to share the date and start time of dose preparation as it is potentially unblinding

Version	Version Date	Summary of changes
		<ul style="list-style-type: none"> • Revised the Preparation Record to allow for unblinded site staff to document and verify preparation steps followed for each syringe • Added page numbers on Preparation Record and corrected date format <p>Appendix 7: Preparation Record for Placebo (0.9% Sodium Chloride Injection, USP) for Intramuscular Injection</p> <ul style="list-style-type: none"> • Revised the qualifications of the unblinded site staff who are performing dose preparation and completing the verification to be consistent with the protocol. • Added the countries who are using the placebo supplies that have a white label • Added a statement to remind the reader not to share the date and start time of dose preparation as it is potentially unblinding • Revised Steps 2 and 3 to simplify the instructions for withdrawing excess volume that is sufficient to allow for priming and ensure a final injection volume of 0.3 mL. Step 3 captures the “final injection volume” of 0.9% sodium chloride that shall be prepared in a syringe. • Added page numbers on Preparation Record and corrected date format

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Source Documents

This section will only be updated if updates to the source documents impact the information included in this IP Manual. Subsequent amendments or updates that do not impact this IP Manual will not be included as a reference and will not require an update to this section.

1. Dosage and Administration Instructions for BNT162b2 (PF-07302048) Vaccine, 0.5 mg/mL (150mcg/0.3 mL and 250mcg/0.5 mL vials): Version C459-INX100407124- V5.0-28JUL2020.
2. C4591001 Final Protocol Amendment 5, 24JUL2020.
3. Impala Quick Reference Guide for Protocol C4591001: V 5.0
4. C4591001 Third Party Investigational Product Blinding Plan, V5.0 06JUL2020.
5. 0.9% Sodium Chloride Injection, USP [package insert]. Lake Forest, IL: Hospira Inc., November 2018.
6. Ezeanolue E, Harriman K, Hunter P, Kroger A, Pellegrini C. General Best Practice Guidelines for Immunization. Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP). [www.cdc.gov/vaccines/hcp/acip-recs/general-recs/downloads/general-recs.pdf]. Accessed on 16APR2020.
7. United States Pharmacopeia and National Formulary (USP 42-NF 37). Rockville, MD: United States Pharmacopeial Convention; 2008.
8. BioNTech RNA Pharmaceuticals GmbH Pharmacy Manual BNT162-01 Version 02 10JUL2020

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1. Acronyms/Terms/Definitions

Acronym / Term	Definition
AE	Adverse Event
BNT	BioNTech developed the RNA-based vaccine candidate referred to as “BNT162b2” throughout this Investigational Product Manual.
CRA	Clinical Research Associate
CRF	Case Report Form
IP/Study Intervention	IP/Study Intervention includes Investigational Product (IP) (may also be referred to as Study Intervention in the protocol) a non-commercial presentation; comparative agents; concomitant medications; background therapies; or commercial products that are supplied by Pfizer Global Clinical Supply or by approved vendors.
IPAL	Investigational Product Accountability Log
IRC	Internal Review Committee
IRT	Interactive Response Technology encompassing an IWRS (Interactive Web Response System)
ISF	Investigator Site File
LNP	Lipid nanoparticle
modRNA	nucleoside modified RNA
P2 S	SARS-CoV-2 full length, P2 mutant, “heads up”, prefusion spike glycoprotein
POR	Proof of Receipt
RBD	Receptor binding domain
RNA	Ribonucleic acid
ROW	Rest of world
SAE	Serious Adverse Event
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SC	Study Coordinator
SDS	Safety Data Sheet

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SSID	Study Subject ID number
Study Management	Refers to Study Manager and applicable study team roles
uCRA	Unblinded Clinical Research Associate
VE	Vaccine Efficacy

2. Study Contacts

Contact your unblinded Clinical Research Associate (uCRA) with any questions. Refer to the Investigator Site File for study contact information.

3. Investigational Product and Study Overview

The investigational product (IP), PF-07302048, consists of RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARSCoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b), that was developed by BioNTech. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, “heads up,” prefusion spike glycoprotein (P2 S) (version 9), or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5).

The vaccine candidate, encoding P2 S, selected for Phase 2/3, evaluation is BNT162b2 at a dose of 30 mcg.

BNT162b2 is provided as a white to off-white frozen concentrate for solution for injection and packaged in a vial that requires dilution with normal saline (0.9% sodium chloride) prior to injection. The dose preparation requires a one-step dilution process that will be performed in a vial. Single or multiple participant doses may be prepared from that dilution. See Section 8 of this IP Manual for dose preparation and administration instructions.

The study is a Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, and vaccine candidate–selection, and efficacy study in healthy adults. The study will evaluate the safety, tolerability, immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule
- At various dose levels in Phase 1 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: 18 to 85 years of age [stratified as ≤55 or >55 years of age]).

The vaccine candidate will comprise 14,643 vaccine recipients. It is intended that a minimum of 40% of participants will be in the 56 to 85 year stratum. An equal number of participants will receive placebo, i.e. randomized in a 1:1 ratio.

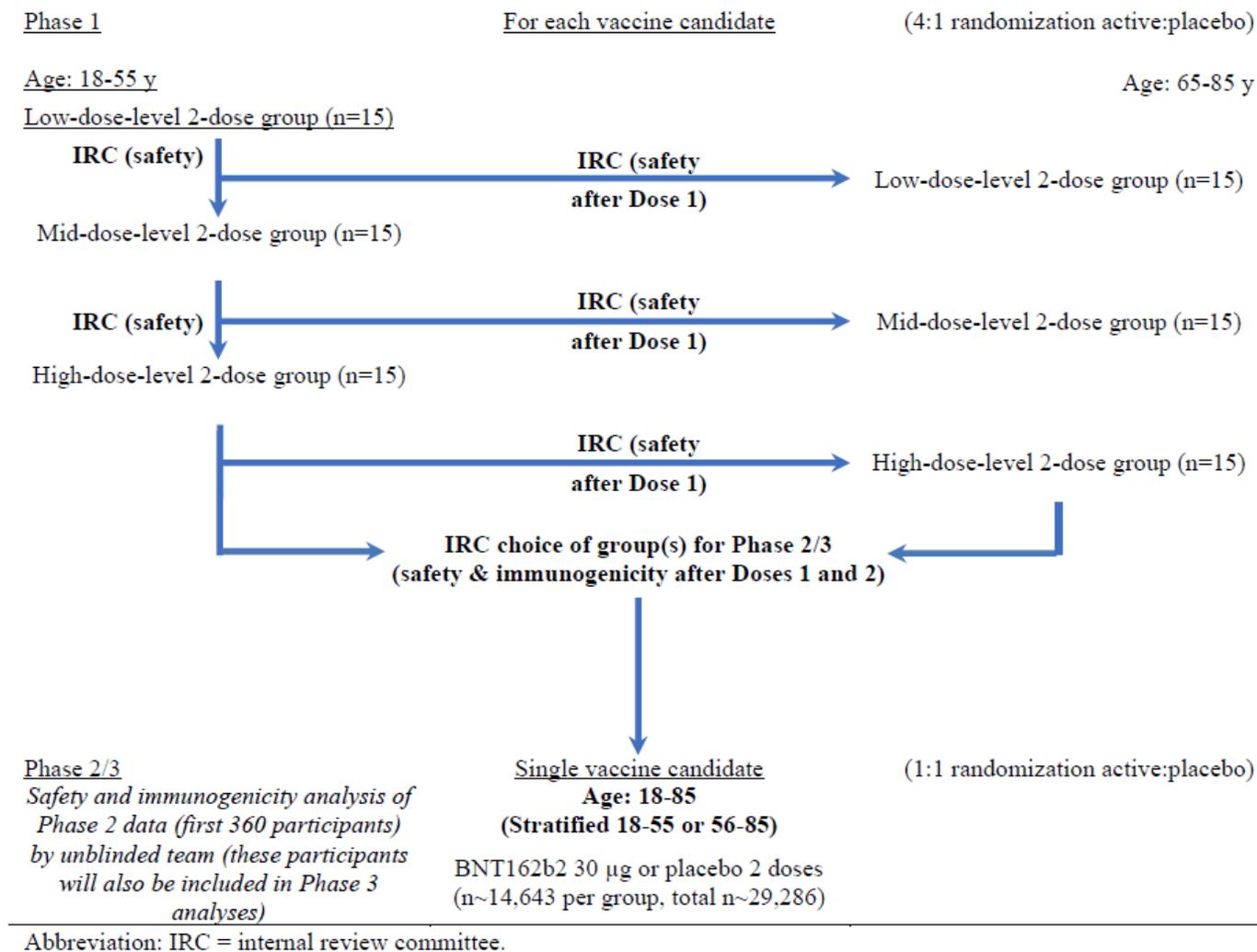
The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator (SC), and other site staff will be

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blinded. Blinded personnel should not have access to the container IDs for the Investigational Product. Only the site staff who will be dispensing, preparing, and administering the IP are unblinded and can have this access.

Please note that this investigational product (IP) manual only covers the Phase 2/3 part of the study.

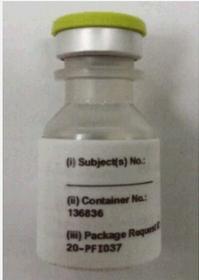
Figure 1. Schema



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3.1. Pfizer Supplied Investigational Products

The table below lists the investigational products (IP, that will be provided during this trial by Pfizer.

Active or Placebo	Product Name	Product Physical Description	Representative Picture of Vial(s)
Active	BNT162 b2 vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial) NOTE: This vial contains a 0.5 mL fill and 0.3 mL extractable volume. The vial has a <i>green</i> flip-off cap.	Concentrate for solution for injection provided as a preservative-free sterile, white to off-white liquid, packaged in a clear glass 2 mL vial.	
	BNT162 b2 vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial) NOTE: This vial contains a 0.2 mL fill volume and 0.2 mL extractable volume. The vial may have a <i>green</i> or <i>purple</i> flip-off cap and the IP containing vials are equivalent to each other.		
Placebo	0.9% Sodium Chloride Injection, USP (10 mL/vial)	Preservative-free, clear colorless solution supplied in a single-dose flip-off plastic vial	

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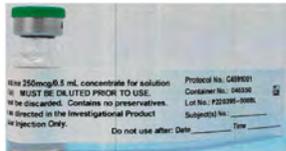
Packaging and Labeling

BNT162b2 Vaccine (Active)

Each BNT162b2 vaccine candidate is packaged into a 2 mL glass vial. Each vial is packaged in a single carton. The vials and cartons are labeled in a way that is consistent with the study design and with the regulatory requirements for each country in which the study is to be performed.

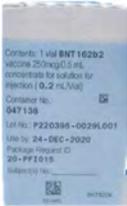
NOTE: All of the BNT162b2 Vaccine labels will describe the contents of the containers. The supply is received at the site as **open labeled** even though the study is **blinded**. Refer to Section 7 for blinding information.

Summary Table of Active, Placebo, and Diluent Product and Configurations

Product Name	Carton Label Color and Type	Vial Label Color/Type and Cap Color	Countries Utilizing Supply
BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial)	Yellow <i>Single Panel</i> 	White <i>Single Panel</i> Green Vial Cap 	Argentina Brazil USA

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Product Name	Carton Label Color and Type	Vial Label Color/Type and Cap Color	Countries Utilizing Supply
<p>BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial)</p>	<p>Blue <i>Single Panel</i></p> 	<p>White <i>Single Panel</i></p> <p>Green or Purple Vial Cap</p> 	<p>Argentina Brazil USA</p>
	<p>White <i>Booklet Label</i></p> 	<p>White <i>Booklet Label</i></p> <p>Purple Vial Cap</p> 	<p>Germany South Africa Turkey</p>
<p>Placebo: 0.9% Sodium Chloride Solution for Injection, USP (10 mL/vial)</p>	<p>White <i>Single Panel</i></p> 	<p>White <i>Single Panel</i></p> 	<p>Argentina Brazil USA</p>
	<p>White <i>Booklet Label</i></p> 	<p>White <i>Booklet Label</i></p> 	<p>Argentina Brazil Germany South Africa Turkey USA</p>

Product Name	Carton Label Color and Type	Vial Label Color/Type and Cap Color	Countries Utilizing Supply
<p>Diluent: 0.9% Sodium Chloride Solution for Injection, USP* (10 mL/vial)</p>	<p>Not Applicable (Bulk Supply, 25 vials per tray)</p> 	<p>Not Applicable (Bulk Supply, 25 vials per tray)</p> 	<p>Argentina Brazil South Africa* USA</p>
	<p>White <i>Booklet Label with Black Dot</i> (1 vial packaged in a single carton)</p> 	<p>White <i>Booklet Label with Black Dot</i></p> 	<p>Germany South Africa* Turkey</p>

*Note: South Africa: Supply configuration for diluent is to be determined

Representative Photos of BNT16b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection

0.3 mL BNT162b2 - Single Panel Label

- **Example of Single Panel Carton Label and Labeled Carton for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.3 mL/Vial)**



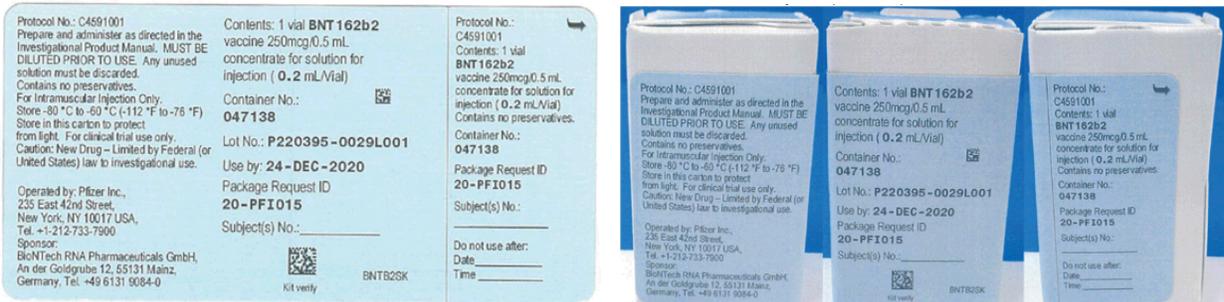
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- Example of Single Panel Vial Label and Labeled Vial for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.3 mL/Vial)



0.2 mL BNT162b2 - Single Panel Label

- Example of Single Panel Carton Label and Labeled Carton for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.2 mL/Vial)



- Examples of Single Panel Vial Label and Labeled Vial for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.2 mL/Vial)



The IP containing green and purple capped vials are equivalent to each other.

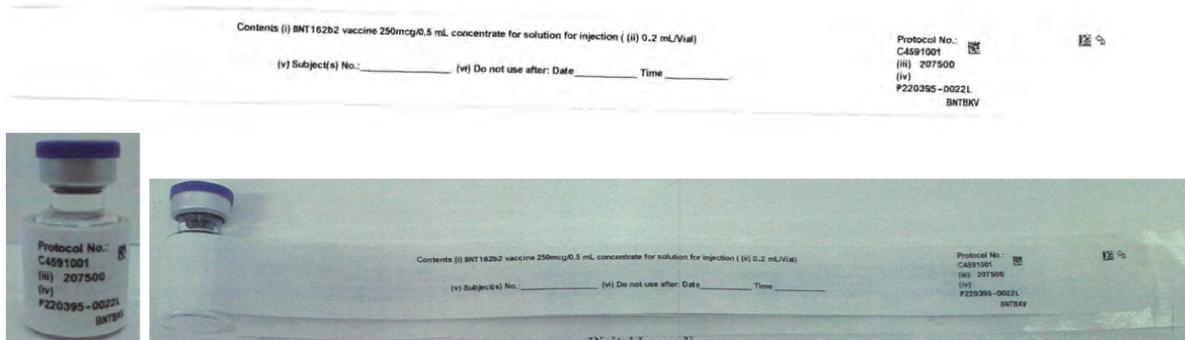
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0.2 mL BNT162b2 - Booklet Label

- **Example Booklet Carton Label and Labeled Carton for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.2 mL/Vial)**



- **Example Booklet Label and Labeled Vial for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.2 mL/Vial)**



**0.9% Sodium Chloride Injection (Placebo) **

0.9% Sodium Chloride Injection, USP (10 mL/vial) will be used as placebo for this study. Each vial is packaged in a single carton. The vials and cartons are labeled in a way that is consistent with the study design and with the regulatory requirements for each country in which the study is to be performed.

NOTE: Supplies will be labeled with a white single panel label that meets US regulatory requirements or with white booklet labels that include separate country panels in the country language that meet the country regulatory requirements. The placebo and labeled diluent presentations are similar in appearance and differ by the presence of a large black dot on the vial and carton label. The placebo vials will be assigned by the IRT based on the container number on the carton label and the diluent vials will not. The contents of the placebo vials should always be confirmed by reading the product description on the label and confirming the container no for the drug assignment (see section 4. Interactive Response Technology).

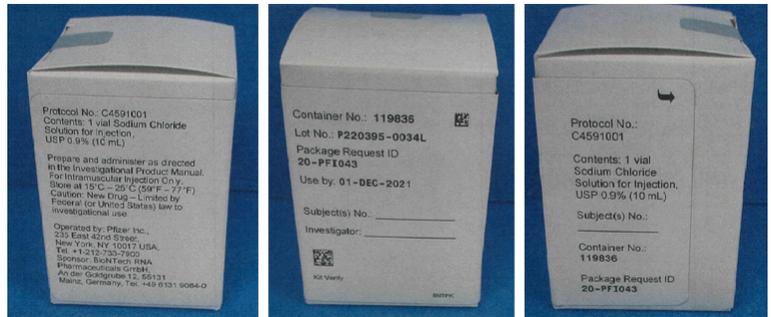
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US single panel labeled supply have been provided for use in Argentina, Brazil, and US. They may be introduced to other countries if agreed to by country regulators. The booklet labeled supplies will be used in all other countries and may be introduced for use in countries currently using the single panel labeled supply.

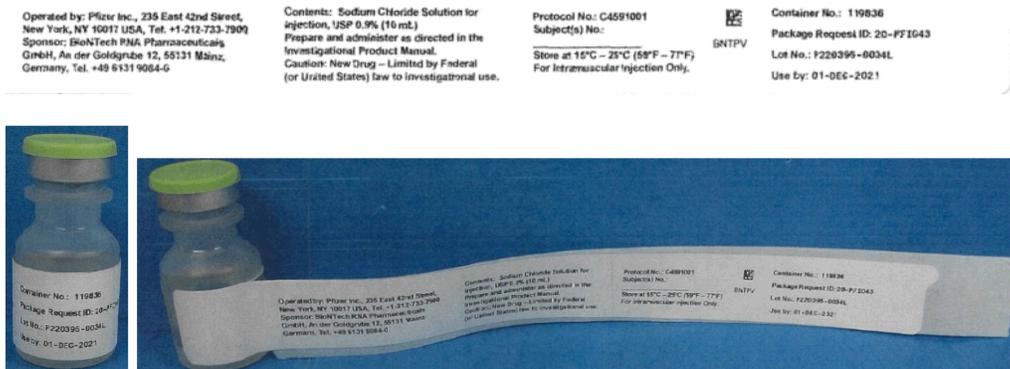
Photo(s) of Placebo (0.9% Sodium Chloride Injection, USP) (10 mL/vial) (Placebo)

0.9% Sodium Chloride, USP (Placebo) - Single Panel Label

- **Example of Single Panel Carton Label and Labeled Carton for 0.9% Sodium Chloride Injection (Placebo)**



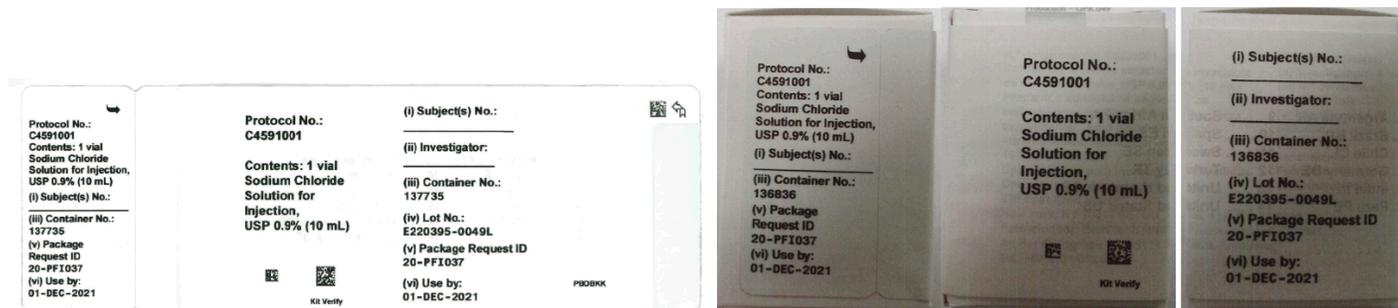
- **Example Single Panel Vial Label and Labeled Vial for 0.9% Sodium Chloride Injection (Placebo)**



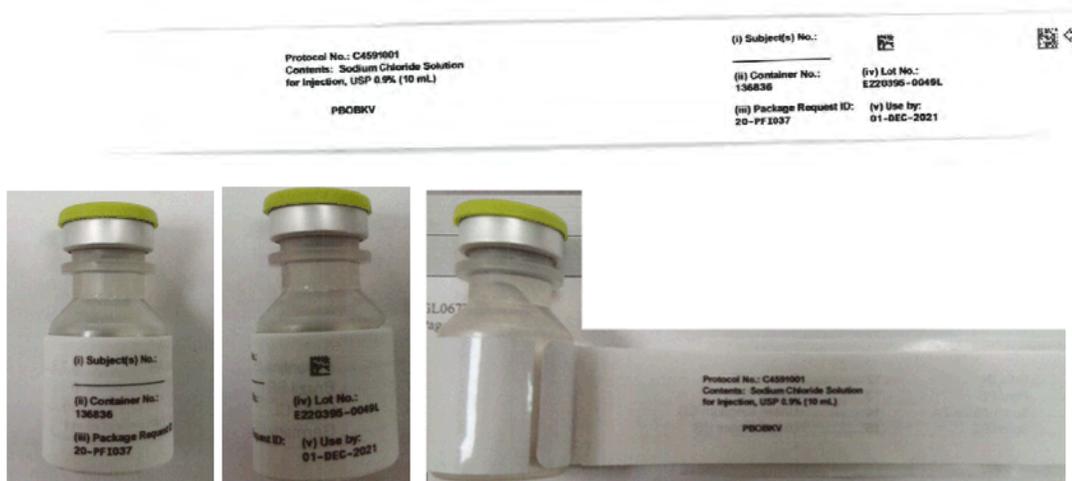
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0.9% Sodium Chloride, USP (Placebo) - Booklet Label

- **Example Booklet Carton Label and Labeled Carton for 0.9% Sodium Chloride Injection (Placebo)**



- **Example Booklet Vial Label and Labeled Vial for 0.9% Sodium Chloride Injection (Placebo)**



3.2. Ancillary Items Required for Investigational Product

In addition to the IP listed previously, the following ancillary items will be required for this study:

0.9% Sodium Chloride Injection, USP to dilute the BNT162b2 concentrate during dose preparation.

Sponsor plans to provide 0.9% Sodium Chloride Injection, USP to dilute the BNT162b2 Vaccine concentrated solution for injection. Initial supply will be provided as trays containing 25 single-dose, (10 mL/vial) plastic flip top vials. Please receive the diluent supplies into Impala to confirm delivery and receipt. If supplies are receipted in as damaged, contact your unblinded CRA to request a new shipment.

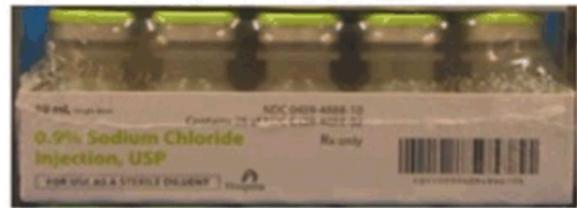
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Under extenuating circumstances, if site does not have access to sponsor provided supplies, they may use their own supply of preservative-free 0.9% Sodium Chloride Injection to dilute the BNT162b2 Vaccine concentrated solution or injection. Sites using their own supply of diluent must track the lot number and manufacturer on the Investigational Product Accountability Log (IPAL)

The US market presentation without any additional labeling for clinical use is being provided for use in Argentina, Brazil, and USA. These supplies may be introduced to other countries if agreed to by country regulators. Other countries, including Germany and Turkey, will be provided diluent that has been labeled for clinical use as summarized below. The diluent vials and cartons will have a large black dot to help distinguish these supplies from the placebo. Although both placebo and diluent supplies include a container ID only the placebo will be assigned by the IRT.

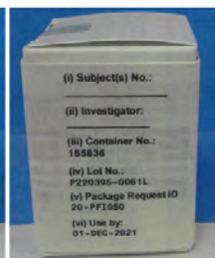
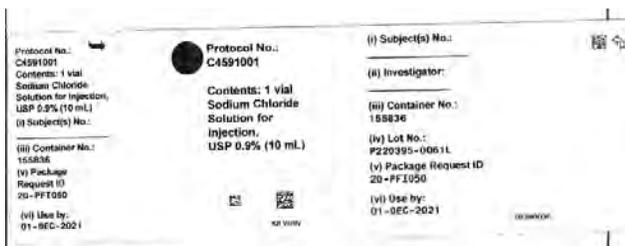
0.9% Sodium Chloride, USP (Diluent) – US Market Presentation

- **US Market Presentation of 0.9% Sodium Chloride Injection (Diluent)**



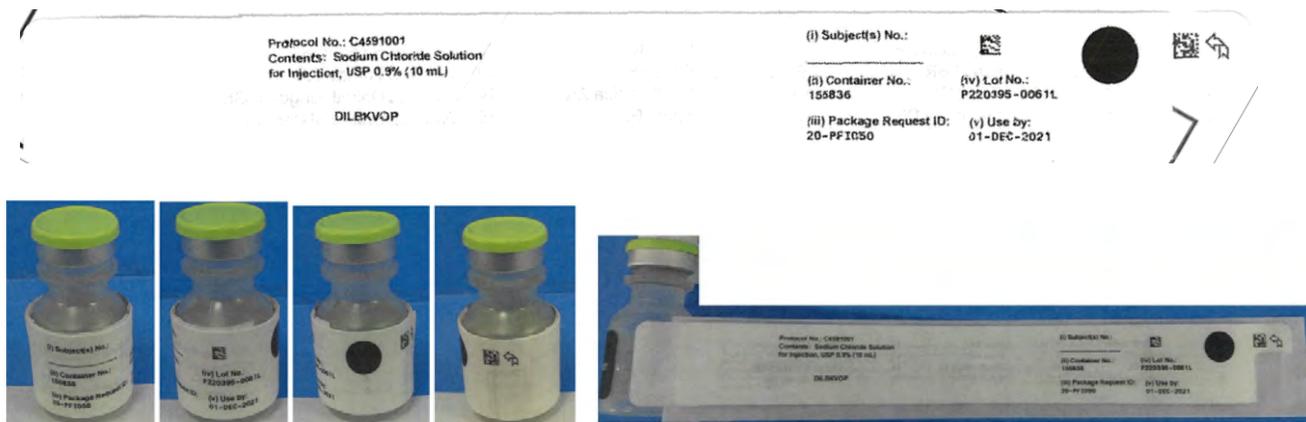
0.9% Sodium Chloride, USP (Diluent) - Booklet Label

- **Example Booklet Carton Label and Labeled Carton for 0.9% Sodium Chloride Injection (Diluent)**



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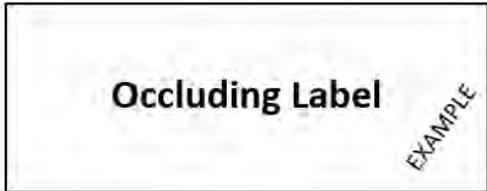
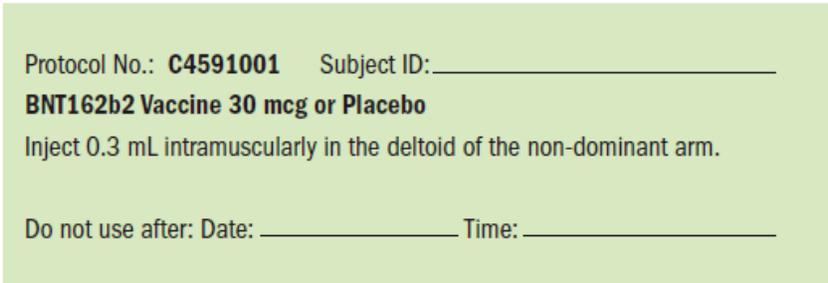
- **Example of Booklet Vial Label and Labeled Vial for 0.9% Sodium Chloride Injection (Diluent)**



In addition to the IP listed previously, the following ancillary items will be required for this study:

Item	Provided By	
	Sponsor	Clinical Site
Alcohol swab/pads	X	
Diluent: 0.9% Sodium Chloride Injection, USP for dilution of BNT162b2 concentrate	X	X
Syringes: Sterile, luer lock, latex free syringes: 1 mL and 3 mL	X	
Sterile Syringe Caps: for storage and transport of prepared syringes	X	
<p>Needles: Sterile, stainless steel needles with appropriate bore size of 25 Gauge (G) or wider.</p> <ul style="list-style-type: none"> • Sterile, stainless steel needles with a bore size of 21 Gauge (1 inch or 1.5 inches in length for dose preparation • Sterile, stainless steel needles with a bore size of 25 G and 1 inch or 1.5 inch length for intramuscular administration <p>NOTE: Sites may also use a 1.5 inch needle for intramuscular administration. Refer to the ACIP guidelines in Section 8.6 (Preparation and Administration) of this IP Manual.</p>	X	

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Item	Provided By	
	Sponsor	Clinical Site
<p>Occluding White Labels: To be applied to the syringe barrel of the prepared BNT162b2 Vaccine or Placebo syringes only. The supplied occluding label must be used for blinding. Do not use other labels or supplies to mask the contents of the syringe.</p> 	X	
<p>Participant Specific Blinded Labels: To be applied to the syringe barrel of all dosing syringes. Use of these supplied Participant Specific Blinded Labels is preferred. However, sites may use their own label if it captures the minimum information shown in the example below and reflects the blinded product name (e.g. BNT162b2 Vaccine 30 mcg or Placebo). The label shall also be blinded to the dose and capture the expiry date and time.</p> <p>Note: Each prepared dosing syringe expires 6 hours from the start of dose preparation. In order to maintain the study blind, the participant specific blinded labels on the final prepared BNT162b2 vaccine and placebo dosing syringes must have the same expiry date and time. See below for recommended expiry times to maintain study blind.</p> 	X	

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4. Interactive Response Technology

The IMPALA Interactive Response Technology (IRT) System is used for participant screening, randomization, shipment receipt acknowledgement, inventory management and for breaking the blind by the blinded site personnel. The IRT system will also manage the expiry of the supplies with regards to dispensing. The system will not allow for dispensing of materials that could potentially be used past the labeled expiry of the materials. Screening will be performed by the blinded site staff, while randomization, review subject information, and drug assignment shall be conducted by unblinded site staff. IMPALA will also be used by the unblinded dispenser to review subject treatment and stratification information. Sites will be provided with two laminated tools to guide unblinded site personnel with the randomization, review subject information, and drug assignment processes in the IRT at Vaccination #1 and Vaccination #2. The unblinded site personnel performing the drug assignment function will be asked a series of questions to identify whether a new active or placebo vial must be assigned by the IRT. In addition, the unblinded site personnel will have the ability to enter a container number when using a previously assigned vial to dose multiple participants. Please refer to the laminated tools as a reference when performing the randomization, review subject information function, and the drug assignment process in the IRT. Refer to the Impala Quick Reference Guide for specific protocol information.

Web Access: <http://impala.pfizer.com>

Pfizer Clinical Support Help Desk: (+1) 877-433-2619

- After you are presented with a set of options to choose, press “3” to reach the Impala Support Help Desk.
- When prompted with another set of options, press “1” for access issues or “2” for all other issues.

An Impala Quick Reference Guide/IRT System Manual is also provided for this protocol. A copy of this guide can be accessed by clicking on the “Help Documents” located above the Main Menu after logging into the Impala End User System or provided by your uCRA.

5. Product Ordering, Receipt, and Inventory Management

5.1. Product Ordering

Initial Shipment

IP Provided by Sponsor

The initial shipment of IP to the clinical site will be manually ordered upon Site Regulatory Approval.

Other Supplies Provided by the Sponsor

Diluent supplies will be provided by the sponsor and included with the shipments of IP.

The initial shipment of ancillary items listed in Section 3.2 will be initiated by Study Management to arrive prior to first participant screened. The order will be processed manually via a manual order form by Study Management.

Re-Supply or Subsequent Shipments

IP supplied by Sponsor

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The IRT system will ensure appropriate levels of IP are present at the site based upon enrollment and the protocol visit schedule. If a site is expecting a significant increase in enrollment rate, Study Management must be alerted.

Other Supplies Provided by the Sponsor

Diluent inventory will be indirectly monitored by the sponsor and additional supplies will be provided as needed.

For re-supply of other ancillary items, these will be ordered through the uCRA.

Shipping Timelines

From the time a shipment order is generated, it will take approximately 5 business days to deliver these supplies to the investigator site. Orders from the distribution warehouses will only be shipped Monday through Wednesday, therefore, the clinical site must plan accordingly. Based on need, site availability, and proximity to the distribution center, special arrangements may be made for a limited number of shipments to deliver on Friday or Monday.

5.2. Product Receipt

The shipment containers will contain dry ice. Precautions must be taken when handling the shipment contents. Upon receipt of IP shipments, the receiving pharmacist or designee must wear insulated gloves and other appropriate personal protective equipment (PPE) (based on local hazardous material guidelines) to unpack, inspect and inventory the shipment contents. The person performing receipt must ensure that the contents match the accompanying shipping documentation Proof of Receipt (POR) and are acceptable for dispensing. Do not store the shipment container containing dry ice in any enclosed spaces (freezers) as this will cause a buildup of pressure that could be dangerous. The shipment should be handled in a well-ventilated space to prevent the buildup of carbon dioxide. Upon opening the shipment, remove the cartons and place them in the freezer -80 to -60 °C (-112 to -76 °F) immediately.

In circumstances where a transfer of IP inventory from one clinical site to another clinical site is required, shipping conditions will be different. Detailed instructions on how to proceed will be sent to both donating and receiving sites, as needed.

The following supplies are shipped on dry ice at ultra-cold of -80 to -60 °C (-112 to -76 °F) with allowable limits programmed into the temperature monitoring device:

Active IP

- BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial)
 - 0.5 mL fill volume and 0.3 mL extractable volume
- BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial)
 - 0.2 mL fill volume and 0.2 mL extractable volume

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Shipments of the BNT162b2 Vaccine vials will include temperature monitoring devices. Follow the temperature monitoring device instructions included in the shipment upon receipt at the clinical site.

NOTE: The temperature monitoring device included in the shipment will only alarm if the temperature is outside of the set range. The shipment is acceptable for use unless the monitor has alarmed. The temperature range for shipping may be expanded for short term temperature spikes and may be different than the labeled site storage parameters.

The following placebo supplies are shipped at 20 to 25°C (68 to 77°F) with allowable limits programmed into the temperature monitoring device:

Placebo and Diluent

- 0.9% Sodium Chloride Injection, USP (10 mL/vial)

Shipments of Placebo (0.9% Sodium Chloride Injection) will include temperature monitoring devices. Follow the temperature monitoring device instructions included in the shipment upon receipt at the clinical site.

NOTE: The temperature monitoring device included in the shipment will only alarm if the temperature is outside of the set range. The shipment is acceptable for use unless the monitor has alarmed. The temperature range for shipping may be expanded for short term temperature spikes and may be different than the labeled site storage parameters.

NOTE: Sites must always follow the instructions in the Temperature Monitoring Instruction Sheet, print and file or file electronically the shipping temperature data report from USB devices whether alarmed or not.

The site must do the following upon the arrival of the shipment as quickly as possible:

- The shipment will contain a temperature monitoring device. Stop the temperature monitoring device immediately upon receipt so it does not record any false high temperatures as it is taken out of the box. Even if the device appears frozen, hit the stop button immediately.
- If the shipment consists of more than one shipper each shipper will have its own temperature monitor, so please take note of which monitoring device ID is associated with which shipper.
- For all shipments of active or placebo, follow the instructions in the Almac Temperature Monitoring Instruction Sheet received with the shipment (see Appendix 2 and 2a for examples). Data from the temperature monitors **must** be downloaded for all shipments, irrespective of the temperature monitor being alarmed or not.
- Inspect the IP (Placebo) and Diluent to ensure they were received in good condition (i.e. undamaged, with tamper seals intact, etc.). See Section 5.3: Lost, Damaged or Incomplete Shipments.
- Check the amount and condition of the IP against the POR or other accompanying document(s).

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- Verify the labels to ensure that they match the protocol number and container numbers (Kit IDs) stated on the POR
- The POR will be located in the first shipper ONLY for shipments that consist of multiple shippers. Each box will have the box number designated (i.e. 1 of 2, 2 of 2 etc.)
- Place the IP in the appropriate labeled storage conditions as quickly as possible.
- Please acknowledge receipt of shipment by answering the questions on page 2 of the POR and sign, date, and file in the Investigator Site File (ISF).
- Once the Temperature Monitor data has been downloaded to Almac TempEZ n any temperature excursions have been evaluated, and it is determined that the IP has arrived in satisfactory condition, log in to the IRT system website to acknowledge the shipment of active, placebo, and diluent supplies per the IRT system manual. Once the shipment is acknowledged via the IRT system, the site must print and maintain a hard copy of the IRT system generated shipment confirmation within the local site files.
- **NOTE:** Failure to complete receipt/acknowledgement in the IRT system for the placebo in a timely manner will impact resupply shipment triggers; thus, potentially putting participants at risk due to IP shortage. In addition, assignment of IP to participants may not be able to occur without proper acknowledgement of IP receipt in the IRT system.

5.2.1. Temperature Excursions During Shipment

In the event of a temperature excursion during shipment to the clinical site:

1. **Do not** confirm shipment receipt in the Impala IRT system.
2. Physically quarantine the supplies at the labeled storage conditions and inform your uCRA.
3. Follow the Almac Temperature Monitor Site Instruction (see Appendix 2 and 2a for examples and Appendix 3A for detailed temperature reporting instructions through the TempEZ Connect website).
4. Do not use the quarantined supplies until you receive confirmation that the shipment is acceptable for use.
5. Once disposition instructions are received, confirm shipment receipt in the Impala IRT system.
 - Confirm shipment as 'Undamaged' if it is determined that the materials are to be designated "acceptable for use"
 - Confirm shipment as 'Damaged' if it is determined that the materials are to be designated "unacceptable for use"
6. If materials are deemed "unacceptable for use", they must be physically quarantined in a way that prevents inadvertent dispensing and a replacement shipment will be sent to the site. Please contact your uCRA for a replacement shipment as soon as possible.

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5.3. Lost, Damaged or Incomplete Shipments

If a shipment is lost or does not arrive in a satisfactory condition, contact the assigned uCRA. Please provide photographs of the damage to your uCRA,. The issue will be escalated to the Sponsor for evaluation and so that disposition instructions can be provided. Damaged materials must be physically quarantined in a way that prevents inadvertent dispensing. Once disposition instructions are received acknowledgement can occur in the IRT system as instructed by the Sponsor. If the assigned Study Manager cannot be reached, call the Help Desk (See Section 4: Interactive Response Technology).

5.4. Inventory Management

Based on the design of this study, the site should expect to have approximately 10 to 100 cartons of the active (BNT162b2 Vaccine vials) which should be stored at -80 C to -60 C (-112 to -76 °F), and 20 to 200 vials of placebo and diluent (0.9% Sodium Chloride Injection) stored at room temperature in inventory at any one time, depending on the site's enrollment.

Each BNT162b2 Vaccine vial is packaged in a carton that has the approximate dimensions of 1.4 inches x 1.4 inches x 2.3 inches (36 mm x 36 mm x 59 mm). The cartons will be shipped in a mylar heat seal pouch, the mylar pouch is used for additional protection during transportation. Upon receipt of shipment, sites may remove the cartons from the mylar pouch and place them in the freezer -80 to -60 °C (-112 to -76 °F) immediately.

Each placebo or packaged diluent vial (0.9% Sodium Chloride Injection, USP (10 mL/vial) is packaged in a carton that has the approximate dimensions of 2 inches x 2 inches x 2 3/4 inches (51 mm x 51 mm x 70 mm).

Ensure that the IP storage location can accommodate this amount of material. See Section 9 for additional information on investigational product accountability.

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6. Storage, Handling and Temperature Monitoring of IP and Diluent at Clinical Site

6.1. Storage and Temperature Monitoring of Investigational Product at a Clinical Site

The following supplies must be stored at -80 to -60 °C (-112 to -76 °F) protected from light and kept in the original packaging prior to use in dose preparation:

Active IP

- BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial)
- BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial)

The following supplies must be stored at 20 to 25 °C (68 to 77 °F) with excursions between 15 to 30 °C (59 to 86 °F) allowed:

Placebo and Diluent

- 0.9% Sodium Chloride Injection, USP (10 mL/vial)

The temperature of all locations where IP is stored at a clinical site must be monitored continuously and verified as appropriate per the site processes, using a temperature monitoring device that measures minimum and maximum temperatures daily. The site may utilize temperature devices with minimum and maximum memory capabilities to monitor temperatures when a site is not operational (e.g. weekends and holidays) however the site must be able to verify and document the minimum and maximum temperatures occurring over the entire non-operational periods once normal operations are resumed. Storage temperature must be recorded and monitored consistently by the site personnel in a site-created or Sponsor-provided temperature log. Sites may apply their own policies and procedures as long as the Sponsor requirements are met.

6.2. Temperature Excursions During Site Storage

If any of the following occur, the site must **immediately** quarantine the IP supply in the appropriate storage conditions as indicated on the product label and inform your uCRA:

- A temperature excursion occurs while any Sponsor supplied product is at the site.
- The temperature is not monitored continuously (for example, a temperature monitoring device malfunctions)
- Advice is needed on whether or not a temperature deviation is considered a temperature excursion
- The documented temperatures and/or duration of an excursion are not available for any reason

Report all temperature excursions, including suspected temperature excursions, by completing the **Almac Clinical Services Site Temperature Excursion Form** provided by your uCRA or located at the Almac TempEZ website at <http://tempezconnect.almacgroup.com>. (see Appendix 3 for an example form and Appendix 3A for detailed temperature reporting instructions through the TempEZ Connect website). The **Almac Clinical Services Site Temperature Excursion Form** will be returned once the final disposition of the material has been determined. Store a copy of the completed form with the TempEZ disposition and temperature records related to the temperature excursion and in

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the Investigator Site File. For assistance you may contact globaltemperatureservices@almacgroup.com and copy your uCRA.

See Appendix 3A for instructions to navigate the TempEZ website.

The site should contact the uCRA if the documented temperatures and/or duration of an excursion are not available for any reason.

The site must not use the quarantined supplies until disposition instructions are received from the Sponsor. If it is determined that the materials are to be designated “unacceptable for use”, the materials must be physically quarantined in a way that prevents inadvertent dispensing and the Sponsor will initiate a replacement shipment to the site.

NOTE: Numeric temperature values may be rounded to the nearest whole number to establish if an excursion has occurred (e.g. Values at or above 0.5 are rounded up. Values at or below 0.49 are rounded down).

For the Active (BNT162b2): Temperature excursions vials of less than 5 minutes that are due to opening and closing of the refrigerator or freezer door do not have to be reported. Vials can be further used.

For the placebo and diluent (0.9% Sodium Chloride Injection, USP): Temperature spikes outside of 15 to 30 °C (59 to 86 °F) for 20 minutes or less are not considered temperature excursions unless the recorded temperature is below 0 °C.

6.3. Special Handling of IP

Recommendations in the Safety Data Sheet (SDS) must be followed. The SDS will be provided separately.

OTHER HANDLING INFORMATION

For clinical sites that have an off-site location for storage, preparation or administration of IP, an IP transport procedure must be provided to the clinical study team for review. At minimum the procedure must identify the designated operators of the dose preparation and transportation steps, a description of the transport container and process to maintain/record temperature during the transit time, and a method to log departure and arrival times

6.4. Expired IP Handling

If your site has received notification from Pfizer that IP has expired, the materials must be physically quarantined in a way that prevents inadvertent dispensing and the Sponsor will initiate a replacement shipment to the site. Do not destroy the quarantined supply until instructed to do so by your uCRA.

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7. Blinding Information

7.1. Definition of Blinded/Unblinded Roles

This is a third-party blind study. The participant, investigator, and study coordinator are blinded to the participant's assignment to BNT162b2 Vaccine or placebo.

Most site staff members are blinded (see table below for exceptions). Site staff members who are unblinded must be aware they are unblinded and must be careful not to inadvertently unblind participant treatment assignments during interactions with staff members, the Sponsor or participants who are blinded.

Only site personnel listed in unblinded roles shall handle shipments, IP, and perform dose preparation, administration, or double verification activities. Unblinded persons may not participate in the evaluation of any study participants. The unblinded site staff members are the only site personnel who can handle the IP packages and document treatment information.

The following table provides an overview of blinded vs. unblinded permissions. Note that there are blinded and unblinded CRAs and Study Managers. It is imperative to clearly identify the distinction **before** any unblinding information is exchanged with these individuals.

Role	Permission
Investigator Site Staff	
Principal Investigator/Sub-Investigator	Blinded
Study Coordinator	Blinded
Receiving IP shipments, performing acknowledgement, and completing proof of receipt	Unblinded
Screening participants	Blinded
Randomizing participants	Unblinded
Dispensing IP	Unblinded
Dose preparation	Unblinded
Another site staff member (witness) performing a second verification of dispensed IP and dose preparation	Unblinded
IP administration	Unblinded
Post-Dose Administration Observer	Blinded

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Role	Permission
ICON and Pfizer Staff*	
ICON Clinical Trial Manager	Blinded and Unblinded
ICON Project Manager	Blinded
Pfizer Study Manager	Blinded and Unblinded
Clinical Research Associates performing study monitoring activities	Blinded and Unblinded
Clinicians	Blinded and Unblinded
Clinical Scientist	Blinded
Site Relationship and Excellence Partners	Unblinded
Supply Chain Lead	Unblinded
Impala Management Analyst	Unblinded

7.2. Notification of Potential Inadvertent Unblinding at Clinical Site

The unblinded site staff must immediately contact the uCRA if the study drug is not stored, handled, or administered according to the protocol and/or other relevant site documentation to adequately maintain the blind. The site must provide details of the incident or any protocol deviations and, assist in resolving the issue and/or determining corrective actions to take.

If the blind is broken or potentially broken, unblinded staff must contact the uCRA immediately. Do not administer or dispense the study drug to any participant and do not randomize a new participant until the Sponsor provides further instructions.

7.3. Breaking the Blind

Whenever possible, the Investigator or Sub-Investigator consults with a member of the Sponsor's study team (e.g., Study Manager, CRA or Clinician) prior to breaking the blind for an individual participant. Refer to the clinical protocol for additional information regarding breaking the blind. If blinding disclosures are received, please note that they must only be opened in an emergency or in cases where, in the judgment of the investigator, the information is necessary for proper participant management.

- Refer to the Quick Reference Guide and or equivalent document for this protocol.

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8. Dosage and Administration Instructions

The BNT162b2 Vaccine is packaged in vials to be diluted and administered intramuscularly into the deltoid muscle, preferably of the non-dominant arm, as a two-dose regimen based on randomization. IP will be prepared, dispensed, and administered by the unblinded study site personnel.

Investigational product (active or placebo) shall be prepared and dispensed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Each participant will receive intramuscular injection in the deltoid muscle of the non-dominant arm.

The BNT162b2 Vaccine candidate is supplied as a white to off-white sterile frozen liquid, packaged in a clear glass 2 mL vial with a rubber stopper, aluminum overseal and flip off cap. The vials contain a 250 mcg/0.5 mL concentrate for solution for injection and require dilution prior to administration. The BNT162b2 Vaccine will be available in two vial configurations:

- BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection **(0.3 mL/vial)**
- BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection **(0.2 mL/vial)**

A single BNT162b2 Vaccine vial will be diluted to prepare doses for multiple participants. The concentrated solution in the vial requires dilution with 0.9% Sodium Chloride Injection, USP. Any unused portion of the diluted solution must be discarded if not used within 6 hours.

Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Any acute reactions shall be recorded in the participant's source documents, on the Adverse Event (AE) page of the Case Report Form (CRF), and on the Serious Adverse Event (SAE) form as applicable.

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8.1. Drug Dispensing per Visit

The table below describes the product to dispense at each dispensing visit for Phase 2/3 only.

Visit/ Vaccination # (Day)	Vials Dispensed at this Visit
<p style="text-align: center;">Visit 1 Vaccination #1 (Day 1)</p> <p style="text-align: center;">AND</p> <p style="text-align: center;">Visit 2 Vaccination #2 (19 to 23 Days after Visit 1)</p>	<p style="text-align: center;">According to cohort and randomization:</p> <div style="border: 2px solid black; border-radius: 15px; padding: 10px; margin: 10px auto; width: 80%;"> <p style="text-align: center;">One of the following BNT162b2 Vaccine Candidate vials (ACTIVE):</p> <ul style="list-style-type: none"> <li style="text-align: center;">• BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial) YELLOW Carton Label <li style="text-align: center;">• BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial) BLUE or WHITE Carton Labels </div> <p style="text-align: center; margin: 10px 0;">OR</p> <div style="border: 2px solid black; border-radius: 15px; padding: 10px; margin: 10px auto; width: 80%;"> <p style="text-align: center;">One vial of Placebo: 0.9% Sodium Chloride Injection, USP (10 mL/vial)</p> </div>

8.2. Investigational Product Dispensing Pilot using Impala Kit Verify Mobile Application

This study will pilot a mobile application (Impala Kit Verify) in the USA only that will be used to verify kits/containers prior to dispensing. Investigator site participation in this pilot is optional. The purpose of this mobile application is to minimize dispensing errors and facilitate the dispensing of the appropriate kit (e.g. vial) to the correct subject.

