MEDSAFE
New Zealand Medicines and Medical Devices Safety Authority

133 Molesworth Street
PO Box 5013
Wellington 6140
New Zealand
T +64 4 496 2000
W www.medsafe.govt.nz

8 November 2023

Name Redacted

Ref: H2023031427

Name Redacted

Response to your request for official information

Thank you for your request under the Official Information Act 1982 (the Act) to Manatū Hauora (the Ministry of Health) on 4 September 2023 for information on the Pfizer new medicine application for Comirnaty COVID-19 vaccine. I apologise for the delay in response, please find an answer to each question below.

> *"I seek further information referred to in the following file received under the OIA . www.health.govt.nz/system/files/documents/information-release/h202106950 - response.pdf*
> *1. I refer to a letter dated 21 October 2020 from Pfizer Australia to Medsafe in respect of the new medicines application for the Covid-19 vaccine on page 35. Under the heading CTD Dossier and Content, there is reference to the fee payable for the evaluation of their application. What is the amount of the fee paid from Pfizer to Medsafe for this evaluation? Who receives this fee payment and what is it used for? Where a product is declined, is the fee refunded to the sponsors or is it retained by Medsafe irrespective of the outcome?*

The fee charged for the application is shown on page 145 of OIA response you refer to, ref H202106950. This was $102,210. Information about Medsafe application fees is publicly available on our website here: www.medsafe.govt.nz/regulatory/Guideline/GRTPNZ/overview-of-medicine-regulation.pdf.

Once the evaluation of an application has begun, the application fee is non-refundable regardless of whether approval is granted or not.

> *2. The document titled Terms of Reference Medsafe COVID-19 Vaccine Advisory Group is set out on page 36. On page 37 condition 5.2 states:*
> *5.2 The commissioning templates will include a section for reports detailing the expert advice provided in response to the question(s) and are to be written. These completed templates will be provided to Medsafe following consideration by the member(s) of the Group. These reports will be stored alongside the Medsafe assessment reports but will not be provided with the assessment reports to sponsors. Templates with the responses are subject to the OIA as per above.*
>
> *Please provide the reports detailing expert advice together with the completed templates referred to under condition 5.2.*

Documents within scope of this part of your request are attached to this letter. All documents are itemised in Appendix 1 and copies of the documents are enclosed. Where information is

withheld under section 9 of the Act, I have considered the countervailing public interest in release in making this decision and consider that it does not outweigh the need to withhold at this time.

> *3. At page 37, condition 5.4 states:*
> *A report to the Health System Improvement and Innovation Deputy Director-General and the appropriate COVID vaccine governance group will be provided at the Group's end date. Please provide a copy of all reports referred to under condition 5.4.*

This part of your request is refused under section 18(e) of the Act as the information requested does not exist.

> *4. I refer to condition 5.1 on page 37. Condition 5.1 states:*
> *5.1 When ad hoc meetings of the Group are held, summaries will be produced by the secretary but not published. Summaries are subject to the Official Information Act 1982 (OIA) but any confidential information will be withheld.*
> *Please provide copies of all ad hoc meeting summaries referred to above."*

No meetings were held regarding the application in question as such Medsafe is unable to provide you with this information. This part of your request is refused under section 18(e) of the Act.

Under section 28(3) of the Act, you have the right to ask the Ombudsman to review any decisions made under this request. The Ombudsman may be contacted by email at: info@ombudsman.parliament.nz or by calling 0800 802 602.

Please note that this response, with your personal details removed, may be published on the Manatū Hauora website at: www.health.govt.nz/about-ministry/information-releases/responses-official-information-act-requests.

Nāku noa, nā

Chris James
Group Manager
Medsafe

Appendix 1: List of documents for release

#	Date	Document details	Decision on release
1	12 January 2021	Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	Some information released under section 9(2)(g)(ii) of the Act to protect Ministers, members of organisations, officers, and employees from improper pressure or harassment.
2	13 January 2021	Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	
3	15 January 2021	Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	
4		Medsafe COVID-19 Vaccine Advisory Group - advice request 120121	
5		Medsafe COVID-19 Vaccine Advisory Group - advice request 120121	
6	17 January 2021	Medsafe COVID-19 Vaccine Advisory Group - advice request 120121	
7		Medsafe COVID-19 Vaccine Advisory Group - advice request 120121	
8		Medsafe COVID-19 Vaccine Advisory Group - advice request 120121	
9	18 January 2021	COVID-19 Vaccine Advisory Group - advice request 180121	
10	19 January 2021	COVID-19 Vaccine Advisory Group - advice request 110121	
11	20 January 2021	Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	
12	21 January 2021	Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	
13		Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	
14		Medsafe COVID-19 Vaccine Advisory Group - advice request 180121	
15	N/A	Medsafe COVID-19 Vaccine Advisory Group - advice request 110121	

Document 1

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii), Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii), Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	11 January 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: 10 working days

Request:
The US FDA recently granted Emergency Use Authorization for Pfizer's COVID-19 vaccine. FDA guidance is that a median of two-months clinical trial follow-up post immunization for emergency use authorization (refer page 10 of the link below).

https://www.fda.gov/media/142749/download

New Zealand currently has no community transmission of SARS-CoV-2, meaning that the benefits of an Emergency Use Authorization would not necessarily be sufficient to outweigh the risks of use based on review of limited data available. Recent research on FDA approval showed that the median follow-up was six months before approval for other vaccines.