Kit Verify is used to verify the container number of a new kit/carton that is dispensed only for the **first** dose of a new active vial and all placebo kits/cartons that are assigned by the IRT. Kit Verify replaces the need for a second verification of the IP container to dispense. The mobile app cannot be used to verify the container number of subsequent doses that are prepared from a previously assigned active kit/container and it is **not** used to support dose preparation.

The verification process will require scanning of the Impala Drug Assignment Confirmation Report and the corresponding kit/container using a smartphone. Use of the Impala Kit Verify mobile application for investigational product dispensing still requires initial single person verification. The Impala Kit Verify application eliminates the need for the second person verification only at the point of dispensing.

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The investigator site may dispense the kits/containers once they have been verified by the Impala Kit Verify mobile application. If an incorrect kit/container is scanned, the user will be alerted by the Impala Kit Verify mobile application not to dispense the scanned kit/container. Any investigator site personnel interested in participating in this pilot must complete the required Impala Kit Verify Mobile Application Training Module located in Firecrest (www.firecrestclinical.com/login) prior to using the mobile application. The Impala Kit Verify Application training will be located in the study training folder and should not take more than 30 minutes to complete. Upon completion of Impala Kit Verify Mobile Application Training Module:

1. Download the training completion certificate from the Firecrest – Pfizer System Training portal. A certificate will also be sent by email to users upon completion of this training.
2. File the training completion certificate in the Investigator Site File for this protocol.

See **Appendix 9** within this IP Manual for more information. If you have questions regarding the use of the Impala Kit Verify mobile application, refer to the Impala Quick Reference Guide or contact the Pfizer Clinical Support Help Desk at 1-877-433-2619; select Option 3 then Option 4.

8.3. General Preparation Guidelines

Only clinical site personnel who are appropriately trained on the procedures detailed in this document may perform the preparation and administration step specified in this IP Manual. Clinical site personnel involved in these procedures must comply with all applicable regulations and standards. The preparation and administration of all sterile products must be performed using aseptic technique. Utilize local site procedures as appropriate.

When preparing single or multiple doses from a single vial using the **in-vial dilution method**, it is *recommended* that all handling and preparations be carried out in a laminar air flow hood using aseptic techniques for sterile products. If a laminar air flow hood is not available, a Class II-III biosafety cabinet or equivalent ISO 5 or better environment may be used. Class I biosafety cabinets should not be used. If sites do not have access to a hood or biosafety cabinet, dose preparation may occur outside of an ISO 5 or better environment, such as on a tabletop or countertop. The in-use period for IP that is prepared within or outside of an ISO5 environment or better will be 6 hours from the point of first stopper puncture to completion of administration. Dose preparation must occur in an isolated area that is away from blinded site personnel and participants to maintain the study blind. Only the necessary materials should be present in the working area during each preparation step.

Utilize local site procedures governing the use of personal protective equipment (e.g. gloves, protective eyewear, gowning, and footwear).

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8.4. In-Use Shelf Life and Storage Requirements for BNT162b2 Vaccine and Placebo Vials

Vials of BNT162b2 Vaccine Concentrate Solution for Injection, 250 mcg/0.5 mL (0.3 mL/vial and 0.2 mL/vial configurations) must be stored in the freezer between -80 and -60°C (-112 to -76°F), protected from light and kept in the original packaging until ready for use in dose preparation. Allow all vials to thaw at room temperature (no more than 25 °C/ 77 °F) for approximately 30 minutes prior to dose preparation. When the contents of the vial are completely thawed, gently invert 10 times to mix thoroughly. Do not shake. If unused vials are left at room temperature for more than 2 hours they should be discarded.

Minimize exposure of BNT162b2 Vaccine vials and prepared dosing solutions to room light during storage. Avoid exposure to direct sunlight and ultraviolet light. Dosing solutions can be prepared and handled in normal room light conditions.

Placebo vials of 0.9% Sodium Chloride, USP (10 mL/vial) shall be stored at 20 to 25 °C (68 to 77 °F).

8.5. In-use Shelf-Life and Storage of Prepared Active and Placebo Dosing Solutions

In Vial Dilutions

Individual dosing syringes that are prepared from diluted solutions in the vial should be used immediately, if possible. Dosing syringes and diluted solutions that cannot be used immediately should be stored at 2 to 8 °C until use. Diluted solutions in vials and the prepared dosing syringes have an in-use period of 6 hours from the start of dose preparation when stored between 2 and 25 °C (36 to 77°F). Start of dose preparation is defined as the time at which the vial stopper is first punctured. If the prepared dosing solution was left for more than 6 hours, contact your unblinded CRA.

Placebo Dosing Solutions

Prepared placebo dosing syringes containing 0.9% Sodium Chloride, USP should be used immediately, if possible. If it cannot be used immediately, it may be stored up to 6 hours if stored between 2 to 25 °C (36 to 77 °F). The expiry time is determined by the environment in which the dose was prepared and from the start time of dose preparation, which is defined as the time at which the vial stopper is first punctured. The prepared placebo dosing syringe expires 6 hours from the start of dose preparation. In order to maintain the study blind, the label on the final prepared BNT162b2 vaccine and placebo dosing syringes must have the same expiry date and time.

Dosing syringes and diluted solutions that are refrigerated should be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution in the syringe is not cold to the touch. Prepared solutions should be administered within the in-use period.

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8.6. Preparation and Administration of IP

This section provides dose preparation and administration instructions for the BNT162b2 30 mcg vaccine or Placebo.

The following video will be available in Firecrest to describe IP dose preparation and administration:

- Dose Preparation and Administration of the BNT162b2 **30 mcg or Placebo Dose** Using the *In-Vial Dilution Method*

Key points to note:

- The BNT162b2 vaccine candidate vials are available in two vial configurations, each with different fill volumes. Since the IP will require in-vial dilutions, it is important to differentiate between the different fill volumes:
 - BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial) has a 0.5 mL fill volume
 - BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial) has a 0.2 mL fill volume
- Read the product description on the label to confirm the contents of the vial prior to dose preparation.
- Dose preparation must be performed using sterile handling techniques in compliance with local, state, and national laws/regulations.
- In order to maintain the study blind, dose preparation must occur in an isolated area where there are no blinded site personnel or participants.
- The prepared dosing solution should be used immediately, if possible. The final IP must be administered within 6 hours of dose preparation if stored between 2 to 25°C (36 to 77°F) Prepared syringes should be kept refrigerated (2 to 8 °C) prior to use if not used immediately.
- Refrigerated dosing solutions in syringes must be allowed to reach room temperature prior to administration to prevent any discomfort resulting from injection of a cold solution. Also, allowing the IP to reach room temperature prior to administration is important for maintaining the blind since the placebo solution is stored at room temperature.
- Each BNT162b2 vial contains a frozen concentrated solution that is preservative-free and must be thawed and diluted prior to administration. The BNT162b2 vaccine concentrate will be diluted using the in-vial method. The diluted solutions in the vial shall be used to prepare doses for multiple participants according to the instructions within this IP Manual.
- Indicate the expiration or “Do not use after date and time” on the BNT162b2 Vaccine Concentrate for Solution for Injection vials or syringes containing the diluted dosing solutions, which is 6 hours from the start of dose preparation

NOTE: Start of dose preparation is defined as the time at which the vial stopper is first punctured.

- In order to maintain the study blind, the label on the final prepared active and placebo dosing syringes must have a blinded product name (e.g. BNT162b2 Vaccine 30 mcg or Placebo) as well as the same expiry date and time.

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- o Note: Each prepared dosing syringe expires 6 hours from the start of dose preparation. In order to maintain the study blind, the participant specific blinded labels on the final prepared BNT162b2 vaccine and placebo dosing syringes must have the same expiry date and time. See below for recommended expiry times to maintain study blind.

Protocol No.: **C4591001** Subject ID: _____
BNT162b2 Vaccine 30 mcg or Placebo
 Inject 0.3 mL intramuscularly in the deltoid of the non-dominant arm.

Do not use after: Date: _____ Time: _____

- o Example of recommended ranges for expiry time for prepared active and placebo syringes.

Preparation Time	Expiry Time
Doses prepared between 08:00 - 10:00	Expiry time is 14:00
Doses prepared between 10:01 – 12:00	Expiry time is 16:00
Doses prepared between 12:01 - 14:00	Expiry time is 18:00

- If the first prepared dose is for placebo, please wait an appropriate amount of time (approximately 30 minutes) after dose preparation before delivering the final dosing syringe to the location of administration in order to prevent any potential unblinding.
- Sponsor-provided occluding label must be applied to all prepared active and placebo dosing syringes to maintain the study blind.
- A confirmation of study blind statement must be documented in the participant’s source documents (see below)
- Document all steps performed as indicated in the Preparation Record (Appendix 5, 6, or 7).

Confirmation of Study Blind

- Investigator sites should have a process/procedure for maintaining study blind to ensure that the IP vials, diluents, and prepared dosing syringe(s) are shielded from the view of BLINDED study staff and the participant during dose preparation, dispensing, transportation, administration, and disposal. The site should ensure that the study blind was maintained and that the IP cartons, preparation records, syringes, and disposal of used supplies were carefully handled prior to and after administration.

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- The unblinded staff member must instruct the participant to look away and document confirmation that the study blind was maintained in the participant’s source document. This is important especially while unwrapping the occluding label on the active or placebo dosing syringes to inspect the contents of the syringe.
- If possible, the unblinded staff administering the dose shall stand behind the participant to prevent the viewing of the syringe during any part of the IP administration process.
- Below is an example of a confirmation of study blind statement that may be used by the clinical site.

<p style="text-align: center;">Confirmation of Study Blind</p> <p style="text-align: center;"><i>EXAMPLE</i></p> <p><i>The prepared dosing syringes were shielded from view of BLINDED study staff and the participant. The participant followed the instructions to look away at the time of injection.</i></p> <p><i>Unblinded Staff Member:</i> _____ <i>Signature:</i> _____ <i>Date:</i> _____</p>
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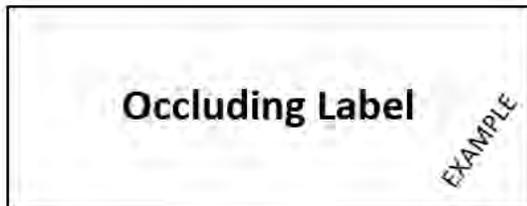
- The participant’s source documents will be reviewed at every monitoring visit to verify that the Confirmation of Study Blind statement has been signed by the unblinded site staff member who administered the dose. Review of this signed statement will be performed by the uCRA.

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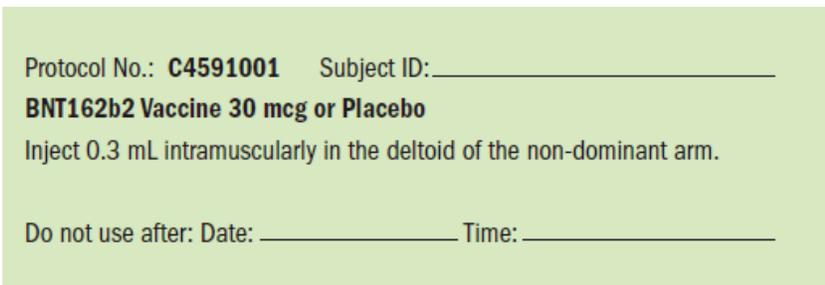
SUPPLIES			
Check that the labelling details on the outer containers of the supplies correspond with these instructions and the clinical protocol. If the supplies available at the site do not correspond with the list below, contact the unblinded CRA.			
Supplies Provided by Pfizer			
Drug product (Active): Labelled as indicated below.			
<ul style="list-style-type: none"> • BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.3 mL/vial) – YELLOW Carton Label • BNT162b2 Vaccine 250 mcg/0.5 mL concentrate for solution for injection (0.2 mL/vial) – BLUE or WHITE Carton Label 			
Placebo: 0.9% Sodium Chloride Injection, USP (10 mL/vial)			
Syringes: 1 mL and 3 mL sterile, luer lock latex-free polypropylene syringes or polycarbonate syringes. Ensure that syringes used have the appropriate gradations to prepare an accurate dose.			
Sterile Syringe cap: If needed for storage and transport of prepared syringes. Should be luer lock, sterile, single use, latex free.			
Needles: Sterile, stainless steel needles with appropriate bore size of 25 Gauge (G) or wider.			
<ul style="list-style-type: none"> • For dose preparation: sterile, stainless steel needles with a bore size of 21 Gauge (G) 1 inch and 1.5 inches in length are recommended. • For intramuscular injection: sterile, stainless steel needles with a bore size of 25 gauge (G) and 1 inch or 1.5 inches in length are recommended. Select the needle for vaccination according to the subject's sex and weight as follows: 			
Recommended Needle for Intramuscular Injection		Male	Female
1 inch (25 mm)	25 G	<130 lbs (<60 kg)*	<130 lbs (<60 kg)*
1 inch (25 mm)	25 G	130-152 lbs (60-70 kg)	130-152 lbs (60-70 kg)
1 or 1.5 inches (25-38 mm)	25 G	152-260 lbs (70-118 kg)	152-200 lbs (70-90 kg)
1.5 inches (38 mm)	25 G	>260 lbs (>118 kg)	>200 lbs (>90 kg)
* Some experts recommend a 5/8-inch needle for men and women who weigh <60 kg. If used, skin must be stretched tightly (do not bunch subcutaneous tissue).			
Reference: <i>General Best Practice Guidelines for Immunization: Best Practices Guidance of the Advisory Committee on Immunization Practices (ACIP)</i>			

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Occluding White Labels: To be applied to the syringe barrel of the prepared BNT162b2 Vaccine or Placebo syringes only. The supplied occluding label must be used for blinding. Do not use other labels or supplies to mask the contents of the syringe.



Participant Specific Blinded Labels: To be applied to the syringe barrel of all dosing syringes. Use of these supplied Participant Specific Blinded Labels is preferred. However, sites may use their own label if it captures the minimum information shown in the example below and reflects the blinded product name (e.g. BNT162b2 Vaccine or Placebo or BNT162b2 Vaccine 30 mcg or Placebo). In order to maintain study blind, the label shall also be blinded to the dose.



Supplies Provided by the Clinical Site

Diluent: 0.9% Sodium Chloride for Injection (Normal Saline). Diluent should meet regional/local compendia requirements and be an authorized product in the local country.

- *Note: Clinical sites that do not have access to this diluent may request sponsor-provided supplies through the uCRA.

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8.6.1. Preparation of BNT162b2 Vaccine (Active) 30 mcg Using the BNT162b2 Vaccine Concentrate for Solution for Injection (0.3 mL/vial) Configuration

**Preparation of BNT162b2 Vaccine (Active) 30 mcg
with the BNT162b2 Vaccine Concentrate for Solution for Injection (0.3 mL/vial)
Using In-Vial Dilution**

Ensure that all materials and equipment required are available before starting the dose preparation. When preparing the BNT162b2 vaccine using this in-vial dilution method, it is recommended that all handling and preparations be carried out in a laminar air flow hood using aseptic techniques for sterile products. If a laminar air flow hood is not available, a Class II-III biosafety cabinet or equivalent ISO 5 or better environment may be used. Class I biosafety cabinets must not be used. If an ISO5 or better environment is not available, preparation may occur on a clean tabletop or countertop that is located in an isolated area where there are no blinded site personnel or participants. Refer to Section 8.5 for in-use stability information. Only the necessary materials should be present in the working area during each preparation step. Document all steps performed as indicated in the Preparation Record.

Step	Instructions								
1	Obtain 1 vial of BNT162b2 Vaccine Concentrate for Solution for Injection (0.3 mL/vial) that has a YELLOW Carton Label from the freezer, and 1 vial of 0.9% Sodium Chloride for Injection (10 mL/vial). NOTE: This BNT162b2 Vaccine vial configuration contains a <u>0.5 mL fill volume</u> .								
2	Thaw the BNT162b2 Vaccine vial for approximately 30 minutes. Once vial is completely thawed, invert gently 10 times to mix. Do not shake.								
3	Per the table below, withdraw 2 mL of 0.9% Sodium Chloride using a new 3 mL syringe and an appropriately sized needle (e.g. 21 G x 1.5 inches). <table border="1" data-bbox="358 1430 1398 1619" style="margin: 10px auto;"> <thead> <tr> <th>Dose Level (mcg)</th> <th>Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial</th> <th>Volume of 0.9% Sodium Chloride Required for Dilution</th> <th>Final Volume of Diluted Dosing Solution</th> </tr> </thead> <tbody> <tr> <td align="center">30 mcg</td> <td align="center">0.5 mL</td> <td align="center">2 mL</td> <td align="center">2.5 mL</td> </tr> </tbody> </table>	Dose Level (mcg)	Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial	Volume of 0.9% Sodium Chloride Required for Dilution	Final Volume of Diluted Dosing Solution	30 mcg	0.5 mL	2 mL	2.5 mL
Dose Level (mcg)	Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial	Volume of 0.9% Sodium Chloride Required for Dilution	Final Volume of Diluted Dosing Solution						
30 mcg	0.5 mL	2 mL	2.5 mL						
4	Carefully transfer the required volume of 0.9% Sodium Chloride into the vial containing BNT162b2 Concentrate for Solution for Injection. Pull back on the plunger to withdraw air and equalize the pressure in the vial. Safely discard the syringe and needle in a sharps container. Gently invert the diluted vial 10 times to mix. Do not shake.								

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Indicate the expiration or “Do not use after: Date _____ and Time _____” on the BNT162b2 Vaccine vial label, which is **6 hours** from the start of dose preparation

Start of dose preparation is defined as the time at which the stopper of the BNT162b2 Vaccine vial is first punctured.

<p>Contents: BNT162__ vaccine 250mcg/0.5 mL concentrate for solution for injection (0.3 mL/Vial) MUST BE DILUTED PRIOR TO USE. Any unused solution must be discarded. Contains no preservatives. Prepare and administer as directed in the Investigational Product Manual. For Intramuscular Injection Only.</p>	<p>Protocol No.: C4591001 Container No.: 046001 Lot No.: P220395-0012L Subject(s) No.: _____</p>
<p>Do not use after: Date _____ Time _____</p>	

EXAMPLE

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Obtain a new 1 mL polycarbonate syringe and attach a sterile needle suitable for dose preparation (e.g. 21 G x 1.5 inch). Withdraw a sufficient excess volume (e.g. 0.35 mL) of the diluted dosing solution into the 1 mL syringe to allow for priming and ensure a final injection volume of 0.3 mL.

Dose	Recommended Excess Volume to Withdraw for Each Prepared Dose to Allow for Priming	Final Injection Volume	Maximum Number of Doses to Prepare from the Diluted Dosing Solution
30 mcg	0.35 mL	0.3 mL	5 doses per vial

To prepare multiple dosing syringes from the diluted dosing solution, repeat this step until the desired number of dosing syringes have been prepared.

7

If the dosing syringe will be stored prior to administration, place a luer cap on the syringe.

If dosing immediately, attach an appropriate size stainless steel needle for intramuscular injection (e.g. 25 G x 1 inch or 1.5 inches needle) to the prepared syringe and prime the needle to ensure a final injection volume of 0.3 mL. Carefully recap the needle.

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8	<p>Apply the white occluding label to the barrel of the prepared syringe for blinding purposes.</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div style="border: 1px solid black; padding: 10px; text-align: center;"> <p>Occluding Label</p> <p style="color: gray; font-size: small;">EXAMPLE</p> </div>  </div> <p>NOTE: Sites <u>must</u> use the Sponsor provided occluding label.</p>
9	<p>Apply a blinded participant specific label (i.e. product name must be blinded) to the prepared syringe. Use the Sponsor provided participant specific label (preferred), or a site-created label according to local site practices. Ensure this label is applied in a manner to allow for unwrapping of the occluding label to perform a visual inspection of the syringe contents. The label should indicate at a minimum:</p> <ul style="list-style-type: none"> • Protocol Number • Subject ID (to be added after randomization) • Blinded Product Name (e.g. BNT162 Vaccine or Placebo <u>or</u> BNT162b2 Vaccine 30 mcg or Placebo) • Label shall also be blinded to the dose • Instructions to inject the dose (0.3 mL) intramuscularly in the non-dominant ARM • Date and Time Prepared (defined as start of dose preparation) • Do not use after date and time <div style="background-color: #e1f5fe; padding: 5px; margin: 10px 0;"> <p>Protocol No.: C4591001 Subject ID: _____ BNT162b2 Vaccine 30 mcg or Placebo Inject 0.3 mL intramuscularly in the deltoid of the non-dominant arm. Do not use after: Date: _____ Time: _____</p> </div> <p><u>Note:</u> The prepared dosing syringe expires 6 hours from the start of dose preparation. In order to maintain the study blind, the label on the final prepared BNT162b2 vaccine and placebo dosing syringes must have the same expiry date and time.</p> 
10	<p>Complete a Preparation Record (See Appendix 5) for each new vial dispensed and add the SSID of each participant who is dosed from the same prepared diluted dosing solution.</p> <p>Carefully dispose of the supplies to maintain the study blind. Retain the empty flattened carton for accountability purposes.</p>

8.6.2. Preparation of BNT162b2 Vaccine (Active) 30 mcg Using the BNT162b2 Vaccine Concentrate for Solution for Injection (0.2 mL/vial) Configuration

**Preparation of BNT162b2 Vaccine (Active) 30 mcg
with the BNT162b2 Vaccine Concentrate for Solution for Injection (0.2 mL/vial)
Using In-Vial Dilution**

Ensure that all materials and equipment required are available before starting the dose preparation. When preparing the BNT162b2 vaccine using this in-vial dilution method, it is recommended that all handling and preparations be carried out in a laminar air flow hood using aseptic techniques for sterile products. If a laminar air flow hood is not available, a Class II-III biosafety cabinet or equivalent ISO 5 or better environment may be used. Class I biosafety cabinets must not be used. If an ISO5 or better environment is not available, preparation may occur on a clean tabletop or countertop that is located in an isolated area where there are no blinded site personnel or participants. Refer to Section 8.5 for in-use stability information. Only the necessary materials should be present in the working area during each preparation step. Document all steps performed as indicated in the Preparation Record.

Step	Instructions								
1	Obtain 1 vial of BNT162b2 Vaccine Concentrate for Solution for Injection (0.2 mL/vial) that has a BLUE or WHITE Carton Label from the freezer, and 1 vial of 0.9% Sodium Chloride for Injection (10 mL/vial). NOTE: This BNT162b2 Vaccine vial configuration contains a <u>0.2 mL fill volume</u> .								
2	Thaw the BNT162b2 Vaccine vial for approximately 30 minutes. Once vial is completely thawed, invert gently 10 times to mix. Do not shake.								
3	Per the table below, withdraw 0.8 mL of 0.9% Sodium Chloride using a new 1 mL syringe and an appropriately sized needle (e.g. 21 G x 1.5 inches). <table border="1" data-bbox="358 1436 1398 1621" style="margin: 10px auto;"> <thead> <tr> <th>Dose Level (mcg)</th> <th>Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial</th> <th>Volume of 0.9% Sodium Chloride Required for Dilution</th> <th>Final Volume of Diluted Dosing Solution</th> </tr> </thead> <tbody> <tr> <td align="center">30 mcg</td> <td align="center">0.2 mL</td> <td align="center">0.8 mL</td> <td align="center">1 mL</td> </tr> </tbody> </table>	Dose Level (mcg)	Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial	Volume of 0.9% Sodium Chloride Required for Dilution	Final Volume of Diluted Dosing Solution	30 mcg	0.2 mL	0.8 mL	1 mL
Dose Level (mcg)	Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial	Volume of 0.9% Sodium Chloride Required for Dilution	Final Volume of Diluted Dosing Solution						
30 mcg	0.2 mL	0.8 mL	1 mL						
4	Carefully transfer the required volume of 0.9% Sodium Chloride into the vial containing BNT162b2 Concentrate for Solution for Injection. Pull back on the plunger to withdraw air and equalize the pressure in the vial. Safely discard the syringe and needle in a sharps container. Gently invert the diluted vial 10 times to mix. Do not shake.								

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Indicate the expiration or “Do not use after: Date _____ and Time _____” on the BNT162b2 Vaccine vial label, which is **6 hours** from the start of dose preparation

Start of dose preparation is defined as the time at which the stopper of the BNT162b2 Vaccine vial is first punctured.



6

Obtain a new 1 mL polycarbonate syringe and attach a sterile needle suitable for dose preparation (e.g. 21 G x 1.5 inch). Withdraw a sufficient excess volume (e.g. 0.35 mL) of the diluted dosing solution into the 1 mL syringe to allow for priming and ensure a final injection volume of 0.3 mL.

Dose	Recommended Excess Volume to Withdraw for Each Prepared Dose to Allow for Priming	Final Injection Volume	Maximum Number of Doses to Prepare from the Diluted Dosing Solution
30 mcg	0.35 mL	0.3 mL	2 doses per vial

To prepare multiple dosing syringes from the diluted dosing solution, repeat this step until the desired number of dosing syringes have been prepared.

7

If the dosing syringe will be stored prior to administration, place a luer cap on the syringe.

If dosing immediately, attach an appropriate size stainless steel needle for intramuscular injection (e.g. 25 G x 1 inch or 1.5 inches needle) to the prepared syringe and prime the needle to ensure a final injection volume of 0.3 mL. Carefully recap the needle.

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8	<p>Apply the white occluding label to the barrel of the prepared syringe for blinding purposes.</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div data-bbox="289 241 812 451" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>Occluding Label</p> <p style="color: gray; font-size: small;">EXAMPLE</p> </div> <div data-bbox="954 268 1214 346" style="text-align: center;">  </div> </div> <p>NOTE: Sites <u>must</u> use the Sponsor provided occluding label.</p>
9	<p>Apply a blinded participant specific label (i.e. product name must be blinded) to the prepared syringe. Use the Sponsor provided participant specific label (preferred), or a site-created label according to local site practices. Ensure this label is applied in a manner to allow for unwrapping of the occluding label to perform a visual inspection of the syringe contents. The label should indicate at a minimum:</p> <ul style="list-style-type: none"> Protocol Number Subject ID (to be added after randomization) Blinded Product Name (e.g. BNT162b2 Vaccine or Placebo <u>or</u> BNT162b2 Vaccine 30 mcg or Placebo) Label shall also be blinded to the dose Instructions to inject the dose (0.3 mL) intramuscularly in the non-dominant ARM Date and Time Prepared (defined as start of dose preparation) Do not use after date and time <div data-bbox="922 653 1469 840" style="background-color: #e0f0e0; padding: 5px; margin: 10px 0;"> <p>Protocol No.: C4591001 Subject ID: _____ BNT162b2 Vaccine 30 mcg or Placebo Inject 0.3 mL intramuscularly in the deltoid of the non-dominant arm. Do not use after: Date: _____ Time: _____</p> </div> <p><u>Note:</u> The prepared dosing syringe expires 6 hours from the start of dose preparation. In order to maintain the study blind, the label on the final prepared BNT162b2 vaccine and placebo dosing syringes must have the same expiry date and time.</p> <div data-bbox="1339 1102 1437 1270" style="text-align: right;">  </div>
10	<p>Complete a Preparation Record (See Appendix 6) for each new vial dispensed and add the SSID of each participant who is dosed from the same prepared diluted dosing solution.</p> <p>Carefully dispose of the supplies to maintain the study blind. Retain the empty flattened carton for accountability purposes.</p>

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8.6.3. Preparation of Placebo for BNT162b2 Vaccine (0.9% Sodium Chloride, USP)

Preparation of Placebo for BNT162b2 Vaccine (0.9% Sodium Chloride, USP)							
<i>Ensure that all materials and equipment required are available before starting the dose preparation. Document all steps performed as indicated in the Preparation Record</i>							
Step	Instructions						
1	Obtain 1 vial of 0.9% Sodium Chloride, USP (10 mL/vial)						
2	<p>Attach an appropriate size needle (e.g. 21 G or wider 1 inch in length) to a new sterile 1 mL polycarbonate syringe. Withdraw a sufficient excess volume of 0.9% Sodium Chloride to allow for priming and ensure a final injection volume that is equivalent to the blinded active dose being administered.</p> <ul style="list-style-type: none"> To prepare placebo doses that are equivalent to the 30 mg active doses prepared from the BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate Solution for Injection (0.3 mL/vial or 0.2 mL/vial) configurations: <table border="1" style="margin-left: auto; margin-right: auto;"> <thead> <tr> <th style="text-align: center;">Dose</th> <th style="text-align: center;">Recommended Excess Volume to Withdraw for Each Prepared Dose to Allow for Priming</th> <th style="text-align: center;">Final Injection Volume</th> </tr> </thead> <tbody> <tr> <td style="text-align: center;">30 mcg</td> <td style="text-align: center;">0.35 mL</td> <td style="text-align: center;">0.3 mL</td> </tr> </tbody> </table>	Dose	Recommended Excess Volume to Withdraw for Each Prepared Dose to Allow for Priming	Final Injection Volume	30 mcg	0.35 mL	0.3 mL
Dose	Recommended Excess Volume to Withdraw for Each Prepared Dose to Allow for Priming	Final Injection Volume					
30 mcg	0.35 mL	0.3 mL					
3	<p>Attach an appropriate size stainless steel dosing needle for intramuscular injection (e.g. 25 G x 1 or 1.5 inch needle) to the syringe, prime the needle to ensure the syringe contains the injection volume equivalent to the blinded active dose and carefully recap the needle.</p> <p>If the prepared syringe will not be administered immediately, place a luer cap on the syringe. Replace the syringe cap with an appropriate size stainless steel needle for intramuscular injection and prime the needle as described above prior to administration.</p>						
4	<p>If the prepared syringe will not be administered immediately, place a luer cap on the syringe. Replace the syringe cap with an appropriate size stainless steel needle for intramuscular injection. Prepared syringes should be kept refrigerated (2 to 8 °C) if not used immediately.</p> <p>NOTE: Dosing syringes and diluted solutions that are refrigerated should be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution in the syringe is not cold to the touch.</p>						

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<p>5</p>	<p>Apply the white occluding label to the barrel of the prepared syringe for blinding purposes.</p> <div style="display: flex; justify-content: space-around; align-items: center;"> <div data-bbox="272 241 797 449" style="border: 1px solid black; padding: 10px; text-align: center;"> <p>Occluding Label</p> <p style="color: gray; transform: rotate(-45deg); font-weight: normal;">EXAMPLE</p> </div> <div data-bbox="938 262 1198 346" style="text-align: center;">  </div> </div> <p>NOTE: Sites <u>must</u> use the Sponsor provided occluding label.</p>
<p>6</p>	<p>Apply a blinded participant specific label (i.e. product name must be blinded) to the prepared syringe. Use the Sponsor provided participant specific label (preferred), or a site-created label according to local site practices. Ensure this label is applied in a manner to allow for unwrapping of the occluding label to perform a visual inspection of the syringe contents. The label should indicate at a minimum:</p> <ul style="list-style-type: none"> • Protocol Number • Subject ID • Blinded Product Name (e.g. BNT162 Vaccine or Placebo <u>or</u> BNT162b2 Vaccine mcg or Placebo) • Instructions to inject the dose (0.3 mL) intramuscularly in the non-dominant ARM • Date and Time Prepared (defined as start of dose preparation) • Do not use after date and time <div data-bbox="834 747 1378 932" style="border: 1px solid gray; background-color: #e0f2e0; padding: 5px; margin: 10px 0;"> <p>Protocol No.: C4591001 Subject ID: _____ BNT162b2 Vaccine 30 mcg or Placebo Inject 0.3 mL intramuscularly in the deltoid of the non-dominant arm. Do not use after: Date: _____ Time: _____</p> </div> <p style="text-align: right; margin-right: 20px;">30</p> <p><u>Note:</u> The prepared dosing syringe expires 6 hours from the start of dose preparation. In order to maintain the study blind, the label on the final prepared BNT162b2 vaccine and placebo dosing syringes must have the same expiry date and time.</p> <p>If the first prepared dose is for placebo, please wait an appropriate amount of time (approximately 30 minutes) after dose preparation before delivering the final dosing syringe to the location of administration in order to prevent any potential unblinding.</p> <div data-bbox="1323 1228 1453 1375" style="text-align: right;">  </div>
<p>7</p>	<p>Complete a Preparation Record (See Appendix 7) for each participant.</p> <p>Carefully dispose of the supplies to maintain the study blind.</p>

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8.6.4. Administration of IP

Step	Intramuscular Administration Instructions
1	<p>Prior to dosing the participant, adhere to normal standard of care and aseptic techniques. Prepared solutions that are refrigerated should be allowed to reach room temperature prior to administration. Make sure the prepared dosing solution is not cold to the touch.</p>
2	<p>The unblinded site staff member designated to administer the investigational products shall prepare the injection site according to local site procedures.</p> <p>IMPORTANT: Immediately prior to administering the dose, the unblinded site staff member will instruct all participants to look away before unwrapping the occluding label on the syringe and performing a visual inspection. If possible, the unblinded staff member may stand behind the participant to prevent viewing of the syringe during any part of the IP administration process.</p> <p>During the visual inspection, the unblinded staff administering the dose shall:</p> <ul style="list-style-type: none"> • Verify the final dosing volume (volume will vary depending on dose prepared) • Confirm there are no particulates and/or discoloration observed. <p>If the visual inspection fails, do not administer the injection. If the visual inspection is successful, rewrap the occluding label to ensure blinding is maintained.</p>
3	<p>Administer the BNT162b2 Vaccine or Placebo in the deltoid muscle of the non-dominant arm.</p>
4	<p>Discard the empty syringe with needle attached into a sharp's disposal container according to local site procedures.</p>
5	<p>Unblinded staff member administering the injection shall also perform the following:</p> <ul style="list-style-type: none"> • Document that study blind was maintained by completing the <i>Confirmation of Study Blind Statement</i> (or similar document) in the participant's source documents <p>Record the injection location and the date and time of administration in the participant's source documents</p>
6	<p>Post-Study Intervention Administration:</p> <p>A blinded staff member shall observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Any acute reactions shall be recorded in the participant's source document and on the AE page of the CRF, and on an SAE form, as applicable</p>

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8.7. Dosing and Dispensing Errors

Any error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or participant harm while in the control of the health care professional, participant or consumer must be reported to the Sponsor and/or Study Monitor immediately. Refer to the study protocol for additional information on how to report a dosing or dispensing error.

8.8. Investigational Product Complaints

Any complaints related to distributed clinical supplies provided by the Sponsor for use in a clinical study that alleges a quality defect of a product, device or its labeling or packaging must immediately be reported. Follow the process below to alert the Sponsor.

Process:

- Upon identification of a product complaint, immediately notify the assigned unblinded Study Manager. Please follow the instructions on the Product Complaint Form (Appendix 8). Quarantine the IP in the appropriate storage conditions and wait for further instructions.
- The site will be notified if additional information or action is needed by the site. *Do not destroy the product as it may need to be returned to the Sponsor.*
- As part of the complaint reporting process the site may be asked to provide digital photographs of the product. The site must work with the unblinded CRA to complete IP complaint documentation for the Sponsor, and/or if requested to ship the material in question back to the Sponsor. If requested to return the product to the Sponsor, the unblinded CRA will support the logistics of this shipment.
The Sponsor will review the complaint and complete an investigation as needed. Once the review/investigation is complete by the Sponsor, the site will be provided a final response by the unblinded CRA.

9. Investigational Product Accountability

IP accountability is the responsibility of the clinical site/investigator. BNT162b2 vaccine, diluents, placebo vials, IP packaging, and used dosing syringes shall be carefully discarded following dose preparation as well as administration, taking into consideration potential unblinding risks. Ensure disposal procedures do not result in any potential unblinding. Blinded personnel must not come into contact with any of the disposed items as they are unblinding. **Only the empty (and flattened) cartons shall be kept for accountability purposes.** Once the unblinded CRA has completed their reconciliation and accountability of the empty, flattened cartons, they may be destroyed. The destruction of the empty cartons shall be documented in the comments section of the Pfizer Investigational Product Accountability Log (IPAL) or equivalent document. Proper documentation shall include the date, time and initials of the unblinded site personnel performing the destruction of the cartons.

Each clinical site will receive prepopulated Pfizer IPAL templates that shall be used to document accountability for each active vaccine candidate, the placebo, and the diluent. For 0.9% sodium chloride for dilution procured by the site, the manufacturer and lot number should be documented in an IPAL. Clinical sites wishing to use a site created equivalent IPAL must receive approval from Pfizer prior to use.

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Clinical sites shall document the disposal of unused dosing solutions in the disposition section of the Pfizer Investigational Product Accountability Log or on a site’s equivalent accountability log. Documentation of the disposal of unused solutions shall include the date and the initials of two unblinded site personnel who witnessed the disposal.

Contact the unblinded CRA for any concerns with regards to accountability. Please see Appendix 4 for an example Pfizer IPAL. A copy of the IPAL can be found in Firecrest.

10. Investigational Product Destruction

If product can be destroyed on site: Once reconciliation and accountability has been performed by the unblinded CRA, the uCRA may authorize the destruction of used, unused, and/or expired IP for destruction by the appropriate site personnel (e.g. Pharmacist or Study Nurse/Coordinator) following local environmental requirements and institutional policies. Please inform your unblinded CRA if this is the case. All destruction must be fully documented at the time of destruction on the Investigational Product Accountability Log or equivalent document at the time of destruction.

If product must be sent for destruction: Once reconciliation and accountability has been performed by the unblinded CRA, the uCRA may authorize the return/shipment for destruction of used, unused, and/or expired IP. These returns/shipments for destruction must be fully documented on the Investigational Product Accountability Log or equivalent document.

Other Supplies Provided by the Sponsor

Destruction of the supplied commercially available diluent (0.9% Sodium Chloride Injection, 10 mL/vial) and ancillary supplies that are remaining or expiring at the clinical sites is the responsibility of Study Management.

Contact the assigned unblinded CRA for any questions related to the return or destruction of IP, the supplied commercially available diluent, or ancillary supplies.

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Appendix 1: Example POR



Drug Shipment & Proof of Receipt



Date Printed:
Page 1 of 2

Shipment ID:	Investigator:	Protocol:
Requested by:	Site:	

Shipped By:	Ship To:
-------------	----------

Shipment Supplies					
Product Description	Packaged Lot	Storage Cond.	Use-By/ Expiry Date	Quantity	Container Number
Not Displayed	Not Displayed	Not Displayed	Not Displayed		10615 10616 10658 10692

This shipment may contain one or more of the following:

EXAMPLE



Drug Shipment & Proof of Receipt



Date Printed:
Page 2 of 2

Shipment ID:	Investigator:	Protocol:
Requested by:	Site:	

Receipt Acknowledgement

Were the contents of the shipment damaged or received in an unacceptable condition?
If yes, contact the Site Monitor. Yes No

Did any of the temperature monitoring devices alarm during shipment?
If yes, follow the provided instructions. Yes No

Signature: _____ Title: _____

Print Name: _____ Date: _____

For non-IRT supplies:
Ensure this drug shipment proof of receipt is signed, dated, and filed in the Investigator Site File (ISF). Copies should be provided to the site monitor. Manually record the serial number of each temperature monitoring device below on this proof of receipt for your records. Follow the temperature monitoring device instructions included in the shipment upon receipt.

For IRT supplies:
This shipment proof of receipt should be filed in the Investigator Site File (ISF). Record receipt in the IRT system. It is not required to complete the receipt acknowledgement section above. Follow the temperature monitoring device instructions included in the shipment.

Shipment receipt must take place in the IRT system. Please refer to the IP manual to identify the appropriate IRT system (Impala or Impala 2.0).
 Impala Web URL: <http://impala.pfizer.com>
 Impala 2.0 Web URL: <https://www.sharedinvestigator.com>
 If assistance is needed, please contact the Pfizer Clinical Support Help Desk.

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Appendix 2: Example Temperature Monitor Site Instruction for 0.9% Sodium Chloride Injection, USP, Placebo and Diluent

This is an example only. Use the instructions provided in the shipment. If there are any queries regarding temperature monitors, please contact: gatewaysupport@almacgroup.com



Important Information for Site Staff



Please continue with your normal receiving procedure. Follow the below iTag4 instruction sheet for guidance.



iTAG4 Bio TEMPERATURE MONITOR SITE INSTRUCTIONS

PLEASE TAKE IMMEDIATE ACTION

IMPORTANT INFORMATION: These symbols on the LCD display will indicate how to proceed with the product.

PROCEED to use as required.

DO NOT USE until you receive confirmation that the shipment is suitable for use.

STEP 1:

1A Locate temperature monitor.
Press the "Start/Stop" button firmly for 3 seconds.
Display shows "STOP".



1B If the monitor does not display "STOP", proceed to continue to place the investigational product in the specified storage conditions immediately.



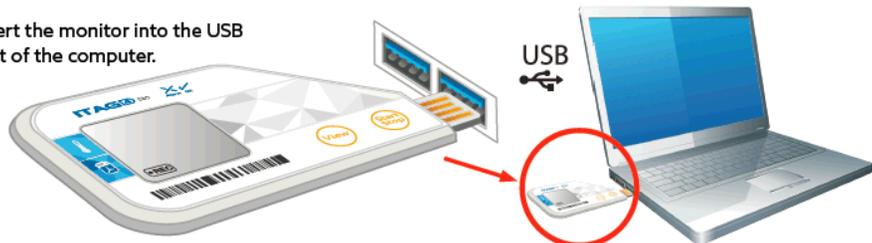
STEP 2:

2A Navigate to TempEZ - <https://tempezconnect.almacgroup.com>

- Follow on-screen instructions to enter contact details and the Order Number or Monitor Serial Number.



2B Insert the monitor into the USB port of the computer.



Any queries regarding temperature monitors please contact: globaltemperatureservices@almacgroup.com

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Appendix 2A: Example Temperature Monitor Site Instruction for BNT162b2 Vaccine (Libero)

This is an example only. Use the instructions provided in the shipment. *If there are any queries regarding temperature monitors, please contact: GlobalTemperatureServices@almacgroup.com*



TT Ultra / TT4 / LIBERO TEMPERATURE MONITOR SITE INSTRUCTIONS

PLEASE TAKE IMMEDIATE ACTION

TempTale Ultra	TempTale4 USB	Libero
<p>Step 1: Hold down the stop button Stop (1) until the stop symbol (2) appears on the display.</p> <p>Step 2: Place the investigational product in the specified storage conditions immediately.</p> <p>Step 3: Is there an X (3) on the display?</p> <p>No: The product has traveled in good conditions within spec and can be used immediately.</p> <p>Yes: If there is an X on the display - DO NOT use the product until you receive confirmation that the shipment is acceptable for use.</p>	<p>Step 1: Hold down the stop button Stop (1) until the stop symbol (2) appears on the display.</p> <p>Place the investigational product in the specified storage conditions immediately.</p> <p>Step 2: Is there a flashing bell symbol (3) on the display?</p> <p>No: The product has traveled in good conditions within spec and can be used immediately.</p> <p>Yes: Bell symbol present -> DO NOT use the product until you receive confirmation that the shipment is acceptable for use.</p>	<p>Step 1: Hold down the Arrived button STOP Arrived (1) until the word "Arrived" (2) appears on the display. There will also be a √ or X on the display (3).</p> <p>Step 2: Place the investigational product in the specified storage conditions immediately.</p> <p>Step 3:</p> <ul style="list-style-type: none"> If there is a √ on the display - the product has traveled in good condition and can be used immediately. If there is an X on the display - DO NOT use the product until you receive confirmation that the shipment is acceptable for use.
<p>Final steps for the TempTale4, TempTale Ultra and Libero monitors:</p> <p>Navigate to TempEZ - https://tempezconnect.almacgroup.com</p> <ul style="list-style-type: none"> Follow on-screen instructions to enter contact details and the Order Number or Monitor Serial Number. <p>Insert the monitor into the USB port of the computer.</p> <p>If you have any queries regarding temperature monitors please contact: globaltemperatureservices@almacgroup.com</p>		

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Appendix 3: Example Almac Clinical Services Site Temperature Monitoring Reporting Form

This is an example only. Obtain a copy of the form from the Sponsor.

Clinical
Services

Site Temperature Excursion Form

Please complete this *Site Temperature Excursion Form* if your site experiences a site temperature excursion and upload the completed form to TempEZ - <https://tempezconnect.almacgroup.com>. Attach a copy of temperature records related to this temperature excursion & store in site file. This form will be returned to you once the final disposition of the material has been determined.

Note: All supplies impacted by the temperature excursion must be segregated and quarantined from unaffected supplies and stored at labeled conditions BUT should not be used until final disposition has been determined.

For assistance, contact globaltemperatureservices@almacgroup.com.

BNT / Pfizer	Customer:	
	Protocol #:	
	Site # / Country:	
	Site Contact Name:	
	Site Contact Telephone:	
	Site Contact Email:	

Product Affected by Excursion:	Total Quantity:
<ul style="list-style-type: none"> - For Numbered studies, include all medication numbers affected - For non-numbered studies, include the Product Name and Lot Number <p><i>Add additional rows if necessary</i></p>	<i>Specify if kits or vials</i>

Excursion Details:	
<i>Sections 1 to 3 can be left blank if this information can be confirmed from the site temperature data</i>	
1. Record the date and time of the temperature excursion: (DDMMYYYY) (HH:MM)	
2. Record the duration of the excursion: (HH:MM)	
3. Record the minimum temperature (Low Excursion)	Minimum: _____
Record the maximum temperature (High Excursion)	Maximum: _____
4. Have any of the materials been relocated to another storage location:	<input type="checkbox"/> Yes <input type="checkbox"/> No If yes, time of relocation: _____ Attach temperature data of relocated material.
5. Were any affected supplies dispensed?	<input type="checkbox"/> Yes <input type="checkbox"/> No
6. Are the supplies being stored correctly?	<input type="checkbox"/> Yes <input type="checkbox"/> No

GL0776.03
Page 1 of 2

Global Temperature Services - GTS.001 Form Type B
Print Date & Time of routing document for approval: 14 Feb. 19 13:54

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Example Almac Clinical Services Site Temperature Excursion Form (Page 2 of 2)

Clinical Services

Site Temperature Excursion Form

Reason for Excursion:	<input type="checkbox"/> Power Failure <input type="checkbox"/> Equipment Malfunction <input type="checkbox"/> Other (detail reason):
Date of next scheduled Patient Visit (if known):	

Excursion Reported By		
Name	Position	Date

REMAINING SECTION TO BE COMPLETED BY ALMAC

Almac Clinical Services Assessment of Temperature Excursion
<input type="checkbox"/> Material is ACCEPTABLE for use. The temperature excursion is not <u>significant</u> and the material is fit for use. <i>The material has been released in the IRT (if applicable).</i>
<input type="checkbox"/> Material is NOT ACCEPTABLE for use. The temperature excursion is <u>significant</u> and the material is NOT fit for use. <i>The IRT vendor has been notified and a replacement shipment will be dispatched if deemed applicable.</i>
<input type="checkbox"/> Material is PARTIALLY ACCEPTABLE for use. The following material is acceptable: The following material has been deemed as NOT ACCEPTABLE for use:

Disposition Performed By			
Signature	Print Name	Position	Date

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Page 2 of 2

Global Temperature Services - GTS.001 Form Type B
Print Date & Time of routing document for approval: 14 Feb. 19 13:54

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Appendix 3A: Temp EZ Upload Instructions

Uploading A Temperature Excursion Form for A Storage Excursion

Access TempEZ Connect <https://tempezconnect.almacgroup.com/TempEZConnect/faces/welcome>

- Click on Facility / Storage Facility



- If you do not already have a form completed and saved you can access it on TempEZ Connect. please [click here](#) to download the form.

Enter your contact information and continue.

Site Monitor/Report Excursion
 If you have a site monitor or a temperature excursion at your facility, please follow the instructions below.
 If a manual "Temperature Excursion Form" is needed for upload, please [click here](#) to download the form.
 For technical assistance, please contact GatewaySupport@almacgroup.com

Please enter your contact information

* First Name * Email Address
 * Last Name * Telephone (numbers only, no dashes)
 *required field Continue

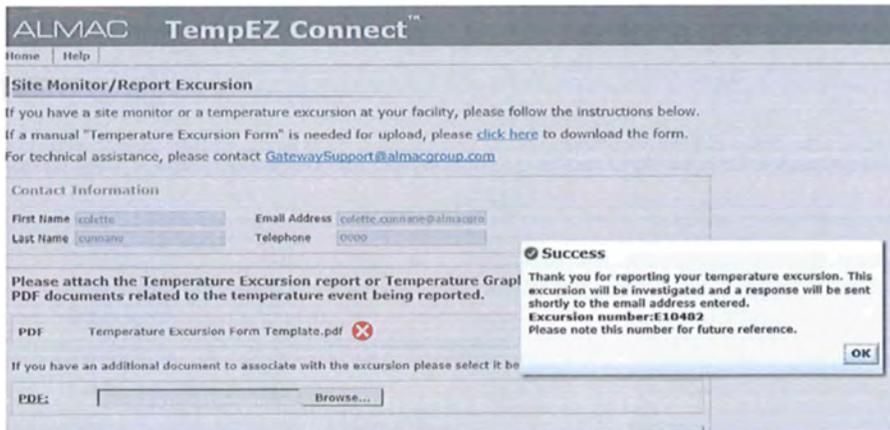
- Upload the pdf completed form and any additional document (logger data) click Done.