In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

Please note that the advice requested is not intended to be specifically informed by the data submitted to date to support the quality, safety and efficacy of this vaccine. Rather it is requested that advice be provided regarding the general limitations of

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relying on a shorter clinical trial follow-up period to make a decision regarding approval, and the risks associated with this. The supporting documents are provided to give context to this request, hence why they include summary overviews as opposed to more in-depth data and analysis.

Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
- Updated data is expected in March 2021, which will include six-month median follow-up data.
- Medsafe is currently reviewing the UK MHRA clinical evaluation report. The report's discussion on clinical efficacy notes the following on page 48.

  The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.
- The current follow-up is shown by the application's Clinical Overview person-years surveillance time in Table 8, the 'No. at risk' in Figure 1, and the safety data for having follow-up after dose two ≥2 months (eg Table 32).

Attached Documents:

- FDA VRBPAC Briefing Document 'Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020' (53 pages)
- MHRA Public Assessment Report COVID-19 mRNA vaccine BNT162 (51 pages).
- CTD Module 2 document: Clinical Overview (257 pages)

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii)

Date Completed: 2021-1-12

Advice:

1. There are two risks of two-month follow-up relating to efficacy: information on **duration** of response and on **asymptomatic infection**.

Duration: Clearly, two-month follow-up cannot provide gold-standard evidence on six-month or 12-month duration of response. However, if the vaccine were conditionally approved based on two-month data, and it turned out that response duration was short, we would know this from the six-month trial data before protection began to expire in NZ.

Asymptomatic infection: In my opinion, this one is more serious. At the moment, there is little information on how well the vaccine prevents asymptomatic infection and secondary transmission. The current vaccine priority group is border workers, for whom prevention of secondary transmission is very important. According to the public Pfizer/BNT trial protocol (p98), presence of antibodies to the nucleocapsid N protein will be measured at the end of the trial, providing information about the total rate of infection, symptomatic and asymptomatic. This information will be valuable in assessing the likely impact of vaccination on border incursions. However, it is important not to overstate the point: while there is no direct evidence on prevention of asymptomatic infection, it seems unlikely that the benefit is zero. In addition, what we care most about is secondary transmission, for which we will not have data from this trial.

2. This is outside my expertise. We would miss adverse reactions that take longer than two months but less than six months to appear, but I have no real idea how plausible these are that's independent of the FDA guidance.

3. The introductory *statement "New Zealand currently has no community transmission of SARS-CoV-2"* is stronger than we have robust evidence for. We have no *detected* community transmission, just as we didn't in early August. It's quite possible that we have undetected community transmission, and have had for a few weeks. That is, the lack of a recognized outbreak in New Zealand is subject to change at no notice. Epidemic simulations also indicate that the new B 1.1.7 variant is about three times as likely as the previous variants to produce an outbreak with no initially known connection to the border (Dr Alex James, personal communication). Such an outbreak might well require a Level 4 alert. While we aren't in the US or UK situation of trying to control a large outbreak by vaccination, the current situation is not reliably stable.

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Document 2

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii) Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii) Manager, Clinical Risk Management
Date:	11 January 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: 10 working days

Request:
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In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

Please note that the advice requested is not intended to be specifically informed by the data submitted to date to support the quality, safety and efficacy of this vaccine. Rather it is requested that advice be provided regarding the general limitations of

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relying on a shorter clinical trial follow-up period to make a decision regarding approval, and the risks associated with this. The supporting documents are provided to give context to this request, hence why they include summary overviews as opposed to more in-depth data and analysis.

Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
- Updated data is expected in March 2021, which will include six-month median follow-up data.
- Medsafe is currently reviewing the UK MHRA clinical evaluation report. The report's discussion on clinical efficacy notes the following on page 48.

  The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.
- The current follow-up is shown by the application's Clinical Overview person-years surveillance time in Table 8, the 'No. at risk' in Figure 1, and the safety data for having follow-up after dose two ≥2 months (eg Table 32).

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- CTD Module 2 document: Clinical Overview (257 pages)

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii)

Date Completed: January 13, 2021

Advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

1
Long term vaccine efficacy is completely uncertain at present, as only time will tell if the virus-vaccine match remains tight, and how long immunity will persist. It will take potentially longer to determine this in low prevalence countries such as NZ where there is little or no virus circulating. It is possible that vaccine efficacy in NZ could be lower than seen in the presented data to hand from high prevalence countries. This could be because there may be a significant delay between vaccination and exposure. The immunogenicity studies provided do however provide reassurance that there are both cellular and humoral responses in apparently all vaccines tested, and it is reasonable to expect that immunity/vaccine efficacy will last longer than the 2 months.