Please attach the Temperature Excursion report or Temperature Graph/Reading or any other PDF documents related to the temperature event being reported.

PDE: Browse...

*required field Done

You will be given a Success to show that it has been uploaded. This will issue you an Excursion Number E..... Please give this to your Adjudicator so that they may make a decision on the suitability of the drugs.



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Appendix 4: Example Pfizer Investigational Product Accountability Log (IPAL)

Contact your uCRA for a copy of the IPAL for this study.

	INVESTIGATIONAL PRODUCT ACCOUNTABILITY LOG (IPAL)
---	--

Protocol Title:							IRT in use: <input type="checkbox"/> Yes <input type="checkbox"/> No			<input type="checkbox"/> Blinded Document <input type="checkbox"/> Unblinded Document¹				
Site Principal Investigator:					Site ID:			Protocol #:						
Investigational Medicinal Product Name:				Strength:			Dosage Form:							
Units Per Container:		Storage Requirement (refer to product label):²												
Receipt or Dispense Date ³ dd/Mmm/yyyy	<input type="checkbox"/> Lot Number <input type="checkbox"/> Kit Number <input type="checkbox"/> Container Number <input type="checkbox"/> Other (specify) Or Shipment ID # ⁴	Study Subject ID Number (SSID) ⁵	Quantity of Containers Received (R) or Dispensed (D) or Undispensed (U) ⁶	Balance (Containers) ⁷	Staff Initials ⁸	Monitor Initials ⁹	Subject Returns ¹⁰			Disposition ¹¹			Monitor Initials	
							Quantity of Units Returned (N/R for not returned)	Date Returned dd/Mmm/yyyy	Staff Initials	Return (R) to Sponsor / Designee or Destroy (D)	Date of Disposition dd/Mmm/yyyy	Staff Initials		

EXAMPLE

Comments:¹² _____ Page¹³ ___ of ___

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Example Pfizer Investigational Product Accountability Log (IPAL) – Continued



INVESTIGATIONAL PRODUCT ACCOUNTABILITY LOG (IPAL)

Instructions for completing Investigational Product Accountability Log (IPAL)

- **This form (or equivalent) is used when Pfizer supplies investigational or commercial products.**
 - Use only blue or black ballpoint pens.
 - If an error is made, draw one line through the incorrect entry, initial, date and enter correction. NEVER USE CORRECTION FLUID.
 - For any fields where data is not applicable; write N/A (not applicable).
 - Perform data entry at the time of occurrence. If late entry of data is necessary, provide both the date of entry and date of occurrence, (e.g., 11Feb2016 for 09Feb2016).
 - The entry of a future date is not allowed.
1. **Blinded or Unblinded Document:** (Pre-populated by study manager or designee). In a blinded study, if unblinded document box is checked, this document is only accessible to unblinded site personnel and requires unblinded site monitor.
 2. **Storage Requirement:** (pre-populated by study manager or designee). Enter appropriate storage requirements (refer to product label).
 3. **Receipt or Dispense Date:** dd/Mmm/yyyy.
 4. **Lot, Kit, Container Number, Other or Shipment ID #:** Check appropriate box (if other, specify). For shipments received, enter shipment ID number (do not list individual container/kit numbers); when dispensing, enter only one kit or container number per page.
 5. **Study Subject ID Number:** Subject's assigned study number (in some cases this will be randomization number).
 6. **Quantity of Containers Received (R) or Dispensed (D) or Undispensed (U):** Indicate as R-10 (for received 10 containers), D-1 (for dispensed 1 container), U-1 for undispensed (accounted for or lost/misplaced).
 7. **Balance (Containers):** Write container balance calculated at each receipt of investigational medicinal product or dispensation to a subject (this number should always reflect the number of undispensed containers available at site); in cases where a bulk bottle is received and dispensing of single units is required from that bottle, change "(containers)" to "(units)" as appropriate (all changes should be indicated by drawing one line through incorrect entry, initial, date and enter correction).
 8. **Site Staff Initials:** Two designated site staff members document dispensing of investigational medicinal product and one or two staff member(s) document receipt of investigational medicinal product by initialing the form.
 9. **Site Monitor Initials:** Monitor initials as verification that accountability was performed at site monitoring visit (this confirms that monitor has verified inventory).
 10. **Subject Returns:** Site staff completes when subject returns unused investigational medicinal product (open bottles, partial blister packs, etc.). Enter N/R if not returned by the subject.
 - Quantity of Units Returned: This is number of "units" (e.g., 31 tablets), not containers OR if product was prepared but not administered to subject and is returned to pharmacy, this should be indicated here (additional comments, if needed may be placed in comment section).
 - Date Returned: dd/Mmm/yyyy (this is the date the subject physically returns the investigational medicinal product to the site).
 - Staff Initials: Site staff performing reconciliation (number of units returned) initials the form.
 11. **Disposition:** The site monitor completes this at time of investigational medicinal product return or destruction.
 - Indicate "R" for return to sponsor/designee, "D" for destruction at site.
 - Date of Disposition: dd/Mmm/yyyy (for investigational product returns, date of disposition is the date that return has been initiated [investigational medicinal product is packed and prepared for shipment]).
 - Staff Initials.
 - Monitor Initials (acknowledgment that investigational medicinal product was destroyed at site, return to sponsor/designee for destruction).
 12. **Comments:** Use this section to comment on any problems or deviations.
 13. **Page ___ of ___:** Number pages consecutively; do not fill in "of ___" until study completion.

Note: Any undispensed containers that are returned or destroyed should be entered on the IPAL. Enter the individual kit, container or lot number as applicable. Documentation of undispensed containers may be completed by the site monitor but requires verification by site personnel.

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Appendix 5: Preparation Record for BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.3 mL/vial) Using In-Vial Dilution for Intramuscular Injection

This form is required for **Phase 2/3 ONLY**. The use of alternative preparation records must be approved by the Sponsor’s Clinical Research Pharmacist. Prepared by and checked by must be completed by two unblinded site personnel. Prepared by must be completed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician’s assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Checked by must be completed by a second unblinded staff member who will verify the dispensing.

Protocol Number: C4591001	List all Single Subject ID Numbers (SSIDs) that were dispensed a dose from this prepared diluted dosing solution. <i>Reminder:</i> Maximum number of 30 mcg doses to prepare = 5 doses, each with 0.3 mL	
BNT162b2 Vaccine Vial Container Number: _____	1.	4.
	2.	5. <i>(MAX 30 mcg doses)</i>
	3.	NOT APPLICABLE

BNT162b2 Vaccine Candidate Vial and Dose-Level (Verify the vial and confirm the desired dose to prepare):

Vial Description and Corresponding Carton Label Color per Country	Dose Level
BNT162b2 (0.3 mL/vial) • Argentina, Brazil, and USA: YELLOW Single Panel Carton Label	<input type="checkbox"/> 30 mcg

Date of dose preparation (DD-MMM-YYYY):	Dose preparation start time (HH:MM): <i>(Time at which the needle is inserted into the BNT162b2 vial)</i>
---	--

Expiry Date and Time of prepared dose (DD-MMM-YYYY; HH:MM): *Expiry is 6 hours from the start of dose preparation.*

NOTE: Prepared dosing solutions should be used immediately. If it cannot be used immediately, it may be stored up to 6 hours between 2 to 25 °C (36 to 77°F). Do not share the date and start time of dose preparation as it is potentially unblinding.

Table 1. BNT162b2 Vaccine In-Vial Dilution Table

Dose Level (mcg)	Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial	Volume of 0.9% Sodium Chloride Required for Dilution	Final Volume of Diluted Dosing Solution	Maximum Number of Doses to Prepare from the Diluted Dosing Solution
30 mcg	0.5 mL	2 mL	2.5 mL	5

Instructions for Preparation		Data
1	Obtain 1 vial of the appropriate BNT162b2 Vaccine concentrate and allow to thaw for approximately 30 minutes.	<input type="checkbox"/> Completed
2	Once BNT162b2 Vaccine vial is completely thawed, invert gently 10 times to mix. Do not shake.	<input type="checkbox"/> Completed

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Instructions for Preparation		Data
Instructions for Preparation		Data
		Page 2 of 3
3	Withdraw the 2 mL of 0.9% Sodium Chloride required for dilution. (Refer to Table 1 above)	Volume of 0.9% Sodium Chloride _____ mL
4	Carefully transfer 2 mL of 0.9% Sodium Chloride into the BNT162b2 Vaccine vial. Pull back on the plunger to withdraw air and equalize the pressure in the vial. Discard the syringe and needle. Gently invert the diluted vial 10 times to mix. Do not shake.	<input type="checkbox"/> Completed
5	Write the "Do not use after: Date ____ and Time ____" on the BNT162b2 Vaccine vial label (expiry is 6 hours from the start of dose preparation – Refer to the expiry information on Page 1 of this record)	<input type="checkbox"/> Completed
6	Obtain a new 1 mL polycarbonate syringe and attach a needle. Withdraw a sufficient volume (e.g 0.35 mL) of the diluted dosing solution into the 1 mL syringe to allow for priming and ensure a final injection volume of 0.3 mL . Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
7	If the syringe will be administered immediately (within 1 hour), attach an appropriate needle for intramuscular injection (e.g. 25 G x 1- or 1.5-inch needle) and prime the needle to a final injection volume of 0.3 mL. Carefully recap the needle. Once completed, check off the appropriate box for each prepared syringe. Note: If the prepared syringe is not used immediately, place a luer lock cap to store the syringe. Attach a suitable needle for intramuscular injection and prime prior to administration.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
8	Verify that the final volume in the syringe is 0.3 mL. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
9	Apply the Sponsor-provided occluding label (required) to the barrel of the syringe to mask the contents. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5
10	Apply a blinded participant-specific label (i.e. product name and dose must be blinded) to the prepared syringe. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2 <input type="checkbox"/> 3 <input type="checkbox"/> 4 <input type="checkbox"/> 5

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The unblinded staff members performing and verifying dose preparation shall print his/her first and last name. The initials of the two unblinded site staff members preparing each syringe (up to 5 syringes) shall be documented in the corresponding column.

Staff Member (Print First and Last Name)	Syringe #1 (Staff initials)	Syringe #2 (Staff initials)	Syringe #3 (Staff initials)	Syringe #4 (Staff initials)	Syringe #5 (Staff initials)
Dose Prepared By:					
Dose Checked By:					

Contact your Clinical Research Associate immediately to report any dose preparation deviations.
 Comments (record any deviations from preparation instructions; storage time and conditions, etc.):

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Appendix 6: BNT162b2 Vaccine 250 mcg/0.5 mL Concentrate for Solution for Injection (0.2 mL/vial) Using In-Vial Dilution for Intramuscular Injection

This form is required for **Phase 2/3 ONLY**. The use of alternative preparation records must be approved by the Sponsor’s Clinical Research Pharmacist. Prepared by and checked by must be completed by two unblinded site personnel. Prepared by must be completed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician’s assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Checked by must be completed by a second unblinded staff member who will verify the dispensing.

Protocol Number: C4591001	BNT162b2 Vaccine Vial Container Number: _____				
List all Single Subject ID Numbers (SSIDs) that were dispensed a dose from this prepared diluted dosing solution. <i>Reminder:</i> Maximum number of 30 mcg doses to prepare = 2 doses, each with 0.3 mL					
1.	2. <i>(MAX 30 mcg doses)</i>				
BNT162b2 Vaccine Candidate Vial and Dose-Level (Verify the vial and confirm the desired dose to prepare): <table border="1" style="width:100%; border-collapse: collapse; margin-top: 10px;"> <thead> <tr style="background-color: #e0e0e0;"> <th style="width:70%;">Vial Description and Corresponding Carton Label Color per Country</th> <th style="width:30%;">Dose Level</th> </tr> </thead> <tbody> <tr> <td> BNT162b2 (0.2 mL/vial) <ul style="list-style-type: none"> Argentina, Brazil, USA: BLUE Single Panel Carton Label Germany, South Africa, Turkey: WHITE <i>Booklet</i> Carton Label </td> <td style="text-align: center;"> <input type="checkbox"/> 30 mcg </td> </tr> </tbody> </table>		Vial Description and Corresponding Carton Label Color per Country	Dose Level	BNT162b2 (0.2 mL/vial) <ul style="list-style-type: none"> Argentina, Brazil, USA: BLUE Single Panel Carton Label Germany, South Africa, Turkey: WHITE <i>Booklet</i> Carton Label 	<input type="checkbox"/> 30 mcg
Vial Description and Corresponding Carton Label Color per Country	Dose Level				
BNT162b2 (0.2 mL/vial) <ul style="list-style-type: none"> Argentina, Brazil, USA: BLUE Single Panel Carton Label Germany, South Africa, Turkey: WHITE <i>Booklet</i> Carton Label 	<input type="checkbox"/> 30 mcg				
Date of dose preparation (DD-MMM-YYYY):	Dose preparation start time (HH:MM): <i>(Time at which the needle is inserted into the BNT162b2 vial)</i>				
Expiry Date and Time of prepared dose (DD-MMM-YYYY; HH:MM): <i>Expiry is 6 hours from the start of dose preparation.</i>					

NOTE: Prepared dosing solution should be used immediately. If it cannot be used immediately, it may be stored up to 6 hours between 2 to 25 °C (36 to 77°F). Do not share the date and start time of dose preparation as it is potentially unblinding.

Table 1. BNT162b2 Vaccine In-Vial Dilution Table

Dose Level (mcg)	Volume of BNT Vaccine Concentrate for Solution for Injection in the Vial	Volume of 0.9% Sodium Chloride Required for Dilution	Final Volume of Diluted Dosing Solution	Maximum Number of Doses to Prepare from the Diluted Dosing Solution
30 mcg	0.2 mL	0.8 mL	1 mL	2

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Instructions for Preparation		Data
1	Obtain 1 vial of the appropriate BNT162b2 Vaccine concentrate and allow to thaw for approximately 30 minutes.	<input type="checkbox"/> Completed
2	Once BNT162b2 Vaccine vial is completely thawed, invert gently 10 times to mix. Do not shake.	<input type="checkbox"/> Completed
3	Withdraw the 0.8 mL of 0.9% Sodium Chloride required for dilution. (Refer to Table 1 above)	Volume of 0.9% Sodium Chloride _____ mL
4	Carefully transfer the required volume of 0.9% Sodium Chloride into the BNT162b2 Vaccine vial. Pull back on the plunger to withdraw air and equalize the pressure in the vial. Discard the syringe and needle. Gently invert the diluted vial 10 times to mix. Do not shake.	<input type="checkbox"/> Completed
5	Write the "Do not use after: Date ____ and Time ____" on the BNT162b2 Vaccine vial label (expiry is 6 hours from the start of dose preparation – Refer to the expiry information on Page 1 of this record)	<input type="checkbox"/> Completed
6	Obtain a new 1 mL polycarbonate syringe and attach a needle. Withdraw a sufficient volume (e.g 0.35 mL) of the diluted dosing solution into the 1 mL syringe to allow for priming and ensure a final injection volume of 0.3 mL. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2
7	If the syringe will be administered immediately (within 1 hour), attach an appropriate needle for intramuscular injection (e.g. 25 G x 1 or 1.5 inch needle) and prime the needle to a final injection volume of 0.3 mL. Carefully recap the needle. Once completed, check off the appropriate box for each prepared syringe. Note: If the prepared syringe is not used immediately, place a luer lock cap to store the syringe. Attach a suitable needle for intramuscular injection and prime prior to administration.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2
8	Verify that the final volume in the syringe is 0.3 mL. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2
9	Apply the Sponsor-provided occluding label (required) to the barrel of the syringe to mask the contents. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2
10	Apply a blinded participant-specific label (i.e. product name, dose, and final injection volume must be blinded) to the prepared syringe. Once completed, check off the appropriate box for each prepared syringe.	<u>Syringe #</u> <input type="checkbox"/> 1 <input type="checkbox"/> 2

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The unblinded staff members performing and verifying dose preparation shall print his/her first and last name. The initials of the two unblinded site staff members preparing each syringe (up to 2 syringes) shall be documented in the corresponding column.

Staff Member (Print First and Last Name)	Syringe #1 (Staff initials)	Syringe #2 (Staff initials)
Dose Prepared By:		
Dose Checked By:		

Contact your Clinical Research Associate immediately to report any dose preparation deviations.

Comments (record any deviations from preparation instructions; storage time and conditions, etc.):

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Appendix 7: Preparation Record for Placebo (0.9% Sodium Chloride Injection, USP) for Intramuscular Injection

This form is required for **Phase 2/3 ONLY**. The use of alternative preparation records must be approved by the Sponsor’s Clinical Research Pharmacist. Prepared by and checked by must be completed by two unblinded site personnel. Prepared by must be completed by an appropriately qualified and experienced member of the study staff (e.g., physician, nurse, physician’s assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. Checked by must be completed by a second unblinded staff member who will verify the dispensing.

Protocol Number: **C4591001**

Subject Number (SSID): _____

0.9% Sodium Chloride (Placebo) Vial Container Number: _____	Date of dose preparation (DD-MMM-YYYY): _____
--	--

Verify the product name on the vial, the desired placebo dose to prepare, and the vaccination # .

Vial Description and Corresponding Carton Label Color per Country	Dose Level	Vaccination # (Select one)
Placebo (0.9% Sodium Chloride, USP 10 mL/Vial) <ul style="list-style-type: none"> Brazil and USA: WHITE <i>Single Panel</i> Carton Label Argentina, Germany, South Africa, Turkey: WHITE <i>Booklet</i> Carton Label 	<input type="checkbox"/> Placebo for 30 mcg	<input type="checkbox"/> #1 <input type="checkbox"/> #2

Dose preparation start time (HH:MM): <i>(Time at which the needle is inserted into vial)</i>	Expiry Date and Time of prepared dose (DD-MMM-YYYY; HH:MM): <i>Expiry is 6 hours from the start of dose preparation.</i>
--	--

NOTE: Prepared dosing solution should be used immediately. If it cannot be used immediately, it may be stored up to 6 hours if stored between 2 to 25 °C (36 to 77 °F). Do not share the date and start time of dose preparation as it is potentially unblinding.

	Instructions for Preparation	Data
1	Obtain 1 vial of 0.9% Sodium Chloride for Injection	<input type="checkbox"/> Complete
2	<ul style="list-style-type: none"> Obtain a new 1 mL polycarbonate syringe and attach an appropriate size needle for dose preparation. Withdraw a sufficient excess volume (e.g. 0.35 mL) to allow for priming and ensure a final injection volume of 0.3 mL. 	<input type="checkbox"/> Complete
3	If dose will be administered immediately (within 1 hour), attach an appropriate needle for intramuscular injection (e.g. 25 G x 1 or 1.5 inch needle) and prime the needle to the final injection volume of 0.3 mL . Carefully recap the needle. Note: If the prepared syringe is not used immediately, place a luer lock cap to store the syringe. Attach a suitable needle for intramuscular injection and prime prior to administration.	Final Injection Volume of 0.9% Sodium Chloride _____ mL
4	Apply the Sponsor-provided occluding label (required) to the barrel of the syringe to mask the contents	<input type="checkbox"/> Complete

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Instructions for Preparation		Data
5	Apply a blinded participant-specific label (i.e. product name and dose must be blinded) to the syringe. The expiry data and time on the label of the placebo dosing syringe must match the same expiry date and time on the label of the active dosing syringe.	<input type="checkbox"/> Complete

Prepared by (Print name/Signature): _____ Date _____ (dd-mmm-yyyy)

Checked by (Print name/Signature): _____ Date _____ (dd-mmm-yyyy)

Contact your Clinical Research Associate immediately to report any dose preparation deviations.

Comments (record any deviations from preparation instructions; storage time and conditions, etc.): _____

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Appendix 8: Example Product Complaint Form

Annex 7 to Pharmacy Manual
BNT162-01

20 APR 2020
Version 01



Internal Reference No.:
(filled in by BioNTech (e.g. Deviation or Complaint No.))

Product Complaint Form			
General Information:	<ul style="list-style-type: none"> Please complete this form for product complaints related to clinical trial supplies provided by BioNTech (e.g. shipped product is damaged, expired or missing). If applicable, keep affected products quarantined until further instructions are given by the sponsor. Temperature Excursions have to be reported via Temperature Excursion Report Form 		
Contact Details Complainant			
Complainant Name			
Address and Site No. (if applicable)			
Country		E-Mail	
Phone		Fax	
Complaint Details			
Batch No.		Box No(s)	
Quantity		Expiry Date	
Shipment No.		Date/line of detection	
Patient No. affected (if applicable)			
Description (what happened/ please provide pictures if relevant)	<div style="font-size: 48px; opacity: 0.3; transform: rotate(-30deg); pointer-events: none;">EXAMPLE</div>		
Sample still available?	<input type="checkbox"/> Yes <input type="checkbox"/> No		
Date & Signature Complainant	I confirm that submitted Complaint is complete and correct.		
After completion and signature please send the completed Form by E-Mail QA@biontech.de			
Received: Date & Signature BioNTech QA			

Strictly confidential

1/2

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Example Product Complaint Form – Continued

Annex 7 to Pharmacy Manual
BNT162-01

20 APR 2020
Version 01



Internal Reference No.:
(filled in by BioNTech (e.g. Deviation or Complaint No.))

Complaint Acknowledgement of Receipt	
Please perform the following additional immediate actions until investigation is completed:	
Date & Signature BioNTech's Subject Matter Expert or Delegate:	
After completion and signature please send back by E-Mail to Complainant	
Complaint Outcome	
Please describe outcome:	
EXAMPLE	
Date & Signature BioNTech's Subject Matter Expert or Delegate	
After completion and signature please send back by E-Mail to Complainant	

Strictly confidential

2/2

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Appendix 9: Impala Kit Verify Mobile Application



The Impala Kit Verify mobile application (app) is a Good Clinical Practices smartphone application that:

- Is available to active clinical sites within the United States using the Impala Interactive Response Technology system.
- Assists clinical site personnel with verification and dispensing of the appropriate kit/container to the correct subject.

Use of the Impala Kit Verify App is optional, yet encouraged.

Use of the Impala Kit Verify App for container dispensing requires the initial single person verification, but eliminates the need for second person verification.

Clinical site personnel must complete the Impala Kit Verify App training in FIRECREST prior to use.

HOW DO I GET THE APP?

The App requires a mobile device with the following system requirements:

- iPhone OS 9.0 or higher
- OR
- Android OS 4.3 or higher

Step 1: Search for "Impala Kit Verify" in the Apple App Store or Google Play.

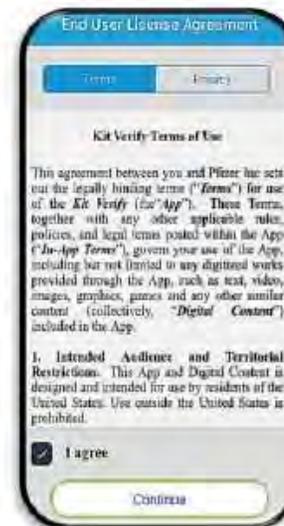


Step 2: Download the Impala Kit Verify App.



Impala Kit Verify App 2.0 Brochure 30-Nov-2018

Step 3: Review and agree to the End User License Agreement Terms & Privacy.



App Support:

If you have questions regarding the App or access to Impala, contact the Pfizer Clinical Support Help Desk:

Tap the icon within the App or call:

1-877-433-2619

Select Option 3 then Option 4.

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EXAMPLE



Before using the App:

Ensure you have completed the Impala Kit Verify App training module in FIRECEST.

Confirm that the user has an active Impala account (contact the study monitor if the site does not have an account).

Register the subject Visit in Impala.

Print out the subject specific Impala Drug Assignment Confirmation Report (DACR).

Obtain the assigned containers from inventory.

Pfizer Inc.
IMPALA ASSIGNMENT CONFIRMATION REPORT
PROTOCOL: 13753333

QR Code: [Barcode]

Contact Email: [Redacted]
 Email Address: [Redacted]

Case Number:	10000000
Principal Investigator:	Jim Zeng
Date of Transmission (DTE):	04-Sep-2019 11:30:12
Date of Transmission (DTE) (GMT):	04-Sep-2019 17:30:12
ASAP:	20190912
Date of Birth:	11-DEC-1988
Randomization Number:	11
Stratum:	1 (Industry-specified)
Visit Number:	1
IMP - Container Number	By Date/Assignment Date (US Eastern)
IMP00110118	01-Sep-2019 04-Sep-2019
IMP00110148	01-Sep-2019 04-Sep-2019
IMP00110200	01-Sep-2019 04-Sep-2019

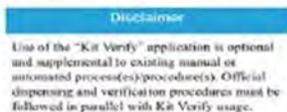
Other fields: First Name, Surname, Date, Date Assigned Name, Date Assigned Surname.

HOW DO I USE THE APP?

Follow the instructions below to begin the verification process:

Complete the initial first person verification per normal procedure and document on the **Investigational Product Accountability Log (IPAL)** and, if required*, on the DACR.

Open the App → Accept the Disclaimer.



Tap "Scan" on the scanning screen.



Impala Kit Verify App 2.0 Brochure 30-Nov-2018

Scan the barcode on the Impala Drug Assignment Confirmation Report.

Pfizer Inc.
IMPALA ASSIGNMENT CONFIRMATION REPORT
PROTOCOL: 13753333

QR Code: [Barcode]

Contact Email: [Redacted]
 Email Address: [Redacted]

Case Number:	10000000
Principal Investigator:	Jim Zeng
Date of Transmission (DTE):	04-Sep-2019 11:30:12
Date of Transmission (DTE) (GMT):	04-Sep-2019 17:30:12
ASAP:	20190912
Date of Birth:	11-DEC-1988
Randomization Number:	11
Stratum:	1 (Industry-specified)
Visit Number:	1
IMP - Container Number	By Date/Assignment Date (US Eastern)
IMP00110118	01-Sep-2019 04-Sep-2019
IMP00110148	01-Sep-2019 04-Sep-2019
IMP00110200	01-Sep-2019 04-Sep-2019

Other fields: First Name, Surname, Date, Date Assigned Name, Date Assigned Surname.

Locate and scan the "Pfizer Kit Verify" barcode on the drug container label.



Enter "KV#2" in the space for the second verification on the **Investigational Product Accountability Log (IPAL)**, including a note in the comments section.

*Check the Impala Quick Reference Guide to see if your study requires signatures on your Drug Assignment Confirmation Report (DACR).

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Document Approval Record

Document Name:	IP Manual for C4591001 Phase 2/3
Document Title:	IP Manual for C4591001 Phase 2/3

Signed By:	Date(GMT)	Signing Capacity
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Weiser, Sarah Elizabeth	28-Aug-2020 23:33:18	Business Line Approver
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Ex. 7

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001



**A PHASE 1/2/3, PLACEBO-CONTROLLED, RANDOMIZED, OBSERVER-BLIND,
DOSE-FINDING STUDY TO EVALUATE THE SAFETY, TOLERABILITY,
IMMUNOGENICITY, AND EFFICACY OF SARS-COV-2 RNA VACCINE
CANDIDATES AGAINST COVID-19 IN HEALTHY INDIVIDUALS**

Study Sponsor: BioNTech
Study Conducted By: Pfizer
Study Intervention Number: PF-07302048
Study Intervention Name: RNA-Based COVID-19 Vaccines
US IND Number: 19736
EudraCT Number: 2020-002641-42
Protocol Number: C4591001
Phase: 1/2/3
Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

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1. PROTOCOL SUMMARY

1.1. Synopsis

Short Title: A Phase 1/2/3 Study to Evaluate the Safety, Tolerability, Immunogenicity, and Efficacy of RNA Vaccine Candidates Against COVID-19 in Healthy Individuals

Rationale

A pneumonia of unknown cause detected in Wuhan, China, was first reported in December 2019. On 08 January 2020, the pathogen causing this outbreak was identified as a novel coronavirus 2019. The outbreak was declared a Public Health Emergency of International Concern on 30 January 2020. On 12 February 2020, the virus was officially named as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and the WHO officially named the disease caused by SARS-CoV-2 as coronavirus disease 2019 (COVID-19). On 11 March 2020, the WHO upgraded the status of the COVID-19 outbreak from epidemic to pandemic, which is now spreading globally at high speed.

There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the rapid transmission of COVID-19 and incidence of disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

BioNTech has developed RNA-based vaccine candidates using a platform approach that enables the rapid development of vaccines against emerging viral diseases, including SARS-CoV-2. Each vaccine candidate is based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b). Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein receptor-binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

BNT162b1 (variant RBP020.3): a modRNA encoding the RBD;

BNT162b2 (variant RBP020.2): a modRNA encoding P2 S.

All candidates are formulated in the same lipid nanoparticle (LNP) composition. This study is intended to investigate the safety, immunogenicity, and efficacy of these prophylactic BNT162 vaccines against COVID-19.

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Objectives, Estimands, and Endpoints

For Phase 1

Objectives	Estimands	Endpoints
Primary:	Primary:	Primary:
To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose Adverse events (AEs) from Dose 1 to 1 month after the last dose Serious AEs (SAEs) from Dose 1 to 6 months after the last dose 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs
	In addition, the percentage of participants with: <ul style="list-style-type: none"> Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2 	Hematology and chemistry laboratory parameters detailed in Section 10.2
Secondary:	Secondary:	Secondary:
To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: <p>7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2</p>	
	<ul style="list-style-type: none"> Geometric mean titers (GMTs) at each time point Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination Proportion of participants achieving ≥ 4-fold rise from before vaccination to each subsequent time point after vaccination 	SARS-CoV-2 neutralizing titers

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Objectives	Estimands	Endpoints
	<ul style="list-style-type: none"> Geometric mean concentrations (GMCs) at each time point GMFR from before vaccination to each subsequent time point after vaccination Proportion of participants achieving ≥ 4-fold rise from before vaccination to each subsequent time point after vaccination 	S1-binding IgG levels and RBD-binding IgG levels
	<ul style="list-style-type: none"> Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point 	<ul style="list-style-type: none"> SARS-CoV-2 neutralizing titers S1-binding IgG levels RBD-binding IgG levels

For Phase 2/3

Objectives ^a	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in <u>the first 360 participants</u> randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from Dose 1 to 7 days after the second dose SAEs from Dose 1 to 7 days after the second dose 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs

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Objectives ^a	Estimands	Endpoints
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose 	<ul style="list-style-type: none"> • AEs • SAEs • In a subset of at least 6000 participants: <ul style="list-style-type: none"> ○ Local reactions (pain at the injection site, redness, and swelling) ○ Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • AEs from Dose 1 to 1 month after the second dose • SAEs from Dose 1 to 6 months after the second dose 	<ul style="list-style-type: none"> • Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection

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Objectives ^a	Estimands	Endpoints
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	<ul style="list-style-type: none"> • S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		<ul style="list-style-type: none"> • N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: <ul style="list-style-type: none"> • Confirmed COVID-19 • Confirmed severe COVID-19 • SARS-CoV-2 infection without confirmed COVID-19 		<ul style="list-style-type: none"> • S1-binding IgG levels and/or RBD-binding IgG levels • SARS-CoV-2 neutralizing titers

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Objectives ^a	Estimands	Endpoints
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		<ul style="list-style-type: none"> All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” or “Process 2” ^b		<ul style="list-style-type: none"> All safety endpoints described above SARS-CoV-2 neutralizing titers

- a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
- b. See [Section 6.1.1](#) for a description of the manufacturing process.

Overall Design

This is a Phase 1/2/3, multicenter, multinational, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts: Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema ([Section 1.2](#)).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥ 12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 μg .

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Number of Participants

Each group in Phase 1 will comprise 15 participants (12 receiving active vaccine and 3 receiving placebo). In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The vaccine candidate selected for Phase 2/3, BNT162b2 at a dose of 30 µg, will comprise 21,999 vaccine recipients. The 12- to 15-year stratum will comprise up to approximately 2000 participants (1000 vaccine recipients) enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55-year stratum. An equal number of participants will receive placebo, ie, randomized in a 1:1 ratio.

Intervention Groups and Duration

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥12 years of age [stratified as 12-15, 16-55, or >55 years of age]):

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD):
10 µg, 20 µg, 30 µg, 100 µg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S):
10 µg, 20 µg, 30 µg

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

Data Monitoring Committee or Other Independent Oversight Committee

The study will utilize an IRC, an internal Pfizer committee that will review data to allow dose escalation or changes to continuation of specific groups.

An external data monitoring committee (DMC) will be formed and will review cumulative unblinded data throughout the study.

Statistical Methods

The sample size for Phase 1 of the study is not based on any statistical hypothesis testing.

For Phase 2/3, the VE evaluation will be the primary objective. The VE is defined as $VE = 100 \times (1 - IRR)$, where IRR is calculated as the ratio of the first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. With assumptions of a true VE of 60% and 4 IAs planned, 164 COVID-19 cases will provide 90%

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power to conclude true VE >30%. This would be achieved with a total 43,998 participants (21,999 vaccine recipients), based on the assumption of a 1.3% per year incidence in the placebo group, accrual of 164 primary-endpoint cases within 6 months, and 20% of the participants being nonevaluable. If the attack rate is much higher, case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

VE will be evaluated using a beta-binomial model and the posterior probability of VE being >30% will be assessed.

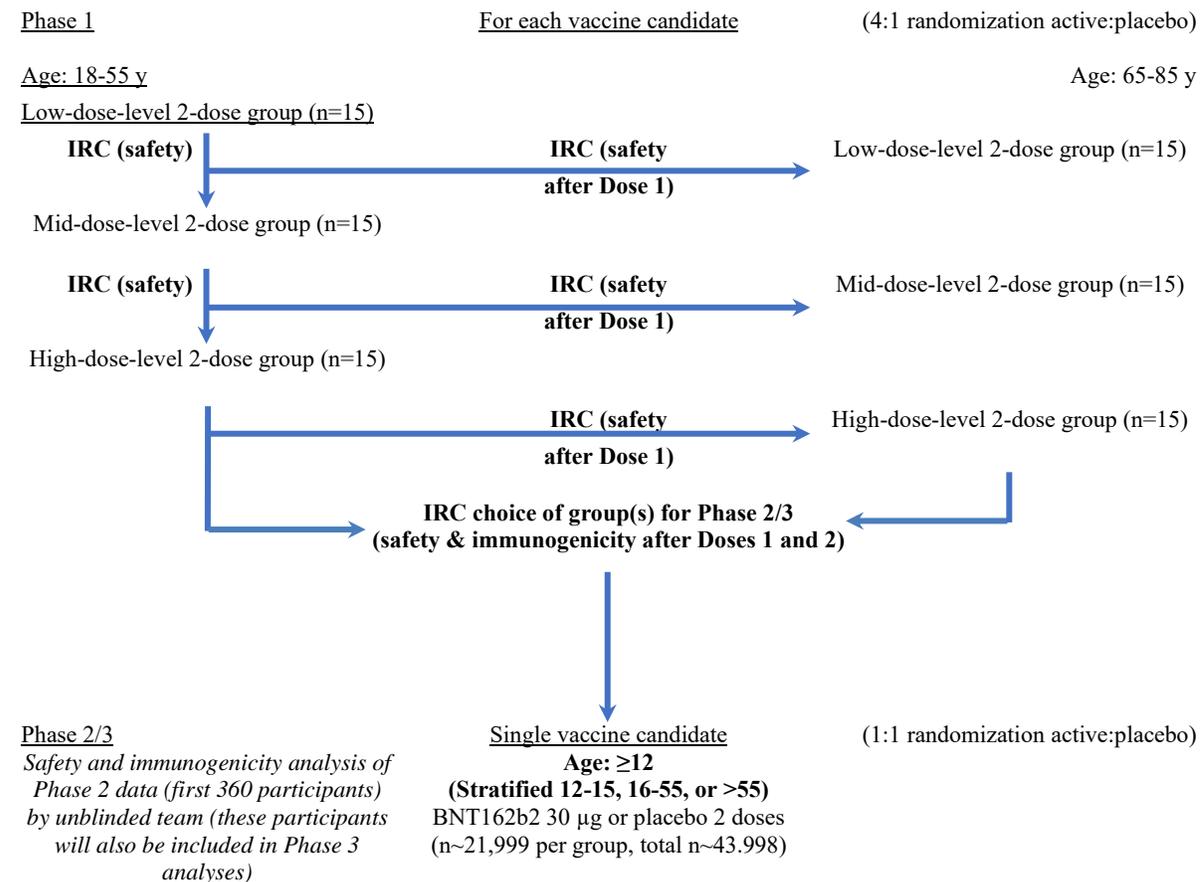
In Phase 3, up to approximately 2000 participants are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR >0.67).

The primary safety objective will be evaluated by descriptive summary statistics for local reactions, systemic events, AEs/SAEs, and abnormal hematology and chemistry laboratory parameters (Phase 1 only), for each vaccine group. A 3-tier approach will be used to summarize AEs in Phase 2/3.

Except for the objective to assess the noninferiority of immune response in participants 12 to 15 years of age compared to participants 16 to 25 years of age, the other immunogenicity objectives will be evaluated descriptively by GMT, GMC, GMFR, percentage of participants with ≥ 4 -fold rise, percentage of participants with \geq specified threshold, and GMC ratio, and the associated 95% confidence intervals (CIs), for SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and/or RBD-binding IgG levels at the various time points.

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1.2. Schema



Abbreviation: IRC = internal review committee.

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1.3. Schedule of Activities

The SoA table provides an overview of the protocol visits and procedures. Refer to the STUDY ASSESSMENTS AND PROCEDURES section of the protocol for detailed information on each procedure and assessment required for compliance with the protocol.

The investigator may schedule visits (unplanned visits) in addition to those listed in the SoA table, in order to conduct evaluations or assessments required to protect the well-being of the participant.

1.3.1. Phase 1

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 10 (24-month follow-up visit) that COVID-19 is suspected.

Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	Screening	Vax 1	Next-Day Follow-up Visit (Vax 1)	1-Week Follow-up Visit (Vax 1)	Vax 2	1-Week Follow-up Visit (Vax 2)	2-Week Follow-up Visit (Vax 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	0 to 28 Days Before Visit 1	Day 1	1 to 3 Days After Visit 1	6 to 8 Days After Visit 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 4	12 to 16 Days After Visit 4	28 to 35 Days After Visit 4	175 to 189 Days After Visit 4	350 to 378 Days After Visit 4	714 to 742 Days After Visit 4	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain informed consent	X												
Assign participant number	X												
Obtain demography and medical history data	X												
Obtain details of medications currently taken	X												
Perform physical examination	X	X	X	X	X	X	X						

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Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	Screening	Vax 1	Next-Day Follow-up Visit (Vax 1)	1-Week Follow-up Visit (Vax 1)	Vax 2	1-Week Follow-up Visit (Vax 2)	2-Week Follow-up Visit (Vax 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	0 to 28 Days Before Visit 1	Day 1	1 to 3 Days After Visit 1	6 to 8 Days After Visit 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 4	12 to 16 Days After Visit 4	28 to 35 Days After Visit 4	175 to 189 Days After Visit 4	350 to 378 Days After Visit 4	714 to 742 Days After Visit 4	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Measure vital signs (including body temperature)	X	X	X	X	X	X	X						
Collect blood sample for hematology and chemistry laboratory tests ^b	~10 mL		~10 mL	~10 mL	~10 mL	~10 mL							
Collect screening blood sample for HIV, HBsAg, HBc Ab, and HCV Ab tests	~10 mL												
Serological test for prior COVID-19 infection	~20 mL												
Perform urine pregnancy test (if appropriate)	X	X			X								
Obtain nasal (midturbinate) swab(s) ^c		X			X							X	
Collect nonstudy vaccine information	X	X	X	X	X	X	X	X	X				
Confirm eligibility	X	X			X								
Collect prohibited medication use			X	X	X	X	X	X	X	X	X	X	X
Review hematology and chemistry results		X		X	X	X	X						
Review temporary delay criteria		X			X								
Confirm use of contraceptives (if appropriate)	X	X	X	X	X	X	X	X					

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Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	Screening	Vax 1	Next-Day Follow-up Visit (Vax 1)	1-Week Follow-up Visit (Vax 1)	Vax 2	1-Week Follow-up Visit (Vax 2)	2-Week Follow-up Visit (Vax 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	0 to 28 Days Before Visit 1	Day 1	1 to 3 Days After Visit 1	6 to 8 Days After Visit 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 4	12 to 16 Days After Visit 4	28 to 35 Days After Visit 4	175 to 189 Days After Visit 4	350 to 378 Days After Visit 4	714 to 742 Days After Visit 4	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain randomization number and study intervention allocation		X											
Collect blood sample for immunogenicity assessment		~50 mL		~50 mL	~50 mL	~50 mL + optional ^e ~170 mL	~50 mL + optional ^e ~170 mL	~50 mL + optional ^e ~170 mL	~20 mL	~20 mL	~20 mL		~20 mL
Administer study intervention		X			X								
Assess acute reactions for at least 30 minutes after study intervention administration ^d		X			X								
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required		X											
Provide thermometer and measuring device		X			X								
Review reactogenicity e-diary data (daily review is optimal during the active diary period)		←→		←→									
Review ongoing reactogenicity e-diary					X		X						

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Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	Screening	Vax 1	Next-Day Follow-up Visit (Vax 1)	1-Week Follow-up Visit (Vax 1)	Vax 2	1-Week Follow-up Visit (Vax 2)	2-Week Follow-up Visit (Vax 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	0 to 28 Days Before Visit 1	Day 1	1 to 3 Days After Visit 1	6 to 8 Days After Visit 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 4	12 to 16 Days After Visit 4	28 to 35 Days After Visit 4	175 to 189 Days After Visit 4	350 to 378 Days After Visit 4	714 to 742 Days After Visit 4	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
symptoms and obtain stop dates													
Collect AEs and SAEs as appropriate	X	X	X	X	X	X	X	X	X	X	X	X	X
Collect e-diary or assist the participant to delete application											X		

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Visit Number	Screening	1	2	3	4	5	6	7	8	9	10	Unplanned	Unplanned
Visit Description	Screening	Vax 1	Next-Day Follow-up Visit (Vax 1)	1-Week Follow-up Visit (Vax 1)	Vax 2	1-Week Follow-up Visit (Vax 2)	2-Week Follow-up Visit (Vax 2)	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	0 to 28 Days Before Visit 1	Day 1	1 to 3 Days After Visit 1	6 to 8 Days After Visit 1	19 to 23 Days After Visit 1	6 to 8 Days After Visit 4	12 to 16 Days After Visit 4	28 to 35 Days After Visit 4	175 to 189 Days After Visit 4	350 to 378 Days After Visit 4	714 to 742 Days After Visit 4	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Collection of COVID-19-related clinical and laboratory information (including local diagnosis)												X	X

Abbreviations: e-diary = electronic diary; HBc Ab = hepatitis B core antibody; HBsAg = hepatitis B surface antigen; HCV Ab = hepatitis C virus antibody; HIV = human immunodeficiency virus; NAAT = nucleic acid amplification test; vax = vaccination.

- a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- b. Hematology: hemoglobin, complete blood count with differential, and platelets. Blood chemistry: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase, total bilirubin, blood urea nitrogen (BUN), and creatinine.
- c. Two swabs will be taken at Visits 1 and 4. One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- d. The first 5 participants in in each group will be observed at the site for at least 4 hours after study intervention administration. Further vaccination will commence no sooner than 24 hours after the fifth participant received his or her vaccination.
- e. An optional blood draw of ~170 mL will be taken at 1 of the visits (from selected participants who consent) for exploratory COVID-19 research.

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1.3.2. Phase 2/3

An unplanned potential COVID-19 illness visit and unplanned potential COVID-19 convalescent visit are required at any time between Visit 1 (Vaccination 1) and Visit 6 (24-month follow-up visit) that potential COVID-19 symptoms are reported, including MIS-C.

Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1 ^b	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain informed consent	X							
Assign participant number	X							
Obtain demography and medical history data	X							
Perform clinical assessment ^c	X							
For participants who are HIV-positive, record latest CD4 count and HIV viral load	X		X	X	X	X		
Measure height and weight	X							
Measure temperature (body)	X	X						
Perform urine pregnancy test (if appropriate)	X	X						
Confirm use of contraceptives (if appropriate)	X	X	X					
Collect nonstudy vaccine information	X	X	X	X				
Collect prohibited medication use		X	X	X	X	X	X	X
Confirm eligibility	X	X						
Review temporary delay criteria	X	X						
Collect blood sample for immunogenicity assessment ^d	~20 mL/ ~10 mL		~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL	~20 mL/ ~10 mL		~20 mL/ ~10 mL
Obtain nasal (midturbinate) swab	X	X					X	

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Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1 ^b	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Obtain randomization number and study intervention allocation	X							
Administer study intervention	X	X						
Assess acute reactions for at least 30 minutes after study intervention administration	X	X						
Explain participant communication methods (including for e-diary completion), assist the participant with downloading the app, or issue provisioned device, if required	X							
Provide/ensure the participant has a thermometer (all participants) and measuring device (reactogenicity subset participants only)	X	X						
Review reactogenicity e-diary data (daily review is optimal during the active diary period) ^e	↔	↔						
Review ongoing reactogenicity e-diary symptoms and obtain stop dates ^e		X	X					
Collect AEs and SAEs as appropriate	X	X	X	X ^f	X ^f	X ^f	X	X ^f
Collect e-diary or assist the participant to delete application						X		

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Visit Number	1	2	3	4	5	6	Unplanned	Unplanned
Visit Description	Vaccination 1	Vaccination 2	1-Month Follow-up Visit	6-Month Follow-up Visit	12-Month Follow-up Visit	24-Month Follow-up Visit	Potential COVID-19 Illness Visit ^a	Potential COVID-19 Convalescent Visit
Visit Window (Days)	Day 1 ^b	19 to 23 Days After Visit 1	28 to 35 Days After Visit 2	175 to 189 Days After Visit 2	350 to 378 Days After Visit 2	714 to 742 Days After Visit 2	Optimally Within 3 Days After Potential COVID-19 Illness Onset	28 to 35 Days After Potential COVID-19 Illness Visit
Collection of COVID-19–related clinical and laboratory information (including local diagnosis)							X	X

Abbreviations: HIV = human immunodeficiency virus; e-diary = electronic diary.

- a. The COVID-19 illness visit may be conducted as an in-person or telehealth visit.
- b. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.
- c. Including, if indicated, a physical examination.
- d. 20 mL is to be collected from participants ≥ 16 years of age; 10 mL is to be collected from participants 12 to 15 years of age.
- e. Reactogenicity subset participants only.
- f. Any AEs occurring up to 48 hours after the blood draw must be recorded (see [Section 8.3.1](#)).

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2. INTRODUCTION

The BNT162 RNA-based COVID-19 vaccines are currently being investigated for prevention of COVID-19 in healthy individuals.

2.1. Study Rationale

The purpose of the study is to rapidly describe the safety, tolerability, and immunogenicity of 2 BNT162 RNA-based COVID-19 vaccine candidates against COVID-19, and the efficacy of 1 candidate, in healthy individuals. There are currently no licensed vaccines to prevent infection with SARS-CoV-2 or COVID-19. Given the global crisis of COVID-19 and fast expansion of the disease in the United States and elsewhere, the rapid development of an effective vaccine is of utmost importance.

2.2. Background

In December 2019, a pneumonia outbreak of unknown cause occurred in Wuhan, China. In January 2020, it became clear that a novel coronavirus (2019-nCoV) was the underlying cause. Later in January, the genetic sequence of the 2019-nCoV became available to the World Health Organization (WHO) and public (MN908947.3), and the virus was categorized in the *Betacoronavirus* subfamily. By sequence analysis, the phylogenetic tree revealed a closer relationship to severe acute respiratory syndrome (SARS) virus isolates than to another coronavirus infecting humans, the Middle East respiratory syndrome (MERS) virus.

SARS-CoV-2 infections and the resulting disease, COVID-19, have spread globally, affecting a growing number of countries.

On 11 March 2020, the WHO characterized the COVID-19 outbreak as a pandemic.¹ The WHO Situation Update Report dated 30 March 2020 noted 693,224 confirmed cases with 33,106 deaths globally, including 142,081 confirmed cases with 2457 deaths in the Americas.² The United States currently has the most reported cases globally. At the time of this communication, the number of confirmed cases continues to rise globally. There are currently no vaccines or effective antiviral drugs to treat SARS-CoV-2 infections or the disease it causes, COVID-19.³

A prophylactic, RNA-based SARS-CoV-2 vaccine provides one of the most flexible and fastest approaches available to immunize against the emerging virus.^{4,5}

The development of an RNA-based vaccine encoding a viral antigen, which is then expressed by the vaccine recipient as a protein capable of eliciting protective immune responses, provides significant advantages over more traditional vaccine approaches. Unlike live attenuated vaccines, RNA vaccines do not carry the risks associated with infection and may be given to people who cannot be administered live virus (eg, pregnant women and immunocompromised persons). RNA-based vaccines are manufactured via a cell-free in vitro transcription process, which allows an easy and rapid production and the prospect of producing high numbers of vaccination doses within a shorter time period than achieved with traditional vaccine approaches. This capability is pivotal to enable the most effective response in outbreak scenarios.

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Two SARS-CoV-2–RNA lipid nanoparticle (RNA-LNP) vaccines based on a platform of nucleoside-modified messenger RNA (modRNA, BNT162b) will be evaluated in this study. Each vaccine candidate expresses 1 of 2 antigens: the SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein (P2 S) (version 9) or a trimerized SARS-CoV-2 spike glycoprotein-receptor binding domain (RBD) (version 5). The 2 SARS-CoV-2 vaccine candidates that will be tested in this study are therefore:

- **BNT162b1** (variant RBP020.3): nucleoside-modified messenger RNA (modRNA) with blunted innate immune sensor–activating capacity and augmented expression encoding the RBD.
- **BNT162b2** (variant RBP020.2): nucleoside-modified messenger RNA (modRNA) as above, but encoding P2 S.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2.

2.2.1. Clinical Overview

Prior to this study, given clinical data from other similarly formulated uRNA liposomal vaccines from BioNTech in oncology trials⁶ and recent published results from clinical trials using modRNA influenza vaccines by Moderna,⁷ the BNT162 vaccines were expected to have a favorable safety profile with mild, localized, and transient effects. BNT162 vaccines based on modRNA have now been administered to humans for the first time in this study and the BNT162-01 study conducted in Germany by BioNTech, at doses between 1 µg and 100 µg. The currently available safety and immunogenicity data are presented in the BNT162 IB.

2.3. Benefit/Risk Assessment

There is an ongoing global pandemic of COVID-19 with no preventative or therapeutic options available. While there were no data available from clinical trials on the use of BNT162 vaccines in humans at the outset of this study, available nonclinical data with these vaccines, and data from nonclinical studies and clinical trials with the same or related RNA components, or antigens, supported a favorable risk/benefit profile. Anticipated AEs after vaccination were expected to be manageable using routine symptom-driven standard of care as determined by the investigators and, as a result, the profile of these vaccine candidates supported initiation of this Phase 1/2/3 clinical study.

Updates as part of protocol amendment 6:

- In order for the overall Phase 3 study population to be as representative and diverse as possible, the inclusion of participants with known chronic stable HIV, HCV, or HBV infection is permitted. Individuals with chronic viral diseases are at increased risk for COVID-19 complications and severe disease. In addition, with the currently available therapies for their treatment, many individuals with chronic stable HIV, HCV, and HBV infections are unlikely to be at higher safety risk as a

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participant in this vaccine study than individuals with other chronic stable medical conditions.

- All participants with chronic stable HIV disease will be included in the reactogenicity subset (see [Section 8.2.2](#)).

Updates as part of protocol amendment 7:

- The minimum age for inclusion in Phase 3 is lowered to 12 years, therefore allowing the inclusion of participants 12 to 15 years of age.
- For individuals 12 to 15 years of age, the immune responses in this age group may be higher and reactogenicity is expected to be similar to younger adults 18 to 25 years of age. Inclusion of individuals 12 to 15 years of age was based upon a satisfactory blinded safety profile in participants 18 to 25 years of age.
- All participants 12 to 15 years of age will be included in the reactogenicity subset (see [Section 8.2.2](#)).

More detailed information about the known and expected benefits and risks and reasonably expected AEs of BNT162 RNA-based COVID-19 vaccines may be found in the IB, which is the SRSD for this study.

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2.3.1. Risk Assessment

Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Intervention: BNT162 RNA-Based COVID-19 Vaccine		
Potential for local reactions (injection site redness, injection site swelling, and injection site pain) and systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, muscle pain, and joint pain) following vaccination.	These are common adverse reactions seen with other vaccines, as noted in the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials. ⁸	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. The study employs the use of a reactogenicity e-diary to monitor local reactions and systemic events in real time. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Unknown AEs and laboratory abnormalities with a novel vaccine.	This study is one of the first 2 parallel-running clinical studies with the BNT162 vaccine candidates and as such there are no clinical data available for this vaccine.	The Phase 1 study design includes the use of controlled vaccination and dose escalation to closely monitor and limit the rate of enrollment to ensure participant safety. An IRC (in Phase 1) and DMC (throughout the study) will also review safety data. Stopping rules are also in place. The first 5 participants in each group in Phase 1 will be observed for 4 hours after vaccination to assess any immediate AEs. All other participants will be observed for at least 30 minutes after vaccination.
Potential for COVID-19 enhancement.	Disease enhancement has been seen following vaccination with respiratory syncytial virus (RSV), feline coronavirus, and Dengue virus vaccines.	Phase 1 excludes participants with likely previous or current COVID-19. In Phase 2/3, temporary delay criteria defer vaccination of participants with symptoms of potential COVID-19. All participants are followed for any potential COVID-19 illness, including markers of severity, and have blood samples taken for potential measurement of SARS-CoV-2 antigen-specific antibody and SARS-CoV-2 neutralizing titers.

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Potential Risk of Clinical Significance	Summary of Data/Rationale for Risk	Mitigation Strategy
Study Procedures		
Participants will be required to attend healthcare facilities during the global SARS-CoV-2 pandemic.	Without appropriate social distancing and PPE, there is a potential for increased exposure to SARS-CoV-2.	Pfizer will work with sites to ensure an appropriate COVID-19 prevention strategy. Potential COVID-19 illness visits can be conducted via telehealth, without the need for an in-person visit, if required, with the participant performing a self-swab.
Venipuncture will be performed during the study.	There is the risk of bleeding, bruising, hematoma formation, and infection at the venipuncture site.	Only appropriately qualified personnel would obtain the blood draw.

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2.3.2. Benefit Assessment

Benefits to individual participants may include:

- Receipt of a potentially efficacious COVID-19 vaccine during a global pandemic
- Access to COVID-19 diagnostic testing
- Contributing to research to help others in a time of global pandemic

2.3.3. Overall Benefit/Risk Conclusion

Taking into account the measures taken to minimize risk to participants participating in this study, the potential risks identified in association with BNT162 RNA-based COVID-19 vaccine are justified by the anticipated benefits that may be afforded to healthy participants.

3. OBJECTIVES, ESTIMANDS, AND ENDPOINTS

3.1. For Phase 1

Objectives	Estimands	Endpoints
Primary: To describe the safety and tolerability profiles of prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses	Primary: In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> • Local reactions for up to 7 days following each dose • Systemic events for up to 7 days following each dose • Adverse events (AEs) from Dose 1 to 1 month after the last dose • Serious AEs (SAEs) from Dose 1 to 6 months after the last dose In addition, the percentage of participants with: <ul style="list-style-type: none"> • Abnormal hematology and chemistry laboratory values 1 and 7 days after Dose 1; and 7 days after Dose 2 • Grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1; and before Dose 2 and 7 days after Dose 2 	Primary: <ul style="list-style-type: none"> • Local reactions (pain at the injection site, redness, and swelling) • Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) • AEs • SAEs Hematology and chemistry laboratory parameters detailed in Section 10.2

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Objectives	Estimands	Endpoints
<p>Secondary: To describe the immune responses elicited by prophylactic BNT162 vaccines in healthy adults after 1 or 2 doses</p>	<p>Secondary: In participants complying with the key protocol criteria (evaluable participants) at the following time points after receipt of study intervention: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2</p> <ul style="list-style-type: none"> • Geometric mean titers (GMTs) at each time point • Geometric mean fold rise (GMFR) from before vaccination to each subsequent time point after vaccination • Proportion of participants achieving ≥ 4-fold rise from before vaccination to each subsequent time point after vaccination • Geometric mean concentrations (GMCs) at each time point • GMFR from prior to first dose of study intervention to each subsequent time point • Proportion of participants achieving ≥ 4-fold rise from before vaccination to each subsequent time point after vaccination • Geometric mean ratio (GMR), estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers to the geometric mean of binding IgG levels at each time point 	<p>Secondary:</p> <p>SARS-CoV-2 neutralizing titers</p> <p>S1-binding IgG levels and RBD-binding IgG levels</p> <ul style="list-style-type: none"> • SARS-CoV-2 neutralizing titers • S1-binding IgG levels • RBD-binding IgG levels

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3.2. For Phase 2/3

Objectives ^a	Estimands	Endpoints
Primary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 7 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 7 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
Primary Safety		
To define the safety profile of prophylactic BNT162b2 in <u>the first 360 participants</u> randomized (Phase 2)	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from Dose 1 to 7 days after the second dose SAEs from Dose 1 to 7 days after the second dose 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs
To define the safety profile of prophylactic BNT162b2 in <u>all participants</u> randomized in Phase 2/3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from Dose 1 to 1 month after the second dose SAEs from Dose 1 to 6 months after the second dose 	<ul style="list-style-type: none"> AEs SAEs In a subset of at least 6000 participants: <ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain)
To define the safety profile of prophylactic BNT162b2 in participants 12 to 15 years of age in Phase 3	In participants receiving at least 1 dose of study intervention, the percentage of participants reporting: <ul style="list-style-type: none"> Local reactions for up to 7 days following each dose Systemic events for up to 7 days following each dose AEs from Dose 1 to 1 month after the second dose SAEs from Dose 1 to 6 months after the second dose 	<ul style="list-style-type: none"> Local reactions (pain at the injection site, redness, and swelling) Systemic events (fever, fatigue, headache, chills, vomiting, diarrhea, new or worsened muscle pain, and new or worsened joint pain) AEs SAEs

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Objectives ^a	Estimands	Endpoints
Secondary Efficacy		
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed COVID-19 occurring from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To evaluate the efficacy of prophylactic BNT162b2 against confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	Confirmed severe COVID-19 incidence per 1000 person-years of follow-up
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT in participants with no serological or virological evidence (up to 7 days and up to 14 days after receipt of the second dose) of past SARS-CoV-2 infection
To describe the efficacy of prophylactic BNT162b2 against confirmed COVID-19 (according to the CDC-defined symptoms) occurring from 7 days and from 14 days after the second dose in participants with and without evidence of infection before vaccination	In participants complying with the key protocol criteria (evaluable participants) <ul style="list-style-type: none"> • at least 7 days and • at least 14 days after receipt of the second dose of study intervention: $100 \times (1 - \text{IRR})$ [ratio of active vaccine to placebo]	COVID-19 incidence per 1000 person-years of follow-up based on central laboratory or locally confirmed NAAT

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Objectives ^a	Estimands	Endpoints
Secondary Immunogenicity		
To demonstrate the noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to participants 16 to 25 years of age	GMR, estimated by the ratio of the geometric mean of SARS-CoV-2 neutralizing titers in the 2 age groups (12-15 years of age to 16-25 years of age) 1 month after completion of vaccination	SARS-CoV-2 neutralizing titers in participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection
Exploratory		
To evaluate the immune response over time to prophylactic BNT162b2 and persistence of immune response in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination	GMC/GMT, GMFR, and percentage of participants with titers greater than defined threshold(s), at baseline and 1, 6, 12, and 24 months after completion of vaccination	<ul style="list-style-type: none"> S1-binding IgG levels and/or RBD-binding IgG levels SARS-CoV-2 neutralizing titers
To evaluate the immune response (non-S) to SARS-CoV-2 in participants with and without confirmed COVID-19 during the study		<ul style="list-style-type: none"> N-binding antibody
To describe the serological responses to the BNT vaccine candidate in cases of: <ul style="list-style-type: none"> Confirmed COVID-19 Confirmed severe COVID-19 SARS-CoV-2 infection without confirmed COVID-19 		<ul style="list-style-type: none"> S1-binding IgG levels and/or RBD-binding IgG levels SARS-CoV-2 neutralizing titers
To describe the safety, immunogenicity, and efficacy of prophylactic BNT162b2 in individuals with confirmed stable HIV disease		<ul style="list-style-type: none"> All safety, immunogenicity, and efficacy endpoints described above
To describe the safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing "Process 1" or "Process 2" ^b		<ul style="list-style-type: none"> All safety endpoints described above SARS-CoV-2 neutralizing titers

- a. HIV-positive participants in Phase 3 will not be included in analyses of the objectives, with the exception of the specific exploratory objective.
- b. See [Section 6.1.1](#) for description of the manufacturing process.

This protocol will use a group of internal case reviewers to determine whether certain investigator-reported events meet the definition of disease-related efficacy endpoints, using predefined endpoint criteria.

For those AEs that are handled as disease-related efficacy endpoints (which may include death), a DMC will conduct unblinded reviews on a regular basis throughout the trial (see [Section 9.6](#)).

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Any AE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. Refer to [Section 8.3.1.1](#) for instructions on how to report any such AE that meets the criteria for seriousness to Pfizer Safety.

4. STUDY DESIGN

4.1. Overall Design

This is a multicenter, multinational, Phase 1/2/3, randomized, placebo-controlled, observer-blind, dose-finding, vaccine candidate–selection, and efficacy study in healthy individuals.

The study consists of 2 parts. Phase 1: to identify preferred vaccine candidate(s) and dose level(s); Phase 2/3: an expanded cohort and efficacy part. These parts, and the progression between them, are detailed in the schema ([Section 1.2](#)).

The study will evaluate the safety, tolerability, and immunogenicity of 2 different SARS-CoV-2 RNA vaccine candidates against COVID-19 and the efficacy of 1 candidate:

- As a 2-dose (separated by 21 days) schedule;
- At various different dose levels in Phase 1;
- In 3 age groups (Phase 1: 18 to 55 years of age, 65 to 85 years of age; Phase 2/3: ≥ 12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups in Phase 1 may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The study is observer-blinded, as the physical appearance of the investigational vaccine candidates and the placebo may differ. The participant, investigator, study coordinator, and other site staff will be blinded. At the study site, only the dispenser(s)/administrator(s) are unblinded.

To facilitate rapid review of data in real time, sponsor staff will be unblinded to vaccine allocation for the participants in Phase 1.

4.1.1. Phase 1

Each group (vaccine candidate/dose level/age group) will comprise 15 participants; 12 participants will be randomized to receive active vaccine and 3 to receive placebo.

For each vaccine candidate/dose level/age group, the following apply:

- Additional safety assessments (see [Section 8.2](#))

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- Controlled enrollment (required only for the first candidate and/or dose level studied):
 - No more than 5 participants (4 active, 1 placebo) can be vaccinated on the first day
 - The first 5 participants must be observed by blinded site staff for at least 4 hours after vaccination for any acute reactions
 - Vaccination of the remaining participants will commence no sooner than 24 hours after the fifth participant received his or her vaccination
- Application of stopping rules
- IRC review of safety data to determine escalation to the next dose level in the 18- to 55-year age cohort:
 - Escalation between dose levels will be based on IRC review of at least 7-day post-Dose 1 safety data in this study and/or the BioNTech study conducted in Germany (BNT162-01)
 - Note that, since both candidates are based upon the same RNA platform, dose escalation for the second candidate studied may be based upon the safety profile of the first candidate studied being deemed acceptable at the same, or a higher, dose level by the IRC

Groups of participants 65 to 85 years of age will not be started until safety data for the RNA platform have been deemed acceptable at the same, or a higher, dose level in the 18- to 55-year age cohort by the IRC.

In this phase, 13 groups will be studied, corresponding to a total of 195 participants.

The IRC will select 1 vaccine candidate that, in Phase 1, has an established dose level per age group based on induction of a post-Dose 2 immune response, including neutralizing antibodies, which is expected to be associated with protection against COVID-19, for progression into Phase 2/3.

4.1.2. Phase 2/3

On the basis of safety and/or immunogenicity data generated during the course of this study, and/or the BioNTech study conducted in Germany (BNT162-01), 1 vaccine candidate was selected to proceed into Phase 2/3. Participants in this phase will be ≥ 12 years of age, stratified as follows: 12 to 15 years, 16 to 55 years, or >55 years. The 12- to 15-year stratum will comprise up to approximately 2000 participants enrolled at selected investigational sites. It is intended that a minimum of 40% of participants will be in the >55 -year stratum. Commencement of each age stratum will be based upon satisfactory post-Dose 2 safety and immunogenicity data from the 18- to 55-year and 65- to 85-year age groups in Phase 1,

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respectively. The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

Phase 2/3 is event-driven. Under the assumption of a true VE rate of $\geq 60\%$, after the second dose of investigational product, a target of 164 primary-endpoint cases of confirmed COVID-19 due to SARS-CoV-2 occurring at least 7 days following the second dose of the primary series of the candidate vaccine will be sufficient to provide 90% power to conclude true VE $> 30\%$ with high probability. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

Assuming a COVID-19 attack rate of 1.3% per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, an estimated 20% nonevaluable rate, and 1:1 randomization, the BNT162b2 vaccine candidate selected for Phase 2/3 is expected to comprise approximately 21,999 vaccine recipients. This is the number of participants initially targeted for Phase 2/3 and may be adjusted based on advice from DMC analyses of case accumulation and the percentage of participants who are seropositive at baseline. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner.

The first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and > 55 to 85 years) will comprise the "Phase 2" portion. Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from these 360 participants will be analyzed by the unblinded statistical team, reviewed by the DMC, and submitted to appropriate regulatory authorities for review. Enrollment may continue during this period and these participants would be included in the efficacy evaluation in the "Phase 3" portion of the study.

In Phase 3, up to approximately 2000 participants, enrolled at selected sites, are anticipated to be 12 to 15 years of age. Noninferiority of immune response to prophylactic BNT162b2 in participants 12 to 15 years of age to response in participants 16 to 25 years of age will be assessed based on the GMR of SARS-CoV-2 neutralizing titers using a 1.5-fold margin. A sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority in terms of GMR (lower limit of 95% CI for GMR > 0.67). A random sample of 250 participants from each of the 2 age groups (12 to 15 years and 16 to 25 years) will be selected as an immunogenicity subset for the noninferiority assessment.

The initial BNT162b2 was manufactured using "Process 1"; however, "Process 2" was developed to support an increased scale of manufacture. In the study, each lot of "Process 2"-manufactured BNT162b2 will be administered to approximately 250 participants 16 to 55 years of age. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with "Process 1" and each lot of "Process 2" study intervention will be described. A random sample of 250 participants from those

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vaccinated with study intervention produced by manufacturing “Process 1” will be selected for this descriptive analysis.

Participants are expected to participate for up to a maximum of approximately 26 months. The duration of study follow-up may be shorter among participants enrolled in Phase 1 dosing arms that are not evaluated in Phase 2/3.

4.2. Scientific Rationale for Study Design

Additional surveillance for COVID-19 will be conducted as part of the study, given the potential risk of disease enhancement. If a participant experiences symptoms, as detailed in [Section 8.13](#), a COVID-19 illness and subsequent convalescent visit will occur. As part of these visits, samples (nasal [midturbinate] swab and blood) will be taken for antigen and antibody assessment as well as recording of COVID-19–related clinical and laboratory information (including local diagnosis).

Human reproductive safety data are not available for BNT162 RNA-based COVID-19 vaccines, but there is no suspicion of human teratogenicity based on the intended mechanism of action of the compound. Therefore, the use of a highly effective method of contraception is required (see [Appendix 4](#)).

4.3. Justification for Dose

Because of the requirement for a rapid response to the newly emerged COVID-19 pandemic, sufficient data were not available to experimentally validate the dose selection and initial starting dose. Therefore, the original planned starting dose of 10 µg (for both BNT162b1 and BNT162b2) in this study was based on nonclinical experience with the same RNAs encoding other viral antigens (such as influenza and HIV antigens). The general safety and effectiveness of uRNA and modRNA platforms have been demonstrated in oncological clinical trials with different administration routes (NCT02410733, NCT03871348). Doses of up to 400 µg total uRNA have been administered IV as RNA lipoplex (RNA-LPX) and doses of up to 1000 µg total naked modRNA have been administered intratumorally, both without signs of unpredictable overstimulation of the immune system.

Based on nonclinical data of the RNA components, with other liposomes or in conjunction with the lipid nanoparticles as will be tested clinically in this study, it was expected that doses in the 1- to 5-µg range would be immunogenic and induce neutralizing antibodies; however, it was anticipated that 3- to 10-fold higher doses would likely be required to elicit a stronger antibody response. Based on previous clinical and nonclinical experience, it was expected that doses of up to 100 µg would be well tolerated.

Update as part of protocol amendment 2: preliminary experience in this study and the BioNTech study conducted in Germany (BNT162-01) suggests that, for vaccine candidates based on the modRNA platform, a dose level between 30 µg and 100 µg warrants consideration. Therefore, a 50-µg dose level is formally included for BNT162b1 and BNT162b2.

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Update as part of protocol amendment 3: as data have become available from this study and the BNT162-01 study in Germany, it was decided:

- To not study the BNT162a1 and BNT162c2 vaccine candidates at this time, so these candidates have been removed from the protocol; and
- That lower dose levels of BNT162b1 and BNT162b2 warrant consideration. Therefore, a 20- μ g dose level is formally included for both candidates.

Update as part of protocol amendment 4: the 50- μ g dose level for BNT162b1 and BNT162b2 is removed and the 100- μ g dose level for BNT162b2 is removed; similar dose levels of BNT162b3 may be studied as for BNT162b1 and BNT162b2.

Update as part of protocol amendment 5: the vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 μ g. BNT162b3 will not be studied.

4.4. End of Study Definition

A participant is considered to have completed the study if he/she has completed all phases of the study, including the last visit. Note that participants enrolled in Phase 1 in groups that do not proceed to Phase 2/3 may be followed for fewer than 24 months (but no less than 6 months after the last vaccination).

The end of the study is defined as the date of last visit of the last participant in the study.

5. STUDY POPULATION

This study can fulfill its objectives only if appropriate participants are enrolled. The following eligibility criteria are designed to select participants for whom participation in the study is considered appropriate. All relevant medical and nonmedical conditions should be taken into consideration when deciding whether a particular participant is suitable for this protocol.

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1. Inclusion Criteria

Participants are eligible to be included in the study only if all of the following criteria apply:

Age and Sex:

1. Male or female participants between the ages of 18 and 55 years, inclusive, and 65 and 85 years, inclusive (Phase 1), or ≥ 12 years (Phase 2/3), at randomization. Note that participants < 18 years of age cannot be enrolled in the EU.
 - Refer to Appendix 4 for reproductive criteria for male ([Section 10.4.1](#)) and female ([Section 10.4.2](#)) participants.

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Type of Participant and Disease Characteristics:

2. Participants who are willing and able to comply with all scheduled visits, vaccination plan, laboratory tests, lifestyle considerations, and other study procedures.
3. Healthy participants who are determined by medical history, physical examination (if required), and clinical judgment of the investigator to be eligible for inclusion in the study.

Note: Healthy participants with preexisting stable disease, defined as disease not requiring significant change in therapy or hospitalization for worsening disease during the 6 weeks before enrollment, can be included. Specific criteria for Phase 3 participants with known stable infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV) can be found in [Section 10.8](#).

4. **Phase 2/3 only:** Participants who, in the judgment of the investigator, are at higher risk for acquiring COVID-19 (including, but not limited to, use of mass transportation, relevant demographics, and frontline essential workers).

Informed Consent:

5. Capable of giving personal signed informed consent/have parent(s)/legal guardian capable of giving signed informed consent as described in [Appendix 1](#), which includes compliance with the requirements and restrictions listed in the ICD and in this protocol.

5.2. Exclusion Criteria

Participants are excluded from the study if any of the following criteria apply:

Medical Conditions:

1. Other medical or psychiatric condition including recent (within the past year) or active suicidal ideation/behavior or laboratory abnormality that may increase the risk of study participation or, in the investigator's judgment, make the participant inappropriate for the study.
2. **Phases 1 and 2 only:** Known infection with human immunodeficiency virus (HIV), hepatitis C virus (HCV), or hepatitis B virus (HBV).
3. History of severe adverse reaction associated with a vaccine and/or severe allergic reaction (eg, anaphylaxis) to any component of the study intervention(s).
4. Receipt of medications intended to prevent COVID-19.
5. Previous clinical (based on COVID-19 symptoms/signs alone, if a SARS-CoV-2 NAAT result was not available) or microbiological (based on COVID-19 symptoms/signs and a positive SARS-CoV-2 NAAT result) diagnosis of COVID-19.

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6. **Phase 1 only:** Individuals at high risk for severe COVID-19, including those with any of the following risk factors:
 - Hypertension
 - Diabetes mellitus
 - Chronic pulmonary disease
 - Asthma
 - Current vaping or smoking
 - History of chronic smoking within the prior year
 - Chronic liver disease
 - Stage 3 or worse chronic kidney disease (glomerular filtration rate <60 mL/min/1.73 m²)
 - Resident in a long-term facility
 - BMI >30 kg/m²
 - Anticipating the need for immunosuppressive treatment within the next 6 months
7. **Phase 1 only:** Individuals currently working in occupations with high risk of exposure to SARS-CoV-2 (eg, healthcare worker, emergency response personnel).
8. Immunocompromised individuals with known or suspected immunodeficiency, as determined by history and/or laboratory/physical examination.
9. **Phase 1 only:** Individuals with a history of autoimmune disease or an active autoimmune disease requiring therapeutic intervention, including but not limited to: systemic or cutaneous lupus erythematosus, autoimmune arthritis/rheumatoid arthritis, Guillain-Barré syndrome, multiple sclerosis, Sjögren's syndrome, idiopathic thrombocytopenia purpura, glomerulonephritis, autoimmune thyroiditis, giant cell arteritis (temporal arteritis), psoriasis, and insulin-dependent diabetes mellitus (type 1).
10. Bleeding diathesis or condition associated with prolonged bleeding that would, in the opinion of the investigator, contraindicate intramuscular injection.
11. Women who are pregnant or breastfeeding.

Prior/Concomitant Therapy:

12. Previous vaccination with any coronavirus vaccine.
13. Individuals who receive treatment with immunosuppressive therapy, including cytotoxic agents or systemic corticosteroids, eg, for cancer or an autoimmune disease, or planned receipt throughout the study. If systemic corticosteroids have been administered short term (<14 days) for treatment of an acute illness, participants should not be enrolled into

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the study until corticosteroid therapy has been discontinued for at least 28 days before study intervention administration. Inhaled/nebulized (except for participants in Phase 1 – see exclusion criterion 14), intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

14. **Phase 1 only:** Regular receipt of inhaled/nebulized corticosteroids.
15. Receipt of blood/plasma products or immunoglobulin, from 60 days before study intervention administration or planned receipt throughout the study.

Prior/Concurrent Clinical Study Experience:

16. Participation in other studies involving study intervention within 28 days prior to study entry and/or during study participation.
17. Previous participation in other studies involving study intervention containing lipid nanoparticles.

Diagnostic Assessments:

18. **Phase 1 only:** Positive serological test for SARS-CoV-2 IgM and/or IgG antibodies at the screening visit.
19. **Phase 1 only:** Any screening hematology and/or blood chemistry laboratory value that meets the definition of a \geq Grade 1 abnormality.

Note: With the exception of bilirubin, participants with any stable Grade 1 abnormalities (according to the toxicity grading scale) may be considered eligible at the discretion of the investigator. (Note: A “stable” Grade 1 laboratory abnormality is defined as a report of Grade 1 on an initial blood sample that remains \leq Grade 1 upon repeat testing on a second sample from the same participant.)

20. **Phase 1 only:** Positive test for HIV, hepatitis B surface antigen (HBsAg), hepatitis B core antibodies (HBc Abs), or hepatitis C virus antibodies (HCV Abs) at the screening visit.
21. **Phase 1 only:** SARS-CoV-2 NAAT-positive nasal swab within 24 hours before receipt of study intervention.

Other Exclusions:

22. Investigator site staff or Pfizer/BioNTech employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator, and their respective family members.

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5.3. Lifestyle Considerations

5.3.1. Contraception

The investigator or his or her designee, in consultation with the participant, will confirm that the participant has selected an appropriate method of contraception for the individual participant and his or her partner(s) from the permitted list of contraception methods (see Appendix 4, [Section 10.4.4](#)) and will confirm that the participant has been instructed in its consistent and correct use. At time points indicated in the SoA, the investigator or designee will inform the participant of the need to use highly effective contraception consistently and correctly and document the conversation and the participant's affirmation in the participant's chart (participants need to affirm their consistent and correct use of at least 1 of the selected methods of contraception). In addition, the investigator or designee will instruct the participant to call immediately if the selected contraception method is discontinued or if pregnancy is known or suspected in the participant or partner.

5.4. Screen Failures

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently randomly assigned to study intervention. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the CONSORT publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAE.

Individuals who do not meet the criteria for participation in this study (screen failure) may be rescreened under a different participant number.

5.5. Criteria for Temporarily Delaying Enrollment/Randomization/Study Intervention Administration

The following conditions are temporary or self-limiting and a participant may be vaccinated once the condition(s) has/have resolved and no other exclusion criteria are met.

1. Current febrile illness (body temperature $\geq 100.4^{\circ}\text{F}$ [$\geq 38^{\circ}\text{C}$]) or other acute illness within 48 hours before study intervention administration. This includes current symptoms that could represent a potential COVID-19 illness:
 - New or increased cough;
 - New or increased shortness of breath;
 - Chills;
 - New or increased muscle pain;
 - New loss of taste/smell;
 - Sore throat;

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- Diarrhea;
 - Vomiting.
2. Receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, before study intervention administration.
 3. Anticipated receipt of any seasonal or pandemic influenza vaccine within 14 days, or any other nonstudy vaccine within 28 days, after study intervention administration.
 4. Receipt of short-term (<14 days) systemic corticosteroids. Study intervention administration should be delayed until systemic corticosteroid use has been discontinued for at least 28 days. Inhaled/nebulized, intra-articular, intrabursal, or topical (skin or eyes) corticosteroids are permitted.

6. STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, medical device(s), or study procedure(s) intended to be administered to a study participant according to the study protocol.

The study will evaluate a 2-dose (separated by 21 days) schedule of various different dose levels of 2 investigational RNA vaccine candidates for active immunization against COVID-19 in 3 age groups (18 to 55 years of age, 65 to 85 years of age, and ≥ 12 years of age [stratified as 12-15, 16-55, or >55 years of age]).

These 2 investigational RNA vaccine candidates, with the addition of saline placebo, are the 3 potential study interventions that may be administered to a study participant:

- BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the RBD):
10 μg , 20 μg , 30 μg , 100 μg
- BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA and encoding the P2 S):
10 μg , 20 μg , 30 μg
- Normal saline (0.9% sodium chloride solution for injection)

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 μg .

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6.1. Study Intervention(s) Administered

Intervention Name	BNT162b1 (BNT162 RNA-LNP vaccine utilizing modRNA)	BNT162b2 (BNT162 RNA-LNP vaccine utilizing modRNA)	Saline Placebo
Type	Vaccine	Vaccine	Placebo
Dose Formulation	modRNA	modRNA	Normal saline (0.9% sodium chloride solution for injection)
Unit Dose Strength(s)	250 µg/0.5 mL	250 µg/0.5 mL	N/A
Dosage Level(s) ^a	10-, 20-, 30-, 100-µg	10-, 20-, 30-µg	N/A
Route of Administration	Intramuscular injection	Intramuscular injection	Intramuscular injection
Use	Experimental	Experimental	Placebo
IMP or NIMP	IMP	IMP	IMP
Sourcing	Provided centrally by the sponsor	Provided centrally by the sponsor	Provided centrally by the sponsor
Packaging and Labeling	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass vial as open-label supply. Each vial will be labeled as required per country requirement	Study intervention will be provided in a glass or plastic vial as open-label supply. Each vial will be labeled as required per country requirement

- a. Dependent upon safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany (BNT162-01), it is possible that groups may be started at the next highest dose, groups may not be started, groups may be terminated early, and/or groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses.

The vaccine candidate selected for Phase 2/3 evaluation is BNT162b2 at a dose of 30 µg.

6.1.1. Manufacturing Process

The scale of the BNT162b2 manufacturing has been increased to support future supply. BNT162b2 generated using the manufacturing process supporting an increased supply (“Process 2”) will be administered to approximately 250 participants 16 to 55 years of age, per lot, in the study. The safety and immunogenicity of prophylactic BNT162b2 in individuals 16 to 55 years of age vaccinated with material generated using the existing manufacturing process “Process 1,” and with material from lots generated using the manufacturing process supporting increased supply, “Process 2,” will be described.

In brief, the process changes relate to the method of production for the DNA template that RNA drug substance is transcribed from, and the RNA drug substance purification method. The BNT162b2 drug product is then produced using a scaled-up LNP manufacturing process.

6.1.2. Administration

Participants will receive 1 dose of study intervention as randomized at each vaccination visit (Visits 1 and 4 for Phase 1 participants, Visits 1 and 2 for Phase 2/3 participants) in accordance with the study’s [SoA](#). The volume to be administered may vary by vaccine candidate and dose level; full details are described in the IP manual.

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Study intervention should be administered intramuscularly into the deltoid muscle, preferably of the nondominant arm, by an **unblinded** administrator.

Standard vaccination practices must be observed and vaccine must not be injected into blood vessels. Appropriate medication and other supportive measures for management of an acute hypersensitivity reaction should be available in accordance with local guidelines for standard immunization practices.

Administration of study interventions should be performed by an appropriately qualified, GCP-trained, and vaccine-experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacist, or medical assistant) as allowed by local, state, and institutional guidance.

Study intervention administration details will be recorded on the CRF.

6.2. Preparation/Handling/Storage/Accountability

1. The investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study interventions received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated recording) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff. At a minimum, daily minimum and maximum temperatures for all site storage locations must be documented and available upon request. Data for nonworking days must indicate the minimum and maximum temperatures since previously documented for all site storage locations upon return to business.
3. Any excursions from the study intervention label storage conditions should be reported to Pfizer upon discovery along with any actions taken. The site should actively pursue options for returning the study intervention to the storage conditions described in the labeling, as soon as possible. Once an excursion is identified, the study intervention must be quarantined and not used until Pfizer provides permission to use the study intervention. Specific details regarding the definition of an excursion and information the site should report for each excursion will be provided to the site in the IP manual.
4. Any storage conditions stated in the SRSD will be superseded by the storage conditions stated on the label.
5. Study interventions should be stored in their original containers.
6. See the IP manual for storage conditions of the study intervention.

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7. The investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records), such as the IPAL or sponsor-approved equivalent. All study interventions will be accounted for using a study intervention accountability form/record.
8. Further guidance and information for the final disposition of unused study interventions are provided in the IP manual. All destruction must be adequately documented. If destruction is authorized to take place at the investigator site, the investigator must ensure that the materials are destroyed in compliance with applicable environmental regulations, institutional policy, and any special instructions provided by Pfizer.

Upon identification of a product complaint, notify the sponsor within 1 business day of discovery as described in the IP manual.

6.2.1. Preparation and Dispensing

See the IP manual for instructions on how to prepare the study intervention for administration. Study intervention should be prepared and dispensed by an appropriately qualified and experienced member of the study staff (eg, physician, nurse, physician's assistant, nurse practitioner, pharmacy assistant/technician, or pharmacist) as allowed by local, state, and institutional guidance. A second staff member will verify the dispensing.

Study intervention and placebo will be prepared by qualified unblinded site personnel according to the IP manual. The study intervention will be administered in such a way to ensure the participants remain blinded.

6.3. Measures to Minimize Bias: Randomization and Blinding

6.3.1. Allocation to Study Intervention

Allocation (randomization) of participants to vaccine groups will proceed through the use of an IRT system (IWR). The site personnel (study coordinator or specified designee) will be required to enter or select information including but not limited to the user's ID and password, the protocol number, and the participant number. The site personnel will then be provided with a vaccine assignment and randomization number. The IRT system will provide a confirmation report containing the participant number, randomization number, and study intervention allocation assigned. The confirmation report must be stored in the site's files.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.3.2. Blinding of Site Personnel

In this observer blinded study, the study staff receiving, storing, dispensing, preparing, and administering the study interventions will be unblinded. All other study and site personnel, including the investigator, investigator staff, and participants, will be blinded to study

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intervention assignments. In particular, the individuals who evaluate participant safety will be blinded. Because the BNT162 RNA-based COVID-19 vaccine candidates and placebo are different in physical appearance, the study intervention syringes will be administered in a manner that prevents the study participants from identifying the study intervention type based on its appearance.

The responsibility of the unblinded dispenser and administrator must be assigned to an individual or individuals who will not participate in the evaluation of any study participants. Contact between the unblinded dispenser and study participants and unblinded administrator and study participants should be kept to a minimum. The remaining site personnel must not know study intervention assignments.

6.3.3. Blinding of the Sponsor

To facilitate rapid review of data in real time, sponsor staff will be unblinded to study intervention allocation for the participants in Phase 1. The majority of sponsor staff will be blinded to study intervention allocation in Phase 2/3. All laboratory testing personnel performing serology assays will remain blinded to study intervention assigned/received throughout the study. The following sponsor staff, who will have no part in the blinded conduct of the study, will be unblinded in Phase 2/3 (further details will be provided in a data blinding plan):

- Those study team members who are involved in ensuring that protocol requirements for study intervention preparation, handling, allocation, and administration are fulfilled at the site will be unblinded for the duration of the study (eg, unblinded study manager, unblinded clinical research associate).
- Unblinded clinician(s), who are not direct members of the study team and will not participate in any other study-related activities, will review unblinded protocol deviations.
- An unblinded team supporting interactions with, and analyses for, the DMC (see [Section 9.6](#)). This will comprise a statistician, programmer(s), a clinical scientist, and a medical monitor who will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 (see [Section 8.2.3](#)).
- An unblinded submissions team will be responsible for preparing unblinded analyses and documents to support regulatory activities that may be required while the study is ongoing. This team will only be unblinded at the group level and not have access to individual participant assignments. The programs that produce the summary tables will be developed and validated by the blinded study team, and these programs will be run by the unblinded DMC team. The submissions team will not have access to unblinded COVID-19 cases unless efficacy is achieved in either an interim analysis or the final analysis, as determined by the DMC.

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6.3.4. Breaking the Blind

The IRT will be programmed with blind-breaking instructions. In case of an emergency, the investigator has the sole responsibility for determining if unblinding of a participant's study intervention assignment is warranted. Participant safety must always be the first consideration in making such a determination. If the investigator decides that unblinding is warranted, the investigator should make every effort to contact the sponsor prior to unblinding a participant's vaccine assignment unless this could delay further management of the participant. If a participant's vaccine assignment is unblinded, the sponsor must be notified within 24 hours after breaking the blind. The date and reason that the blind was broken must be recorded in the source documentation and CRF.

The study-specific IRT reference manual and IP manual will provide the contact information and further details on the use of the IRT system.

6.4. Study Intervention Compliance

When participants are dosed at the site, they will receive study intervention directly from the investigator or designee, under medical supervision. The date and time of each dose administered in the clinic will be recorded in the source documents and recorded in the CRF. The dose of study intervention and study participant identification will be confirmed at the time of dosing by a member of the study site staff other than the person administering the study intervention.

6.5. Concomitant Therapy

The following concomitant medications and vaccinations will be recorded in the CRF:

- All vaccinations received from 28 days prior to study enrollment until the 6-month follow-up visit (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).
- Prohibited medications listed in Section 6.5.1 will be recorded, to include start and stop dates, name of the medication, dose, unit, route, and frequency.
- In addition, for participants enrolled in Phase 1, all current medication at baseline will be recorded, to include start date, name of the medication, dose, unit, route, and frequency.

6.5.1. Prohibited During the Study

Receipt of the following vaccines and medications during the time periods listed below may exclude a participant from the per-protocol analysis from that point onwards, and may require vaccinations to be discontinued in that participant; however, it is anticipated that the participant would not be withdrawn from the study (see [Section 7](#)). Medications should not be withheld if required for a participant's medical care.

Unless considered medically necessary, no vaccines other than study intervention should be administered within 28 days before and 28 days after each study vaccination. One exception

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to this is that seasonal and pandemic influenza vaccine can be given at least 14 days after, or at least 14 days prior to, the administration of study intervention.

Receipt of chronic systemic treatment with known immunosuppressant medications, or radiotherapy, within 60 days before enrollment through conclusion of the study.

Receipt of systemic corticosteroids (≥ 20 mg/day of prednisone or equivalent) for ≥ 14 days is prohibited from 28 days prior to enrollment to Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants).

Receipt of inhaled/nebulized corticosteroids from 28 days prior to enrollment to Visit 7 (1-month follow-up visit) for Phase 1 participants.

Receipt of blood/plasma products or immunoglobulins within 60 days before enrollment through conclusion of the study.

Receipt of any other (nonstudy) coronavirus vaccine at any time prior to or during study participation is prohibited.

Prophylactic antipyretics and other pain medication to prevent symptoms associated with study intervention administration are not permitted. However, if a participant is taking a medication for another condition, even if it may have antipyretic or pain-relieving properties, it should not be withheld prior to study vaccination.

6.5.2. Permitted During the Study

The use of antipyretics and other pain medication to treat symptoms associated with study intervention administration or ongoing conditions is permitted.

Medication other than that described as prohibited in [Section 6.5.1](#) required for treatment of preexisting stable conditions is permitted.

Inhaled (except in Phase 1 participants – see [Section 6.5.1](#)), topical, or localized injections of corticosteroids (eg, intra-articular or intrabursal administration) are permitted.

6.6. Dose Modification

This protocol allows some alteration of vaccine dose for individual participants and/or dose groups from the currently outlined dosing schedule. For reasons of reactogenicity, tolerability, or safety, the IRC may recommend to reduce the second dose of study intervention and/or increase the interval between doses.

If, due to a medication error, a participant receives 1 dose of BNT162b2 at Visit 1 and 1 dose of placebo at Visit 2 (or vice versa), the participant should be offered the possibility to receive a second dose of BNT162b2 at an unscheduled visit. In this situation:

- Obtain informed consent for administration of the additional dose.

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- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.6](#).
- Discuss contraceptive use as described in [Section 10.4](#).
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- The participant should continue to adhere to the normal visit schedule but must be followed for nonserious AEs for 1 month and SAEs for 6 months after the second dose of BNT162b2. This will require AEs to be elicited either by unscheduled telephone contact(s) and/or in-person visit(s).

6.7. Intervention After the End of the Study

No intervention will be provided to study participants at the end of the study.

7. DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1. Discontinuation of Study Intervention

In rare instances, it may be necessary for a participant to permanently discontinue study intervention (definitive discontinuation). Reasons for definitive discontinuation of study intervention may include the following: AEs; participant request; investigator request; pregnancy; protocol deviation (including no longer meeting all the inclusion criteria, or meeting 1 or more exclusion criteria). In general, unless the investigator considers it unsafe to administer the second dose, or the participant does not wish to receive it, it is preferred that the second dose be administered. Note that a positive SARS-CoV-2 NAAT result without symptoms does not meet exclusion criterion 5 and should not result in discontinuation of study intervention, whereas a COVID-19 diagnosis does meet exclusion criterion 5 and should result in discontinuation of study intervention (see [Section 8.15](#)).

Note that discontinuation of study intervention does not represent withdrawal from the study. Per the study estimands, if study intervention is definitively discontinued, the participant will remain in the study to be evaluated for safety, immunogenicity, and efficacy. See the [SoA](#) for data to be collected at the time of discontinuation of study intervention and follow-up for any further evaluations that need to be completed.

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In the event of discontinuation of study intervention, it must be documented on the appropriate CRF/in the medical records whether the participant is discontinuing further receipt of study intervention or also from study procedures, posttreatment study follow-up, and/or future collection of additional information.

7.2. Participant Discontinuation/Withdrawal From the Study

A participant may withdraw from the study at any time at his/her own request. Reasons for discontinuation from the study may include the following:

- Refused further follow-up;
- Lost to follow-up;
- Death;
- Study terminated by sponsor;
- AEs;
- Participant request;
- Investigator request;
- Protocol deviation.

If a participant does not return for a scheduled visit, every effort should be made to contact the participant. All attempts to contact the participant and information received during contact attempts must be documented in the participant's source document. In any circumstance, every effort should be made to document participant outcome, if possible.

The investigator or his or her designee should capture the reason for withdrawal in the CRF for all participants.

If a participant withdraws from the study, he/she may request destruction of any remaining samples taken and not tested, and the investigator must document any such requests in the site study records and notify the sponsor accordingly.

If the participant withdraws from the study and also withdraws consent (see [Section 7.2.1](#)) for disclosure of future information, no further evaluations should be performed and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

Lack of completion of all or any of the withdrawal/early termination procedures will not be viewed as protocol deviations so long as the participant's safety was preserved.

7.2.1. Withdrawal of Consent

Participants who request to discontinue receipt of study intervention will remain in the study and must continue to be followed for protocol-specified follow-up procedures. The only exception to this is when a participant specifically withdraws consent for any further contact

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with him or her or persons previously authorized by the participant to provide this information. Participants should notify the investigator in writing of the decision to withdraw consent from future follow-up, whenever possible. The withdrawal of consent should be explained in detail in the medical records by the investigator, as to whether the withdrawal is only from further receipt of study intervention or also from study procedures and/or posttreatment study follow-up, and entered on the appropriate CRF page. In the event that vital status (whether the participant is alive or dead) is being measured, publicly available information should be used to determine vital status only as appropriately directed in accordance with local law.

7.3. Lost to Follow-up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to attend a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study;
- Before a participant is deemed lost to follow-up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record;
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

8. STUDY ASSESSMENTS AND PROCEDURES

The investigator (or an appropriate delegate at the investigator site) must obtain a signed and dated ICD before performing any study-specific procedures.

The full date of birth will be collected to critically evaluate the immune response and safety profile by age.

Study procedures and their timing are summarized in the [SoA](#). Protocol waivers or exemptions are not allowed.

Safety issues should be discussed with the sponsor immediately upon occurrence or awareness to determine whether the participant should continue or discontinue study intervention.

Adherence to the study design requirements, including those specified in the [SoA](#), is essential and required for study conduct.

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All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.

Every effort should be made to ensure that protocol-required tests and procedures are completed as described. However, it is anticipated that from time to time there may be circumstances outside the control of the investigator that may make it unfeasible to perform the test. In these cases, the investigator must take all steps necessary to ensure the safety and well-being of the participant. When a protocol-required test cannot be performed, the investigator will document the reason for the missed test and any corrective and preventive actions that he or she has taken to ensure that required processes are adhered to as soon as possible. The study team must be informed of these incidents in a timely manner.

For samples being collected and shipped, detailed collection, processing, storage, and shipment instructions and contact information will be provided to the investigator site prior to initiation of the study.

The total blood sampling volume for individual participants in this study is approximately up to: 515 mL for participants in Phase 1, 110 mL for Phase 2/3 participants ≥ 16 years of age, and 50 mL for participants in the 12- to 15-year age stratum. Additionally, 20 mL of blood for participants ≥ 16 years of age and 10 mL for participants in the 12- to 15-year age stratum will be taken at an unplanned convalescent visit at any time a participant develops respiratory symptoms indicating a potential COVID-19 infection. Select participants in Phase 1 will also be asked to provide an additional blood sample of approximately 170 mL at either Visit 5, 6, or 7. These participants would therefore have a total blood sampling volume of 700 mL during the 24-month study period. Other additional blood samples may be taken for safety assessments at times specified by Pfizer, provided the total volume taken during the study does not exceed 550 mL during any period of 60 consecutive days.

8.1. Efficacy and/or Immunogenicity Assessments

Efficacy will be assessed throughout a participant's involvement in the study through surveillance for potential cases of COVID-19. If, at any time, a participant develops acute respiratory illness (see [Section 8.13](#)), for the purposes of the study he or she will be considered to potentially have COVID-19 illness.⁹ In this circumstance, the participant should contact the site, an in-person or telehealth visit should occur, and assessments should be conducted as specified in the SoA. The assessments will include a nasal (midturbinate) swab, which will be tested at a central laboratory using a reverse transcription–polymerase chain reaction (RT-PCR) test (Cepheid; FDA approved under EUA), or other equivalent nucleic acid amplification–based test (ie, NAAT), to detect SARS-CoV-2. In addition, clinical information and results from local standard-of-care tests (as detailed in [Section 8.13](#)) will be assessed. The central laboratory NAAT result will be used for the case definition, unless no result is available from the central laboratory, in which case a local NAAT result may be used if it was obtained using 1 of the following assays:

- Cepheid Xpert Xpress SARS-CoV-2

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- Roche cobas SARS-CoV-2 real-time RT-PCR test (EUA200009/A001)
- Abbott Molecular/RealTime SARS-CoV-2 assay (EUA200023/A001)

Two definitions of SARS-CoV-2–related cases, and SARS-CoV-2–related severe cases, will be considered (for both, the onset date of the case will be the date that symptoms were first experienced by the participant; if new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness):

- Confirmed COVID-19: presence of at least 1 of the following symptoms and SARS-CoV-2 NAAT-positive during, or within 4 days before or after, the symptomatic period, either at the central laboratory or at a local testing facility (using an acceptable test):
 - Fever;
 - New or increased cough;
 - New or increased shortness of breath;
 - Chills;
 - New or increased muscle pain;
 - New loss of taste or smell;
 - Sore throat;
 - Diarrhea;
 - Vomiting.

The second definition, which may be updated as more is learned about COVID-19, will include the following additional symptoms defined by the CDC (listed at <https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html>):

- Fatigue;
- Headache;
- Nasal congestion or runny nose;
- Nausea.
- Confirmed severe COVID-19: confirmed COVID-19 and presence of at least 1 of the following:

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- Clinical signs at rest indicative of severe systemic illness (RR \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ <300 mm Hg);
- Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO);
- Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors);
- Significant acute renal, hepatic, or neurologic dysfunction*;
- Admission to an ICU;
- Death.

The DMC may recommend modification of the definition of severe disease according to emerging information.

* Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of this criterion, the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

In addition, a serological definition will be used for participants without clinical presentation of COVID-19:

- Confirmed seroconversion to SARS-CoV-2 without confirmed COVID-19: positive N-binding antibody result in a participant with a prior negative N-binding antibody result

Serum samples will be obtained for immunogenicity testing at the visits specified in the [SoA](#). The following assays will be performed:

- SARS-CoV-2 neutralization assay
- S1-binding IgG level assay
- RBD-binding IgG level assay
- N-binding antibody assay

Note that all immunogenicity analyses will be based upon samples analyzed at the central laboratory; the rapid test will only be performed at screening by all sites recruiting participants in Phase 1 (see [Section 8.11.1.1](#)) to determine eligibility.