2.
The timelines of AE developing are not clearly presented, but it appears that almost all AE occur within 2 days of vaccination. It is reasonable to assume that there will be no predictable late AE. Bell's palsy appears to a late AE that occurs in vaccine recipients, but in numbers too small to say that are causally related to vaccination itself. At this stage, having only 2 months of AE monitoring data does not concern me. Safety data will emerge more quickly from the widespread use of BNT162b overseas than from completing the followup of the existing cohort.

3.
It will be important to perform some immunogenicity studies in NZ as Pasifika and Maori subjects were under-represented in the trials. It will also provide reassurance that the vaccine's efficacy has not been affected by shipping. Assuming that HCW will be prioritized to receive the Pfizer vaccine, it will be also important to know that staff seroconvert or develop other markers of immunity.

My recommendation is the two month safety data provide sufficient reassurance for efficacy and safety. The huge numbers of people receiving the vaccine overseas at the moment also provide reassurance, despite the appearance of a small number of anaphylaxis.

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Document 3

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) , Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii) , Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii) , Manager, Clinical Risk Management
Date:	21 December 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: within 10 working days

Request:
FDA recently granted Emergency Use Authorization for Pfizer's COVID-19 vaccine. FDA guidance is that a median of two-months clinical trial follow-up post immunization for emergency use authorization (refer page 10 of the link below).

https://www.fda.gov/media/142749/download

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In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments on what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

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Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
- Updated data is expected in March 2021, which will have six-month median follow-up data.
- Medsafe is currently reviewing the MHRA clinical evaluation report. The report's discussion on clinical efficacy notes the following on page 48.

  The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.
- The current follow-up is shown by the application's Clinical Overview person-years surveillance time in Table 8, the 'No. at risk' in Figure 1, and the safety data for having follow-up after dose two ≥2 months (eg Table 32).

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member(s): s 9(2)(g)(ii)

Reviewing Member(s): [Name]

Date Completed: 15 January 2021

Advice:
With regard to answering the questions Medsafe has posed I would prefer to use the term uncertainties as opposed to risks.

Brief Summary of Efficacy

The applicant provides data from a single pivotal study to demonstrate the effectiveness of BNT162b2 30 µg mRNA COVID-19 Vaccine. (Study C4591001). The study was undertaken in males and females aged 18 to 85-years'.

The primary endpoint was symptomatic COVID-19 incidence per 1000 person-years of follow-up based on centrally or locally confirmed nucleic acid amplification test participants without serological or virological evidence of SARS-CoV-2 infection before and during vaccination regimen (cases confirmed >7 days after Dose 2), and in participants with and without evidence of SARS-CoV-2 infection before and during vaccination regimen.

The study was event-driven, and the final efficacy analysis was to be triggered by 162 cases of infection, 170 cases were reached.

Vaccine efficacy after dose 1 to before dose 2 was 52.4% (95% CI 29.5, 68.4). Vaccine efficacy from 10 days after dose 1 to before dose 2 was estimated to be 86. 7% (95% CI 68.6, 95).

The overall vaccine efficacy against symptomatic laboratory confirmed COVID-19 from 7 days after dose 2 was 95.0% (95% CI 90.0, 97.9

Phase 1 and phase 2 immunogenicity data was obtained form both the pivotal study and a supportive study, BNT162-01.

Immunological responses after vaccination with 2 doses of BNT162b2 at 30 µg was demonstrated in pre-defined groups of adults younger (18-55 years) and older adults (age groups 56-85 years and 65-85 years).

Neutralising antibodies and IgG-antigen binding antibodies were seen in participants.

The second dose given 21- days post-dose 1 resulted in a boosted humoral response in both younger and older adults.

The levels of neutralizing antibodies titres were moderate 21 days after dose 1. The peak of neutralizing antibodies titres was reached 14 days post-dose 2 in older adults versus 7 days post-dose 2 in younger adults. Immune responses were maintained up to 1-month post-dose 2..

The pivotal study is ongoing and due to the timing of submission an interim analysis was undertaken with data cut-off at 2-months.

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Uncertainties Regarding 2-months Efficacy data

A single dose of the vaccine does appear to confer a degree of protection that is augmented by a second dose, however the data are limited and this needs to be confirmed by longer term data.

As the data are limited due to the timing of the submission, efficacy of the vaccine against severe COVID-19 7 days after the second dose (a secondary endpoint of the pivotal study) can not be established.

Long term effectiveness after a single dose has not been established, generally speaking the efficacy should be established over six-months to establish the need or otherwise for a booster dose, which may vary amongst a younger and older population.

Although not directly related to the question with regard to duration of efficacy the pivotal study was not designed to demonstrate that immunisation with BNT162b2 prevents the spread of SARS-CoV-2.

Brief Summary of Safety

The safety evaluation is based on one ongoing Phase 2/3 study that at the time of data cut-off included 43,448 subjects who received either two doses of BNT162b2 (n=21 720) or placebo (n=21 728).

The data cut-off date for was 14 November 2020 for additional follow-up to at least 2 months after administration of the second dose of BNT162b2.

More participants in the BNT162b2 group reported at least 1 AE and at least 1 related AE compared with the placebo group.

The rates of withdrawal were low (approx. 0.2%) in both active and placebo groups.

The most frequent adverse events could be considered reactions that are common to vaccine administration such as injection site pain, fever, fatigue, myalgia and arthralgia, nausea and lymphadenopathy.

The rate of allergic reaction was low, one case was observed in active and once case in placebo. The subject in the treatment group had a history of atopy and was allergic to tree pollen. The reaction was reported on day 1 of dose-1 and the participant did not receive dose 2.

Four cases of facial paralysis were observed in the treatment arm versus none in the placebo arm Time to onset after injection with BNT162b2 was 3, 9 and 48 days after Dose 2 and 37 days after Dose 1. Two participants who experienced this had no history of Bell's palsy. Although limited the data suggest a causal relationship between vaccine administration and development of facial paralysis.

Serious adverse events were generally balanced across the groups.

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Six deaths (2 in the BNT162b2 group and 4 in the placebo group) were reported in the Phase 2/3 study up to the cut-off date of 14-Nov-20. None of the deaths were considered related to study intervention.

Elderly

Approximately 40% of participants were older than 55-years . No specific safety concern is anticipated for tis population, noting, due to the inclusion criteria for the study there were only a handful of participants older than 85-years

Pregnancy

A total of 23 participants reported pregnancies at the time of data cut-off. 9 participants withdrew from the vaccination period of the study due to pregnancy. These participants are being followed for pregnancy outcomes.

Immunocompromised participants

Safety data are available for 196 participants with stable HIV infection. The most frequent adverse events in the BNT162b2 group were injection site pain, pyrexia, chills, fatigue, injection site erythema, and injection site swelling.

There are no data available on the interactions when BNT 162b2 is co-administered with, or close to other vaccines.

Uncertainties Regarding Two-month Safety Data

Long term safety data is not available, and clearly there are risks associated with this.

Uncertainties remain regarding the association of facial paralysis due to vaccination there are a limited number of cases all of which are in the vaccination arm, the aetiology is unknown and more cases may be come apparent.

This is a novel mRNA vaccine and although the mRNA should denture rapidly the long term effects of administration of non-host mRNA remain unknown.

No autoimmune adverse events have been identified as causally related to administration of BNT162b2, rare events of this nature cannot be excluded and may become apparent in the longer term.

There were a small number of pregnancies in participants who received BNT162b2. The safety of the vaccine s clearly unestablished in this group and given the current limited duration of follow-up the outcomes remain unknown.

This vaccine contains two new excipients (cationic lipid ALC-0315 and PEGylated liquid ALC-0159 these are novel and there is limited experience. ALC-0159 as an apparent terminal half-life of two to three days. ALC-0315 has an apparent terminal half-life of six to eight days. Long-term effects of these excipients are theoretically possible and remain uncertain.

Summary and Conclusions

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It is clear that there are inadequate long-term efficacy and safety data. The planned duration of follow-up in the clinical study is 2-years and the evaluation of this data is necessary to fully assess the benefit-risk of this product.

Should the product be granted Consent I assume his will be under Section 23 of the Medicines Act as the data appear insufficient for full consent. The applicant should be asked to provide these data expediently following completion of the study, and consideration should be given to making this a condition of approval.

The data does demonstrate sustained protection from sever Covid-19 at two months given the humoral response it may be anticipated that this may be sustained beyon this time but the duration remains uncertain.

There are clearly a number of safety issues that remain unquantified including long-term safety, safety in pregnancy and at the extremes of age.

With regard to the third question:

I think this is asking whether we should wait for the six month data to become available in March as rates of Covid-19 infection currently remain low. Whereas this may provide reassurance from an efficacy point of view, evidence of sustained immunity over six-months is always going to be, preferable to only two-months, this is unlikely to move us further forward from a safety point of view. This also needs to be balanced with the demand for immunisation and Covid-19 cases continue to arrive in the country exposing airline, border and managed isolation facility workers to risk and this vaccine does appear to confer protection.

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Document 3

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Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) , Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii) , Manager Clinical Risk
Approving Manager:	s 9(2)(g)(ii) , Manager, Clinical Risk Management
Date:	12 January 2021
Product:	Comiranty/ BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Risk Management Plan (RMP)
Expertise Required:	Clinical /Statistical (re planned studies)
Requested Urgency:	**Urgent**: by 18 January 2021

Request:

A Risk Management Plan (RMP) for Pfizer's COVID-19 vaccine (Comiranty) has been submitted to Medsafe as part of their New Medicine Application. This has been assessed by Medsafe and a list of questions/requests for further information is proposed for Pfizer. Medsafe would appreciate the following advice related to the RMP:

- Are the proposed questions/requests related to the RMP reasonable?
- Are any changes needed to the proposed questions/requests?
- Are there any additional questions/requests that should be addressed by the company?