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Serum obtained from the additional ~170-mL blood sample from select participants in Phase 1 at either Visit 5, 6, or 7 will be used for exploratory COVID-19 research, intended to establish a surrogate endpoint that is reasonably likely to predict clinical benefit.

8.1.1. Biological Samples

Blood and nasal swab samples will be used only for scientific research. Each sample will be labeled with a code so that the laboratory personnel testing the samples will not know the participant's identity. Samples that remain after performing assays outlined in the protocol may be stored by Pfizer. Unless a time limitation is required by local regulations or ethical requirements, the samples will be stored for up to 15 years after the end of the study and then destroyed. If allowed by the ICD, stored samples may be used for additional testing to better understand the immune responses to the vaccine(s) under study in this protocol, to inform the development of other products, and/or for vaccine-related assay work supporting vaccine programs. No testing of the participant's DNA will be performed.

The participant may request that his or her samples, if still identifiable, be destroyed at any time; however, any data already collected from those samples will still be used for this research. The biological samples may be shared with other researchers as long as confidentiality is maintained and no testing of the participant's DNA is performed.

8.2. Safety Assessments

Planned time points for all safety assessments are provided in the [SoA](#). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

A clinical assessment, including medical history, will be performed on all participants at his/her first visit to establish a baseline. Significant medical history and observations from any physical examination, if performed, will be documented in the CRF.

AEs and SAEs are collected, recorded, and reported as defined in [Section 8.3](#).

Acute reactions within the first 4 hours after administration of the study intervention (for the first 5 participants vaccinated in each Phase 1 group), and within the first 30 minutes (for the remainder of participants), will be assessed and documented in the AE CRF.

The safety parameters also include reactogenicity e-diary reports of local reactions and systemic events (including fever), and use of antipyretic medication that occur in the 7 days after administration of the study intervention in a subset of participants. These prospectively self-collected occurrences of local reactions and systemic events are graded as described in [Section 8.2.2](#). For participants who are not in the reactogenicity subset, these local reactions and systemic events should be detected and reported as AEs, in accordance with [Section 8.3.2](#).

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8.2.1. Clinical Safety Laboratory Assessments (Phase 1 Participants Only)

See [Appendix 2](#) for the list of clinical safety laboratory tests to be performed and the [SoA](#) for the timing and frequency. All protocol-required laboratory assessments, as defined in [Appendix 2](#), must be conducted in accordance with the laboratory manual and the [SoA](#). Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

The investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the CRF. See [Appendix 2](#) for the grading scale for assessment of clinically significant abnormal laboratory findings. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant's condition.

All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 28 days after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the investigator or medical monitor.

If such values do not return to normal/baseline within a period of time judged reasonable by the investigator, the etiology should be identified and the sponsor notified.

See [Appendix 5](#) for suggested actions and follow-up assessments in the event of potential drug-induced liver injury (DILI).

8.2.2. Electronic Diary

Participants will be required to complete a reactogenicity e-diary through an application (see [Section 8.14](#)) installed on a provisioned device or on the participant's own personal device. All participants in Phase 1, and a subset of at least the first 6000 randomized in Phase 2/3, will be asked to monitor and record local reactions, systemic events, and antipyretic medication usage for 7 days following administration of the study intervention. All participants in Phase 3 who are HIV-positive or 12 to 15 years of age will be included in this subset. In addition, participants 16 through 17 years of age enrolled under protocol amendment 9 and onwards will be included in the reactogenicity subset. The reactogenicity e-diary allows recording of these assessments only within a fixed time window, thus providing the accurate representation of the participant's experience at that time. Data on local reactions and systemic events reported in the reactogenicity e-diary will be transferred electronically to a third-party vendor, where they will be available for review by investigators and the Pfizer clinicians at all times via an internet-based portal.

At intervals agreed to by the vendor and Pfizer, these data will be transferred electronically into Pfizer's database for analysis and reporting. These data do not need to be reported by the investigator in the CRF as AEs.

Investigators (or designee) will be required to review the reactogenicity e-diary data online at frequent intervals as part of the ongoing safety review.

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The investigator or designee must obtain stop dates from the participant for any ongoing local reactions, systemic events, or use of antipyretic medication on the last day that the reactogenicity e-diary was completed. The stop dates should be documented in the source documents and the information entered in the CRF.

8.2.2.1. Grading Scales

The grading scales used in this study to assess local reactions and systemic events as described below are derived from the FDA Center for Biologics Evaluation and Research (CBER) guidelines on toxicity grading scales for healthy adult volunteers enrolled in preventive vaccine clinical trials.⁸

8.2.2.2. Local Reactions

During the reactogenicity e-diary reporting period, participants will be asked to assess redness, swelling, and pain at the injection site and to record the symptoms in the reactogenicity e-diary. If a local reaction persists beyond the end of the reactogenicity e-diary period following vaccination, the participant will be requested to report that information. The investigator will enter this additional information in the CRF.

Redness and swelling will be measured and recorded in measuring device units (range: 1 to 21) and then categorized during analysis as absent, mild, moderate, or severe based on the grading scale in Table 1. Measuring device units can be converted to centimeters according to the following formula: 1 measuring device unit = 0.5 cm. Pain at the injection site will be assessed by the participant as absent, mild, moderate, or severe according the grading scale in Table 1.

If a Grade 3 local reaction is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's local reaction as Grade 4. If a participant experiences a confirmed Grade 4 local reaction, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 1. Local Reaction Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Pain at the injection site	Does not interfere with activity	Interferes with activity	Prevents daily activity	Emergency room visit or hospitalization for severe pain
Redness	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis or exfoliative dermatitis
Swelling	>2.0 cm to 5.0 cm (5 to 10 measuring device units)	>5.0 cm to 10.0 cm (11 to 20 measuring device units)	>10 cm (≥21 measuring device units)	Necrosis

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8.2.2.3. Systemic Events

During the reactogenicity e-diary reporting period, participants will be asked to assess vomiting, diarrhea, headache, fatigue, chills, new or worsened muscle pain, and new or worsened joint pain and to record the symptoms in the reactogenicity e-diary. The symptoms will be assessed by the participant as absent, mild, moderate, or severe according to the grading scale in Table 2.

If a Grade 3 systemic event is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to classify a participant's systemic event as Grade 4. If a participant experiences a confirmed Grade 4 systemic event, the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 2. Systemic Event Grading Scale

	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Vomiting	1-2 times in 24 hours	>2 times in 24 hours	Requires IV hydration	Emergency room visit or hospitalization for hypotensive shock
Diarrhea	2 to 3 loose stools in 24 hours	4 to 5 loose stools in 24 hours	6 or more loose stools in 24 hours	Emergency room visit or hospitalization for severe diarrhea
Headache	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe headache
Fatigue/ tiredness	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe fatigue
Chills	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe chills
New or worsened muscle pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened muscle pain
New or worsened joint pain	Does not interfere with activity	Some interference with activity	Prevents daily routine activity	Emergency room visit or hospitalization for severe new or worsened joint pain

Abbreviation: IV = intravenous.

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8.2.2.4. Fever

In order to record information on fever, a thermometer will be given to participants with instructions on how to measure oral temperature at home. Temperature will be collected in the reactogenicity e-diary in the evening daily during the reactogenicity e-diary reporting period. It will also be collected at any time during the reactogenicity e-diary data collection periods when fever is suspected. Fever is defined as an oral temperature of $\geq 38.0^{\circ}\text{C}$ (100.4°F). The highest temperature for each day will be recorded in the reactogenicity e-diary. Temperature will be measured and recorded to 1 decimal place and then categorized during analysis according to the scale shown in Table 3.

If a fever of $\geq 39.0^{\circ}\text{C}$ (102.1°F) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. Only an investigator or medically qualified person is able to confirm a participant's fever as $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$). If a participant experiences a confirmed fever $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$), the investigator must immediately notify the sponsor and, if it is determined to be related to the administration of the study intervention, further vaccinations will be discontinued in that participant.

Table 3. Scale for Fever

$\geq 38.0\text{-}38.4^{\circ}\text{C}$ ($100.4\text{-}101.1^{\circ}\text{F}$)
$>38.4\text{-}38.9^{\circ}\text{C}$ ($101.2\text{-}102.0^{\circ}\text{F}$)
$>38.9\text{-}40.0^{\circ}\text{C}$ ($102.1\text{-}104.0^{\circ}\text{F}$)
$>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$)

8.2.2.5. Antipyretic Medication

The use of antipyretic medication to treat symptoms associated with study intervention administration will be recorded in the reactogenicity e-diary daily during the reporting period (Day 1 to Day 7).

8.2.3. Phase 1 Stopping Rules

The following stopping rules are in place for all Phase 1 participants, based on review of AE data and e-diary reactogenicity data, until the start of Phase 2/3 or 30 days after the last dose of study intervention in Phase 1, whichever is later. These data will be monitored on an ongoing basis by the investigator (or medically qualified designee) and sponsor in order to promptly identify and flag any event that potentially contributes to a stopping rule.

The sponsor study team will be unblinded during Phase 1, so will be able to assess whether or not a stopping rule has been met on the basis of a participant's individual study intervention allocation.

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In the event that sponsor personnel confirm that a stopping rule is met, the following actions will commence:

- The IRC will review all appropriate data.
- The stopping rule will PAUSE randomization and study intervention administration for the impacted vaccine candidate all dose levels and age groups.
- The DMC will review all appropriate data.
- For all participants vaccinated, all other routine study conduct activities, including ongoing data entry, reporting of AEs, participant reactogenicity e-diary completion, blood sample collection, and participant follow-up, will continue during the pause.

A stopping rule is met if any of the following rules occur after administration of investigational BNT162 vaccine; data from placebo recipients will not contribute to the stopping rules. Reactogenicity e-diary data confirmed by the investigator as being entered by the participant in error will not contribute toward a stopping rule.

The BNT162b RNA platform will be evaluated for contribution to stopping rules overall; vaccine candidate dose levels within the platform and age groups will contribute to stopping rules together. However, it is possible that the recommendations may include halting or continuing randomization with any of the BNT162 vaccine candidates.

Stopping Rule Criteria for Each BNT162 Vaccine Candidate:

1. If any participant vaccinated with the BNT162 candidate (at any dose level) develops an SAE that is assessed by the investigator as possibly related, or for which there is no alternative, plausible, attributable cause.
2. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a Grade 4 local reaction or systemic event after vaccination (see [Section 8.2.2](#)) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
3. If any participant vaccinated with the BNT162 candidate (at any dose level) develops a fever $>40.0^{\circ}\text{C}$ ($>104.0^{\circ}\text{F}$) for at least 1 daily measurement after vaccination (see [Section 8.2.2.4](#)) that is assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.
4. If any 2 participants vaccinated with the BNT162 candidate (at any dose level) report the same or similar severe (Grade 3) AE (including laboratory abnormalities) after vaccination, assessed as possibly related by the investigator, or for which there is no alternative, plausible, attributable cause.

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5. If any participant dies or requires ICU admission due to SARS-CoV-2 infection; if this stopping rule is met, all available clinical and preclinical safety and immunogenicity data should be reviewed to evaluate for enhanced COVID-19.

8.2.4. Surveillance of Events That Could Represent Enhanced COVID-19 and Phase 2/3 Stopping Rule

Participants in all phases of the study will be surveilled for potential COVID-19 illness from Visit 1 onwards (see [Section 8.13](#)).

As this is a sponsor open-label study during Phase 1, the sponsor will conduct unblinded reviews of the data during the course of the study, including for the purpose of safety assessment. All NAAT-confirmed cases in Phase 1 will be reviewed contemporaneously by the IRC and the DMC (see [Section 9.6](#)).

In Phase 2/3, the unblinded team supporting the DMC, including an unblinded medical monitor, will review cases of severe COVID-19 as they are received and will review AEs at least weekly for additional potential cases of severe COVID-19. At any point, the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups.

The purpose of these reviews will be to identify whether any features of each case appear unusual, in particular greater in severity, compared to available information at the time of review. Indicators of severity may include accelerated deterioration, need for hospitalization, need for ventilation, or death. Observed rates of these indicators will be compared with what could be expected in a similar population to the study participants based upon available information at the time of review.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%. Further details can be found in [Section 10.7](#).

8.2.5. Randomization and Vaccination After a Stopping Rule Is Met

Once the IRC (if in Phase 1) and DMC (all phases) have reviewed the safety data and provided guidance, a notification will be sent from the sponsor to the sites with guidance on how to proceed.

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8.2.6. Pregnancy Testing

Pregnancy tests may be urine or serum tests, but must have a sensitivity of at least 25 mIU/mL. Pregnancy tests will be performed in WOCBP at the times listed in the [SoA](#), immediately before the administration of each vaccine dose. A negative pregnancy test result will be required prior to the participant's receiving the study intervention. Pregnancy tests may also be repeated if requested by IRBs/ECs or if required by local regulations. In the case of a positive confirmed pregnancy, the participant will be withdrawn from administration of study intervention but may remain in the study.

8.3. Adverse Events and Serious Adverse Events

The definitions of an AE and an SAE can be found in [Appendix 3](#).

AEs will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's parent(s)/legal guardian).

The investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible to pursue and obtain adequate information both to determine the outcome and to assess whether the event meets the criteria for classification as an SAE or caused the participant to discontinue the study intervention (see [Section 7.1](#)).

Each participant/parent(s)/legal guardian will be questioned about the occurrence of AEs in a nonleading manner.

In addition, the investigator may be requested by Pfizer Safety to obtain specific follow-up information in an expedited fashion.

8.3.1. Time Period and Frequency for Collecting AE and SAE Information

The time period for actively eliciting and collecting AEs and SAEs ("active collection period") for each participant begins from the time the participant/parent(s)/legal guardian provides informed consent, which is obtained before the participant's participation in the study (ie, before undergoing any study-related procedure and/or receiving study intervention), through and including Visit 7 for Phase 1 participants, and Visit 3 for Phase 2/3 participants. In addition, any AEs occurring up to 48 hours after each subsequent blood draw must be recorded on the CRF.

SAEs will be collected from the time the participant/parent(s)/legal guardian provides informed consent to approximately 6 months after the last dose of study intervention (Visit 8 for Phase 1 participants, and Visit 4 for Phase 2/3 participants).

Follow-up by the investigator continues throughout and after the active collection period and until the AE or SAE or its sequelae resolve or stabilize at a level acceptable to the investigator and Pfizer concurs with that assessment.

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For participants who are screen failures, the active collection period ends when screen failure status is determined.

If the participant withdraws from the study and also withdraws consent for the collection of future information, the active collection period ends when consent is withdrawn.

If a participant definitively discontinues or temporarily discontinues study intervention because of an AE or SAE, the AE or SAE must be recorded on the CRF and the SAE reported using the Vaccine SAE Report Form.

Investigators are not obligated to actively seek AEs or SAEs after the participant has concluded study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has completed the study, and he/she considers the event to be reasonably related to the study intervention, the investigator must promptly report the SAE to Pfizer using the Vaccine SAE Report Form.

8.3.1.1. Reporting SAEs to Pfizer Safety

All SAEs occurring in a participant during the active collection period as described in [Section 8.3.1](#) are reported to Pfizer Safety on the Vaccine SAE Report Form immediately upon awareness and under no circumstance should this exceed 24 hours, as indicated in [Appendix 3](#). The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

8.3.1.2. Recording Nonserious AEs and SAEs on the CRF

All nonserious AEs and SAEs occurring in a participant during the active collection period, which begins after obtaining informed consent as described in [Section 8.3.1](#), will be recorded on the AE section of the CRF.

The investigator is to record on the CRF all directly observed and all spontaneously reported AEs and SAEs reported by the participant.

8.3.2. Method of Detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AEs and SAEs and the procedures for completing and transmitting SAE reports are provided in [Appendix 3](#).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3. Follow-up of AEs and SAEs

After the initial AE/SAE report, the investigator is required to proactively follow each participant at subsequent visits/contacts. For each event, the investigator must pursue and obtain adequate information until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in [Section 7.3](#)).

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In general, follow-up information will include a description of the event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses, must be provided. In the case of a participant death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer Safety.

Further information on follow-up procedures is given in [Appendix 3](#).

8.3.4. Regulatory Reporting Requirements for SAEs

Prompt notification by the investigator to the sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.

The sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, IRBs/ECs, and investigators.

Investigator safety reports must be prepared for SUSARs according to local regulatory requirements and sponsor policy and forwarded to investigators as necessary.

An investigator who receives SUSARs or other specific safety information (eg, summary or listing of SAEs) from the sponsor will review and then file it along with the SRSD(s) for the study and will notify the IRB/EC, if appropriate according to local requirements.

8.3.5. Exposure During Pregnancy or Breastfeeding, and Occupational Exposure

Exposure to the study intervention under study during pregnancy or breastfeeding and occupational exposure are reportable to Pfizer Safety within 24 hours of investigator awareness.

8.3.5.1. Exposure During Pregnancy

An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
 - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

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- A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- If EDP occurs in a participant or a participant's partner, the investigator must report this information to Pfizer Safety on the Vaccine SAE Report Form and an EDP Supplemental Form, regardless of whether an SAE has occurred. Details of the pregnancy will be collected after the start of study intervention and until 6 months after the last dose of study intervention.
- If EDP occurs in the setting of environmental exposure, the investigator must report information to Pfizer Safety using the Vaccine SAE Report Form and EDP Supplemental Form. Since the exposure information does not pertain to the participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

Follow-up is conducted to obtain general information on the pregnancy and its outcome for all EDP reports with an unknown outcome. The investigator will follow the pregnancy until completion (or until pregnancy termination) and notify Pfizer Safety of the outcome as a follow-up to the initial EDP Supplemental Form. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless preprocedure test findings are conclusive for a congenital anomaly and the findings are reported).

Abnormal pregnancy outcomes are considered SAEs. If the outcome of the pregnancy meets the criteria for an SAE (ie, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly), the investigator should follow the procedures for reporting SAEs. Additional information about pregnancy outcomes that are reported to Pfizer Safety as SAEs follows:

- Spontaneous abortion including miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to the study intervention.

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Additional information regarding the EDP may be requested by the sponsor. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays). In the case of paternal exposure, the investigator will provide the participant with the Pregnant Partner Release of Information Form to deliver to his partner. The investigator must document in the source documents that the participant was given the Pregnant Partner Release of Information Form to provide to his partner.

8.3.5.2. Exposure During Breastfeeding

An exposure during breastfeeding occurs if:

- A female participant is found to be breastfeeding while receiving or after discontinuing study intervention.
- A female is found to be breastfeeding while being exposed or having been exposed to study intervention (ie, environmental exposure). An example of environmental exposure during breastfeeding is a female family member or healthcare provider who reports that she is breastfeeding after having been exposed to the study intervention by inhalation or skin contact.

The investigator must report exposure during breastfeeding to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The information must be reported using the Vaccine SAE Report Form. When exposure during breastfeeding occurs in the setting of environmental exposure, the exposure information does not pertain to the participant enrolled in the study, so the information is not recorded on a CRF. However, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an SAE associated with such a drug, the SAE is reported together with the exposure during breastfeeding.

8.3.5.3. Occupational Exposure

An occupational exposure occurs when a person receives unplanned direct contact with the study intervention, which may or may not lead to the occurrence of an AE. Such persons may include healthcare providers, family members, and other roles that are involved in the trial participant's care.

The investigator must report occupational exposure to Pfizer Safety within 24 hours of the investigator's awareness, regardless of whether there is an associated SAE. The information must be reported using the Vaccine SAE Report Form. Since the information does not pertain to a participant enrolled in the study, the information is not recorded on a CRF; however, a copy of the completed Vaccine SAE Report Form is maintained in the investigator site file.

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8.3.6. Cardiovascular and Death Events

Not applicable.

8.3.7. Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as AEs or SAEs

Potential COVID-19 illnesses and their sequelae that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.

Potential COVID-19 illnesses and their sequelae will not be reported according to the standard process for expedited reporting of SAEs, even though the event may meet the definition of an SAE. These events will be recorded on the COVID-19 illness pages in the participant's CRF within 1 day.

NOTE: However, if either of the following conditions applies, then the event must be recorded and reported as an SAE (instead of a disease-related event):

The event is, in the investigator's opinion, of greater intensity, frequency, or duration than expected for the individual participant.

OR

The investigator considers that there is a reasonable possibility that the event was related to study intervention.

Potential COVID-19 illness events and their sequelae will be reviewed by a group of internal blinded case reviewers. Any SAE that is determined by the internal case reviewers NOT to meet endpoint criteria is reported back to the investigator site of incidence. The investigator must report the SAE to Pfizer Safety within 24 hours of being made aware that the SAE did not meet endpoint criteria. The investigator's SAE awareness date is the date on which the investigator site of incidence receives the SAE back from the internal case reviewers.

8.3.8. Adverse Events of Special Interest

Not applicable.

8.3.8.1. Lack of Efficacy

Lack of efficacy is reportable to Pfizer Safety only if associated with an SAE.

8.3.9. Medical Device Deficiencies

Not applicable.

8.3.10. Medication Errors

Medication errors may result from the administration or consumption of the study intervention by the wrong participant, or at the wrong time, or at the wrong dosage strength.

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Exposures to the study intervention under study may occur in clinical trial settings, such as medication errors.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
Medication errors	All (regardless of whether associated with an AE)	Only if associated with an SAE

Medication errors include:

- Medication errors involving participant exposure to the study intervention;
- Potential medication errors or uses outside of what is foreseen in the protocol that do or do not involve the study participant;
- The administration of expired study intervention;
- The administration of an incorrect study intervention;
- The administration of an incorrect dosage;
- The administration of study intervention that has undergone temperature excursion from the specified storage range, unless it is determined by the sponsor that the study intervention under question is acceptable for use.

Such medication errors occurring to a study participant are to be captured on the medication error page of the CRF, which is a specific version of the AE page.

In the event of a medication dosing error, the sponsor should be notified within 24 hours.

Whether or not the medication error is accompanied by an AE, as determined by the investigator, the medication error is recorded on the medication error page of the CRF and, if applicable, any associated AE(s), serious and nonserious, are recorded on the AE page of the CRF.

Medication errors should be reported to Pfizer Safety within 24 hours on a Vaccine SAE Report Form **only when associated with an SAE**.

8.4. Treatment of Overdose

For this study, any dose of study intervention greater than 1 dose of study intervention within a 24-hour time period will be considered an overdose.

Pfizer does not recommend specific treatment for an overdose.

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In the event of an overdose, the investigator should:

1. Contact the medical monitor within 24 hours.
2. Closely monitor the participant for any AEs/SAEs.
3. Document the quantity of the excess dose as well as the duration of the overdose in the CRF.
4. Overdose is reportable to Safety **only when associated with an SAE.**

Decisions regarding dose interruptions or modifications will be made by the investigator in consultation with the medical monitor based on the clinical evaluation of the participant.

8.5. Pharmacokinetics

Pharmacokinetic parameters are not evaluated in this study.

8.6. Pharmacodynamics

Pharmacodynamic parameters are not evaluated in this study.

8.7. Genetics

Genetics (specified analyses) are not evaluated in this study.

8.8. Biomarkers

Biomarkers are not evaluated in this study.

8.9. Immunogenicity Assessments

Immunogenicity assessments are described in [Section 8.1](#).

8.10. Health Economics

Health economics/medical resource utilization and health economics parameters are not evaluated in this study.

8.11. Study Procedures

8.11.1. Phase 1

8.11.1.1. Screening: (0 to 28 Days Before Visit 1)

Before enrollment and before any study-related procedures are performed, voluntary, written study-specific informed consent will be obtained from the participant. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant. The source data must reflect that the informed consent was obtained before participation in the study.

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It is anticipated that the procedures below will be conducted in a stepwise manner; however, the visit can occur over more than 1 day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance.
- Obtain details of any medications currently taken.
- Perform physical examination including vital signs (weight, height, body temperature, pulse rate, and seated blood pressure), evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 20 mL) for potential future serological assessment and to perform a rapid test for prior COVID-19 infection.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in [Section 10.2](#).
- Collect a blood sample (approximately 10 mL) for HIV, HBsAg, HBc Ab, and HCV Ab tests.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.6](#).
- Discuss contraceptive use as described in [Section 10.4](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Record AEs as described in [Section 8.3](#). AEs that occur prior to dosing should be noted on the Medical History CRF.
- Ask the participant to contact the site staff or investigator immediately if any significant illness or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.

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- Complete the source documents.
- Complete the CRF.

8.11.1.2. Visit 1 – Vaccination 1: (Day 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in [Section 8.3](#).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.6](#).
- Discuss contraceptive use as described in [Section 10.4](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Review screening laboratory results (hematology and chemistry, and HIV, HBsAg, HBc Ab, and HCV Ab tests).
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will proceed only if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Obtain the participant's randomization number and study intervention allocation using the IRT system. Only an unblinded site staff member may obtain this information.
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

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- The first 5 participants vaccinated in each group must be observed by blinded site staff for any acute reactions for at least 4 hours after vaccination. For participants enrolled thereafter, blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.
- Explain the e-diary technologies available for this study (see [Section 8.14](#)), and assist the participant in downloading the study application onto the participant's own device or issue a provisioned device if required. Provide instructions on e-diary completion and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination and, if utilized, the COVID-19 illness e-diary (to be completed if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly).

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- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
 - Severe pain at the injection site.
 - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.3. Visit 2 – Next-Day Follow-up Visit (Vaccination 1): (1 to 3 Days After Visit 1)

- Record AEs as described in [Section 8.3](#).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in [Section 10.2](#).

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- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 10.4](#).
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
 - Severe pain at the injection site.
 - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

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8.11.1.4. Visit 3 – 1-Week Follow-up Visit (Vaccination 1): (6 to 8 Days After Visit 1)

- Record AEs as described in [Section 8.3](#).
- Review hematology and chemistry laboratory results and record any AEs in accordance with [Appendix 2](#).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in [Section 10.2](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 10.4](#).
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
 - Severe pain at the injection site.
 - Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.

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- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.5. Visit 4 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with [Appendix 2](#).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.6](#).
- Discuss contraceptive use as described in [Section 10.4](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Obtain 2 nasal (midturbinate) swabs (collected by site staff). One will be tested (if possible at the site, otherwise at the central laboratory) within 24 hours and vaccination will only proceed if it is NAAT-negative for SARS-CoV-2 genomes. The second will be sent to the central laboratory for potential later testing.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant should not receive further study intervention

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- but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
 - Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in [Section 10.2](#).
 - Collect a blood sample (approximately 50 mL) for immunogenicity testing.
 - Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
 - Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
 - Ensure the participant has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
 - Ensure the participant remains comfortable with his or her chosen e-diary platform, confirm instructions on e-diary completion, and ask the participant to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
 - Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
 - Severe pain at the injection site.
 - Any severe systemic event.
 - Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
 - Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).

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- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.6. Visit 5 – 1-Week Follow-up Visit (Vaccination 2): (6 to 8 Days After Visit 4)

- Record AEs as described in [Section 8.3](#).
- Review hematology and chemistry laboratory results and record any AEs in accordance with [Appendix 2](#).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Collect a blood sample (approximately 10 mL) for hematology and chemistry laboratory tests as described in [Section 10.2](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 10.4](#).
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170 mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:

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- Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
- Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
- Severe pain at the injection site.
- Any severe systemic event.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant to bring the e-diary to the next visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- The investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.1.7. Visit 6 – 2-Week Follow-up Visit (Vaccination 2): (12 to 16 Days After Visit 4)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Review hematology and chemistry laboratory results and record any AEs in accordance with [Appendix 2](#).
- Measure vital signs (body temperature, pulse rate, and seated blood pressure), and, if indicated by any change in the participant's health since the previous visit, perform a physical examination, evaluating any clinically significant abnormalities within the following body systems: general appearance; skin; head, eyes, ears, nose, and throat; heart; lungs; abdomen; musculoskeletal; extremities; neurological; and lymph nodes.
- Record nonstudy vaccinations as described in [Section 6.5](#).

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- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 10.4](#).
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator immediately (this could be via the COVID-19 illness e-diary) if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.8. Visit 7 – 1-Month Follow-up Visit: (28 to 35 Days After Visit 4)

- Record AEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Discuss contraceptive use as described in [Section 10.4](#).
- Collect a blood sample (approximately 50 mL) for immunogenicity testing.
- If not collected at Visit 5 or 6, and the participant (select participants only, details will be provided by the sponsor) consents, collect an additional 170-mL blood sample for exploratory COVID-19 research.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).

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- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.11.1.9. Visit 8 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 4)

- Record SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Ask the participant to contact the site staff or investigator if a medically attended event (eg, doctor’s visit, emergency room visit) or hospitalization occurs.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.11.1.10. Visit 9 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

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- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.11.1.11. Visit 10 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 4)

- Collect a blood sample (approximately 20 mL) for immunogenicity testing.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.11.2. Phase 2/3

8.11.2.1. Visit 1 – Vaccination 1: (Day 1)

Before enrollment and before any study-related procedures are performed, voluntary, written, study-specific informed consent will be obtained from the participant or his/her parent(s)/legal guardian, as appropriate. Each signature on the ICD must be personally dated by the signatory. The investigator or his or her designee will also sign the ICD. A copy of the signed and dated ICD must be given to the participant/participant's parent(s)/legal guardian. The source data must reflect that the informed consent was obtained before participation in the study.

It is anticipated that the procedures below will be conducted in a stepwise manner. The visit may be conducted across 2 consecutive days; if so, all steps from assessing the inclusion and exclusion criteria onwards must be conducted on the same day.

- Assign a single participant number using the IRT system.
- Obtain the participant's demography (including date of birth, sex, race, and ethnicity). The full date of birth will be collected to critically evaluate the immune response and safety profile by age.
- Obtain any medical history of clinical significance. For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed in the previous 6 months.

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- Perform a clinical assessment. If the clinical assessment indicates that a physical examination is necessary to comprehensively evaluate the participant, perform a physical examination and record any findings in the source documents and, if clinically significant, record on the medical history CRF.
- Measure the participant's height and weight.
- Measure the participant's body temperature.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.6](#).
- Discuss contraceptive use as described in [Section 10.4](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Record AEs as described in [Section 8.3](#).
- Collect a blood sample (approximately 20 mL for participants ≥ 16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Obtain the participant's randomization number and study intervention allocation number using the IRT system. Only an unblinded site staff member may obtain this information.
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.
- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- For participants in the reactogenicity subset, issue a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures and provide instructions on their use.

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- For participants not in the reactogenicity subset, issue a thermometer to monitor for fever (for COVID-19 surveillance) and provide instructions on its use.
- Explain the e-diary technologies available for this study (see [Section 8.14](#)), and assist the participant or his/her parent(s)/legal guardian, as appropriate, in downloading the study application onto the participant's own device or issue a provisioned device if required.
 - For participants in the reactogenicity subset, provide instructions on reactogenicity e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
 - For all participants, provide instructions on COVID-19 illness e-diary completion and ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the COVID-19 illness e-diary if the participant is diagnosed with COVID-19 or has possible new or increased symptoms, and when he/she receives a reminder, at least weekly. See [Section 8.14](#) for further details.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
 - Severe pain at the injection site.
 - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if he or she experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.

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- Complete the source documents.
- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.2. Visit 2 – Vaccination 2: (19 to 23 Days After Visit 1)

It is anticipated that the procedures below will be conducted in a stepwise manner; ensure that procedures listed prior to administration of the vaccine are conducted prior to vaccination.

- Record AEs as described in [Section 8.3](#).
- If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Perform urine pregnancy test on WOCBP as described in [Section 8.2.6](#).
- Discuss contraceptive use as described in [Section 10.4](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ensure and document that all of the inclusion criteria and none of the exclusion criteria are met. If not, the participant may not receive further study intervention but will remain in the study to be evaluated for safety, immunogenicity, and efficacy (see [Section 7.1](#)).
- Measure the participant's body temperature.
- Ensure that the participant meets none of the temporary delay criteria as described in [Section 5.5](#).
- Obtain a nasal (midturbinate) swab (collected by site staff).
- Unblinded site staff member(s) will dispense/administer 1 dose of study intervention into the deltoid muscle of the preferably nondominant arm. Please refer to the IP manual for further instruction on this process.

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- Blinded site staff must observe the participant for at least 30 minutes after study intervention administration for any acute reactions. Record any acute reactions (including time of onset) in the participant's source documents and on the AE page of the CRF, and on an SAE form as applicable.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, has a measuring device to measure local reactions at the injection site and a thermometer for recording daily temperatures.
- Ensure the participant or his/her parent(s)/legal guardian, as appropriate, remains comfortable with the chosen e-diary platform, confirm instructions on e-diary completion, and, if the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to complete the reactogenicity e-diary from Day 1 to Day 7, with Day 1 being the day of vaccination.
- If the participant is part of the reactogenicity subset, ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator immediately if the participant experiences any of the following from Day 1 to Day 7 after vaccination (where Day 1 is the day of vaccination) to determine if an unscheduled reactogenicity visit is required:
 - Fever $\geq 39.0^{\circ}\text{C}$ ($\geq 102.1^{\circ}\text{F}$).
 - Redness or swelling at the injection site measuring greater than 10 cm (>20 measuring device units).
 - Severe pain at the injection site.
 - Any severe systemic event.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Remind the participant or his/her parent(s)/legal guardian, as appropriate, to bring the e-diary to the next visit.
- Complete the source documents.

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- The investigator or an authorized designee completes the CRFs and an unblinded dispenser/administrator updates the study intervention accountability records.

If the participant is part of the reactogenicity subset, the investigator or appropriately qualified designee reviews the reactogenicity e-diary data online following vaccination to evaluate participant compliance and as part of the ongoing safety review. Daily review is optimal during the active diary period.

8.11.2.3. Visit 3 – 1-Month Follow-up Visit (After Vaccination 2): (28 to 35 Days After Visit 2)

- Record AEs as described in [Section 8.3](#).
- Review the participant's reactogenicity e-diary data. If the participant is part of the reactogenicity subset, review the participant's reactogenicity e-diary data. Collect stop dates of any reactogenicity e-diary events ongoing on the last day that the reactogenicity e-diary was completed and record stop dates in the CRF if required.
- Record nonstudy vaccinations as described in [Section 6.5](#).
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 1 (if any).
- Discuss contraceptive use as described in [Section 10.4](#).
- Collect a blood sample (approximately 20 mL for participants ≥ 16 years of age, and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator if a medically attended event (eg, doctor's visit, emergency room visit) or hospitalization occurs.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

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8.11.2.4. Visit 4 – 6-Month Follow-up Visit: (175 to 189 Days After Visit 2)

- Record SAEs as described in [Section 8.3](#).
- Record nonstudy vaccinations as described in [Section 6.5](#).
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 3 (if any).
- Collect a blood sample (approximately 20 mL for participants ≥ 16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 8.3](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.11.2.5. Visit 5 – 12-Month Follow-up Visit: (350 to 378 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥ 16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 4 (if any).
- Ask the participant or his/her parent(s)/legal guardian, as appropriate, to contact the site staff or investigator (this could be via the COVID-19 illness e-diary) immediately if the participant experiences any respiratory symptoms as detailed in [Section 8.13](#).
- Schedule an appointment for the participant to return for the next study visit.
- Complete the source documents.

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- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.11.2.6. Visit 6 – 24-Month Follow-up Visit: (714 to 742 Days After Visit 2)

- Collect a blood sample (approximately 20 mL for participants ≥ 16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- For participants who are HIV-positive, record HIV viral load and CD4 count results from the most recent test performed since Visit 5 (if any).
- Collect the participant's e-diary or assist the participant to remove the study application from his or her own personal device.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.12. Unscheduled Visit for a Grade 3 or Suspected Grade 4 Reaction

If a Grade 3 local reaction ([Section 8.2.2.2](#)), systemic event ([Section 8.2.2.3](#)), or fever ([Section 8.2.2.4](#)) is reported in the reactogenicity e-diary, a telephone contact should occur to ascertain further details and determine whether a site visit is clinically indicated. If suspected Grade 4 local reaction ([Section 8.2.2.2](#)), systemic event ([Section 8.2.2.3](#)), or fever ([Section 8.2.2.4](#)) is reported in the reactogenicity e-diary, a telephone contact or site visit should occur to confirm whether the event meets the criteria for Grade 4.

A site visit must be scheduled as soon as possible to assess the participant unless any of the following is true:

- The participant is unable to attend the unscheduled visit.
- The local reaction/systemic event is no longer present at the time of the telephone contact.
- The participant or his/her parent(s)/legal guardian, as appropriate, recorded an incorrect value in the reactogenicity e-diary (confirmation of a reactogenicity e-diary data entry error).

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- The PI or authorized designee determined it was not needed.

This telephone contact will be recorded in the participant's source documentation and the CRF.

If the participant is unable to attend the unscheduled visit, or the PI or authorized designee determined it was not needed, any ongoing local reactions/systemic events must be assessed at the next study visit.

During the unscheduled visit, the reactions should be assessed by the investigator or a medically qualified member of the study staff such as a study physician or a study nurse, as applicable to the investigator's local practice, who will:

- Measure body temperature (°F/°C).
- Measure minimum and maximum diameters of redness (if present).
- Measure minimum and maximum diameters of swelling (if present).
- Assess injection site pain (if present) in accordance with the grades provided in [Section 8.2.2.2](#).
- Assess systemic events (if present) in accordance with the grades provided in [Section 8.2.2.3](#).
- Assess for other findings associated with the reaction and record on the AE page of the CRF, if appropriate.

The investigator or an authorized designee will complete the unscheduled visit assessment page of the CRF.

8.13. COVID-19 Surveillance (All Participants)

If a participant experiences any of the following (irrespective of perceived etiology or clinical significance), he or she is instructed to contact the site immediately and, if confirmed, participate in an in-person or telehealth visit as soon as possible, optimally within 3 days of symptom onset (and at the latest 4 days after symptom resolution). Note that:

- If new symptoms are reported within 4 days after resolution of all previous symptoms, they will be considered as part of a single illness and a second illness visit is not required;
- Surveillance of potential COVID-19 symptoms should continue even if a participant has a positive SARS-CoV-2 test earlier in the study.

During the 7 days following each vaccination, potential COVID-19 symptoms that overlap with specific systemic events (ie, fever, chills, new or increased muscle pain, diarrhea, vomiting) should not trigger a potential COVID-19 illness visit unless, in the investigator's

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opinion, the clinical picture is more indicative of a possible COVID-19 illness than vaccine reactogenicity. If, in the investigator's opinion, the symptoms are considered more likely to be vaccine reactogenicity, but a participant is required to demonstrate that they are SARS-CoV-2–negative, a local SARS-CoV-2 test may be performed: if positive, the symptoms should be recorded as a potential COVID-19 illness; if not, the symptoms should be recorded as AEs (unless already captured in the reactogenicity e-diary).

Participants may utilize a COVID-19 illness e-diary through an application (see [Section 8.14](#)) installed on a provisioned device or on the participant's own personal device to prompt him/her to report any symptoms. Note that this does not substitute for a participant's routine medical care. Therefore, participants should be encouraged to seek care, if appropriate, from their usual provider.

- A diagnosis of COVID-19;
- Fever;
- New or increased cough;
- New or increased shortness of breath;
- Chills;
- New or increased muscle pain;
- New loss of taste/smell;
- Sore throat;
- Diarrhea;
- Vomiting.

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8.13.1. Potential COVID-19 Illness Visit: (Optimally Within 3 Days After Potential COVID-19 Illness Onset)

This visit may be conducted as an in-person or telehealth visit; a telehealth visit involves the sharing of healthcare information and services via telecommunication technologies (eg, audio, video, video-conferencing software) remotely, thus allowing the participant and investigator to communicate on aspects of clinical care.

As a participant's COVID-19 illness may evolve over time, several contacts may be required to obtain the following information:

- Record AEs, as appropriate as described in [Section 8.3](#). Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- If the visit is conducted in person, obtain a nasal (midturbinate) swab (collected by site staff). Alternatively, if conducted by telehealth, instruct the participant to self-collect a nasal (midturbinate) swab and ship for assessment at the central laboratory.
- Collect COVID-19–related standard-of-care clinical and laboratory information. This includes, but is not limited to:
 - Symptoms and signs, including
 - Clinical signs at rest indicative of severe systemic illness (RR \geq 30 breaths per minute, HR \geq 125 beats per minute, SpO₂ \leq 93% on room air at sea level, or PaO₂/FiO₂ <300 mm Hg)
 - Evidence of shock (SBP <90 mm Hg, DBP <60 mm Hg, or requiring vasopressors)
 - Significant acute renal, hepatic, or neurologic dysfunction
 - Respiratory failure (defined as needing high-flow oxygen, noninvasive ventilation, mechanical ventilation, or ECMO)
 - Clinical diagnosis
 - Local laboratory SARS-CoV-2 test result(s). Note that if it is routine practice to perform a repeat local SARS-CoV-2 test for any reason, then a repeat nasal (midturbinate) swab should also be obtained and shipped for assessment at the central laboratory.

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- Full blood count
- Blood chemistry, specifically creatinine, urea, liver function tests, and C-reactive protein
- Imaging results (eg, CT or MRI scan) to document neurologic dysfunction
- Number and type of any healthcare contact; duration of hospitalization and ICU stay
- Death
- Schedule an appointment for the participant to return for the potential COVID-19 convalescent visit once he or she has recovered.
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.

8.13.2. Potential COVID-19 Convalescent Visit: (28 to 35 Days After Potential COVID-19 Illness Visit)

- Record AEs, as appropriate as described in [Section 8.3](#). Note: Potential COVID-19 illnesses that are consistent with the clinical endpoint definition should not be recorded as AEs. These data will be captured as efficacy assessment data only on the relevant pages of the CRF, as these are expected endpoints.
- Record details of any of the prohibited medications specified in [Section 6.5.1](#) received by the participant if required for his or her clinical care.
- Collect a blood sample (approximately 20 mL for participants ≥ 16 years of age and approximately 10 mL for participants in the 12- to 15-year age stratum) for immunogenicity testing.
- Collect/update COVID-19–related clinical and laboratory information (detailed in [Section 8.13.1](#)).
- Complete the source documents.
- The investigator or an authorized designee completes the CRFs.
- Record any AEs that occur within the 48 hours after the blood draw as described in [Section 8.3](#).

8.14. Communication and Use of Technology

In a study of this nature that requires illness events to be reported outside of scheduled study visits, it is vital that communication between the study site and the participant or his/her

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parent(s)/legal guardian, as appropriate, is maintained to ensure that endpoint events are not missed. This study will employ various methods, tailored to the individual participant, to ensure that communication is maintained and study information can be transmitted securely. Using appropriate technology, such as a study application, a communication pathway between the participant or his/her parent(s)/legal guardian, as appropriate, and the study site staff will be established. The participant or his/her parent(s)/legal guardian, as appropriate, may be able to utilize his or her own devices to access this technology, or use a device provided by the sponsor. Traditional methods of telephone communication will also be available. The technology solution may facilitate the following:

- Contact with the investigator, including the ability of the participant or his/her parent(s)/legal guardian, as appropriate, to report whether or not the participant has experienced symptoms that could represent a potential COVID-19 illness (COVID-19 illness e-diary; see [Section 8.13](#)).
- An alert in the event that the participant is hospitalized.
- Visit reminders.
- Messages of thanks and encouragement from the study team.
- A platform for recording local reactions and systemic events (reactogenicity e-diary) – see [Section 8.2.2](#).

If a participant or his/her parent(s)/legal guardian, as appropriate, is not actively completing either the reactogenicity or COVID-19 illness e-diary, the investigator or designee is required to contact the participant or his/her parent(s)/legal guardian, as appropriate, to ascertain why and also to obtain details of any missed events.

8.15. SARS-CoV-2 NAAT Results From Visits 1 and 2 and Potential COVID-19 Illness Visits

Nasal (midturbinate) swabs for SARS-CoV-2 NAAT are obtained at:

- Visits 1 and 2: To determine whether a participant will be included in efficacy analyses of those with no serological or virological evidence (up to 7 or 14 days after receipt of the second dose, depending on the objective) of past SARS-CoV-2 infection.
- Potential COVID-19 illness visits: To determine whether symptoms experienced by the participant fulfill the COVID-19 case definition.

Research laboratory-generated positive results from the Visit 1 and Visit 2 swabs, and all results from the illness visit swabs, will be provided to the site once available, but this will not be in real time and cannot be relied upon to direct clinical care. Therefore, the participant should be directed to seek additional testing through his/her primary healthcare providers at a licensed clinical laboratory when exhibiting potential COVID-19 symptoms or otherwise

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receiving a positive result and counseled on whether to take any precautionary measures pending confirmatory testing.

Participants who have a positive SARS-CoV-2 NAAT result prior to Visit 2 should be handled as follows:

- Positive SARS-CoV-2 test with no symptoms, either at Visit 1 or any time between Visit 1 and Visit 2: A positive test in an asymptomatic participant does not meet exclusion criterion 5; therefore, Vaccination 2 should proceed as normal.
- Confirmed COVID-19 (ie, symptoms and positive SARS-CoV-2 test): This meets exclusion criterion 5; therefore, Vaccination 2 should not be given but the participant should remain in the study.

9. STATISTICAL CONSIDERATIONS

Methodology for summary and statistical analyses of the data collected in this study is described here and further detailed in a statistical analysis plan (SAP), which will be maintained by the sponsor. The SAP may modify what is outlined in the protocol where appropriate; however, any major modifications of the primary endpoint definitions or their analyses will also be reflected in a protocol amendment.

9.1. Estimands and Statistical Hypotheses

9.1.1. Estimands

The estimand corresponding to each primary, secondary, and tertiary/exploratory objective is described in the table in [Section 3](#).

In the primary safety objective evaluations, missing reactogenicity e-diary data will not be imputed. Missing AE dates will be imputed according to Pfizer safety rules. No other missing information will be imputed in the safety analysis.

The estimands to evaluate the immunogenicity objectives are based on evaluable populations for immunogenicity ([Section 9.3](#)). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. Missing antibody results will not be imputed. Immunogenicity results that are below the LLOQ will be set to $0.5 \times \text{LLOQ}$ in the analysis; this may be adjusted once additional data on the assay characteristics become available.

The estimands to evaluate the efficacy objectives are based on evaluable populations for efficacy ([Section 9.3](#)). These estimands estimate the vaccine effect in the hypothetical setting where participants follow the study schedules and protocol requirements as directed. In addition, VE will also be analyzed by all-available efficacy population. Missing laboratory results will not be imputed for the primary analysis, but missing data imputation for the efficacy endpoint may be performed as a sensitivity analysis.

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9.1.2. Statistical Hypotheses

9.1.2.1. Statistical Hypothesis Evaluation for Efficacy

Phase 2/3 of the study has 2 primary efficacy endpoints evaluating VE, which is defined as $VE = 100 \times (1 - IRR)$. IRR is calculated as the ratio of first confirmed COVID-19 illness rate in the vaccine group to the corresponding illness rate in the placebo group. In Phase 2/3, the assessment of VE will be based on posterior probabilities of $VE_1 > 30\%$ and $VE_2 > 30\%$. VE_1 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in participants without evidence of infection before vaccination, and VE_2 represents VE for prophylactic BNT162b2 against confirmed COVID-19 in all participants after vaccination.

For participants with multiple confirmed cases, only the first case will contribute to the VE calculation for each hypothesis. VE_1 and VE_2 will be evaluated sequentially to control the overall type I error to the desired level of 2.5%. VE is demonstrated if there is sufficient evidence (posterior probability) that either $VE_1 > 30\%$ or both VE_1 and VE_2 are $> 30\%$. The assessment for the primary analysis will be based on posterior probability using a Bayesian model.

9.1.2.2. Statistical Hypothesis Evaluation for Immunogenicity

One of the secondary objectives in the Phase 3 part of the study is to evaluate noninferiority of the immune response to prophylactic BNT162b2 in participants 12 to 15 years of age compared to the response in participants 16 to 25 years of age at 1 month after Dose 2. The (Dose 2) evaluable immunogenicity population will be used for the following hypothesis testing:

$$H_0: \ln(\mu_2) - \ln(\mu_1) \leq \ln(0.67)$$

where $\ln(0.67)$ corresponds to a 1.5-fold margin for noninferiority, $\ln(\mu_2)$ and $\ln(\mu_1)$ are the natural log of the geometric mean of SARS-CoV-2 neutralizing titers from BNT162b2 recipients 12 to 15 years of age and 16 to 25 years of age, respectively, measured 1 month after Dose 2. If the lower limit of the 95% CI for the GMR (12-15 years of age to 16-25 years of age) is > 0.67 , the noninferiority objective is met.

9.2. Sample Size Determination

The study sample size for Phase 1 of the study is not based on any statistical hypothesis testing. Phase 1 comprises 15 participants (randomization ratio of 4:1 so that 12 receive active vaccine and 3 receive placebo) per group; 13 vaccine groups are studied, corresponding to a total of 195 participants.

For Phase 2/3, with assumptions of a true VE of 60% after the second dose of investigational product, a total of approximately 164 first confirmed COVID-19 illness cases will provide 90% power to conclude true $VE > 30\%$ with high probability, allowing early stopping for efficacy at the IA. This would be achieved with 17,600 evaluable participants per group or 21,999 vaccine recipients randomized in a 1:1 ratio with placebo, for a total sample size of 43,998, based on the assumption of a 1.3% illness rate per year in the placebo group, accrual of 164 first primary-endpoint cases within 6 months, and 20% of the participants being

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nonevaluable or having serological evidence of prior infection with SARS-CoV-2, potentially making them immune to further infection. Dependent upon the evolution of the pandemic, it is possible that the COVID-19 attack rate may be much higher, in which case accrual would be expected to be more rapid, enabling the study's primary endpoint to be evaluated much sooner. The total number of participants enrolled in Phase 2/3 may vary depending on the incidence of COVID-19 at the time of the enrollment, the true underlying VE, and a potential early stop for efficacy or futility.