Background:

- The Risk Management Plan for a medicine is supposed to summarise the known information on risks of harm identified from the pre-clinical studies and clinical trials.
- The risks are categorized as important identified risks, important potential risks and missing information. Missing information pre-approval is generally judged according to the inclusion/exclusion criteria for the clinical trials and the exposure in the trials.
- RMP guidance issued by the EMA is available here

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https://www.ema.europa.eu/en/news/ema-publishes-safety-monitoring-plan-guidance-risk-management-planning-covid-19-vaccines

Attached Documents:

- RMP assessment report as a Medicines Adverse Reactions Committee (MARC) report including questions and requests for the company
- BNT162b2 RMP version 0.1

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member(s): s 9(2)(g)(ii)

Date Completed: [15/01/2021]

Advice:

Thank you for the opportunity to comment on the Risk Management Plan for BNT162b2 (Tozinameran/Comirnaty). The current questions/requests that will be put to the company (Pfizer) cover important identified risks, important potential risks, and missing information; these questions should be asked. Of particular importance is the request that long-term safety data on BNT162b2 be considered missing information.

My suggested edit/additions to the current RMP questions, and additional questions (which may fall outside of the scope of this RMP) that could be put to the company, are:

- Given anaphylaxis has been identified as an important risk, with rates seemingly slightly higher than seen with other vaccines, does the company have data on patient characteristics that predispose to anaphylaxis? If yes, does the company have recommendations on how this information should inform special warnings and precautions for the use of BNT162b2? Does the company have other suggested risk mitigation strategies to reduce the risk of poor outcomes due to anaphylaxis as a rare AESI following vaccination with BNT162b2?

- The company could be asked to confirm that emerging data on both the efficacy and the risk of vaccine-enhanced disease, with regards to new variants of SARS-CoV-2 with mutations that render the spike glycoprotein antigenically distinct from the spike glycoprotein encoded by BNT162b2, will be provided to Medsafe.

- It is increasingly apparent that, following registration in other countries, BNT162b2 may be administered with dosing intervals that differ from the dosing schedule studied in NCT04368728; will Medsafe seek data on the efficacy and safety (and immunogenicity, if it is known) from any post-authorisation surveillance of these different regimens?

- In addition to the general lack of information on interactions, specific data on how immunisation with the influenza vaccine, given concurrently with, or in close proximity, to, either dose of BNT162b2 affects efficacy and safety (and immunogenicity, if known) could be considered missing information. In addition to important safety information, this has logistical implications for the rollout of a COVID-19 immunisation programme.

- Data in pregnant and breastfeeding women are considered missing information. How does the company intend to gather more information on safety and efficacy in these two groups? I note C4591015 plans to study BNT162b2 in pregnant women but is it hoped that sufficient information on breastfeeding women will be obtained from other more general post-authorisation studies? These data should be provided to Medsafe

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when they become available. There are likely to be a significant number of breastfeeding women in groups that could be prioritised for immunisation in New Zealand (border works, healthcare workers, etc). A lack of clarity on safety in this population has created difficulties with the rollout of COVID-19 immunisation programmes overseas.

As a minor point, 'immunosuppressed' should be spelt correctly or replaced with one of the broader terms used elsewhere 'immunocompromised individuals' or ', immunocompromised individuals including those receiving immunosuppressive therapy or systemic corticosteroids'.

Is this the correct forum to ask whether data on the risks associated with multi-dose vials (e.g. the transmission of infective agents), in the post-authorisation phase (outside of the controlled clinical trial environment) will be collected by the company and, if so, whether that data will be provided to Medsafe?

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Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) , Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii) , Manager Clinical Risk
Approving Manager:	s 9(2)(g)(ii) Manager, Clinical Risk Management
Date:	12 January 2021
Product:	Comiranty/ BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Risk Management Plan (RMP)
Expertise Required:	Clinical /Statistical (re planned studies)
Requested Urgency:	**Urgent**: by 18 January 2021

Request:

A Risk Management Plan (RMP) for Pfizer's COVID-19 vaccine (Comiranty) has been submitted to Medsafe as part of their New Medicine Application. This has been assessed by Medsafe and a list of questions/requests for further information is proposed for Pfizer. Medsafe would appreciate the following advice related to the RMP:

- Are the proposed questions/requests related to the RMP reasonable?
- Are any changes needed to the proposed questions/requests?
- Are there any additional questions/requests that should be addressed by the company?

Background:

- The Risk Management Plan for a medicine is supposed to summarise the known information on risks of harm identified from the pre-clinical studies and clinical trials.
- The risks are categorized as important identified risks, important potential risks and missing information. Missing information pre-approval is generally judged according to the inclusion/exclusion criteria for the clinical trials and the exposure in the trials.
- RMP guidance issued by the EMA is available here

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https://www.ema.europa.eu/en/news/ema-publishes-safety-monitoring-plan-guidance-risk-management-planning-covid-19-vaccines

Attached Documents:

- RMP assessment report as a Medicines Adverse Reactions Committee (MARC) report including questions and requests for the company
- BNT162b2 RMP version 0.1

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member(s): s 9(2)(g)(ii)

Date Completed: 17/1/20

Advice:
Write report detailing advice in response to Medsafe request and include:
- summary of supporting information, data, documents, guidelines referenced
- final opinion/recommendation regarding issues raised
- identification of any deficiencies in data and recommendations of any requests for information that may be made of the sponsor, including an indication of what would be an acceptable response.

I support all Medsafe's comments on the vaccine and append some additional views.

1. The vaccine licensure is for those aged 16 years and older. However, a substantial proportion of the population is aged less than 16 years. It is estimated that in 2020 those aged 0-14 years comprised approximately 18% of the population (NZ stats.Govt). If one of the purposes of vaccination is to prevent community spread and achieve herd immunity, then not vaccinating a substantial minority of the population will make it difficult to achieve especially as this age group mixes regularly in large groups. Do the company have any plans to study Covid-19 vaccination in those aged less than 16 years?
2. This comment is for the data sheet. Adverse events following vaccination should always be reported with placebo events in parallel. These data are available in the document, though not obvious, and for most placebo caused fewer events, though for some events the incidence following vaccine and placebo was similar.
3. This comment is about the real-world administration on which the Ministry will have to give advice to vaccinators. It is inevitable that the interval between dose 1 and dose 2 will not always be 21 days. In fact, in some countries, it

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seems that a decision has been made to prioritise dose 1 and as a result there will be a longer interval between the two doses. Does the company plan any immunogenicity studies to compare the response of differing intervals between doses 1 and 2?

4. A further real-world concern. It is highly likely that, on occasion, the vaccine used for the first dose will not be available for the second, but another Covid-19 vaccine will be available. This is even more likely to apply for booster doses if any are recommended, which I consider highly probable. Does the company plan any immunogenicity studies, with the collaboration of other vaccine companies, to compare immune response in the event two different vaccines are used for the primary course? A similar question will arise for booster doses. It will be necessary for the Ministry to provide advice to vaccinators on how to deal with these real-world administration issues.
5. Follow up of adverse events. Several studies are proposed, and the vaccine data capture tool looks very comprehensive. There is an emphasis on vaccine enhanced disease which is appropriate. However, I do have concerns about the older age group and coincidental events. Thrombotic events are more likely to occur in the older age group and with a large number being vaccinated it is inevitable that some events will occur in a close temporal relationship to receipt of Covid-19 vaccination. Whilst I could see that considerable efforts will be made to detect and report such events, using a passive reporting system, I could not see any evidence of any method to distinguish between causal and coincidental events. My fear is that some coincidental serious adverse events, thought by sufferers to be causal events, could be published on social media and could significantly increase the number of individuals refusing Covid-19

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vaccination. Has the Company established a method of distinguishing between causal and coincidental events?

6. Finally, I could not see any evidence of an approach to assess efficacy against asymptomatic infection or whether the vaccine could prevent transmission. These two issues should be considered missing data.

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Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) , Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii) , Manager Clinical Risk
Approving Manager:	s 9(2)(g)(ii) , Manager, Clinical Risk Management
Date:	12 January 2021
Product:	Comiranty/ BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Risk Management Plan (RMP)
Expertise Required:	Clinical /Statistical (re planned studies)
Requested Urgency:	**Urgent**: by 18 January 2021

Request:

A Risk Management Plan (RMP) for Pfizer's COVID-19 vaccine (Comiranty) has been submitted to Medsafe as part of their New Medicine Application. This has been assessed by Medsafe and a list of questions/requests for further information is proposed for Pfizer. Medsafe would appreciate the following advice related to the RMP:

- Are the proposed questions/requests related to the RMP reasonable?
- Are any changes needed to the proposed questions/requests?
- Are there any additional questions/requests that should be addressed by the company?

Background:

- The Risk Management Plan for a medicine is supposed to summarise the known information on risks of harm identified from the pre-clinical studies and clinical trials.
- The risks are categorized as important identified risks, important potential risks and missing information. Missing information pre-approval is generally judged according to the inclusion/exclusion criteria for the clinical trials and the exposure in the trials.
- RMP guidance issued by the EMA is available here

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https://www.ema.europa.eu/en/news/ema-publishes-safety-monitoring-plan-guidance-risk-management-planning-covid-19-vaccines

Attached Documents:

- RMP assessment report as a Medicines Adverse Reactions Committee (MARC) report including questions and requests for the company
- BNT162b2 RMP version 0.1

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member(s): s 9(2)(g)(ii)

Date Completed: 17/1/21

Advice:

I agree with the points raised by Medsafe, and I would also add some further questions/comments

As for the Medsafe questions, I am not sure whether the monitoring and risk management is the responsibility of the vaccine manufacturer or government agencies. There may be little incentive to establish an elaborate RMP in a small market like NZ.

My concerns around COVID vaccines for healthcare and border workers is that the vaccination will be given as part of an occupational health programme, and it will be important to know which vaccinees develop an immune response. This is critical information when planning rosters etc, as it would not be wise to place non-responders in front line care directly caring for COVID patients.

I would like to know if the COVID vaccination register will have fields not only for adverse events, but also for immunogenicity for critical workers.

These comments also apply to Maori/Pasifika: there are insufficient data for both safety and immunogenicity.