In Phase 3, approximately 2000 participants are anticipated to be 12 to 15 years of age. A random sample of 250 participants will be selected for each of the 2 age groups (12 to 15 years and 16 to 25 years) as an immunogenicity subset for the noninferiority assessment. With the standard deviation and observed GMT difference assumed in the power analysis below, a sample size of 200 evaluable participants (or 250 vaccine recipients) per age group will provide a power of 90.8% to declare the noninferiority of adolescents to 16- to 25-year-olds in terms of neutralizing antibody GMR, 1 month after the second dose (see Table 4).

Table 4. Power Analysis for Noninferiority Assessment

Criteria	Standard Deviation (Log Value) ^a	Assumed Observed GMT Difference (Log Scale)	Number of Evaluable Participants per Age Group	Power ^b
Lower limit of 95% CI for GMR (12-15/16-25) >0.67	0.623	-0.2	200	90.8%

Abbreviation: GMR = geometric mean ratio.

- a. Reference: 1 month after Dose 2, BNT162b2 (30 µg), 18- to 55-year age group (C4591001 Phase 1, N=12). Calculation may be updated if additional information becomes available to better estimate the standard deviation.
- b. At 0.05 alpha level (2-sided).

For safety outcomes, Table 5 shows the probability of observing at least 1 AE for a given true event rate of a particular AE, for various sample sizes. For example, if the true AE rate is 10%, with 12 participants in a vaccine group, there is 72% probability of observing at least 1 AE.

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Table 5. Probability of Observing at Least 1 AE by Assumed True Event Rates With Different Sample Sizes

Assumed True Event Rate of an AE	N=12	N=45	N=180	N=1000	N=3000	N=6000	N=9000	N=15000
0.01%	0.00	0.00	0.02	0.10	0.26	0.45	0.59	0.78
0.02%	0.00	0.01	0.04	0.18	0.45	0.70	0.83	0.95
0.04%	0.00	0.02	0.07	0.33	0.70	0.91	0.97	>0.99
0.06%	0.01	0.03	0.10	0.45	0.83	0.97	0.99	>0.99
0.08%	0.01	0.04	0.13	0.55	0.91	0.99	0.99	>0.99
0.10%	0.01	0.04	0.16	0.63	0.95	0.99	0.99	>0.99
0.15%	0.02	0.07	0.24	0.78	0.99	0.99	>0.99	>0.99
0.20%	0.02	0.09	0.30	0.86	>0.99	>0.99	>0.99	>0.99
0.25%	0.03	0.11	0.36	0.92	>0.99	>0.99	>0.99	>0.99
0.30%	0.04	0.13	0.42	0.95	>0.99	>0.99	>0.99	>0.99
0.35%	0.04	0.15	0.47	0.97	>0.99	>0.99	>0.99	>0.99
0.50%	0.06	0.20	0.59	0.99	>0.99	>0.99	>0.99	>0.99
1.00%	0.11	0.36	0.84	>0.99	>0.99	>0.99	>0.99	>0.99
2.00%	0.22	0.60	0.97	>0.99	>0.99	>0.99	>0.99	>0.99
3.00%	0.31	0.75	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
5.00%	0.46	0.90	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
7.00%	0.58	0.96	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99
10.00%	0.72	0.99	>0.99	>0.99	>0.99	>0.99	>0.99	>0.99

Note: N = number in sample.

9.3. Analysis Sets

For purposes of analysis, the following populations are defined:

Population	Description
Enrolled	All participants who have a signed ICD.
Randomized	All participants who are assigned a randomization number in the IWR system.
Dose 1 evaluable immunogenicity	For Phase 1 only, all eligible randomized participants who receive the vaccine to which they are randomly assigned at the first dose, have at least 1 valid and determinate immunogenicity result after Dose 1, have blood collection within an appropriate window after Dose 1, and have no other important protocol deviations as determined by the clinician.
Dose 2 evaluable immunogenicity	All eligible randomized participants who receive 2 doses of the vaccine to which they are randomly assigned, within the predefined window, have at least 1 valid and determinate immunogenicity result after Dose 2, have blood collection within an appropriate window after Dose 2, and have no other important protocol deviations as determined by the clinician.

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Population	Description
Dose 1 all-available immunogenicity	For Phase 1 only: all randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 1 but before Dose 2.
Dose 2 all-available immunogenicity	All randomized participants who receive at least 1 dose of the study intervention with at least 1 valid and determinate immunogenicity result after Dose 2.
Evaluable efficacy	All eligible randomized participants who receive all vaccination(s) as randomized within the predefined window and have no other important protocol deviations as determined by the clinician.
All-available efficacy	<ol style="list-style-type: none"> 1. All randomized participants who receive at least 1 vaccination. 2. All randomized participants who complete 2 vaccination doses.
Safety	All randomized participants who receive at least 1 dose of the study intervention.

9.4. Statistical Analyses

The SAP will be developed and finalized before database lock for any of the planned analyses in [Section 9.5.1](#). It will describe the participant populations to be included in the analyses and the procedures for accounting for missing, unused, and spurious data. This section provides a summary of the planned statistical analyses of the primary, secondary, and tertiary/exploratory endpoints.

9.4.1. Immunogenicity Analyses

Immunogenicity samples will be drawn for all participants. Immunogenicity analyses will be based upon results from appropriately sized subsets of samples, according to the purpose.

The statistical analysis of immunogenicity results will be primarily based on the evaluable immunogenicity populations as defined in [Section 9.3](#). Serology data after a postbaseline positive SARS-CoV-2 test result will not be included in the analysis based on the evaluable immunogenicity populations.

An additional analysis will be performed based on the all-available populations if there is a large enough difference in sample size between the all-available immunogenicity population and the evaluable immunogenicity population. Participants will be summarized according to the vaccine group to which they were randomized.

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Endpoint	Statistical Analysis Methods
Secondary immunogenicity	<p data-bbox="513 260 1419 369">Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level</p> <p data-bbox="513 405 1419 548">For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points:</p> <ul data-bbox="558 583 1419 653" style="list-style-type: none"> • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12 and 24 months after Dose 2 <p data-bbox="513 688 1419 905">Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits.</p> <p data-bbox="513 940 1419 1010">GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level</p> <p data-bbox="513 1045 1419 1188">For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points:</p> <ul data-bbox="558 1224 1419 1293" style="list-style-type: none"> • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 <p data-bbox="513 1329 1419 1619">GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student’s t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.</p> <p data-bbox="513 1654 1419 1766">Percentage of participants with ≥ 4-fold rise in SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level</p> <p data-bbox="513 1801 1419 1871">For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, percentages (and 2-sided 95% CIs) of</p>

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Endpoint	Statistical Analysis Methods
	<p>participants with ≥ 4-fold rise will be provided for each investigational product within each group at each of the following time points:</p> <ul style="list-style-type: none"> • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 <p>The Clopper-Pearson method will be used to calculate the CIs.</p> <p>GMR of SARS-CoV-2 neutralizing titer to S1-binding IgG level and to RBD-binding IgG level</p> <p>For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points:</p> <ul style="list-style-type: none"> • Phase 1: 7 and 21 days after Dose 1; 7 and 14 days and 1, 6, 12, and 24 months after Dose 2 <p>GMRs will be limited to participants with nonmissing values for both SARS-CoV-2 neutralizing titers and S1-binding IgG level/RBD-binding IgG level at each time point. The GMR will be calculated as the mean of the difference of logarithmically transformed assay results (eg, SARS-CoV-2 neutralizing titers minus S1-binding IgG level for each participant) and exponentiating the mean. Two-sided CIs will be obtained by calculating CIs using Student's t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.</p> <p>For all the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.</p>
<p>Secondary immunogenicity (noninferiority in the 12- to 15-year age group compared to the</p>	<p>GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those 16 to 25 years of age</p> <p>For participants with no serological or virological evidence (up to 1 month after receipt of the second dose) of past SARS-CoV-2 infection, the GMR of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age to those in participants 16 to 25 years of age and</p>

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Endpoint	Statistical Analysis Methods
16- to 25-year age group)	<p>2-sided 95% CIs will be provided at 1 month after Dose 2 for noninferiority assessment.</p> <p>The GMR and its 2-sided 95% CI will be derived by calculating differences in means and CIs on the natural log scale of the titers based on the Student's t-distribution and then exponentiating the results. The difference in means on the natural log scale will be 12 to 15 years minus 16 to 25 years. Noninferiority will be declared if the lower bound of the 2-sided 95% CI for the GMR is greater than 0.67.</p> <p>This analysis will be based on Dose 2 evaluable immunogenicity populations. An additional analysis may be performed based on the Dose 2 all-available immunogenicity population if needed. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.</p>
Exploratory immunogenicity	<p>Geometric mean titers/concentrations (GMTs/GMCs) of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level</p> <p>For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, GMTs/GMCs and 2-sided 95% CIs will be provided for each investigational product within each group before vaccination and at each of the following time points in Phase 2/3:</p> <ul style="list-style-type: none"> • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination <p>Geometric means will be calculated as the mean of the assay results after making the logarithm transformation and then exponentiating the mean to express results on the original scale. Two-sided 95% CIs will be obtained by taking natural log transforms of concentrations/titers, calculating the 95% CI with reference to the t-distribution, and then exponentiating the confidence limits.</p> <p>GMFRs of SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level</p> <p>For SARS-CoV-2 neutralizing titers, S1-binding IgG levels, and RBD-binding IgG levels, the GMFRs and 2-sided 95% CIs will be provided for each investigational product within each group at each of the following time points in Phase 2/3:</p>

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Endpoint	Statistical Analysis Methods
	<ul style="list-style-type: none"> • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination <p>GMFRs will be limited to participants with nonmissing values prior to the first dose and at the postvaccination time point. The GMFR will be calculated as the mean of the difference of logarithmically transformed assay results (later time point – earlier time point) and exponentiating the mean. The associated 2-sided CIs will be obtained by calculating CIs using Student’s t-distribution for the mean difference of the logarithmically transformed assay results and exponentiating the confidence limits.</p> <p>Percentage of participants with antibody levels \geq predefined threshold(s) for SARS-CoV-2 serological parameters</p> <p>For SARS-CoV-2 neutralizing titers, S1-binding IgG levels and/or RBD-binding IgG levels, N-binding antibody, and SARS-CoV-2 detection by NAAT, percentages (and 2-sided 95% CIs) of participants with antibody levels \geq predefined threshold(s) will be provided for each investigational product within each group at baseline and each of the following time points in Phase 2/3:</p> <ul style="list-style-type: none"> • 1, 6, 12, and 24 months after completion of vaccination in participants with and without serological or virological evidence of SARS-CoV-2 infection before vaccination <p>The Clopper-Pearson method will be used to calculate the CIs.</p> <p>Percentage of participants with the immune response (non-S) to SARS-CoV-2 for N-binding antibody at the time points when data are available</p> <p>The Clopper-Pearson method will be used to calculate the CIs.</p> <p>For all of the immunogenicity endpoints, the analysis will be based on the Dose 1 and Dose 2 evaluable immunogenicity populations. An additional analysis will be performed based on the all-available immunogenicity populations if there is a large enough difference in sample size between the all-available immunogenicity populations and the evaluable immunogenicity populations. Participants will be summarized according to the vaccine group to which they were randomized. Missing serology data will not be imputed.</p>

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Endpoint	Statistical Analysis Methods
	<p>RCDCs for immunogenicity results</p> <p>Empirical RCDCs will be provided for SARS-CoV-2 neutralizing titers, S1-binding IgG level, and RBD-binding IgG level after Dose 1 and after Dose 2.</p>

9.4.2. Efficacy Analyses

The evaluable efficacy population will be the primary analysis population for all efficacy analyses. Additional analyses based on the all-available efficacy population will be performed.

Endpoint	Statistical Analysis Methods
Primary efficacy	<p>Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p>VE will be estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model.</p> <p>After the above objective is met, the second primary endpoint will be evaluated as below.</p> <p>Ratio of confirmed COVID-19 illness from 7 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p>VE will be estimated by $100 \times (1 - \text{IRR})$, where IRR is the calculated ratio of confirmed COVID-19 illness per 1000 person-years follow-up in the active vaccine group to the corresponding illness rate in the placebo group from 7 days after the second dose. VE will be analyzed using a beta-binomial model.</p> <p>The efficacy analysis for the first primary objective evaluation will be based on the participants without evidence of infection before vaccination and included in the evaluable efficacy population and in the all-available efficacy population.</p>

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Endpoint	Statistical Analysis Methods
	<p>The efficacy analysis for the second primary objective evaluation will be based on all participants included in the evaluable efficacy population and in the all-available efficacy population.</p> <p>For the primary endpoint analysis, missing efficacy data will not be imputed. A sensitivity analysis will be performed by imputing missing values with the assumption of MAR. A missing efficacy endpoint may be imputed based on predicted probability using the fully conditional specification method. Other imputation methods without the MAR assumption may be explored. The details will be provided in the SAP.</p>
Secondary	<p>First: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p>Second: Ratio of confirmed COVID-19 illness from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 14 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p>Third and fourth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p>Fifth and sixth: Ratios of confirmed severe COVID-19 illness from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p>These secondary efficacy objectives will be evaluated sequentially in the order specified above after the primary objectives are met. The analysis will be based on the evaluable efficacy population and the all-available efficacy population. The analysis methodology used for the primary efficacy endpoints will be applied for the analysis of the above secondary efficacy endpoints.</p> <p>The following secondary efficacy endpoints will be evaluated descriptively with 95% CIs.</p> <p>Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the</p>

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Endpoint	Statistical Analysis Methods
	<p data-bbox="513 264 1360 405">second dose per 1000 person-years of follow-up in participants without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p data-bbox="513 443 1409 657">Ratios of confirmed COVID-19 illness (according to the CDC-defined symptoms) from 7 days and from 14 days after the second dose per 1000 person-years of follow-up in participants with and without evidence of infection (prior to 7 days or 14 days after receipt of the second dose) for the active vaccine group to the placebo group</p> <p data-bbox="513 695 1390 835">VE = $100 \times (1 - \text{IRR})$ will be estimated with confirmed COVID-19 illness according to the CDC-defined symptoms from 7 days or from 14 days after the second dose. The 2-sided 95% CI for VE will be derived using the Clopper-Pearson method as described by Agresti.⁹</p> <p data-bbox="513 873 1049 905">Missing efficacy data will not be imputed.</p>

9.4.3. Safety Analyses

Endpoint	Statistical Analysis Methods
Primary	<p data-bbox="513 1104 1409 1350">Descriptive statistics will be provided for each reactogenicity endpoint for each dose and vaccine group. Local reactions and systemic events from Day 1 through Day 7 after each vaccination will be presented by severity and cumulatively across severity levels. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 95% CIs.</p> <p data-bbox="513 1388 1377 1675">For Phase 1, descriptive statistics will be provided for abnormal hematology and chemistry laboratory values at 1 and 7 days after Dose 1 and 7 days after Dose 2, including grading shifts in hematology and chemistry laboratory assessments between baseline and 1 and 7 days after Dose 1, and before Dose 2 and 7 days after Dose 2. Descriptive summary statistics will include counts and percentages of participants with the indicated endpoint and the associated Clopper-Pearson 2-sided 95% CIs.</p> <p data-bbox="513 1713 1401 1879">AEs will be categorized according to the Medical Dictionary for Regulatory Activities (MedDRA) terms. A 3-tier approach will be used to summarize AEs in Phase 2/3. Under this approach AEs are classified into 1 of 3 tiers: (1) Tier 1 events are prespecified events of clinical importance and are identified in a list in the product's safety</p>

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Endpoint	Statistical Analysis Methods
	<p>review plan; (2) Tier 2 events are those that are not Tier 1 but are considered “relatively common”; a MedDRA preferred term is defined as a Tier 2 event if there are at least 1% of participants in at least 1 vaccine group reporting the event; and (3) Tier 3 events are those that are neither Tier 1 nor Tier 2 events. For both Tier 1 and Tier 2 events, 2-sided 95% CIs for the difference between the vaccine and placebo groups in the percentage of participants reporting the events based on the Miettinen and Nurminen method¹⁰ will be provided. In addition, for Tier 1 events, the asymptotic p-values will also be presented for the difference between groups in the percentage of participants reporting the events, based on the same test statistic and under the assumption that the test statistic is asymptotically normally distributed.</p> <p>Descriptive summary statistics (counts, percentages, and associated Clopper-Pearson 95% CIs) will be provided for any AE events for each vaccine group.</p> <p>SAEs will be categorized according to MedDRA terms. Counts, percentages, and the associated Clopper-Pearson 95% CIs of SAEs from Dose 1 to 6 months after the last dose will be provided for each vaccine group.</p> <p>The safety analyses are based on the safety population. Participants will be summarized by vaccine group according to the investigational products they actually received. Missing reactogenicity e-diary data will not be imputed; missing AE dates will be handled according to the Pfizer safety rules.</p>
Secondary	Not applicable (N/A)
Exploratory	N/A

9.4.4. Other Analyses

The ratios of (GMFR A to GMFR B) and (GMFR A to GMFR C) may be explored, where GMFR A is the geometric mean of the ratio of the SARS-CoV-2 neutralizing titer at the postvaccination time point to the corresponding titer at the prevaccination time point, GMFR B is the geometric mean of the ratio of the S1-binding IgG level at the postvaccination time point to the corresponding IgG level at the prevaccination time point, and GMFR C is the geometric mean of the ratio of the RBD-binding IgG level at the postvaccination time point to the corresponding antibody level at the prevaccination time point.

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The safety data and immunogenicity results for individuals with confirmed stable HIV disease will be summarized descriptively. Furthermore, VE may be assessed if there is a sufficient number of COVID-19 cases in this group of participants.

The safety and immunogenicity results for individuals 16 to 55 years of age vaccinated with study intervention produced by manufacturing “Process 1” and each lot of “Process 2” will be summarized descriptively. A random sample of 250 participants from those vaccinated with study intervention produced by manufacturing “Process 1” will be selected randomly for the analysis.

9.5. Interim Analyses

As this is a sponsor open-label study during Phase 1, the sponsor may conduct unblinded reviews of the data during the course of the study for the purpose of safety assessment, facilitating dose escalation decisions, and/or supporting clinical development.

During Phase 2/3, 4 IAs were planned to be performed by an unblinded statistical team after accrual of at least 32, 62, 92, and 120 cases. However, for operational reasons, the first planned IA was not performed. Consequently, 3 IAs are now planned to be performed after accrual of at least 62, 92, and 120 cases. At these IAs, futility and VE with respect to the first primary endpoint will be assessed as follows:

- VE for the first primary objective will be evaluated. Overwhelming efficacy will be declared if the first primary study objective is met. The criteria for success at an interim analysis are based on the posterior probability (ie, $P[VE > 30\% | \text{data}]$) at the current number of cases. Overwhelming efficacy will be declared if the posterior probability is higher than the success threshold. The success threshold for each interim analysis will be calibrated to protect overall type I error at 2.5%. Additional details about the success threshold or boundary calculation at each interim analysis will be provided in the SAP.
- The study will stop for lack of benefit (futility) if the predicted probability of success at the final analysis or study success is $< 5\%$. The posterior predictive POS will be calculated using a beta-binomial model. The futility assessment will be performed for the first primary endpoint and the futility boundary may be subject to change to reflect subsequent program-related decisions by the sponsor.
- Efficacy and futility boundaries will be applied in a nonbinding way.

Bayesian approaches require specification of a prior distribution for the possible values of the unknown vaccine effect, thereby accounting for uncertainty in its value. A minimally informative beta prior, $\text{beta}(0.700102, 1)$, is proposed for $\theta = (1-VE)/(2-VE)$. The prior is centered at $\theta = 0.4118$ (VE=30%) which can be considered pessimistic. The prior allows considerable uncertainty; the 95% interval for θ is (0.005, 0.964) and the corresponding 95% interval for VE is (-26.2, 0.995).

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Table 6 illustrates the boundary for efficacy and futility if, for example, IAs are performed after accrual of 32, 62, 92, and 120 cases in participants without evidence of infection before vaccination. Note that although the first IA was not performed, the statistical criterion for demonstrating success (posterior probability threshold) at the interim (>0.995) and final (>0.986) analyses remains unchanged. Similarly, the futility boundaries are not changed.

Table 6. Interim Analysis Plan and Boundaries for Efficacy and Futility

Analysis	Number of Cases	Success Criteria ^a	Futility Boundary
		VE Point Estimate (Case Split)	VE Point Estimate (Case Split)
IA1	32	76.9% (6:26)	11.8% (15:17)
IA2	62	68.1% (15:47)	27.8% (26:36)
IA3	92	62.7% (25:67)	38.6% (35:57)
IA4	120	58.8% (35:85)	N/A
Final	164	52.3% (53:111)	

Abbreviations: IA = interim analysis; N/A = not applicable; VE = vaccine efficacy.

Note: Case split = vaccine : placebo.

- a. Interim efficacy claim: $P(\text{VE} > 30\% | \text{data}) > 0.995$; success at the final analysis: $P(\text{VE} > 30\% | \text{data}) > 0.986$.

Additional design operating characteristics (the boundary based on the number of cases observed in the vaccine group; the probabilities for efficacy and futility given assumed various VEs with a 1:1 randomization ratio) are listed in Table 7 and Table 8, for IAs conducted at 32, 62, 92, and 120 cases and the final analysis at 164 cases. Although the IA at 32 cases was not performed, the overall Type I error (overall probability of success when true $\text{VE}=30\%$) will still be strictly controlled at 0.025 with the originally proposed success/futility boundaries.

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Table 7. Statistical Design Operating Characteristics: Probability of Success or Failure for Interim Analyses

Vaccine Efficacy (%)	Interim Analysis 1 (Total Cases = 32)		Interim Analysis 2 (Total Cases = 62)		Interim Analysis 3 (Total Cases = 92)		Interim Analysis 4 (Total Cases = 120)
	Probability of Success (Cases in Vaccine Group ≤6)	Probability of Failure (Cases in Vaccine Group ≥15)	Probability of Success (Cases in Vaccine Group ≤15)	Probability of Failure (Cases in Vaccine Group ≥26)	Probability of Success (Cases in Vaccine Group ≤25)	Probability of Failure (Cases in Vaccine Group ≥35)	Probability of Success (Cases in Vaccine Group ≤35)
30	0.006	0.315	0.003	0.231	0.002	0.239	0.002
50	0.054	0.078	0.051	0.056	0.063	0.103	0.075
60	0.150	0.021	0.160	0.010	0.175	0.019	0.160
70	0.368	0.003	0.310	<0.001	0.195	0.001	0.085
80	0.722	<0.001	0.238	<0.001	0.037	<0.001	0.003

Table 8. Statistical Design Operating Characteristics: Probability of Success for Final Analysis and Overall

Vaccine Efficacy (%)	Final Analysis (Total Cases = 164)	Overall Probability of Success
	Probability of Success (Cases in Vaccine Group ≤53)	
30	0.007	0.021
50	0.196	0.439
60	0.220	0.866
70	0.036	>0.999
80	<0.001	>0.999

If neither success nor futility has been declared after all IAs, the final analysis will be performed and the first primary objective will have been met if there are 53 or fewer cases observed in the vaccine group out of a total of 164 first confirmed cases from 7 days after receipt of the second dose of investigational product onwards.

Only the first primary endpoint will be analyzed at IA. If the first primary objective is met, the second primary objective will be evaluated at the final analysis. After the primary objectives are met, the first 6 secondary VE endpoints (confirmed COVID-19 occurring from 14 days after the second dose in participants without evidence of infection and in all participants, confirmed severe COVID-19 occurring from 7 days and from 14 days after the second dose in participants without evidence of infection and in all participants) will be evaluated sequentially in the stated order, by the same method used for the evaluation of primary VE endpoints. Success thresholds for secondary VE endpoints will be appropriately chosen to control overall Type I error at 2.5%. Further details will be provided in the SAP. The remaining secondary VE endpoints will be evaluated descriptively to calculate the observed VE with 95% CIs.

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9.5.1. Analysis Timing

Statistical analyses will be carried out when the following data are available:

- Complete safety and immunogenicity analysis approximately 1 month after Dose 2 for Phase 1.
- Safety data through 7 days after Dose 2 and immunogenicity data through 1 month after Dose 2 from the first 360 participants enrolled (180 to active vaccine and 180 to placebo, stratified equally between 18 to 55 years and >55 to 85 years) in Phase 2/3.
- Safety data through 1 month after Dose 2 from at least 6000 participants enrolled (3000 to active vaccine and 3000 to placebo) in Phase 2/3. Additional analyses of safety data (with longer follow-up and/or additional participants) may be conducted if required for regulatory purposes.
- IAs for efficacy after accrual of at least 62, 92, and 120 cases and fertility after accrual of at least 62 and 92 cases.
- Safety data through 1 month after Dose 2 and noninferiority comparison of SARS-CoV-2 neutralizing titers in participants 12 to 15 years of age compared to those in participants 16 to 25 years of age, 1 month after Dose 2.
- Descriptive analysis of immunogenicity and safety of “Process 1” and “Process 2” material, 1 month after Dose 2.
- Complete safety and immunogenicity analysis approximately 6 months after Dose 2 for all participants in Phase 2/3.
- Complete efficacy and persistence-of-immunogenicity analysis after complete data are available or at the end of the study.

All analyses conducted on Phase 2/3 data while the study is ongoing will be performed by an unblinded statistical team.

9.6. Data Monitoring Committee or Other Independent Oversight Committee

This study will use an IRC, a DMC, and a group of internal case reviewers. The IRC is independent of the study team and includes only internal members. The DMC is independent of the study team and includes only external members. The IRC and DMC charters describe the role of the IRC and DMC in more detail.

The responsibilities of the IRC are only in Phase 1 and will include:

- Review of safety data to permit dose escalations in the 18- to 55-year age cohort
- Review of safety data in the case of a stopping rule being met

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- Review of safety and/or immunogenicity data to:
 - Allow groups of participants of 65 to 85 years of age to proceed
 - Select vaccine candidate/dose level(s) to proceed into Phase 2/3. Data supporting the selection, including results for both binding antibody levels and neutralizing titers, and the ratio between them, will also be submitted to the FDA for review
- Review of any available safety and/or immunogenicity data generated during the course of this study, or the BioNTech study conducted in Germany, to determine:
 - Whether any groups may not be started
 - Whether any groups may be terminated early
 - Whether any groups may be added with dose levels below the lowest stated dose or intermediate between the lowest and highest stated doses
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1

The DMC will be responsible for ongoing monitoring of the safety of participants in the study according to the charter. This may include, but is not limited to:

- Contemporaneous review of related AEs up to 1 month after completion of the vaccination schedule
- Contemporaneous review of all SAEs up to 6 months after completion of the vaccination schedule
- Contemporaneous review of all NAAT-confirmed COVID-19 illnesses in Phase 1
- At the time of the planned IAs, and ad hoc if requested by the unblinded team, review of cases of COVID-19 for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups

The recommendations made by the DMC to alter the conduct of the study will be forwarded to the appropriate Pfizer personnel for final decision. Pfizer will forward such decisions, which may include summaries of aggregate analyses of safety data, to regulatory authorities, as appropriate.

Three blinded case reviewers (medically qualified Pfizer staff members) will review all potential COVID-19 illness events. If a NAAT-confirmed case in Phase 2/3 may be considered severe, or not, solely on the basis of “significant acute renal, hepatic, or neurologic dysfunction,” the blinded data will be reviewed by the case reviewers to assess whether the criterion is met; the majority opinion will prevail.

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10. SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1. Appendix 1: Regulatory, Ethical, and Study Oversight Considerations

10.1.1. Regulatory and Ethical Considerations

This study will be conducted in accordance with the protocol and with the following:

- Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and CIOMS International Ethical Guidelines;
- Applicable ICH GCP guidelines;
- Applicable laws and regulations, including applicable privacy laws.

The protocol, protocol amendments, ICD, SRSD(s), and other relevant documents (eg, advertisements) must be reviewed and approved by the sponsor and submitted to an IRB/EC by the investigator and reviewed and approved by the IRB/EC before the study is initiated.

Any amendments to the protocol will require IRB/EC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

The investigator will be responsible for the following:

- Providing written summaries of the status of the study to the IRB/EC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/EC;
- Notifying the IRB/EC of SAEs or other significant safety findings as required by IRB/EC procedures;
- Providing oversight of the conduct of the study at the site and adherence to requirements of 21 CFR, ICH guidelines, the IRB/EC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations.

10.1.1.1. Reporting of Safety Issues and Serious Breaches of the Protocol or ICH GCP

In the event of any prohibition or restriction imposed (ie, clinical hold) by an applicable regulatory authority in any area of the world, or if the investigator is aware of any new information that might influence the evaluation of the benefits and risks of the study intervention, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study participants against any immediate hazard, and of any serious breaches of this protocol or of ICH GCP that the investigator becomes aware of.

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10.1.2. Informed Consent Process

The investigator or his/her representative will explain the nature of the study to the participant or his or her parent(s)/legal guardian and answer all questions regarding the study. The participant or his or her parent(s)/legal guardian should be given sufficient time and opportunity to ask questions and to decide whether or not to participate in the trial.

Participants must be informed that their participation is voluntary. Participants or their parent(s)/legal guardian will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, HIPAA requirements, where applicable, and the IRB/EC or study center.

The investigator must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about the nature and objectives of the study, the sharing of data related to the study, and possible risks associated with participation, including the risks associated with the processing of the participant's personal data.

The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the sponsor, by appropriate IRB/EC members, and by inspectors from regulatory authorities.

The investigator further must ensure that each study participant or his or her parent(s)/legal guardian is fully informed about his or her right to access and correct his or her personal data and to withdraw consent for the processing of his or her personal data.

The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICD.

Participants must be reconsented to the most current version of the ICD(s) during their participation in the study.

A copy of the ICD(s) must be provided to the participant or his or her parent(s)/legal guardian. Participants who are rescreened are required to sign a new ICD.

Unless prohibited by local requirements or IRB/EC decision, the ICD will contain a separate section that addresses the use of samples for optional additional research. The optional additional research does not require the collection of any further samples. The investigator or authorized designee will explain to each participant the objectives of the additional research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period.

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10.1.3. Data Protection

All parties will comply with all applicable laws, including laws regarding the implementation of organizational and technical measures to ensure protection of participant data.

Participants' personal data will be stored at the study site in encrypted electronic and/or paper form and will be password protected or secured in a locked room to ensure that only authorized study staff have access. The study site will implement appropriate technical and organizational measures to ensure that the personal data can be recovered in the event of disaster. In the event of a potential personal data breach, the study site will be responsible for determining whether a personal data breach has in fact occurred and, if so, providing breach notifications as required by law.

To protect the rights and freedoms of participants with regard to the processing of personal data, participants will be assigned a single, participant-specific numerical code. Any participant records or data sets that are transferred to the sponsor will contain the numerical code; participant names will not be transferred. All other identifiable data transferred to the sponsor will be identified by this single, participant-specific code. The study site will maintain a confidential list of participants who participated in the study, linking each participant's numerical code to his or her actual identity and medical record identification. In case of data transfer, the sponsor will protect the confidentiality of participants' personal data consistent with the clinical study agreement and applicable privacy laws.

10.1.4. Dissemination of Clinical Study Data

Pfizer fulfills its commitment to publicly disclose clinical study results through posting the results of studies on www.clinicaltrials.gov (ClinicalTrials.gov), the EudraCT, and/or www.pfizer.com, and other public registries in accordance with applicable local laws/regulations. In addition, Pfizer reports study results outside of the requirements of local laws/regulations pursuant to its SOPs.

In all cases, study results are reported by Pfizer in an objective, accurate, balanced, and complete manner and are reported regardless of the outcome of the study or the country in which the study was conducted.

www.clinicaltrials.gov

Pfizer posts clinical trial results on www.clinicaltrials.gov for Pfizer-sponsored interventional studies (conducted in patients) that evaluate the safety and/or efficacy of a product, regardless of the geographical location in which the study is conducted. These results are submitted for posting in accordance with the format and timelines set forth by US law.

[EudraCT](#)

Pfizer posts clinical trial results on EudraCT for Pfizer-sponsored interventional studies in accordance with the format and timelines set forth by EU requirements.

www.pfizer.com

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Pfizer posts public disclosure synopses (CSR synopses in which any data that could be used to identify individual participants have been removed) on www.pfizer.com for Pfizer-sponsored interventional studies at the same time the corresponding study results are posted to www.clinicaltrials.gov.

Documents within marketing authorization packages/submissions

Pfizer complies with the European Union Policy 0070, the proactive publication of clinical data to the EMA website. Clinical data, under Phase 1 of this policy, includes clinical overviews, clinical summaries, CSRs, and appendices containing the protocol and protocol amendments, sample CRFs, and statistical methods. Clinical data, under Phase 2 of this policy, includes the publishing of individual participant data. Policy 0070 applies to new marketing authorization applications submitted via the centralized procedure since 01 January 2015 and applications for line extensions and for new indications submitted via the centralized procedure since 01 July 2015.

Data Sharing

Pfizer provides researchers secure access to patient-level data or full CSRs for the purposes of “bona-fide scientific research” that contributes to the scientific understanding of the disease, target, or compound class. Pfizer will make available data from these trials 24 months after study completion. Patient-level data will be anonymized in accordance with applicable privacy laws and regulations. CSRs will have personally identifiable information redacted.

Data requests are considered from qualified researchers with the appropriate competencies to perform the proposed analyses. Research teams must include a biostatistician. Data will not be provided to applicants with significant conflicts of interest, including individuals requesting access for commercial/competitive or legal purposes.

10.1.5. Data Quality Assurance

All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (eg, laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must ensure that the CRFs are securely stored at the study site in encrypted electronic and/or paper form and are password protected or secured in a locked room to prevent access by unauthorized third parties.

The investigator must permit study-related monitoring, audits, IRB/EC review, and regulatory agency inspections and provide direct access to source data documents. This verification may also occur after study completion. It is important that the investigator(s)

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and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as risk management and mitigation strategies and analytical risk-based monitoring), methods, responsibilities, and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring), are provided in the monitoring plan.

The sponsor or designee is responsible for the data management of this study, including quality checking of the data.

Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.

Records and documents, including signed ICDs, pertaining to the conduct of this study must be retained by the investigator for 15 years after study completion unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the sponsor. No records may be transferred to another location or party without written notification to the sponsor. The investigator must ensure that the records continue to be stored securely for as long as they are maintained.

When participant data are to be deleted, the investigator will ensure that all copies of such data are promptly and irrevocably deleted from all systems.

The investigator(s) will notify the sponsor or its agents immediately of any regulatory inspection notification in relation to the study. Furthermore, the investigator will cooperate with the sponsor or its agents to prepare the investigator site for the inspection and will allow the sponsor or its agent, whenever feasible, to be present during the inspection. The investigator site and investigator will promptly resolve any discrepancies that are identified between the study data and the participant's medical records. The investigator will promptly provide copies of the inspection findings to the sponsor or its agent. Before response submission to the regulatory authorities, the investigator will provide the sponsor or its agents with an opportunity to review and comment on responses to any such findings.

10.1.6. Source Documents

Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the investigator site.

Data reported on the CRF or entered in the eCRF that are from source documents must be consistent with the source documents or the discrepancies must be explained. The

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investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.

Definition of what constitutes source data can be found in the study monitoring plan.

Description of the use of computerized system is documented in the Data Management Plan.

10.1.7. Study and Site Start and Closure

The study start date is the date on which the clinical study will be open for recruitment of participants.

The first act of recruitment is the date of the first participant's first visit and will be the study start date.

The sponsor designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The investigator may initiate study-site closure at any time upon notification to the sponsor or designee if requested to do so by the responsible IRB/EC or if such termination is required to protect the health of study participants.

Reasons for the early closure of a study site by the sponsor may include but are not limited to:

- Failure of the investigator to comply with the protocol, the requirements of the IRB/EC or local health authorities, the sponsor's procedures, or GCP guidelines;
- Inadequate recruitment of participants by the investigator;
- Discontinuation of further study intervention development.

If the study is prematurely terminated or suspended, the sponsor shall promptly inform the investigators, the ECs/IRBs, the regulatory authorities, and any CRO(s) used in the study of the reason for termination or suspension, as specified by the applicable regulatory requirements. The investigator shall promptly inform the participant and should assure appropriate participant therapy and/or follow-up.

Study termination is also provided for in the clinical study agreement. If there is any conflict between the contract and this protocol, the contract will control as to termination rights.

10.1.8. Sponsor's Qualified Medical Personnel

The contact information for the sponsor's appropriately qualified medical personnel for the study is documented in the study contact list located in the supporting study documentation.

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To facilitate access to appropriately qualified medical personnel on study-related medical questions or problems, participants are provided with a contact card at the time of informed consent. The contact card contains, at a minimum, protocol and study intervention identifiers, participant numbers, contact information for the investigator site, and contact details for a contact center in the event that the investigator site staff cannot be reached to provide advice on a medical question or problem originating from another healthcare professional not involved in the participant's participation in the study. The contact number can also be used by investigator staff if they are seeking advice on medical questions or problems; however, it should be used only in the event that the established communication pathways between the investigator site and the study team are not available. It is therefore intended to augment, but not replace, the established communication pathways between the investigator site and the study team for advice on medical questions or problems that may arise during the study. The contact number is not intended for use by the participant directly, and if a participant calls that number, he or she will be directed back to the investigator site.

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10.2. Appendix 2: Clinical Laboratory Tests

The following safety laboratory tests will be performed at times defined in the [SoA](#) section of this protocol. Additional laboratory results may be reported on these samples as a result of the method of analysis or the type of analyzer used by the clinical laboratory, or as derived from calculated values. These additional tests would not require additional collection of blood. Unscheduled clinical laboratory measurements may be obtained at any time during the study to assess any perceived safety issues.

Hematology	Chemistry	Other
Hemoglobin Hematocrit RBC count MCV MCH MCHC Platelet count WBC count Total neutrophils (Abs) Eosinophils (Abs) Monocytes (Abs) Basophils (Abs) Lymphocytes (Abs)	BUN and creatinine AST, ALT Total bilirubin Alkaline phosphatase	<ul style="list-style-type: none"> • Urine pregnancy test (β-hCG) <u>At screening only:</u> <ul style="list-style-type: none"> • Hepatitis B core antibody • Hepatitis B surface antigen • Hepatitis C antibody • Human immunodeficiency virus

Investigators must document their review of each laboratory safety report.

Clinically significant abnormal laboratory findings should be recorded in the AE CRF in accordance with the following grading scale (Table 9).

Table 9. Laboratory Abnormality Grading Scale

Hematology	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
Hemoglobin (Female) - g/dL	11.0 – 12.0	9.5 – 10.9	8.0 – 9.4	<8.0
Hemoglobin (Male) - g/dL	12.5 – 13.5	10.5 – 12.4	8.5 – 10.4	<8.5
WBC increase - cells/mm ³	10,800 – 15,000	15,001 – 20,000	20,001 – 25,000	>25,000
WBC decrease - cells/mm ³	2,500 – 3,500	1,500 – 2,499	1,000 – 1,499	<1,000
Lymphocytes decrease - cells/mm ³	750 – 1,000	500 – 749	250 – 499	<250
Neutrophils decrease - cells/mm ³	1,500 – 2,000	1,000 – 1,499	500 – 999	<500
Eosinophils - cells/mm ³	650 – 1500	1501 - 5000	>5000	Hypereosinophilic
Platelets decreased - cells/mm ³	125,000 – 140,000	100,000 – 124,000	25,000 – 99,000	<25,000

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Table 9. Laboratory Abnormality Grading Scale

Chemistry	Mild (Grade 1)	Moderate (Grade 2)	Severe (Grade 3)	Potentially Life Threatening (Grade 4)
BUN - mg/dL	23 – 26	27 – 31	> 31	Requires dialysis
Creatinine – mg/dL	1.5 – 1.7	1.8 – 2.0	2.1 – 2.5	> 2.5 or requires dialysis
Alkaline phosphate – increase by factor	1.1 – 2.0 x ULN	2.1 – 3.0 x ULN	3.1 – 10 x ULN	>10 x ULN
Liver function tests – ALT, AST increase by factor	1.1 – 2.5 x ULN	2.6 – 5.0 x ULN	5.1 – 10 x ULN	>10 x ULN
Bilirubin – when accompanied by any increase in liver function test - increase by factor	1.1 – 1.25 x ULN	1.26 – 1.5 x ULN	1.51 – 1.75 x ULN	>1.75 x ULN
Bilirubin – when liver function test is normal - increase by factor	1.1 – 1.5 x ULN	1.6 – 2.0 x ULN	2.0 – 3.0 x ULN	>3.0 x ULN

Abbreviations: ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; ULN = upper limit of normal; WBC = white blood cell.

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10.3. Appendix 3: Adverse Events: Definitions and Procedures for Recording, Evaluating, Follow-up, and Reporting

10.3.1. Definition of AE

AE Definition
<ul style="list-style-type: none"> • An AE is any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention. • NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events <u>Meeting</u> the AE Definition
<ul style="list-style-type: none"> • Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital sign measurements), including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the investigator. Any abnormal laboratory test results that meet any of the conditions below must be recorded as an AE: <ul style="list-style-type: none"> • Is associated with accompanying symptoms. • Requires additional diagnostic testing or medical/surgical intervention. • Leads to a change in study dosing (outside of any protocol-specified dose adjustments) or discontinuation from the study, significant additional concomitant drug treatment, or other therapy. • Exacerbation of a chronic or intermittent preexisting condition including either an increase in frequency and/or intensity of the condition. • New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study. • Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction. • Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication. Overdose per se will not be reported as an AE/SAE unless it is an intentional overdose taken with possible suicidal/self-harming intent. Such overdoses should be reported regardless of sequelae.

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Events <u>NOT</u> Meeting the AE Definition
<ul style="list-style-type: none"> • Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the investigator to be more severe than expected for the participant’s condition. • The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant’s condition. • Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE. • Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital). • Anticipated day-to-day fluctuations of preexisting disease(s) or condition(s) present or detected at the start of the study that do not worsen.

10.3.2. Definition of SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

An SAE is defined as any untoward medical occurrence that, at any dose:
a. Results in death
b. Is life-threatening The term “life-threatening” in the definition of “serious” refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.
c. Requires inpatient hospitalization or prolongation of existing hospitalization In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician’s office or outpatient setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether “hospitalization” occurred or was necessary, the AE should be considered serious.

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Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered an AE.

d. Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

e. Is a congenital anomaly/birth defect

f. Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.
- Suspected transmission via a Pfizer product of an infectious agent, pathogenic or nonpathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by pharmacovigilance personnel. Such cases are also considered for reporting as product defects, if appropriate.

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10.3.3. Recording/Reporting and Follow-up of AEs and/or SAEs

AE and SAE Recording/Reporting

The table below summarizes the requirements for recording adverse events on the CRF and for reporting serious adverse events on the Vaccine SAE Report Form to Pfizer Safety. These requirements are delineated for 3 types of events: (1) SAEs; (2) nonserious adverse events (AEs); and (3) exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure.

It should be noted that the Vaccine SAE Report Form for reporting of SAE information is not the same as the AE page of the CRF. When the same data are collected, the forms must be completed in a consistent manner. AEs should be recorded using concise medical terminology and the same AE term should be used on both the CRF and the Vaccine SAE Report Form for reporting of SAE information.

Safety Event	Recorded on the CRF	Reported on the Vaccine SAE Report Form to Pfizer Safety Within 24 Hours of Awareness
SAE	All	All
Nonserious AE	All	None
Exposure to the study intervention under study during pregnancy or breastfeeding, and occupational exposure	All AEs/SAEs associated with exposure during pregnancy or breastfeeding Occupational exposure is not recorded.	All (and EDP supplemental form for EDP) Note: Include all SAEs associated with exposure during pregnancy or breastfeeding. Include all AEs/SAEs associated with occupational exposure.

- When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostic reports) related to the event.
- The investigator will then record all relevant AE/SAE information in the CRF.
- It is **not** acceptable for the investigator to send photocopies of the participant's medical records to Pfizer Safety in lieu of completion of the Vaccine SAE Report Form/AE/SAE CRF page.
- There may be instances when copies of medical records for certain cases are requested by Pfizer Safety. In this case, all participant identifiers, with the

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exception of the participant number, will be redacted on the copies of the medical records before submission to Pfizer Safety.

- The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of Intensity

The investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

GRADE	If required on the AE page of the CRF, the investigator will use the adjectives MILD, MODERATE, SEVERE, or LIFE-THREATENING to describe the maximum intensity of the AE. For purposes of consistency, these intensity grades are defined as follows:	
1	MILD	Does not interfere with participant's usual function.
2	MODERATE	Interferes to some extent with participant's usual function.
3	SEVERE	Interferes significantly with participant's usual function.
4	LIFE-THREATENING	Life-threatening consequences; urgent intervention indicated.

Assessment of Causality

- The investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A “reasonable possibility” of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration, will be considered and investigated.

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- The investigator will also consult the IB and/or product information, for marketed products, in his/her assessment.
- For each AE/SAE, the investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the investigator has minimal information to include in the initial report to the sponsor. However, **it is very important that the investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the sponsor.**
- The investigator may change his/her opinion of causality in light of follow-up information and send an SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.
- If the investigator does not know whether or not the study intervention caused the event, then the event will be handled as “related to study intervention” for reporting purposes, as defined by the sponsor. In addition, if the investigator determines that an SAE is associated with study procedures, the investigator must record this causal relationship in the source documents and CRF, and report such an assessment in the dedicated section of the Vaccine SAE Report Form and in accordance with the SAE reporting requirements.

Follow-up of AEs and SAEs

- The investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the sponsor to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other healthcare providers.
- If a participant dies during participation in the study or during a recognized follow-up period, the investigator will provide Pfizer Safety with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed CRF.
- The investigator will submit any updated SAE data to the sponsor within 24 hours of receipt of the information.

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10.3.4. Reporting of SAEs

SAE Reporting to Pfizer Safety via Vaccine SAE Report Form

- Facsimile transmission of the Vaccine SAE Report Form is the preferred method to transmit this information to Pfizer Safety.
- In circumstances when the facsimile is not working, notification by telephone is acceptable with a copy of the Vaccine SAE Report Form sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the investigator to complete and sign the Vaccine SAE Report Form pages within the designated reporting time frames.

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10.4. Appendix 4: Contraceptive Guidance

10.4.1. Male Participant Reproductive Inclusion Criteria

Male participants are eligible to participate if they agree to the following requirements during the intervention period and for at least 28 days after the last dose of study intervention, which corresponds to the time needed to eliminate reproductive safety risk of the study intervention(s):

- Refrain from donating sperm.

PLUS either:

- Be abstinent from heterosexual intercourse with a female of childbearing potential as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agree to remain abstinent.

OR

- Must agree to use a male condom when engaging in any activity that allows for passage of ejaculate to another person.
- In addition to male condom use, a highly effective method of contraception may be considered in WOCBP partners of male participants (refer to the list of highly effective methods below in [Section 10.4.4](#)).

10.4.2. Female Participant Reproductive Inclusion Criteria

A female participant is eligible to participate if she is not pregnant or breastfeeding, and at least 1 of the following conditions applies:

- Is not a WOCBP (see definitions below in [Section 10.4.3](#)).

OR

- Is a WOCBP and using an acceptable contraceptive method as described below during the intervention period (for a minimum of 28 days after the last dose of study intervention). The investigator should evaluate the effectiveness of the contraceptive method in relationship to the first dose of study intervention.

The investigator is responsible for review of medical history, menstrual history, and recent sexual activity to decrease the risk for inclusion of a woman with an early undetected pregnancy.

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10.4.3. Woman of Childbearing Potential

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before the first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP:

1. Premenarchal.
2. Premenopausal female with 1 of the following:
 - Documented hysterectomy;
 - Documented bilateral salpingectomy;
 - Documented bilateral oophorectomy.

For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), investigator discretion should be applied to determining study entry.

Note: Documentation for any of the above categories can come from the site personnel's review of the participant's medical records, medical examination, or medical history interview. The method of documentation should be recorded in the participant's medical record for the study.

3. Postmenopausal female:
 - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. In addition, a
 - high FSH level in the postmenopausal range must be used to confirm a postmenopausal state in women under 60 years of age and not using hormonal contraception or HRT.
 - Female on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

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10.4.4. Contraception Methods

Contraceptive use by men or women should be consistent with local availability/regulations regarding the use of contraceptive methods for those participating in clinical trials.

1. Implantable progestogen-only hormone contraception associated with inhibition of ovulation.
2. Intrauterine device.
3. Intrauterine hormone-releasing system.
4. Bilateral tubal occlusion.
5. Vasectomized partner:
 - Vasectomized partner is a highly effective contraceptive method provided that the partner is the sole sexual partner of the woman of childbearing potential and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used. The spermatogenesis cycle is approximately 90 days.
6. Combined (estrogen- and progestogen-containing) hormonal contraception associated with inhibition of ovulation:
 - Oral;
 - Intravaginal;
 - Transdermal;
 - Injectable.
7. Progestogen-only hormone contraception associated with inhibition of ovulation:
 - Oral;
 - Injectable.
8. Sexual abstinence:
 - Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.

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9. Progestogen-only oral hormonal contraception where inhibition of ovulation is not the primary mode of action.
10. Male or female condom with or without spermicide.
11. Cervical cap, diaphragm, or sponge with spermicide.
12. A combination of male condom with either cervical cap, diaphragm, or sponge with spermicide (double-barrier methods).