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Document 7

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii), Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii), Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	11 January 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: 10 working days

Request:
The US FDA recently granted Emergency Use Authorization for Pfizer's COVID-19 vaccine. FDA guidance is that a median of two-months clinical trial follow-up post immunization for emergency use authorization (refer page 10 of the link below).

https://www.fda.gov/media/142749/download

New Zealand currently has no community transmission of SARS-CoV-2, meaning that the benefits of an Emergency Use Authorization would not necessarily be sufficient to outweigh the risks of use based on review of limited data available. Recent research on FDA approval showed that the median follow-up was six months before approval for other vaccines.

In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

Please note that the advice requested is not intended to be specifically informed by the data submitted to date to support the quality, safety and efficacy of this vaccine. Rather it is requested that advice be provided regarding the general limitations of

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relying on a shorter clinical trial follow-up period to make a decision regarding approval, and the risks associated with this. The supporting documents are provided to give context to this request, hence why they include summary overviews as opposed to more in-depth data and analysis.

Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
- Updated data is expected in March 2021, which will include six-month median follow-up data.
- Medsafe is currently reviewing the UK MHRA clinical evaluation report. The report's discussion on clinical efficacy notes the following on page 48.

  The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.
- The current follow-up is shown by the application's Clinical Overview person-years surveillance time in Table 8, the 'No. at risk' in Figure 1, and the safety data for having follow-up after dose two ≥2 months (eg Table 32).

Attached Documents:

- FDA VRBPAC Briefing Document 'Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020' (53 pages)
- MHRA Public Assessment Report COVID-19 mRNA vaccine BNT162 (51 pages).
- CTD Module 2 document: Clinical Overview (257 pages)

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii)

Date Completed: 17/1/20

Advice:
Write report detailing advice in response to Medsafe request and include:
- summary of supporting information, data, documents, guidelines referenced
- final opinion/recommendation regarding issues raised
- identification of any deficiencies in data and recommendations of any requests for information that may be made of the sponsor, including an indication of what would be an acceptable response.

Regarding efficacy. I do not expect Covid-19 vaccines to provide long term protection and I expect booster doses will be required. I anticipate that by the end of 2021 there will be sufficient data to indicate when a booster dose will be required – hopefully no more frequently than annually. Therefore, in the first instance having data indicating that efficacy is sustained over 2 months is acceptable. However, I would expect regular updates on the duration of protection as time passes. The Company(ies) should be required, as a condition of licensure, to provide regular updates on the duration of efficacy and the requirement for booster doses.

Being unaware of the duration of protection of a vaccine when it is licensed is by no means unusual as was the case for HPV vaccine when it was licensed, for example. Changes in booster policy as more data are available are also not unusual. This is perhaps best exemplified by pertussis vaccines.

Regarding safety. In general, 2 months of follow up for safety prior to licensure is acceptable. In a recent article I drew attention to vaccines that had been withdrawn for safety concerns. All of the events, resulting in withdrawal, occurred within 2 months of vaccine receipt (Reid S Vaccine Safety NZMJ 21 February 2020 Vol 133 No 1510. www.nzma.org.nz/journal-articles/vaccine-safety).

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Auto-immune events are challenging. Unless very common they are not likely to be seen in prelicensure studies. However, there will be some auto-immune events which will occur following vaccination and will be considered by the sufferer, and possibly their medical advisors, to have been caused by vaccination. These events are challenging to assess and require comprehensive post licensure safety monitoring, including establishing the expected rate of such an event in the community from historical data.
My response to the concern about auto-immune events is to ensure that at least there is adequate capacity to investigate such events and assess whether there is a causal or coincidental link to the vaccine.

Safety Concern. My main concern with regard to safety is the adequacy of age-related data. One of the key target groups is those aged >65 years. Whilst there will be some individuals in that age-group in the pre-licensure studies, I imagine the numbers will be relatively small and that they will require careful post-licensure safety monitoring. Covid-19 has been reported to cause vascular problems, e.g. strokes. It is inevitable that some strokes will occur in those aged >65 years in a close temporal relationship to receipt of Covid-19 vaccination and will be attributed to Covid-19 vaccine by the sufferer; such events will require very careful evaluation and explanation to ensure public confidence in the vaccination programme is sustained.

However, there will be substantial use of the vaccine(s) in the Northern hemisphere prior to their use here. Vaccine companies should be asked (required?) to provide regular updates on vaccine safety from the post-licensure experience in other countries.

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Document 8

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii), Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii), Manager Clinical Risk
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	12 January 2021
Product:	Comiranty/ BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Risk Management Plan (RMP)
Expertise Required:	Clinical /Statistical (re planned studies)
Requested Urgency:	**Urgent**: by 18 January 2021

Request:

A Risk Management Plan (RMP) for Pfizer's COVID-19 vaccine (Comiranty) has been submitted to Medsafe as part of their New Medicine Application. This has been assessed by Medsafe and a list of questions/requests for further information is proposed for Pfizer. Medsafe would appreciate the following advice related to the RMP:

- Are the proposed questions/requests related to the RMP reasonable?
- Are any changes needed to the proposed questions/requests?
- Are there any additional questions/requests that should be addressed by the company?