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10.5. Appendix 5: Liver Safety: Suggested Actions and Follow-up Assessments

Potential Cases of Drug-Induced Liver Injury

Humans exposed to a drug who show no sign of liver injury (as determined by elevations in transaminases) are termed “tolerators,” while those who show transient liver injury, but adapt are termed “adaptors.” In some participants, transaminase elevations are a harbinger of a more serious potential outcome. These participants fail to adapt and therefore are “susceptible” to progressive and serious liver injury, commonly referred to as DILI. Participants who experience a transaminase elevation above $3 \times \text{ULN}$ should be monitored more frequently to determine if they are an “adaptor” or are “susceptible.”

LFTs are not required as a routine safety monitoring procedure for all participants in this study. However, should an investigator deem it necessary to assess LFTs because a participant presents with clinical signs/symptoms, such LFT results should be managed and followed as described below.

In the majority of DILI cases, elevations in AST and/or ALT precede TBili elevations ($>2 \times \text{ULN}$) by several days or weeks. The increase in TBili typically occurs while AST/ALT is/are still elevated above $3 \times \text{ULN}$ (ie, AST/ALT and TBili values will be elevated within the same laboratory sample). In rare instances, by the time TBili elevations are detected, AST/ALT values might have decreased. This occurrence is still regarded as a potential DILI. Therefore, abnormal elevations in either AST OR ALT in addition to TBili that meet the criteria outlined below are considered potential DILI (assessed per Hy’s law criteria) cases and should always be considered important medical events, even before all other possible causes of liver injury have been excluded.

The threshold of laboratory abnormalities for a potential DILI case depends on the participant’s individual baseline values and underlying conditions. Participants who present with the following laboratory abnormalities should be evaluated further as potential DILI (Hy’s law) cases to definitively determine the etiology of the abnormal laboratory values:

- Participants with AST/ALT and TBili baseline values within the normal range who subsequently present with AST OR ALT values $>3 \times \text{ULN}$ AND a TBili value $>2 \times \text{ULN}$ with no evidence of hemolysis and an alkaline phosphatase value $<2 \times \text{ULN}$ or not available.
- For participants with baseline AST **OR** ALT **OR** TBili values above the ULN, the following threshold values are used in the definition mentioned above, as needed, depending on which values are above the ULN at baseline:
 - Preexisting AST or ALT baseline values above the normal range: AST or ALT values >2 times the baseline values AND $>3 \times \text{ULN}$; or $>8 \times \text{ULN}$ (whichever is smaller).

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- Preexisting values of TBili above the normal range: TBili level increased from baseline value by an amount of at least $1 \times \text{ULN}$ **or** if the value reaches $>3 \times \text{ULN}$ (whichever is smaller).

Rises in AST/ALT and TBili separated by more than a few weeks should be assessed individually based on clinical judgment; any case where uncertainty remains as to whether it represents a potential Hy's law case should be reviewed with the sponsor.

The participant should return to the investigator site and be evaluated as soon as possible, preferably within 48 hours from awareness of the abnormal results. This evaluation should include laboratory tests, detailed history, and physical assessment.

In addition to repeating measurements of AST and ALT and TBili for suspected cases of Hy's law, additional laboratory tests should include albumin, CK, direct and indirect bilirubin, GGT, PT/INR, total bile acids, and alkaline phosphatase. Consideration should also be given to drawing a separate tube of clotted blood and an anticoagulated tube of blood for further testing, as needed, for further contemporaneous analyses at the time of the recognized initial abnormalities to determine etiology. A detailed history, including relevant information, such as review of ethanol, acetaminophen/paracetamol (either by itself or as a coformulated product in prescription or over-the-counter medications), recreational drug, supplement (herbal) use and consumption, family history, sexual history, travel history, history of contact with a jaundiced person, surgery, blood transfusion, history of liver or allergic disease, and potential occupational exposure to chemicals, should be collected. Further testing for acute hepatitis A, B, C, D, and E infection and liver imaging (eg, biliary tract) and collection of serum samples for acetaminophen/paracetamol drug and/or protein adduct levels may be warranted.

All cases demonstrated on repeat testing as meeting the laboratory criteria of AST/ALT and TBili elevation defined above should be considered potential DILI (Hy's law) cases if no other reason for the LFT abnormalities has yet been found. **Such potential DILI (Hy's law) cases are to be reported as SAEs, irrespective of availability of all the results of the investigations performed to determine etiology of the LFT abnormalities.**

A potential DILI (Hy's law) case becomes a confirmed case only after all results of reasonable investigations have been received and have excluded an alternative etiology.

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10.6. Appendix 6: Abbreviations

The following is a list of abbreviations that may be used in the protocol.

Abbreviation	Term
2019-nCoV	novel coronavirus 2019
Abs	absolute (in Appendix 2)
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
β -hCG	beta-human chorionic gonadotropin
BMI	body mass index
BUN	blood urea nitrogen
CBER	Center for Biologics Evaluation and Research
CDC	Centers for Disease Control and Prevention (United States)
CFR	Code of Federal Regulations
CI	confidence interval
CIOMS	Council for International Organizations of Medical Sciences
CLIA	Clinical Laboratory Improvement Amendments
CONSORT	Consolidated Standards of Reporting Trials
COVID-19	coronavirus disease 2019
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CT	computed tomography
DBP	diastolic blood pressure
DILI	drug-induced liver injury
DMC	data monitoring committee
DNA	deoxyribonucleic acid
DU	dosing unit
EC	ethics committee
ECMO	extracorporeal membrane oxygenation
ECG	electrocardiogram
eCRF	electronic case report form
e-diary	electronic diary
EDP	exposure during pregnancy
EMA	European Medicines Agency
EU	European Union
EUA	emergency use authorization
EudraCT	European Clinical Trials Database
FDA	Food and Drug Administration
FiO ₂	fraction of inspired oxygen
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma-glutamyl transferase

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Abbreviation	Term
GMC	geometric mean concentration
GMFR	geometric mean fold rise
GMR	geometric mean ratio
GMT	geometric mean titer
HBc Ab	hepatitis B core antibody
HBe	hepatitis B e
HBeAg	hepatitis B e antigen
HBsAg	hepatitis B surface antigen
HBV	hepatitis B virus
HCV	hepatitis C virus
HCV Ab	hepatitis C virus antibody
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
HR	heart rate
HRT	hormone replacement therapy
IA	interim analysis
IB	investigator's brochure
ICD	informed consent document
ICH	International Council for Harmonisation
ICU	intensive care unit
ID	identification
Ig	immunoglobulin
IgG	immunoglobulin G
IgM	immunoglobulin M
IMP	investigational medicinal product
IND	investigational new drug
INR	international normalized ratio
IP manual	investigational product manual
IPAL	Investigational Product Accountability Log
IRB	institutional review board
IRC	internal review committee
IRR	illness rate ratio
IRT	interactive response technology
ISO	International Organization for Standardization
IV	intravenous(ly)
IWR	interactive Web-based response
LFT	liver function test
LL	lower limit
LLOQ	lower limit of quantitation
LNP	lipid nanoparticle
LPX	lipoplex
MAR	missing at random
MCH	mean corpuscular hemoglobin

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Abbreviation	Term
MCHC	mean corpuscular hemoglobin concentration
MCV	mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MERS	Middle East respiratory syndrome
MIS-C	multisystem inflammatory syndrome in children
modRNA	nucleoside-modified messenger ribonucleic acid
MRI	magnetic resonance imaging
N	SARS-CoV-2 nucleoprotein
N/A	not applicable
NAAT	nucleic acid amplification test
non-S	nonspike protein
P2 S	SARS-CoV-2 full-length, P2 mutant, prefusion spike glycoprotein
PaO ₂	partial pressure of oxygen, arterial
PCR	polymerase chain reaction
PI	principal investigator
POS	probability of success
PPE	personal protective equipment
PT	prothrombin time
RBC	red blood cell
RBD	receptor-binding domain
RCDC	reverse cumulative distribution curve
RNA	ribonucleic acid
RR	respiratory rate
RSV	respiratory syncytial virus
RT-PCR	reverse transcription–polymerase chain reaction
S1	spike protein S1 subunit
SAE	serious adverse event
SAP	statistical analysis plan
saRNA	self-amplifying messenger ribonucleic acid
SARS	severe acute respiratory syndrome
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SBP	systolic blood pressure
SoA	schedule of activities
SOP	standard operating procedure
SpO ₂	oxygen saturation as measured by pulse oximetry
SRSD	single reference safety document
SUSAR	suspected unexpected serious adverse reaction
TBD	to be determined
TBili	total bilirubin
ULN	upper limit of normal
uRNA	unmodified messenger ribonucleic acid
US	United States
vax	vaccination

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Abbreviation	Term
VE	vaccine efficacy
WBC	white blood cell
WHO	World Health Organization
WOCBP	woman/women of childbearing potential

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10.7. Appendix 7: Stopping and Alert Rules for Enhanced COVID-19

In Phase 2/3, the unblinded team supporting the DMC (reporting team), including an unblinded medical monitor, will review cases of severe COVID-19 as they are received, and will review AEs at least weekly for additional potential cases of severe COVID-19 and will contact the DMC in the event that the stopping rule or an alert is met. Specifically, the unblinded reporting team will contact the DMC chair, who will then convene the full DMC as soon as possible. The DMC will review all available safety and/or efficacy data at the time of the review. The DMC will make one of the following recommendations to Pfizer: withhold final recommendation until further information/data are provided, continue the study as designed, modify the study and continue, or stop the study. The final decision to accept or reject the committee's recommendation resides with Pfizer management and will be communicated to the committee chairperson in writing.

At any point the unblinded team may discuss with the DMC chair whether the DMC should review cases for an adverse imbalance of cases of COVID-19 and/or severe COVID-19 between the vaccine and placebo groups (see [Section 9.6](#)). In addition, at the time of the IAs after accrual of at least 62, 92, and 120 cases, the number of severe COVID-19 cases in the vaccine and placebo groups will be assessed.

Stopping and alert rules will be applied as follows. The stopping rule will be triggered when the 1-sided probability of observing the same or a more extreme case split is 5% or less when the true incidence of severe disease is the same for vaccine and placebo participants, and alert criteria are triggered when this probability is less than 11%. In addition, when the total number of severe cases is low (15 or less), the unblinded team supporting the DMC will implement the alert rule when a reverse case split of 2:1 or worse is observed. For example, at 3 cases 2:1, at 4 cases 3:1, etc. Below 15 cases, this rule is more rigorous than requiring the probability of an observed adverse split or worse be <11%.

The stopping rule and alert rules are illustrated in Table 10 and Table 11, respectively, when the total number of severe cases is 20 or less. For example, when there are 7 severe cases, the adverse split has to be 7:0 to stop the study, but a split of 5:2 would trigger the alert rule. Similarly, when there is a total of 9 severe cases, an adverse split of 9:0 triggers the stopping rule, while a split of 6:3 or worse triggers the alert rule. The alert rule may be triggered with as few as 2 cases, with a split of 2:0.

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Table 10. Stopping Rule: Enrollment Is Stopped if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Stopping Rule Value (S)

Total Severe Cases	Prespecified Stopping Rule Value (S): Number of Severe Cases in the Vaccine Group to Stop	If the True Ratio of Severe Cases Between Vaccine and Placebo Groups Is 1:1, Probability of S or More Being Observed in the Vaccine Group
4	4	N/A
5	5	3.13%
6	6	1.56%
7	7	0.78%
8	7	3.52%
9	8	1.95%
10	9	1.07%
11	9	3.27%
12	10	1.93%
13	10	4.61%
14	11	2.87%
15	12	1.76%
16	12	3.84%
17	13	2.45%
18	13	4.81%
19	14	3.18%
20	15	2.07%

Abbreviation: N/A = not applicable.

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Table 11. Alert Rule: Further Action Is Taken if the Number of Severe Cases in the Vaccine Group Is Greater Than or Equal to the Prespecified Alert Rule Value (A)

Total Severe Cases	Prespecified Alert Rule Value (A): Number of Severe Cases in the Vaccine Group to Trigger Further Action	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 1:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 2:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 3:1, Probability of A or More Being Observed in the Vaccine Group	If the True Ratio of Severe Cases Between the Vaccine and Placebo Groups Is 4:1, Probability of A or More Being Observed in the Vaccine Group
2	2	25.00%	25.00%	44.49%	56.25%	64.00%
3	2	37.50%	50.00%	74.12%	84.38%	89.60%
4	3	25.00%	31.25%	59.32%	73.83%	81.92%
5	4	15.63%	18.75%	46.16%	63.28%	73.73%
6	4	23.44%	34.38%	68.10%	83.06%	90.11%
7	5	16.41%	22.66%	57.14%	75.64%	85.20%
8	6	10.94%	14.45%	46.90%	67.85%	79.69%
9	6	16.41%	25.39%	65.11%	83.43%	91.44%
10	7	11.72%	17.19%	56.02%	77.59%	87.91%
11	8	8.06%	11.33%	47.35%	71.33%	83.89%
12	8	12.08%	19.38%	63.25%	84.24%	92.74%
13	9	8.73%	13.34%	55.31%	79.40%	90.09%
14	10	6.11%	8.98%	47.66%	74.15%	87.02%
15	10	9.16%	15.09%	61.94%	85.16%	93.89%
16	11	6.67%	10.51%	54.81%	81.03%	91.83%
17	12	4.72%	7.17%	47.88%	76.53%	89.43%
18	13	3.27%	4.81%	41.34%	71.75%	86.71%
19	13	5.18%	8.35%	54.43%	82.51%	93.24%
20	14	3.70%	5.77%	48.06%	78.58%	91.33%

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

10.8. Appendix 8: Criteria for Allowing Inclusion of Participants With Chronic Stable HIV, HCV, or HBV Infection

Potential participants with chronic stable HIV, HCV, or HBV infection may be considered for inclusion if they fulfill the following respective criteria.

Known HIV infection

- Confirmed stable HIV disease defined as documented viral load <50 copies/mL and CD4 count >200 cells/mm³ within 6 months before enrollment, and on stable antiretroviral therapy for at least 6 months.

Known HCV infection

- History of chronic HCV with evidence of sustained virological response (defined as undetectable HCV RNA) for ≥12 weeks following HCV treatment or without evidence of HCV RNA viremia (undetectable HCV viral load).

Known HBV infection

Confirmed inactive chronic HBV infection, defined as HBsAg present for ≥6 months and the following:

- HBeAg negative, anti-HBe positive
- Serum HBV DNA <2000 IU/mL
- Persistently normal ALT and/or AST levels
- In those who have had a liver biopsy performed, findings that confirm the absence of significant necroinflammation.

PF-07302048 (BNT162 RNA-Based COVID-19 Vaccines)
Protocol C4591001

11. REFERENCES

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- ³ Centers for Disease Control and Prevention. Coronavirus disease 2019 (COVID-19): information for clinicians on investigational therapeutics for patients with COVID-19. Available from: <https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html>. Updated: 25 Apr 2020. Accessed: 26 Jun 2020.
- ⁴ Rauch S, Jasny E, Schmidt KE, et al. New vaccine technologies to combat outbreak situations. *Front Immunol* 2018;9:1963.
- ⁵ Sahin U, Karikó K, Türeci Ö. mRNA-based therapeutics—developing a new class of drugs. *Nat Rev Drug Discov* 2014;13(10):759-80.
- ⁶ BioNTech RNA Pharmaceuticals GmbH. CorVAC/BNT162 Investigator's Brochure. Mainz, Germany: BioNTech RNA Pharmaceuticals GmbH; 25 Mar 2020.
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- ⁸ US Food and Drug Administration. Guidance for industry: toxicity grading scale for healthy adult and adolescent volunteers enrolled in preventive vaccine clinical trials. Rockville, MD: Center for Biologics Evaluation and Research; September 2007.
- ⁹ Agresti A. Introduction: distributions and inference for categorical data. In: Agresti A, ed. *Categorical data analysis*. 2nd ed. Hoboken, NJ: John Wiley & Sons; 2002:1-35.
- ¹⁰ Miettinen O, Nurminen M. Comparative analysis of two rates. *Stat Med* 1985;4(2):213-26.

Ex. 8



Pfizer and BioNTech Conclude Phase 3 Study of COVID-19 Vaccine Candidate, Meeting All Primary Efficacy Endpoints

- *Primary efficacy analysis demonstrates BNT162b2 to be 95% effective against COVID-19 beginning 28 days after the first dose; 170 confirmed cases of COVID-19 were evaluated, with 162 observed in the placebo group versus 8 in the vaccine group*
- *Efficacy was consistent across age, gender, race and ethnicity demographics; observed efficacy in adults over 65 years of age was over 94%*
- *Safety data milestone required by U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved*
- *Data demonstrate vaccine was well tolerated across all populations with over 43,000 participants enrolled; no serious safety concerns observed; the only Grade 3 adverse event greater than 2% in frequency was fatigue at 3.8% and headache at 2.0%*
- *Companies plan to submit within days to the FDA for EUA and share data with other regulatory agencies around the globe*
- *The companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021*
- *Pfizer is confident in its vast experience, expertise and existing cold-chain infrastructure to distribute the vaccine around the world*



November 18, 2020 06:59 AM Eastern Standard Time

NEW YORK & MAINZ, Germany--(BUSINESS WIRE)--Pfizer Inc. (NYSE: PFE) and BioNTech SE (Nasdaq: BNTX) today announced that, after conducting the final efficacy analysis in their ongoing Phase 3 study, their mRNA-based COVID-19 vaccine candidate, BNT162b2, met all of the study's primary efficacy endpoints. Analysis of the data indicates a vaccine efficacy rate of 95% ($p < 0.0001$) in participants without prior SARS-CoV-2 infection (first primary objective) and also in participants with and without prior SARS-CoV-2 infection (second primary objective), in each case measured from 7 days after the second dose. The first primary objective analysis is based on 170 cases of COVID-19, as specified in the study protocol, of which 162 cases of COVID-19 were observed in the placebo group versus 8 cases in the BNT162b2 group. Efficacy was consistent across age, gender, race and ethnicity demographics. The observed efficacy in adults over 65 years of age was over 94%.

There were 10 severe cases of COVID-19 observed in the trial, with nine of the cases occurring in the placebo group and one in the BNT162b2 vaccinated group.

To date, the Data Monitoring Committee for the study has not reported any serious safety concerns related to the vaccine. A review of unblinded reactogenicity data from the final analysis which consisted of a randomized subset of at least 8,000 participants 18 years and older in the phase 2/3 study demonstrates that the vaccine was well tolerated, with most solicited adverse events resolving shortly after vaccination. The only Grade 3 (severe) solicited adverse events greater than or equal to 2% in frequency after the first or second dose was fatigue at 3.8% and headache at 2.0% following dose 2. Consistent with earlier shared results, older adults tended to report fewer and milder solicited adverse events following vaccination.

In addition, the companies announced that the safety milestones required by the U.S. Food and Drug Administration (FDA) for Emergency Use Authorization (EUA) has been achieved. Pfizer and BioNTech plan to submit a request within days to the FDA for an EUA based on the totality of safety and efficacy data collected to date, as well as manufacturing data relating to the quality and consistency of the vaccine. These data also will be submitted to other regulatory agencies around the world.

"The study results mark an important step in this historic eight-month journey to bring forward a vaccine capable of helping to end this devastating pandemic. We continue to move at the speed of science to compile all the data collected thus far and share with regulators around the world," said Dr. Albert Bourla, Pfizer Chairman and CEO. "With hundreds of thousands of people around the globe infected every day, we urgently need to get a safe and effective vaccine to the world."

"We are grateful that the first global trial to reach the final efficacy analysis mark indicates that a high rate of protection against COVID-19 can be achieved very fast after the first 30 µg dose, underscoring the power of BNT162 in providing early protection," said Ugur Sahin, M.D., CEO and Co-founder of BioNTech. "These achievements highlight the potential of mRNA as a new drug class. Our objective from the very beginning was to design and develop a vaccine that would generate rapid and potent protection against COVID-19 with a benign tolerability profile across all ages. We believe we have achieved this with our vaccine candidate BNT162b2 in all age groups studied so far and look forward to sharing further details with the regulatory authorities. I want to thank all the devoted women and men who contributed to this historically unprecedented achievement. We will continue to work with our partners and governments around the world to prepare for global distribution in 2020 and beyond."

The Phase 3 clinical trial of BNT162b2 began on July 27 and has enrolled 43,661 participants to date, 41,135 of whom have received a second dose of the vaccine candidate as of November 13, 2020. Approximately 42% of global participants and 30% of U.S. participants have racially and ethnically diverse backgrounds, and 41% of global and 45% of U.S. participants are 56-85 years of age. A breakdown of the diversity of clinical trial participants can be found [here](#) from approximately 150 clinical trials sites in United States, Germany, Turkey, South Africa, Brazil and Argentina. The trial will continue to collect efficacy and safety data in participants for an additional two years.

Based on current projections, the companies expect to produce globally up to 50 million vaccine doses in 2020 and up to 1.3 billion doses by the end of 2021. Four of Pfizer's facilities are part of the manufacturing and supply chain; St. Louis, MO; Andover, MA; and Kalamazoo, MI in the U.S.; and Puurs in Belgium. BioNTech's German sites will also be leveraged for global supply.

Pfizer is confident in its vast experience, expertise and existing cold-chain infrastructure to distribute the vaccine around the world. The companies have developed specially designed, temperature-controlled thermal shippers utilizing dry ice to maintain temperature conditions of $-70^{\circ}\text{C}\pm 10^{\circ}\text{C}$. They can be used as temporary storage units for 15 days by refilling with dry ice. Each shipper contains a GPS-enabled thermal sensor to track the location and temperature of each vaccine shipment across their pre-set routes leveraging Pfizer's broad distribution network.

Pfizer and BioNTech plan to submit the efficacy and safety data from the study for peer-review in a scientific journal once analysis of the data is completed.

About Pfizer: Breakthroughs That Change Patients' Lives

At Pfizer, we apply science and our global resources to bring therapies to people that extend and significantly improve their lives. We strive to set the standard for quality, safety and value in the discovery, development and manufacture of health care products, including innovative medicines and vaccines. Every day, Pfizer colleagues work across developed and emerging markets to advance wellness, prevention, treatments and cures that challenge the most feared diseases of our time. Consistent with our responsibility as one of the world's premier innovative biopharmaceutical companies, we collaborate with health care providers, governments and local communities to support and expand access to reliable, affordable health care around the world. For more than 150 years, we have worked to make a difference for all who rely on us. We routinely post information that may be important to investors on our website at www.Pfizer.com. In addition, to learn more, please visit us on www.Pfizer.com and follow us on Twitter at [@Pfizer](https://twitter.com/Pfizer) and [@Pfizer News](https://twitter.com/PfizerNews), [LinkedIn](#), [YouTube](#) and like us on Facebook at [Facebook.com/Pfizer](https://www.facebook.com/Pfizer).

The information contained in this release is as of November 18, 2020. Pfizer assumes no obligation to update forward-looking statements contained in this release as the result of new information or future events or developments.

This release contains forward-looking information about Pfizer's efforts to combat COVID-19, the collaboration between BioNTech and Pfizer to develop a potential COVID-19 vaccine, the BNT162 mRNA vaccine program, and modRNA candidate BNT162b2 (including qualitative assessments of available data, potential benefits, expectations for clinical trials, anticipated timing of regulatory submissions and anticipated manufacturing, distribution and supply), that involves substantial risks and uncertainties that could cause actual results to differ materially from those expressed or implied by such statements. Risks and uncertainties include, among other things, the uncertainties inherent in research and development, including the ability to meet anticipated clinical endpoints, commencement and/or completion dates for clinical trials, regulatory submission dates, regulatory approval dates and/or launch dates, as well as risks associated with clinical data (including the Phase 3 data that is the subject of this release), including the possibility of unfavorable new preclinical or clinical trial data and further analyses of existing preclinical or clinical trial data; the ability to produce comparable clinical or other results, including the rate of vaccine effectiveness and safety and tolerability profile observed to date, in additional analyses of the Phase 3 trial or in larger, more diverse populations upon commercialization; the risk that clinical trial data are subject to differing interpretations and assessments, including during the peer review/publication process, in the scientific community generally, and by regulatory authorities; whether and when data from the BNT162 mRNA vaccine program will be published in scientific journal publications and, if so, when and with what modifications; whether regulatory authorities will be satisfied with the design of and results from these and any future preclinical and clinical studies; whether and when any biologics license and/or emergency use authorization applications may be filed in any jurisdictions for BNT162b2 or any other potential vaccine candidates; whether and when any such applications may be approved by regulatory authorities, which will depend on myriad factors, including making a determination as to whether the vaccine candidate's benefits outweigh its known risks and determination of the vaccine candidate's efficacy and, if approved, whether it will be commercially successful; decisions by regulatory authorities impacting labeling, manufacturing processes, safety and/or other matters that could affect the availability or commercial potential of a vaccine, including development of products or therapies by other companies; disruptions in the relationships between us and our collaboration partners or third-party suppliers; risks related to the availability of raw materials to manufacture a vaccine; challenges related to our vaccine candidate's ultra-low temperature formulation and attendant storage, distribution and administration requirements, including risks related to handling after delivery by Pfizer; the risk that we may not be able to successfully develop non-frozen formulations; the risk that we may not be able to create or scale up manufacturing capacity on a timely basis or have access to logistics or supply channels commensurate with global demand for any potential approved vaccine, which would negatively impact our ability to supply the estimated numbers of doses of our vaccine candidate within the projected time periods indicated; whether and when additional supply agreements will be reached; uncertainties regarding the ability to obtain recommendations from vaccine technical committees and other public health authorities and uncertainties regarding the commercial impact of any such recommendations; uncertainties regarding the impact of COVID-19 on Pfizer's business, operations and financial results; and competitive developments.

A further description of risks and uncertainties can be found in Pfizer's Annual Report on Form 10-K for the fiscal year ended December 31, 2019 and in its subsequent reports on Form 10-Q, including in the sections thereof captioned "Risk Factors" and "Forward-Looking Information and Factors That May Affect Future Results", as well as in its subsequent reports on Form 8-K, all of which are filed with the U.S. Securities and Exchange Commission and available at www.sec.gov and www.pfizer.com.

About BioNTech

Biopharmaceutical New Technologies is a next generation immunotherapy company pioneering novel therapies for cancer and other serious diseases. The Company exploits a wide array of computational discovery and therapeutic drug platforms for the rapid development of novel biopharmaceuticals. Its broad portfolio of oncology product candidates includes individualized and off-the-shelf mRNA-based therapies, innovative chimeric antigen receptor T cells, bi-specific checkpoint immuno-modulators, targeted cancer antibodies and small molecules. Based on its deep expertise in mRNA vaccine development and in-house manufacturing capabilities, BioNTech and its collaborators are developing multiple mRNA vaccine candidates for a range of infectious diseases alongside its diverse oncology pipeline. BioNTech has established a

BioNTech Forward-looking statements

This press release contains “forward-looking statements” of BioNTech within the meaning of the Private Securities Litigation Reform Act of 1995. These forward-looking statements may include, but may not be limited to, statements concerning: BioNTech’s efforts to combat COVID-19; the collaboration between BioNTech and Pfizer to develop a potential COVID-19 vaccine; our expectations regarding the potential characteristics of BNT162b2 in our Phase 2/3 trial and/or in commercial use based on data observations to date; the expected timepoint for additional readouts on efficacy data of BNT162b2 in our Phase 2/3 trial; the nature of the clinical data, which is subject to ongoing peer review, regulatory review and market interpretation; the timing for submission of data for, or receipt of, any potential Emergency Use Authorization; the timing for submission of manufacturing data to the FDA; and the ability of BioNTech to supply the quantities of BNT162 to support clinical development and, if approved, market demand, including our production estimates for 2020 and 2021. Any forward-looking statements in this press release are based on BioNTech current expectations and beliefs of future events, and are subject to a number of risks and uncertainties that could cause actual results to differ materially and adversely from those set forth in or implied by such forward-looking statements. These risks and uncertainties include, but are not limited to: the ability to meet the pre-defined endpoints in clinical trials; competition to create a vaccine for COVID-19; the ability to produce comparable clinical or other results, including our stated rate of vaccine effectiveness and safety and tolerability profile observed to date, in the remainder of the trial or in larger, more diverse populations upon commercialization; the ability to effectively scale our productions capabilities; and other potential difficulties. For a discussion of these and other risks and uncertainties, see BioNTech’s Annual Report on Form 20-F filed with the SEC on March 31, 2020, which is available on the SEC’s website at www.sec.gov. All information in this press release is as of the date of the release, and BioNTech undertakes no duty to update this information unless required by law.

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Ex. 9

To: Brook Jackson[bjackson@ventaviaresearch.com]
Cc: Jailyn Reyes[jailynreyes@ventaviaresearch.com]
From: Kandy Downs[kdowns@ventaviaresearch.com]
Sent: Fri 9/18/2020 12:09:03 AM (UTC)
Subject: FW: IP thaw time

Please review.

Warmest Regards;

Lovica “Kandy” Downs

Regional Director
RMA, BBA, CCRC

Ventavia Research Group

1307 8th Ave Suite #202

Fort Worth, TX 76104

Cell Number: 817-269-5997
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From: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>
Sent: Thursday, September 17, 2020 7:08 PM
To: Kandy Downs <kdowns@ventaviaresearch.com>
Subject: Fwd: IP thaw time

Mercedes Livingston
Chief Operating Officer

[img alt="Small square icon with a grid pattern, possibly a placeholder for a logo or image."/>

Ventavia Research Group
1307 8th Avenue Suite 202

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From: Alfaro, Arturo A. <Arturo.Alfaro@pfizer.com>
Sent: Tuesday, August 18, 2020 9:08:06 AM
To: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>
Subject: RE: IP thaw time

I would try to keep it at 30 minutes since that is what the manual states.

Arturo A. Alfaro, M.D.

Site Relationship Partner II

Global Site & Study Operations

Clinical Development & Operations, GPD

Location: North America, United States, C.S.T.

Office / Cell: 512-638-2188

Fax: 845-474-5793

arturo.alfaro@pfizer.com



From: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>

Sent: Tuesday, August 18, 2020 8:35 AM

To: Alfaro, Arturo A. <Arturo.Alfaro@pfizer.com>

Subject: [EXTERNAL] RE: IP thaw time

Hi Arturo

I see that it says for **approximately** 30 minutes. So my question is still if it thaws before the “approximate 30 min” can we move forward before the 30 min.

Thanks,

Mercedes Livingston, CCRC

Chief Operating Officer

Ventavia Research Group

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JSN0290

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From: Alfaro, Arturo A. <Arturo.Alfaro@pfizer.com>
Sent: Monday, August 17, 2020 4:33 PM
To: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>
Subject: RE: IP thaw time

Could you please check the version you are reading? In the most current version the thawing time was increased to 30 minutes.

Arturo A. Alfaro, M.D.
Site Relationship Partner II
Global Site & Study Operations
Clinical Development & Operations, GPD
Location: North America, United States, C.S.T.
Office / Cell: 512-638-2188
Fax: 845-474-5793
arturo.alfaro@pfizer.com



From: Mercedes Livingston <mercedeslivingston@ventaviaresearch.com>
Sent: Monday, August 17, 2020 4:26 PM
To: Alfaro, Arturo A. <Arturo.Alfaro@pfizer.com>
Subject: [EXTERNAL] IP thaw time

Hi Arturo

In the IP manual, it states the study drug should thaw for approximately 20 minutes. Also, that subjects assigned to Placebo should be given the vaccine about 30 minutes after drawing up to prevent unblinded (no thaw time with Placebo).

My question is, if the drug thaws in about 15 minutes due to being in a room, closed with fridge and freezer in there making the room warmer, the un-blinded personnel handling the vials, etc since the drug manual says approximately would this be considered a deviation?

We had a previous Pfizer study that read similar to this and the drug was not taking the amount of time suggested in the drug manual and we did an NTF with our process for bringing it to room temp.

Of course, if it was not taking the full 20 minutes to thaw, we would also adjust the placebo prep time to be inline with study drug prep to maintain the blind.

Regards,

Mercedes Livingston, CCRC
Chief Operating Officer

JSN0291

Ventavia Research Group

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Ex. 10



**DEPARTMENT OF THE ARMY
U.S. ARMY CONTRACTING COMMAND – NEW JERSEY
PICATINNY ARSENAL, NEW JERSEY 07806-5000**

REPLY TO
ATTENTION OF

21 July 2020

Army Contracting Command – New Jersey
ACC-NJ, Building 9
Picatinny Arsenal, NJ 07806

SUBJECT: Technical Direction Letter for Medical CRBN Defense Consortium (MCDC), Request for Prototype Proposals (RPP) 20-11, Objective PRE-20-11 for “COVID-19 Pandemic – Large Scale Vaccine Manufacturing Demonstration” (Pfizer, Inc.)

REF: Prizer Request for Technical Direction Letter, RPP 20-11 under OTA W15QKN-16-9-1002 for Objective PRE-20-11, dated 20 July 2020

Advanced Technology International
ATTN: (b) (6), Sr. Contracts Manager
315 Sigma Drive
Summerville, SC 29486

Dear (b) (6),

The Army Contracting Command – New Jersey (ACC-NJ), in supporting the Joint Project Manager – Medical Countermeasure Systems (JPM-MCS), issued MCDC RPP 20-11 on 09 June 2020. Members of the MCDC submitted proposals in accordance with this RPP. The Government received and evaluated all proposal(s) submitted and a Basis of Selection has been executed, selecting Pfizer, Inc. as the awardee. The Government requests that a Firm-Fixed-Price Project Agreement be issued to Pfizer, Inc. to award this proposal under Other Transaction Agreement W15QKN-16-9-1002, to be performed in accordance with the attached Government Statement of Work (SOW).

Based upon the acceptable update of Pfizer, Inc.’s proposal for “COVID-19 Pandemic – Large Scale Vaccine Manufacturing Demonstration” and 1) The Project Agreement Recipient’s concurrence with the requirements included in the Government SOW; 2) An acceptable milestone schedule that meets SOW requirements, and; 3) The price proposed that has been analyzed by the Government, you are hereby directed to issue a Project Agreement to Pfizer, Inc. for the subject project. The total project value has been determined fair and reasonable and Pfizer, Inc.’s proposal has been selected IAW the above referenced Basis of Selection.

The total approved cost to the Government for this effort is not to exceed \$1,950,097,500.00. The break-out of the costs is as follows: \$1,950,000,000.00 to perform project efforts included in the SOW and \$97,500.00 for the Consortium Management Firm (CMF) Administrative Cost. The CMF Administrative Cost was approved as a “Special Allocation” for Operation Warp Speed (OWS) Prototype Projects executed under the MCDC OTA. The effort currently has \$1,950,097,500.00 of available funding, comprised of \$1,950,000,000.00 for the Project Agreement, \$67,500.00 for the CMF Special Allocation, and \$30,000 for other, non G&A, ATI costs, which will be incurred, tracked,

JSN0293

and invoiced in accordance with Article V of the OTA. The COVID-19 work shall be tracked separately using the funding obligated via modification P00076. In alignment with the special allocation conditions, it is noted that this project has a base period of performance (b) (4), with a projected completion date of (b) (4). A customized clause for the special allocation, will be incorporated into the funding modification for this prototype project.

The prime contractor is considered a small business, nontraditional defense contractor, or nonprofit research institution and determined to be providing a significant contribution. The affirmation of business status certifications submitted as part of the proposal are hereby incorporated into the agreement. The contractor shall notify the MCDC CMF of any deviation from the final proposed affirmation of business status certifications that would affect the contributions of the small business, nontraditional defense contractor, or nonprofit research institution as proposed.

In accordance with 10.U.S.C. 2371b(f), and upon a determination that the prototype project for this transaction has been successfully completed, this competitively awarded prototype OTA may result in the award of a follow-on production contract or transaction without the use of competitive procedures.

Points of Contact:

Agreements Specialist:

(b) (6)

E-mail: (b) (6)

Phone: (b) (6)

Agreements Officer:

(b) (6)

E-mail: (b) (6)

Phone: (b) (6)

Regards,

X (b) (6)

(b) (6)

Agreements Officer

Signed by: (b) (6)

Attachments:

Attachment 1: MCDC2011-003 – Pfizer - 7-21-2020

Attachment 2: SOW Appendix 1 Clause for MCDC Consortium Other Transaction Authority Agreements

**Statement of Work
For
COVID-19 PANDEMIC--LARGE SCALE VACCINE MANUFACTURING
DEMONSTRATION**

RPP #: 20-11

Project Identifier: 2011-003

Consortium Member: Member

Title of Proposal: COVID-19 Pandemic--Large Scale Vaccine Manufacturing Demonstration

Requiring Activity: Joint mission between the Department of Health and Human Services and Department of Defense to combat COVID-19

1.0 INTRODUCTION, SCOPE, AND OBJECTIVES

1.1 Introduction

This Statement of Work (the "Statement of Work") is hereby entered into, effective as of July 21, 2020, pursuant to that certain Project Agreement by and between MCDC and Pfizer dated as of July 21, 2020 ("this Agreement" or "Project Agreement").

An outbreak of respiratory disease caused by a novel coronavirus was first detected in China in late 2019 and has now spread worldwide, including the United States ("US"). The virus has been named Severe Acute Respiratory Disease Coronavirus-2 ("SARS-CoV-2") and causes Coronavirus Disease 2019 ("COVID-19"). On January 30, 2020, the International Health Regulations Emergency Committee of the World Health Organization ("WHO"), declared the outbreak a "Public Health Emergency of International Concern". On January 31, the US Department of Health and Human Services Secretary ("HHS"), Alex M. Azar II, declared a Public Health Emergency for the US to aid the nation's healthcare community in responding to COVID-19. On March 11, 2020, WHO publicly characterized COVID-19 as a pandemic. On March 13, 2020 the President of the United States declared the COVID-19 outbreak a national emergency. The Government has identified COVID-19 vaccine candidates that are progressing rapidly through advanced research and development activities.

Therefore, in response to a request by the Government, Pfizer is proposing to manufacture at-scale and fill-finish, for provision to the Government, a state-of-the-art candidate vaccine, developed in collaboration with BioNTech and capable of providing protection against the SARS-CoV-2 threat and related coronaviruses, subject to technical, clinical and regulatory success.

Pfizer and BioNTech's program aims to revolutionize the vaccine field by providing an mRNA candidate that, itself, has several key advantages, including the efficiency and flexibility of the platform – which is apparent by the pace of the vaccine development and the unprecedented phase

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1/2/3 trial design that it supports. A clear fundamental difference of this candidate over more traditional modalities, such as viral vector vaccines, is that mRNA is delivered by protein-free lipid nanoparticles, which is believed to abolish the risk of anti-vector immunity and permit boosting to maximize the level and duration of immune responses.

The mRNA vaccine technology is also intended to enable quick scale up of production, which is critical for bringing a COVID-19 vaccine to market to address this urgent medical need while preserving high quality and safety standards.

The intent of this prototype project is to demonstrate that Pfizer has the business and logistics capability to manufacture 100M doses of its currently unapproved mRNA-based COVID-19 vaccine for the Government (b) (4), using the Pfizer/BioNTech unique mRNA delivery system and its associated cold chain requirements, under pandemic conditions. This prototype project aims to significantly accelerate and secure US access to this promising medical countermeasure based on domestic manufacturing.

1.1.1 BACKGROUND

(b) (4), Pfizer and BioNTech entered into an agreement for the co-development and distribution (excluding China) of a potential mRNA-based coronavirus vaccine aimed at preventing COVID-19 infection (the "Pfizer/BioNTech Agreement"). Under the Pfizer/BioNTech Agreement, (b) (4)

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(b) (4)

The collaboration has rapidly advanced multiple COVID-19 vaccine candidates into human clinical testing based on BioNTech's proprietary mRNA vaccine platforms, with the objective of ensuring rapid worldwide access to the vaccine, if approved. The collaboration leverages Pfizer's broad expertise in vaccine research and development, regulatory capabilities, and global manufacturing and distribution network. The two companies are jointly conducting clinical trials, and will also work jointly to commercialize the vaccine upon regulatory approval.

Pfizer and BioNTech have already made substantial progress, outside this Statement of Work and without use of any Government funding, towards the demonstration of technical and manufacturing feasibility, including through the initiation of Phase 1/2 studies evaluating the likelihood of safety, tolerability and immunogenicity in the US and in Germany. The goal of the program is to rapidly develop and obtain regulatory licensure for a vaccine for use in adults ≥ 18 years of age, followed by a possible pediatric and/ or maternal indication (to protect ~4M US pregnant women at risk each year). Both companies aspire to have an FDA-approved or authorized vaccine ready for administration in the US by October 31, 2020. Based on current information, Pfizer and BioNTech anticipate a 2-dose per patient regimen.

This Statement of Work is designed toward establishing production capacity and distribution infrastructure sufficient to ensure that doses of the vaccine manufactured under this Agreement can be made available immediately for administration in the US, if clinical trials are successful and the FDA grants an Emergency Use Authorization ("EUA") under Section 564 of the Federal Food, Drug, and Cosmetic Act or Biologics License Application ("BLA") licensure under Section 351(a) of the Public Health Service Act (hereafter "FDA-approved or authorized").

1.1.2 ACTIVITIES UNDERTAKEN WITHOUT GOVERNMENT FUNDING

This section describes activities that Pfizer and BioNTech have been performing and will continue to perform without use of Government funding. These activities are described solely for background and context for the Government-funded deliverables itemized in Section 4.

A. Regulatory Planning

Pfizer will meet the necessary FDA requirements for conducting ongoing and planned clinical trials, and with its collaboration partner, BioNTech, will seek FDA approval or authorization for the vaccine, assuming the clinical data supports such application for approval or authorization. Given that these clinical trials are regulated by the FDA and HHS, there is no need for separate regulation by the U.S. Army Medical Research and Materiel Command. BioNTech is the Investigational New Drug ("IND") holder, while Pfizer is the designated agent for all interactions with the FDA and is taking the lead on all communications with and submissions to FDA.

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B. Clinical and Regulatory Approach

BioNTech is the regulatory sponsor for trials of the vaccine and will be the applicant in the US for an EUA and/or a BLA, and will ultimately be the holder of any such approval issued in the US. Pfizer is BioNTech's authorized agent to FDA. As noted above, Pfizer is the designated agent for all interactions with the FDA and is taking the lead on all communications with and submissions to FDA.

Prior to commencing clinical development, on February 6, 2020, BioNTech obtained feedback from the Paul Ehrlich Institute ("PEI") on plans for rapid vaccine development in response to the COVID-19 outbreak following a Scientific Advice Meeting. Based on the PEI feedback, BioNTech refined the clinical program plan and prepared a detailed protocol for FIH clinical study (BNT162). Additionally, a meeting was held by BioNTech on February 24, 2020 with the Chinese CDC to discuss a possible Special Review Procedure.

In Germany, BioNTech began a Phase 1/2 study (BNT162-01) in late April 2020. BNT162-01 is a dose-escalation trial investigating the safety and immunogenicity of COVID-19 mRNA vaccine candidates in healthy adults. The primary objective of the study is to describe the safety and tolerability profiles of prophylactic BNT162 vaccine candidates after a single dose (for saRNA) or two doses separated by 21 days (uRNA and modRNA candidates). The secondary objective of the study is to describe the immune response to the vaccine in healthy adults, as measured by a functional antibody assay, such as virus neutralization.

Informed by BNT162-01, the Phase 1/2 US study (C4591001) of the vaccine candidates started in May 2020. Pfizer and BioNTech utilized this approach to efficiently optimize formulation and dose selection in the clinic. Study C4591001 is a single, multistage and multi-phase trial (including the pivotal efficacy portion) designed to generate the data needed to achieve FDA approval or authorization for use of one of the vaccine candidates. This is a randomized, placebo-controlled, observer-blind, dose-finding and vaccine candidate-selection study in healthy adults. The study is evaluating the safety, tolerability, and immunogenicity of the COVID-19 mRNA vaccine candidates.

The study consists of 3 stages:

Stage 1: to identify preferred vaccine candidate(s), dose level(s), number of doses, and schedule of administration (with the first 15 participants at each dose level of each vaccine candidate comprising a sentinel cohort);

Stage 2: an expanded-cohort stage; and

Stage 3: a final candidate/dose large-scale stage.

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Using this approach, Pfizer and BioNTech are efficiently working towards selection of final candidate/dose level.

The study currently is being amended to incorporate a pivotal efficacy study design. Therefore, the study would be converted to a single Phase 1/2/3 study. The pivotal study portion (*i.e.*, Phase 2b/3) is expected to enroll up to ~30,000 subjects (1:1 randomized between vaccine and placebo).

Upon gathering adequate safety and immunogenicity/efficacy data in a sufficient number of subjects, Pfizer believes the vaccine candidate could, with FDA's agreement, be administered under EUA.

As background, Pfizer's and BioNTech's activities to ensure provision of vaccine on a timely schedule may include the following discrete activities, depending on emerging data and regulatory guidance.

Activity	Success Criteria	Estimated Timing
Candidate, dose, and regimen selection	Decision endorsed by Pfizer-BioNTech Joint Steering Committee	(b) (4)
Phase 2b/3 Study Start	Requires FDA (CBER) approval	(b) (4)
Phase 1/2/3 Demonstration of immunogenicity, efficacy (interim analysis) and safety	Adequate efficacy and safety data supports EUA application	(b) (4)
EUA Submission to Support Use in American Population	Acceptance of EUA submission	(b) (4)
BLA Submission to Support Use in American Population	Agreement from FDA (CBER) that proposed licensure package (preclinical, clinical, CMC) is acceptable	(b) (4)
EUA Issuance to Support Use in American Population	EUA issued	(b) (4)
BLA Approval to Support Use in American Population	BLA approval	(b) (4)
Post-Approval Commitments Agreed	Agreement with FDA	(b) (4)

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C. Chemistry Manufacturing Controls (CMC)

Pfizer will complete the necessary CMC and scale-up activities to demonstrate the ability to manufacture 100M doses (b) (4). Pfizer will use diligent efforts to manufacture and quality release (using Pfizer's quality system) 100M doses within the US in a non-preservative multi-dose vial (b) (4).

Pfizer currently estimates potential production rates (b) (4). With GMP production expected to commence (b) (4) for drug product, this plan would allow for ~40M doses to be supplied under this Statement of Work in (b) (4). As Pfizer validates the facilities and makes continuous process improvements, Pfizer currently anticipates such production rate to increase starting in (b) (4). Should clinical data indicate that a lesser amount of dosage may be needed, there could be an increase in the anticipated potential number of doses supplied in (b) (4).

As background, to help ensure delivery of the doses, Pfizer is undertaking the following CMC activities:

1. Continue with BioNTech to manufacture initial clinical trial material for EU and US Phase 1/2/3 studies, through mRNA production in Germany and EU (Puurs, Belgium for fill-finish) and drug product/labelling operations at EU CMOs and establish EU based supply chain for lipid nanoparticle (LNP) formulation, fill, finish and distribution for commercial supply.

2. Complete knowledge transfer of the technology and manufacturing process from BioNTech (and its CMO partners) to Pfizer in order to establish the process at Pfizer in the US, (b) (4)

3. Obtain all raw material supplies for manufacturing. This may include support of existing third-party suppliers of raw materials, qualifying new third-party suppliers and/or in-house production of certain raw materials, (b) (4)

4. Establish (b) (4) mRNA (drug substance), lipid nanoparticle (LNP) formulation/fill finish (drug product) capacity for GMP Covid-19 pandemic supply of the RNA-based COVID-19 vaccine on US soil.

5. Develop the shipping model for the -80 °C drug product in consultation with CDC.

In parallel, Pfizer is prepared to also evaluate alternative options including:

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1. Conduct necessary stability and development studies to establish (b) (4)

[Redacted]

2. Conduct necessary formulation and stability studies to develop (b) (4)

[Redacted]

The CMC program may include, but not be limited to: (a) (b) (4); (b) drug substance development; (c) drug product development (LNP formulation, fill-finish); (d) analytical development in GLP and GMP setting; (e) GLP and GMP manufacturing; and (f) and shipping of -80 °C frozen product.

(a) (b) (4)

[Redacted]

(b) Drug Substance Development: Pfizer shall scale-up its capabilities for process optimization, manufacture, analysis, release of GMP materials (mRNA) and securing necessary raw materials from third party providers. For drug substance manufacture, Pfizer seeks to build-out the existing purification suite located at Pfizer's (b) (4)

[Redacted]

Pfizer shall supply incremental resources to transfer/implement new technology and GMP manufacturing processes, including technical experts, quality professionals, analytical technicians, and trained operational staff.

(c) Drug Product Development (Lipid Nanoparticle (LNP Formulation, Fill-Finish)): Activities Pfizer shall perform may include, but are not be limited to, securing of necessary lipids for formulation and manufacturing process development for BNT162; defining the formulation; and initial development of manufacturing process and analytical methods. Pfizer will undertake to

(b) (4)
[Redacted]

(d) Analytical Development: Analytical development may include, but not be limited to: methods transfer participation at receiving site and in-process testing support; process verification on commercial equipment; media fill runs; engineering trials; registration batch manufacture; and registration batch stability (pivotal stability) testing. (b) (4)

[Redacted]

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(e) GLP and GMP Manufacturing: Packaging, storage and distribution of clinical trial supplies for Phase 1/2 will be conducted by (b) (4)

(f) Shipping of -80 °C frozen product: Pfizer is evaluating extension of current clinical packaging configuration using soft boxes and dry ice. (b) (4)

As background, to maintain a timely completion schedule of the vaccine, Pfizer is aspiring to undertake the following discrete activities, without Government funding:

(b) (4)

1.2 Scope

The scope of this prototype project is the demonstration by Pfizer of the supply and logistics capability to manufacture and distribute to the Government of 100M doses of a novel mRNA-based vaccine that has received FDA-approval or authorization based on demonstration of efficacy (hereafter FDA-approved or authorized). The criteria for successful Emergency Use Authorization (EUA) are described in *Emergency Use Authorization of Medical Products and Related Authorities: Guidance for Industry and Other Stakeholders, January 2017*; and *Development and Licensure of Vaccine to Prevent COVID-19: Guidance for Industry June 2020*. The successful provision of these doses shall establish the effectiveness of a technology capable of potentially providing immediate and long-term solutions to coronavirus infections. While pre-clinical, clinical, and chemistry/manufacturing/controls (CMC) activities are described in the Background section of this Statement of Work, the Parties acknowledge and agree that such activities not related to the large-scale manufacturing demonstration are out-of-scope for this prototype project as Pfizer and BioNTech have and will continue to fund these activities, without the use of Government funding.

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1.3 Objective

(a) Prototype Project

As set forth more fully in Section 11.7, the provisions of this Section 1.3 hereby supersede and replace, in their entirety, the provisions of Section 21.15 of the MCDC Base Agreement, 2020-532 (July 2018) (“Base Agreement”).

Consistent with the Government’s objectives under Operation Warp Speed, Pfizer intends to employ its proprietary manufacturing technology and processes, in a manner compliant with applicable laws and regulations, including 21 CFR 210 and 211 and the Drug Supply Chain Security Act (to the extent required for COVID-19 medical countermeasures, as defined by relevant FDA guidance), to manufacture and deliver vaccine. Success of the prototype project is defined as manufacture of 100M doses of Pfizer and BioNTech’s mRNA-based COVID-19 vaccine and, upon FDA-approval or authorization as described above, delivery of those doses in accordance with Section 6.0.

This effort constitutes a prototype project because it will be used to evaluate the technical feasibility of completion of the prototype project during the ongoing COVID-19 pandemic and unprecedented threats to several components of the prototype project. In addition, this is a prototype project because Pfizer will demonstrate and prove-out the at-scale, multi-lot proprietary manufacturing activities in order to assess the feasibility to support the necessary quantity of safe and effective doses required for vaccination of the U.S. population and deliver those doses within challenging cold chain requirements in accordance with Section 6.0. Successful completion of the prototype project will demonstrate Pfizer’s capability to (i) rapidly manufacture product, which can be further scaled-up to meet mutually agreed to surge requirements with limited advance notification and (ii) distribute large quantities of the FDA-approved or authorized drug product in accordance with Section 6.0. For clarity, any manufacturing and delivery of drug product in excess of the specific quantities set forth in Section 4.0 of this Statement of Work, shall be subject to a separate mutually acceptable production agreement between Pfizer and the Government.

(b) Follow-On Production Contract/Options

In accordance with 10.U.S.C. § 2371b(f), and upon a determination that the prototype project is successful, or at the accomplishment of particularly favorable or unexpected results that would justify transition to production, the Government and Pfizer may enter into a non-competitive, mutually-acceptable, follow-on production agreement for additional manufacturing of the vaccine without the use of competitive procedures, which agreement shall reflect an unfunded option on the basis set forth in the following paragraph (the “Option”).

Under the Option, the Government may request that Pfizer produce and deliver up to 500M additional doses for purchase by the Government for delivery (b) (4)

Any order placed pursuant to the Option Agreement will provide for a

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minimum of 100M doses, provided that the aggregate number of doses ordered under the Option shall not exceed 500M.

Upon any request pursuant to the Option, Pfizer shall inform the Government of appropriate lead times based on purchase of raw materials, capacity reservation and other factors, and Pfizer and the Government shall mutually agree on an appropriate estimated delivery schedule. Each order under the Option will be subject to the reasonable acceptance of Pfizer, it being understood that Pfizer shall have no obligation to accept any order pursuant to the Option that would involve (b) (4)

As promptly as practicable following the effective date of this Agreement, the Government and Pfizer will agree in principle upon a form of production agreement reflecting the Option that can be executed as a binding agreement promptly upon Government request following such determination, demonstration, or accomplishment.

2.0 APPLICABLE REFERENCES

Current Good Manufacturing Procedures, 21 CFR 210 and 211.

3.0 REQUIREMENTS

Pfizer shall conduct manufacturing activities to support production and distribution of vaccine doses after the final vaccine candidate from its development program is selected (currently expected to occur in July 2020). Subject to the terms and conditions of this Agreement, including without limitation Sections 3.1, 6.0, 11.5 and 11.6, Pfizer shall use diligent efforts to manufacture, quality release (using Pfizer's quality system), and deliver 100M doses of an FDA-approved or authorized vaccine in a preservative-free, multi-dose vial no later than the end of the period of performance (as defined in Section 3.1).

Pfizer anticipates providing the vaccine, subject to FDA approval or authorization, as -80 °C frozen product that needs to be maintained at or below that temperature prior to dosing. The Government acknowledges that Pfizer's responsibility for cold chain will cease upon delivery in accordance with Section 6.0.

Pfizer anticipates providing the vaccine, subject to FDA-approval or authorization, as a concentrate that needs to be diluted at point of use prior to dosing. Vaccinators will need to use locally sourced 0.9% Sodium Chloride Injection, USP (Normal Saline), syringes and needles.

3.1 Period of Performance

The total proposed duration of this prototype initiative is (b) (4) with an expected completion date (b) (4) (the "period of performance"). If FDA-approval or authorization is not issued by October 31, 2020

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as estimated in Section 1.1.2 above, and Pfizer expects it will be unable to timely complete performance, then the Parties will discuss in good faith a contract modification to shift forward the estimated delivery schedule to reflect the difference in time period between October 31, 2020 and the date of actual regulatory approval or authorization.

As a result of these discussions, the Government shall have the unilateral ability to extend the Period of Performance of this prototype project in increments of up to thirty (30) days at a time. In no event can this unilateral right to extend the period of performance require performance (b) (4) or result in a requirement for Pfizer to demonstrate the ability to manufacture more than 100M doses.

Notwithstanding the efforts and estimated dates set forth throughout this Statement of Work, and as set out more fully in Sections 11.5 and 11.6, both Parties recognize that the vaccine is currently in Phase 1/2 clinical trials and that, despite the diligent efforts of Pfizer and BioNTech in research, and development and manufacturing, the prototype project may not be successful due to technical, clinical, regulatory or manufacturing challenges or failures.

3.2 Management and Reporting

As set forth more fully in Section 11.7, the provisions of this Section 3.2 hereby supersede and replace, in their entirety, Section 1.05 of the Base Agreement.

Pfizer will not employ any new or other Project Management components and Pfizer shall have no obligation to provide any custom reports to the Government except as provided herein. The Government acknowledges that Pfizer plans to utilize existing Pfizer-formatted reports to provide this information to the Government as described in the Deliverable table below at Section 4.0.

Pfizer shall provide (b) (4) technical reports providing an update of relevant ongoing non-Government funded activities.

Pfizer shall provide, (b) (4) a synopsis of the Phase 2b/3 clinical trial protocol, which synopsis shall include [Overview of the Protocol, Objectives and Endpoints, Statistical Methods, and Schedule of Activities].

Pfizer shall provide copies of EUA and BLA filings, as well as interim and final data updates from clinical studies in a format determined by Pfizer.

Pfizer shall provide weekly prototype production status reports, including the number of batches produced, doses in the batch, and release status of the finished doses.

In addition to regular reporting requirements, during the period of performance, Pfizer shall use diligent efforts to notify the Government (b) (4) of any event, risk, formal or informal

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FDA communication, or other issue that would be reasonably expected to materially change the anticipated schedule by one week or more.

Except for reports expressly contemplated in this Statement of Work, Pfizer and the Government agree that Pfizer will not be subject to any reporting requirements contemplated in Section 1.05 of the Base Agreement.

4.0 DELIVERABLES

As set forth more fully in Sections 11.5 and 11.6, the Government understands that the dates set forth below are Pfizer’s best estimate, as of the Execution Date of this Agreement, of its development and manufacturing timelines, and that these timeframes are subject to significant risks and uncertainties. Pfizer will promptly notify the Government of any event(s) that would be reasonably expected to materially alter projected Estimated Due Date for Deliverables 4.1 through 4.20.

The Government agrees that it will not resell any of the deliverables to any third party.

Deliverables

Del. #	Deliverable Description	Estimated Due Date	Format	SOW Reference	Government Role	Data Rights
4.1	Project Kick-Off materials	(b) (4)	Telecon. and related slides	--	Review	(b) (4)
4.2	Phase 2b/3 Clinical Trial Synopsis	(b) (4)	Pfizer-determined format	(b) (4)	Review	(b) (4)
4.3	Provision of PL 115-92 Sponsor Authorization Letter	(b) (4)	--	--	Review/ Approve	(b) (4)
4.4	(b) (4) Updates on Prototype Production Status	(b) (4)	Pfizer-determined format	(b) (4)	Review	(b) (4)
4.5	(b) (4) Business and Technical Report	(b) (4)	Pfizer-determined format	(b) (4)	Review	(b) (4)

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4.6	EUA Filing	[REDACTED]	Pfizer-determined format	[REDACTED]	Review	(b) (4)
4.7	BLA Filing	[REDACTED]	Pfizer-determined format	[REDACTED]	Review	(b) (4)
4.8	Delivery of 100M doses	(b) (4)	--	[REDACTED]	Receipt	(b) (4)
4.9	Release documentation for delivered doses	(b) (4)	Pfizer-determined format	[REDACTED]	Review	(b) (4)
4.10	Supply Chain Resiliency Plan or Pfizer Equivalent	(b) (4)	Pfizer-determined format	[REDACTED]	Review & Comment	(b) (4)
4.11	Manufacturing Data Requirement or Pfizer Equivalent	(b) (4)	Pfizer - determined format	[REDACTED]	Review & Comment	(b) (4)
4.12	Product Development Source Material & Manufacturing Reports and Projections	(b) (4)	Pfizer-determined format	[REDACTED]	Review & Comment	(b) (4)
4.13	Work Location Report or Pfizer Equivalent	(b) (4)	Pfizer-determined format	[REDACTED]	Review & Comment	(b) (4)
4.14	Facility Security Plan or Pfizer Equivalent	(b) (4)	Pfizer-determined format	[REDACTED]	Review & Comment	(b) (4)
4.15	Confirmation of Registration and Listing with FDA	(b) (4)		[REDACTED]	Review	(b) (4)

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4.16	Formal Written Responses from the FDA	(b) (4)		(b) (4)	Review	(b) (4)
4.17	FDA Inspection and Compliance Notices, Observations and Responses	(b) (4)		(b) (4)	Review	(b) (4)
4.18	Manufacturing Development Plan*	(b) (4)		(b) (4)	Review	(b) (4)
4.19	Quality Management Plan**	(b) (4)		(b) (4)	Review	(b) (4)
4.20	Shipping Specifications and Details	(b) (4)		(b) (4)	Review	(b) (4)

* Manufacturing Development Plan. Pfizer will, (b) (4) describe the manufacturing process for the vaccine product to ensure conformity with §501(a)(2)(B) of the Food, Drug, and Cosmetics Act (FD&C Act, Title 21 United States Code (“U.S.C.”) §351 (a)(2)(B)), regarding good manufacturing practices (“GMP”). This plan shall describe (b) (4)

** Quality Management Plan. Pfizer will, (b) (4) provide a quality management plan (b) (4)

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The Government acknowledges that, as set forth more fully in Section 1.1.2, the above deliverables (other than the delivery of doses contemplated by Section 4.5) are being prepared without the use of Government funding.

As used herein, the term “Limited” means “limited rights” as that term is defined in DFARS 252.227.7013(a)(14).

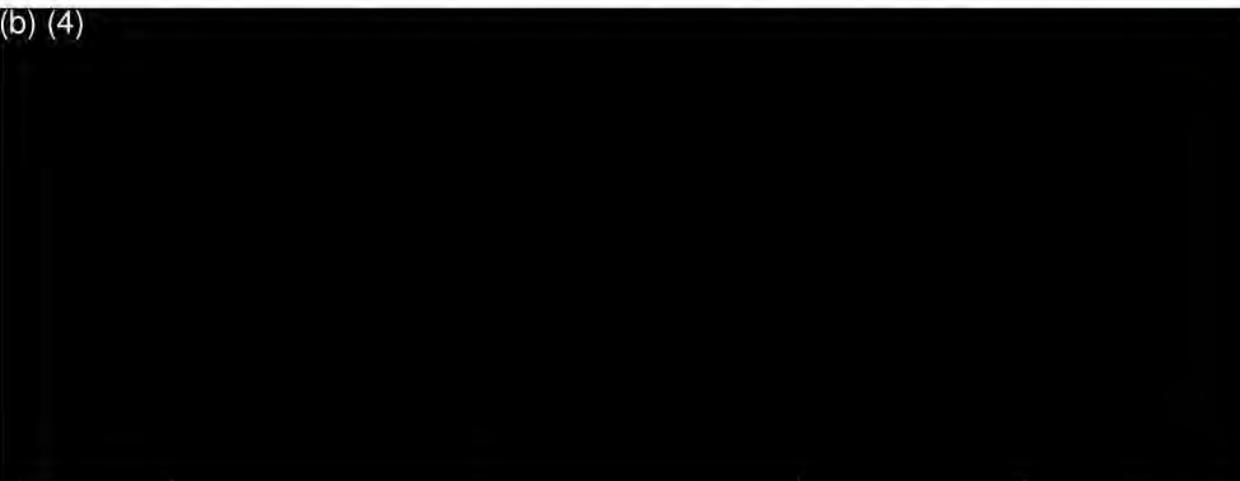
5.0 MILESTONE PAYMENT SCHEDULE

As set forth more fully in Section 11.7, the provisions of this Section 5 supersede and replace, in their entirety, the provisions of 5.04b of the Base Agreement.

As the clinical trials and validation of the product presentation are ongoing, the estimated timing of delivery of doses is subject to change. Provided the FDA has granted approval or authorization, the 100M doses will be provided by Pfizer to the Government on a Firm Fixed Price per dose basis in accordance with the Milestone Payment Schedule. Due to variances in fill/finish yield, Pfizer shall invoice for and the Government, through the Consortium Management Firm (CMF), shall pay for actual quantities delivered, at a rate of \$19.50 per dose. Subject to regulatory and technical success, Pfizer shall use its diligent efforts to provide the Government the full 100M doses on or before the final delivery date.

Upon release, Pfizer will ship the doses to the Government as set forth in Section 6.0, below. Pfizer expects to invoice the Government (through the CMF) every month for released doses that have been shipped during each such monthly period. The CMF will pay all such invoices within thirty (30) days of receipt thereof. Pfizer shall submit invoices via email to MCDC-invoices@ati.org.

(b) (4)



Total (Include Payment Type; FFP):	\$1.95B
(b) (4)	(b) (4)

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Except as contemplated by the Option, the price per dose set forth in this Statement of Work is provided in connection with Operation Warp Speed and this specific Statement of Work only. This price shall not serve as the basis for pricing under any separate government contracts between Pfizer and HHS, the Department of Defense, or any other Department or agency of the Government by application of most favored customer, most favored nations, or any other contract or program-specific terms.

For clarity, the Government will have no right to withhold payment in respect of any delivered doses, unless the FDA has withdrawn approval or authorization of the vaccine. In such event, the Parties will work in good faith to establish an appropriate course of action for delivered doses which have not yet been administered. By way of illustrative example only, (b) (4)

[REDACTED]

6.0 SHIPPING PROVISIONS

In coordination with the Government, Pfizer will conduct a demonstration of the shipping process prior to the first delivery of doses at a time mutually agreed by the Parties. As set forth in Section 4.0, Pfizer agrees to share specifications and details associated with the shipping process and containers to enable the Government to adequately plan and prepare for potential distribution of the vaccine.

Pfizer will notify the Government the date by which doses will become available for delivery. The Government will confirm dosage orders by ship-to location (b) (4) in advance of those dates; *provided* that each such ship-to location will abide by the specifications provided by Pfizer or will otherwise be agreed by Pfizer and the Government. The number of ship-to locations and the manner of delivery shall be identified to create an efficient delivery of the doses, subject to mutual agreement of the parties. The recommended delivery quantity for each ship-to location is (b) (4)

[REDACTED]

(b) (4)

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7.0 INTELLECTUAL PROPERTY, DATA RIGHTS, AND COPYRIGHTS

As set forth more fully in Section 11.7, the provisions of this Section 7.0 supersede and replace, in their entirety, the provisions of Article X (Patent Rights), Article XI (Data Rights) of the Base Agreement.

7.1 Inventions

As between Pfizer and the Government, Pfizer shall hereby retain all of its rights, titles and interests in and to any and all inventions conceived and reduced to practice by Pfizer and/or BioNTech (i) as of the Effective Date of this Agreement, or (ii) after the Effective Date of this Agreement, outside the scope of this Statement of Work (“Background Inventions”). Pfizer does not grant to the Government any license to practice the Background Inventions under this Agreement.

As between Pfizer and the Government, all inventions conceived or first actually reduced to practice in the performance of this Statement of Work (“Subject Inventions”) shall be owned by Pfizer. If invented solely by Pfizer, Pfizer will be able to elect, in its discretion, whether to hold Subject Inventions as trade secrets, and holding a Subject Invention as a trade secret will not forfeit title to the Government. Pfizer does not grant to the Government a license to practice any Subject Inventions on behalf of the Government.

Notwithstanding the foregoing, and as set forth more fully in Section 1.1.2, the Government acknowledges that it is not funding the research or development of the vaccine, or CMC/process development in respect thereof. As such, neither Pfizer nor the Government anticipate the conception or reduction to practice of any Subject Inventions.

The Government acknowledges that the Bayh-Dole Act does not apply to or govern this Agreement. Given that the Government will not fund the conception or reduction to practice of Background Inventions or Subject Inventions hereunder, this Agreement shall neither (i) give the Government any rights to “march-in,” as that term is defined in 35 U.S.C. § 203, nor (ii) subject Pfizer to the manufacturing requirements of 35 U.S.C. § 204.

7.2 Data

The Government recognizes that all data relating to the vaccine has been and will continue to be generated by Pfizer and its collaboration partner, BioNTech, without the use of Government funding.

As between Pfizer and the Government, Pfizer shall own any and all data generated by Pfizer and/or BioNTech (i) as of the Effective Date of this Statement of Work, or (ii) after the Effective Date of this Statement of Work, outside the scope of this Statement of Work (“Background Data”). As between Pfizer and the Government, Pfizer also shall own any and all data generated by Pfizer

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within the scope of this Statement of Work (“Subject Data”). For the avoidance of doubt, the parties do not anticipate Pfizer generating any Subject Data using Government funding.

Pfizer hereby grants the Government a non-exclusive license to use any Background Data and Subject Data contained in the deliverables pursuant to Section 4, but solely to the extent necessary for the Government to perform its obligations under this Agreement and arrange administration of the doses delivered in accordance with FDA and other applicable regulations.

The Government will provide Pfizer with no less than thirty (30) days’ written notice prior to releasing, in response to a Freedom of Information Act (FOIA) request, any document submitted by Pfizer to Government. During this 30-day period, Pfizer shall have the right to notify Government which documents, if any, contain trade secrets of Pfizer, BioNTech or their respective collaboration partners (or other information legally withholdable from release under FOIA).

7.3 Regulatory Rights

Pfizer will seek and anticipates that it will achieve FDA-approval or authorization and commercialization of Pfizer and BioNTech’s mRNA-based Vaccine against SARS-CoV-2 Coronavirus (the “Technology”).

Pfizer and the Government agree to the following:

Communications. Pfizer will provide the Government with all formal written responses from the FDA regarding the Technology (b) (4).

Pfizer also shall use diligent efforts to provide to the USG Government any and all FDA inspection and compliance notices, observations, and responses from Pfizer (b) (4). The Government shall limit distribution of these documents to HHS and DoD regulatory personnel, and may share the substance of the documents to others within the DoD and HHS that have a need to know.

DoD Medical Product Priority. PL 115-92 allows the DoD to request, and FDA to provide, assistance to expedite development of products to diagnose, treat, or prevent serious or life-threatening diseases or conditions facing American military personnel. Pfizer recognizes that only the DoD can utilize PL 115-92. (b) (4)

Pfizer shall submit Public Law 115-92 Sponsor Authorization Letter that will be delivered to the designated OWS POC(s) (b) (4).

8.0 SECURITY / EXPORT CONTROL

As set forth more fully in Section 11.7, the provisions of this Section 8 supersede the provisions of Article XII (Export Controls). The following requirements of Article XVII (Security and

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OPSEC) of the Base Agreement are not applicable and are therefore self-deleting and replaced by this Section: all references to CUI and CDI, sub-paragraphs (1) through (20) excepting sub-Paragraphs (3)(e), (4), and (20)(d).

The security classification for this effort is Unclassified. As it is currently not anticipated that any Controlled Unclassified Information (“CUI”) will be obtained under this Statement of Work, other than Pfizer proprietary information, DFARS 252.204-8012 shall not apply. In addition, the training requirements of Article XVII of the Base Agreement shall not apply. However, if CUI is provided, Pfizer will keep all such information confidential and will only give access to such information to persons with a legitimate need for such access.

Pfizer agrees to comply with all applicable laws regarding commodities and technology subject to this Statement of Work. Pfizer will submit plans and reports as set forth in Section 4.0 above addressing the security topics generally contemplated by Appendix 1 to this Statement of Work. The Government acknowledges that these plans will reflect Pfizer’s established security procedures in place with respect to its facilities and information security, which are at least as protective as would be customary for a global company. Pfizer will use commercially reasonable efforts to implement any further procedures/precautions reasonably requested by the Government with respect to Statement of Work and Appendix 1, at Pfizer’s sole discretion and as long as such implementation would not adversely impact Pfizer’s ordinary operation of its facilities and systems in connection with its other business and products.

9.0 MISCELLANEOUS REQUIREMENTS (SAFETY, ENVIRONMENTAL, ETC.)

Intentionally Left Blank.

10.0 GOVERNMENT FURNISHED PROPERTY/MATERIAL/INFORMATION

As set forth more fully in Section 11.7, the provisions of this Section 10.0 supersede and replace, in their entirety, the provisions of Article XIII (Title and Disposition of Property) of the Base Agreement.

There will be no Government furnished equipment, and no equipment will be funded by the Government under this Statement of Work.

11.0 OTHER

11.1 PREP Act.

In accordance with the Public Readiness and Emergency Preparedness Act (“PREP Act”), Pub. L. No. 109-148, Division C, Section 2, as amended (codified at 42 U.S.C. § 247d-6d and 42 U.S.C. § 247d-6e), as well as the Secretary of HHS’s Declaration Under the Public Readiness and

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Emergency Preparedness Act for Medical Countermeasures Against COVID-19, 85 Fed. Reg. 15198 (Mar. 17, 2020, effective Feb. 4, 2020), and amended on April 15, 2020, 85 Fed. Reg. 21012, and on June 8, 2020, 85 Fed. Reg. 34740 (together, the “Prep Act Declaration”):

- (i) This Agreement is being entered into for purposes of facilitating the manufacture, testing, development, distribution, administration, and use of “Covered Countermeasures” for responding to the COVID-19 public health emergency, in accordance with Section VI of the PREP Act Declaration;
- (ii) Pfizer’s performance of this Agreement falls within the scope of the “Recommended Activities” for responding to the COVID-19 public health emergency in accordance with Section III of the PREP Act Declaration; and
- (iii) Pfizer is a “Covered Person” per Section V of the PREP Act Declaration.

Therefore, in accordance with Sections IV and VII of the PREP Act Declaration as well as the PREP Act (42 U.S.C. § 247d-6d), the Department of Defense contracting via assisted acquisition on behalf of the HHS, expressly acknowledges and agrees that the HHS Declaration cited above, specifically its language providing immunity from suit and liability is applicable to this Agreement, as long as Pfizer’s activities fall within the terms and conditions of the PREP Act and the PREP Act Declaration.

The Government may not use, or authorize the use of, any products or materials provided under this Agreement, unless such use occurs in the United States and is protected from liability under a declaration issued under the PREP Act, or a successor COVID-19 PREP Act declaration of equal or greater scope.

11.2 Terminations. As set forth more fully in Section 11.7, the provisions of this Section 11.2 hereby supersede and replace, in their entirety, Sections 2.03 and 2.06 of the Base Agreement:

(a) (b) (4)



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(b) Stop-Work Orders. Except as required by applicable law or regulation, or judicial or administrative order, the Government shall not have the authority to issue a Stop-Work Order to halt the work contemplated under this Statement of Work.

(c) Consequences of Termination. In the event of termination of this Agreement pursuant to this Section 11.2, or expiration of this Agreement at the end of the period of performance as set forth in Section 3.1, this Agreement shall forthwith become null and void and have no effect, without any liability on the part of any Party; *provided, however*, that Sections 7, 11 and 12 hereof, and Article VIII (Confidential Information) of the Base Agreement, shall survive any termination or expiration of this Agreement; and *provided, further*, that the termination or expiration of this Agreement shall not release any Party hereto of any liability, including any outstanding payments of the Government for doses previously delivered hereunder, which at the time of termination or expiration had already accrued to the other party in respect to any act or omission prior thereto.

11.3 Audits. As set forth more fully in Section 11.7, the provisions of this Section 11.3 hereby supersede and replace, in their entirety, the provisions of Section 5.07 (Financial Records and Reports) of the Base Agreement.

Pfizer's relevant financial records shall not be subject to audit until the Government has provided funds to Pfizer. These records will be subject to audit for a period not to exceed three (3) years after final payment under this Agreement. Pfizer shall have the right to request use of a third-party audit firm to audit Pfizer's books and records maintained in connection with this Agreement; however, in accordance with 10 U.S.C. § 2371b(c) for a period not to exceed three (3) years after final payment under this Agreement, the Comptroller General shall have access to examine the records of any party to the agreement or any entity that participates in the performance of the agreement.

11.4 Disputes. As set forth more fully in Section 11.7, Section 7.02 of the Base Agreement is hereby amended to add the following at the end of said section:

The Government's breach of this Statement of Work may result in money damages and nothing in the Project Agreement (if any) or Base Agreement prevents Pfizer from seeking relief in the United States Court of Federal Claims pursuant to 28 U.S.C. § 1491.

11.5 Timing Estimates. All timing estimates set forth in this Statement of Work are subject to change based on emerging data, regulatory guidance, and manufacturing and technical developments, among other risks.

11.6 Limitation of Liability. The Government acknowledges and agrees that Pfizer's efforts to develop and manufacture a vaccine intended to prevent COVID-19 disease caused by SARS-CoV-2 are aspirational in nature and subject to significant risks and uncertainties. Accordingly, notwithstanding anything to the contrary in this Statement of Work or the Base Agreement, Pfizer shall have no liability for any failure to develop, obtain or maintain U.S. regulatory approval or authorization of such a vaccine in accordance with the estimated schedule described in this Statement of Work.

Even if a vaccine is successfully developed and obtains U.S. regulatory approval or authorization, Pfizer shall have no liability for any failure to deliver doses in accordance with the estimated delivery dates set forth in this Statement of Work to the extent any such change in delivery dates is based on emerging data, regulatory guidance, manufacturing and technical developments, or other risks outside Pfizer's control; *provided, however*, Government retains the right to terminate this Agreement or to issue a Stop-Work Order, as specifically contemplated in Sections 11.2(1) and 11.2(b).

(b) (4)

. This Section 11.6 supersedes the Base Agreement's other liability provisions solely to the extent they are inconsistent with this Statement of Work.

11.7 Order of Precedence. Notwithstanding the provisions of Article XXIII (Order of Precedence) of the Base Agreement, the Parties hereby expressly agree that to the extent any provision of the Project Agreement (if any) or this Statement of Work conflicts with any provision of the Base Agreement, the provision of the Project Agreement (if any) or this Statement of Work, as applicable, shall supersede and replace, in the entirety, the conflicting provision of the Base Agreement and control the relationship of the Parties.

Without limiting the generality of the foregoing, this Section 11.7 shall supersede Article XXIII (Order of Precedence) of the Base Agreement and the terms of this Statement of Work shall constitute "specifically negotiated Project Agreement terms" referenced in the last sentence thereof.

This Statement of Work hereby supersedes, without limitation, the following provisions of the Base Agreement: Section 1.05 (Reporting Requirements), Section 2.03 (Termination Provisions), Section 2.06 (Stop-Work), Section 5.07 (Financial Records and Reports), Section 8.05 (Term), Article IX (Publications), Article X (Patent Rights), Article XI (Data Rights), XII (Export Controls), Article XIII (Title and Disposition of Property), Article XVII (Security and OPSEC), and Sections 21.6-21.15 (Regulations) and the integration clause above the signature block to the Base Agreement.

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11.8 (b) (4)

11.9 Non-Traditional Defense Contractor. Pfizer has self-certified that Pfizer meets the definition of a “Nontraditional Defense Contractor” as defined in the Base Agreement and therefore is not subject to the cost-sharing requirement referenced in Article VI of the Base Agreement.

11.10 Confidentiality. As set forth more fully in Section 11.7, the provisions of this Section 11.10 hereby supersede and replace, in their entirety, the provisions of Section 8.05 of the Base Agreement.

The obligations of the Receiving Party under this Section shall continue for a period of ten (10) years from the conveyance of Confidential Information. If Pfizer shall need to disclose trade secret information to the Government, Pfizer and the Government will first determine in good faith whether the Government desires to receive any such trade secret information and if the Government so desires to receive such trade secret information, all such information shall be held by the Government in confidence in perpetuity.

11.11 Announcements. Neither Pfizer nor the Government shall make, or permit any person to make, any public announcement concerning the existence, subject matter or terms of this Agreement, the transactions contemplated by it, or the relationship between the Pfizer and the Government hereunder, without the prior written consent of the other, such consent not to be unreasonably withheld or delayed, except as required by law, any governmental or regulatory authority (including, without limitation, any relevant securities exchange), any court or other authority of competent jurisdiction. Notwithstanding the foregoing, Pfizer and (its collaboration partners) shall have the right, but not the obligation, to prepare and submit scientific publications and release information to the public about its Covid-19 development program, without the Government’s consent or involvement. This section supersedes and replaces Article IX of the Base Agreement.

12.0 AGREEMENTS OFFICER’S REPRESENTATIVE (AOR) AND ALTERNATE AOR CONTACT INFORMATION

AOR

NAME: (b) (6)

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MAILING ADDRESS:

EMAIL: (b) (6)

PHONE: (b) (6)

AGENCY NAME/DIVISION/SECTION: BARDA/ASPR/HHS

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Appendix 1: Clause for MCDC Consortium Other Transaction Authority Agreements

Standard Language OWS for Consortium OTA

Required MCDC Base Agreement Modifications

The Medical CBRN Consortium (MCDC) Base Agreement, Article XVII, SECURITY & OPSEC shall apply to this Project Agreement. In addition, the below language shall replace Paragraph 6 of Article XVII of the MCDC Base Agreement.

(6) Access and General Protection/Security Policy and Procedures. This standard language text is applicable to ALL PAH employees working on critical program information or covered defense information related to Operation Warp Speed (OWS), and to those with an area of performance within an Army controlled installation, facility or area. PAH employees shall comply with applicable installation, facility and area commander installation/facility access and local security policies and procedures (provided by government representative). The PAH also shall provide all information required for background checks necessary to access critical program information or covered defense information related to OWS, and to meet installation access requirements to be accomplished by installation Provost Marshal Office, Director of Emergency Services or Security Office. The PAH workforce must comply with all personal identity verification requirements as directed by DOD, HQDA and/or local policy. In addition to the changes otherwise authorized by the changes clause of this agreement, should the Force Protection Condition (FPCON) at any individual facility or installation change, the Government may require changes in PAH security matters or processes.

Required SOW Language for Deliverables (in body of SOW or Deliverables Section)

Information Security

Classification guidance for Operation Warp Speed - The security level for this agreement is UNCLASSIFIED.

“Controlled technical information,” “covered contractor information system,” “covered defense information,” “cyber incident,” “information system,” and “technical information” are defined in DFARS Clause 252.204-7012, Safeguarding Covered Defense Information and Cyber Incident Reporting.

Personnel Security

In addition to the industry standards for employment background checks, The Contractor must be willing to have key individuals, in exceptionally sensitive positions, identified for additional vetting by the United States Government.

Supply Chain Resiliency Plan

The contractor shall develop and submit within 30 calendar days after contract award, a comprehensive Supply Chain Resiliency Program that provides identification and reporting of critical components associated with the secure supply of drug substance, drug product, and work-in-process through to finished goods.

- a) A critical component is defined as any material that is essential to the product or the manufacturing process associated with that product. Included in the definition are consumables and disposables associated with manufacturing. NOT included in the definition are facility and capital equipment.

Consideration of critical components includes the evaluation and potential impact of raw materials, excipients, active ingredients, substances, pieces, parts, software, firmware, labeling, assembly, testing, analytical and environmental componentry, reagents, or utility materials which are used in the manufacturing of a drug, cell banks, seed stocks, devices and key processing components and equipment. A clear example of a critical component is one where a sole supplier is utilized.

The contractor shall identify key equipment suppliers, their locations, local resources, and the associated control processes at the time of award. This document shall address planning and scheduling for active pharmaceutical ingredients, upstream, downstream, component assembly, finished drug product and delivery events as necessary for the delivery of product.

- a) Communication for these requirements shall be updated as part of an annual review, or as necessary, as part of regular contractual communications.
- b) For upstream and downstream processing, both single-use and re-usable in-place processing equipment, and manufacturing disposables also shall be addressed. For finished goods, the inspection, labeling, packaging, and associated machinery shall be addressed taking into account capacity capabilities.
- c) The focus on the aspects of resiliency shall be on critical components and aspects of complying with the contractual delivery schedule. Delivery methods shall be addressed, inclusive of items that are foreign-sourced, both high and low volume, which would significantly affect throughput and adherence to the contractually agreed deliveries.

The contractor shall articulate in the plan, the methodology for inventory control, production planning, scheduling processes and ordering mechanisms, as part of those agreed deliveries.

- a) Production rates and lead times shall be understood and communicated to the Contracting/Agreement Officer or the Contracting/Agreement Officer's Representative as necessary.
- b) Production throughput critical constraints should be well understood by activity and by design, and communicated to contractual personnel. As necessary, communication should focus on identification, exploitation, elevation, and secondary constraints of throughput, as appropriate.

Reports for critical items should include the following information:

- a) Critical Material
- b) Vendor
- c) Supplier, Manufacturing / Distribution Location
- d) Supplier Lead Time
- e) Shelf Life
- f) Transportation / Shipping restrictions

The CO and COR reserve the right to request un-redacted copies of technical documents, during the period of performance, for distribution within the Government. Documents shall be provided within ten (10) days after CO issues the request. The Contractor may arrange for additional time if deemed necessary, and agreed to by the CO.

Manufacturing Data Requirements:

The Contractor shall submit within 30 calendar days after award detailed data regarding project materials, sources, and manufacturing sites, including but not limited to: physical locations of sources of raw and processed material by type of material; location and nature of work performed at manufacturing, processing, and fill/finish sites; and location and nature of non-clinical and clinical studies sites. The Government may provide a table in tabular format for Contractor to be used to submit such data which would include but not be limited to the following:

- Storage/inventory of ancillary materials (vials, needles, syringes, etc.)
- Shipment of ancillary materials (vials, needles, syringes, etc.)
- Disposal of ancillary materials (vials, needles, syringes, etc.)
- Seed development or other starting material manufacturing
- Bulk drug substance and/or adjuvant production
- Fill, finish, and release of product or adjuvant
- Storage/inventory of starting materials, bulk substance, or filled/final product or adjuvant
- Stability information of bulk substance and/or finished product
- Shipment of bulk substance of final product
- Disposal of bulk substance or final product

Product Development Source Material and Manufacturing Reports and Projections:

The Contractor shall submit a detailed spreadsheet regarding critical project materials that are sourced from a location other than the United States, sources, and manufacturing sites, including but not limited to: physical locations of sources of raw and processed material by type of material; location and nature of work performed at manufacturing sites; and location and nature of non-clinical and clinical study sites.

The Contractor will provide manufacturing reports and manufacturing dose tracking projections/actuals utilizing the "COVID-19 Dose Tracking Templates", on any contract/agreement that is manufacturing product

- Contractor will submit Product Development Source Material Report
 - Within month of contract award
 - Within 30 days of substantive changes are made to sources and/or materials
 - Or on the 6th month contract anniversary.
- Contractor will update the Dose Tracking Template weekly, during manufacturing campaigns and COVID response, with the first deliverable submission within 15 days of award/modification.
- The Government will provide written comments to the Product Development Source Material and Manufacturing Report within 15 business days after the submission
- If corrective action is recommended, Contractor must address all concerns raised by the Government in writing

Contractor Locations:

The contractor shall submit detailed data regarding locations where work will be performed under this contract, including addresses, points of contact, and work performed per location, to include sub-contractors.

Contractor will submit Work Locations Report:

- Within 5 business days of contract award
- Within 30 business days after a substantive location or capabilities change
- Within 2 business days of a substantive change if the work performed supports medical countermeasure development that addresses a threat that has been declared a Public Health Emergency by the HHS Secretary or a Public Health Emergency of International Concern (PHEIC) by the WHO

Required SOW Language for Security Section

This project requires an OPSEC Plan and a Security Plan.

The contractor shall develop a comprehensive security program that provides overall protection of personnel, information, data, and facilities associated with fulfilling the Government requirement. This plan shall establish security practices and procedures that demonstrate how the contractor will meet and adhere to the security requirements outlined below prior to the commencement of product manufacturing, and shall be delivered to the Government within 30 calendar days of award. The contractor shall also ensure all subcontractors, consultants, researchers, etc. performing work on behalf of this effort, comply with all Operation Warp Speed and Project Agreement security requirements and prime contractor security plans.

- a) The Government will review in detail and submit comments within ten (10) business days to the Contracting Officer (CO) to be forwarded to the Contractor. The Contractor shall review the Draft Security Plan comments, and, submit a Final Security Plan to the U.S. Government within thirty (10) calendar days after receipt of the comments.
- b) The Security Plan shall include a timeline for compliance of all the required security measures outlined by the Government.
- c) Upon completion of initiating all security measures, the Contractor shall supply to the Contracting Officer a letter certifying compliance to the elements outlined in the Final Security Plan.

At a minimum, the Final Security Plan shall address the following items:

Security Requirements:

1. Facility Security Plan Description: As part of the partner facility's overall security program, the contractor shall submit a written security plan with their proposal to the Agreement Officer for review and approval by Operation Warp Speed security subject matter experts. The performance of work under the Project Agreement will be in accordance with the approved security plan. The security plan will include the following processes and procedures at a minimum:	
Security Administration	<ul style="list-style-type: none"> • organization chart and responsibilities • written security risk assessment for site • threat levels with identification matrix (High, Medium, or Low) • enhanced security procedures during elevated threats • liaison procedures with law enforcement • annual employee security education and training program
Personnel Security	<ul style="list-style-type: none"> • policies and procedures • candidate recruitment process • background investigations process • employment suitability policy • employee access determination • rules of behavior/ conduct • termination procedures • non-disclosure agreements
Physical Security Policies and Procedures	<ul style="list-style-type: none"> • internal/external access control • protective services • identification/badging • employee and visitor access controls • parking areas and access control • perimeter fencing/barriers • product shipping, receiving and transport security procedures • facility security lighting • restricted areas • signage • intrusion detection systems • alarm monitoring/response • closed circuit television • product storage security • other control measures as identified
Information Security	<ul style="list-style-type: none"> • identification and marking of sensitive information • access control • storage of information • document control procedures • retention/ destruction requirements
Information Technology/Cyber Security Policies and Procedures	<ul style="list-style-type: none"> • intrusion detection and prevention systems • threat identification • employee training (initial and annual) • encryption systems • identification of sensitive information/media • password policy (max days 90) • lock screen time out policy (minimum time 20 minutes) • removable media policy • laptop policy • removal of IT assets for domestic/foreign travel • access control and determination • VPN procedures • WiFi and Bluetooth disabled when not in use

	<ul style="list-style-type: none"> • system document control • system backup • system disaster recovery • incident response • system audit procedures • property accountability
<p>2. Site Security Master Plan</p> <p>Description: The partner facility shall provide a site schematic for security systems which includes: main access points; security cameras; electronic access points; IT Server Room; Product Storage Freezer/Room; and bio-containment laboratories.</p>	
<p>3. Site Threat / Vulnerability / Risk Assessment</p> <p>Description: The partner facility shall provide a written risk assessment for the facility addressing: criminal threat, including crime data; foreign/domestic terrorist threat; industrial espionage; insider threats; natural disasters; and potential loss of critical infrastructure (power/water/natural gas, etc.) This assessment shall include recent data obtained from local law enforcement agencies. The assessment should be updated annually.</p>	
<p>4. Physical Security</p> <p>Description:</p>	
Closed Circuit Television (CCTV) Monitoring	<ul style="list-style-type: none"> a) Layered (internal/external) CCTV coverage with time-lapse video recording for buildings and areas where critical assets are processed or stored. b) CCTV coverage must include entry and exits to critical facilities, perimeters, and areas within the facility deemed critical to the execution of the contract. c) Video recordings must be maintained for a minimum of 30 days. d) CCTV surveillance system must be on emergency power backup. e) CCTV coverage must include entry and exits to critical facilities, perimeters, and areas within the facility deemed critical to the execution of the contract. f) Video recordings must be maintained for a minimum of 30 days. g) CCTV surveillance system must be on emergency power backup.
Facility Lighting	<ul style="list-style-type: none"> a) Lighting must cover facility perimeter, parking areas, critical infrastructure, and entrances and exits to buildings. b) Lighting must have emergency power backup. c) Lighting must be sufficient for the effective operation of the CCTV surveillance system during hours of darkness.
Shipping and Receiving	<ul style="list-style-type: none"> a) Must have CCTV coverage and an electronic access control system. b) Must have procedures in place to control access and movement of drivers picking up or delivering shipments. c) Must identify drivers picking up Government products by government issued photo identification.
Access Control	<ul style="list-style-type: none"> a) Must have an electronic intrusion detection system with centralized monitoring. b) Responses to alarms must be immediate and documented in writing. c) Employ an electronic system (i.e., card key) to control access to areas where assets critical to the contract are located (facilities, laboratories, clean rooms, production facilities, warehouses, server rooms, records storage, etc.). d) The electronic access control should signal an alarm notification of unauthorized attempts to access restricted areas. e) Must have a system that provides a historical log of all key access transactions and kept on record for a minimum of 12 months.

	<ul style="list-style-type: none"> f) Must have procedures in place to track issuance of access cards to employees and the ability to deactivate cards when they are lost or an employee leaves the company. g) Response to electronic access control alarms must be immediate and documented in writing and kept on record for a minimum of 12 months. h) Should have written procedures to prevent employee piggybacking access i) to critical infrastructure (generators, air handlers, fuel storage, etc.) should be controlled and limited to those with a legitimate need for access. j) Must have a written manual key accountability and inventory process. k) Physical access controls should present a layered approach to critical assets within the facility.
Employee/Visitor Identification	<ul style="list-style-type: none"> a) Should issue company photo identification to all employees. b) Photo identification should be displayed above the waist anytime the employee is on company property. c) Visitors should be sponsored by an employee and must present government issued photo identification to enter the property. d) Visitors should be logged in and out of the facility and should be escorted by an employee while on the premises at all times.
Security Fencing	Requirements for security fencing will be determined by the criticality of the program, review of the security plan, threat assessment, and onsite security assessment.
Protective Security Forces	Requirements for security officers will be determined by the criticality of the program, review of the security plan, threat assessment, and onsite security assessment.
Protective Security Forces Operations	<ul style="list-style-type: none"> a) Must have in-service training program. b) Must have Use of Force Continuum. c) Must have communication systems available (i.e., landline on post, cell phones, handheld radio, and desktop computer). d) Must have Standing Post Orders. e) Must wear distinct uniform identifying them as security officers.
5. Security Operations	
Description:	
Information Sharing	<ul style="list-style-type: none"> a) Establish formal liaison with law enforcement. b) Meet in person at a minimum annually. Document meeting notes and keep them on file for a, minimum of 12 months. POC information for LE Officer that attended the meeting must be documented. c) Implement procedures for receiving and disseminating threat information.
Training	<ul style="list-style-type: none"> a) Conduct new employee security awareness training. b) Conduct and maintain records of annual security awareness training.
Security Management	<ul style="list-style-type: none"> a) Designate a knowledgeable security professional to manage the security of the facility. b) Ensure subcontractor compliance with all Government security requirements.
6. Personnel Security	
Description:	
Records Checks	Verification of social security number, date of birth, citizenship, education credentials, five-year previous employment history, five-year previous residence history, FDA disbarment, sex offender registry, credit check based upon position within the company; motor vehicle records check as appropriate; and local/national criminal history search.
Hiring and Retention Standards	<ul style="list-style-type: none"> a) Detailed policies and procedures concerning hiring and retention of employees, employee conduct, and off boarding procedures.

	b) Off Boarding procedures should be accomplished within 24 hour of employee leaving the company. This includes termination of all network access.
7. Information Security	
Description:	
Physical Document Control	<ul style="list-style-type: none"> a) Applicable documents shall be identified and marked as procurement sensitive, proprietary, or with appropriate government markings. b) Sensitive, proprietary, and government documents should be maintained in a lockable filing cabinet/desk or other storage device and not be left unattended. c) Access to sensitive information should be restricted to those with a need to know.
Document Destruction	Documents must be destroyed using approved destruction measures (i.e., shredders/approved third party vendors / pulverizing / incinerating).
8. Information Technology & Cybersecurity	
Description:	
Identity Management	<ul style="list-style-type: none"> a) Physical devices and systems within the organization are inventoried and accounted for annually. b) Organizational cybersecurity policy is established and communicated. c) Asset vulnerabilities are identified and documented. d) Cyber threat intelligence is received from information sharing forums and sources. e) Threats, vulnerabilities, likelihoods, and impacts are used to determine risk. f) Identities and credentials are issued, managed, verified, revoked, and audited for authorized devices, users and processes. g) Users, devices, and other assets are authenticated (e.g., single-factor, multifactor) commensurate with the risk of the transaction (e.g., individuals' security and privacy risks and other organizational risks)
Access Control	<ul style="list-style-type: none"> a) Limit information system access to authorized users. b) Identify information system users, processes acting on behalf of users, or devices and authenticate identities before allowing access. c) Limit physical access to information systems, equipment, and server rooms with electronic access controls. d) Limit access to/ verify access to use of external information systems.
Training	a) Ensure that personnel are trained and are made aware of the security risks associated with their activities and of the applicable laws, policies, standards, regulations, or procedures related to information technology systems.
Audit and Accountability	<ul style="list-style-type: none"> a) Create, protect, and retain information system audit records to the extent needed to enable the monitoring, analysis, investigation, and reporting of unlawful, unauthorized, or inappropriate system activity. Records must be kept for minimum must be kept for 12 months. b) Ensure the actions of individual information system users can be uniquely traced to those users. c) Update malicious code mechanisms when new releases are available. d) Perform periodic scans of the information system and real time scans of files from external sources as files are downloaded, opened, or executed.
Configuration Management	<ul style="list-style-type: none"> a) Establish and enforce security configuration settings. b) Implement sub networks for publically accessible system components that are physically or logically separated from internal networks.

Contingency Planning	a) Establish, implement, and maintain plans for emergency response, backup operations, and post-disaster recovery for information systems to ensure the availability of critical information resources at all times.
Incident Response	a) Establish an operational incident handling capability for information systems that includes adequate preparation, detection, analysis, containment, and recovery of cybersecurity incidents. Exercise this capability annually.
Media and Information Protection	a) Protect information system media, both paper and digital. b) Limit access to information on information systems media to authorized users. c) Sanitize and destroy media no longer in use. d) Control the use of removable media through technology or policy.
Physical and Environmental Protection	a) Limit access to information systems, equipment, and the respective operating environments to authorized individuals. b) Intrusion detection and prevention system employed on IT networks. c) Protect the physical and support infrastructure for all information systems. d) Protect information systems against environmental hazards. e) Escort visitors and monitor visitor activity.
Network Protection	Employ intrusion prevention and detection technology with immediate analysis capabilities.
9. Transportation Security	
Description: Adequate security controls must be implemented to protect materials while in transit from theft, destruction, manipulation, or damage.	
Drivers	a) Drivers must be vetted in accordance with the Government Personnel Security Requirements. b) Drivers must be trained on specific security and emergency procedures. c) Drivers must be equipped with backup communications. d) Driver identity must be 100 percent confirmed before the pick-up of any Government product. e) Drivers must never leave Government products unattended, and two drivers may be required for longer transport routes or critical products during times of emergency. f) Truck pickup and deliveries must be logged and kept on record for a minimum of 12 months.
Transport Routes	a) Transport routes should be pre-planned and never deviated from except when approved or in the event of an emergency. b) Transport routes should be continuously evaluated based upon new threats, significant planned events, weather, and other situations that may delay or disrupt transport.
Product Security	a) Government products must be secured with tamper resistant seals during transport, and the transport trailer must be locked and sealed. <ul style="list-style-type: none"> • Tamper resistant seals must be verified as "secure" after the product is placed in the transport vehicle. b) Government products should be continually monitored by GPS technology while in transport, and any deviations from planned routes should be investigated and documented. c) Contingency plans should be in place to keep the product secure during emergencies such as accidents and transport vehicle breakdowns.
10. Security Reporting Requirements	
Description: The partner facility shall notify the Agreement Officer within 24 hours of any activity or incident that is in violation of established security standards or indicates the loss or theft of government products. The facts and circumstances associated with these incidents will be documented in writing for government review.	
11. Security Audits	

Description: The partner facility agrees to formal security audits conducted at the discretion of the government. Security audits may include both prime and subcontractor.	