Background:

- The Risk Management Plan for a medicine is supposed to summarise the known information on risks of harm identified from the pre-clinical studies and clinical trials.
- The risks are categorized as important identified risks, important potential risks and missing information. Missing information pre-approval is generally judged according to the inclusion/exclusion criteria for the clinical trials and the exposure in the trials.
- RMP guidance issued by the EMA is available here

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https://www.ema.europa.eu/en/news/ema-publishes-safety-monitoring-plan-guidance-risk-management-planning-covid-19-vaccines

Attached Documents:

- RMP assessment report as a Medicines Adverse Reactions Committee (MARC) report including questions and requests for the company
- BNT162b2 RMP version 0.1

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member(s): s 9(2)(g)(ii)

Date Completed: 17/01/2021

Advice:

I am in agreement with the risks and missing information that have been included in the RMP.

I am in agreement with the proposed additional questions of the Sponsor, as detailed in the MARC briefing document.

In addition, I propose the following as Important Missing Information:

Immunogenicity of excipients: Some of the excipients used in Comirnaty (COVID-19 mRNA) Vaccine may be used in other vaccines and might induce an immune response (specifically ALC-0159). The extent to which this could sensitize to immunologically medicated adverse reactions to future doses of Comirnaty (COVID-19 mRNA) Vaccine or other vaccines containing these excipients is unknown. This should be included as Important Missing Information. (See **DOI: 10.1056/NEJMra2035343)**

Efficacy and safety in the Maori and Pacific Peoples populations: The populations currently studied are not representative of the New Zealand population, specifically because there are no Māori or Pacific Peoples included in the studies. This should be included as Important Missing Information in a New Zealand Specific Annex to the Risk Management Plan. New Zealand is unique in having the Treaty of Waitangi, which outlines the relationship between Māori and the Crown. This includes the principles of partnership and equality. A vaccine that does not work in the Māori population has limited utility in New Zealand: it would not confer acceptable community immunity, would not prevent community spread and would not allow normalization of international movement. Hence, as part of any initial vaccine implementation, it would be essential to perform an immunogenicity study in the Māori and Pacific Peoples populations. The Sponsor could facilitate such a study by providing resources, including their laboratory assays for anti-COVID-19 and neutralizing antibodies.

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Medsafe COVID-19 Vaccine Advisory Group – Request for Advice

To: s 9(2)(g)(ii) , Chair, Medsafe Vaccine Advisory Group, s 9(2)(g)(ii)

From: s 9(2)(g)(ii) Principal Technical Specialist, Product Regulation

Approving Manager: s 9(2)(g)(ii) Team Leader – Medicines Assessment, Product Regulation

Date: 18 January 2021

Product: Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech)

Subject: Residual enzyme levels

Expertise Required: Biochemistry/pharmaceutics/immunology

Requested Urgency: **Urgent**: 3-5 working days

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Background:
Various enzymes (T7 RNA polymerase, RNase inhibitor, pyrophosphatase, DNase I, Proteinase K) are added during the drug substance (mRNA) manufacturing process.

Proteinase K is added towards the end of the manufacturing process, with its primary objective to digest the proteins (i.e. enzymes) added throughout the manufacturing process to small polypeptides so that they can be removed in the following ultrafiltation/diafiltration step.

A copy of the manufacturing process is attached.

Enzyme removal from the drug substance has been evaluated as part of the process design and characterisation. Due to a lack of safety data on enzymes, the company has leveraged studies on ovalbumin (a common egg-derived protein impurity in commercialised vaccines) to assess the risk of the enzyme impurities. Studies have shown that ovalbumin was tolerated in patients with egg allergies up to a dose of 1.2 µg/mL with no significant allergic reactions. Assuming a typical vaccine dose of 0.5 mL, this equates to a 0.6 µg ovalbumin/dose, or 0.6 µg protein/dose. Applying a 10-fold uncertainty factor for the difference in ovalbumin versus the proteins used in the drug substance manufacturing process, the company has established a safety concern threshold of 0.06 µg/dose (60 ng/dose). The theoretical worst case of nanograms of enzyme per dose (assuming no removal) is shown in Table 1.

Table 1: Enzyme safety risk assessment (theoretical worst-case dose)

Impurity	ng Protein / Dose	Safety Concern Threshold (ng Protein/dose)
RNase Inhibitor	2.4	60
DNase I	39.4	60
T7 RNA Polymerase	140.8	60
Proteinase K	95.8	60
Pyrophosphatase	1.4	60

The safety risk assessment calculations identified that RNase inhibitor, DNase I, and pyrophosphatase are below the safety concern threshold of 60 ng/dose with no removal, and therefore do not pose a safety concern. T7 RNA Polymerase and Proteinase K levels with no removal would exceed the safety concern threshold of 60 ng/dose.

The levels of T7 RNA polymerase and Proteinase K that have been monitored in drug substance batches manufactured to date and are shown in Table 2 and 3 below. (Note there are two drug substance manufacturing sites associated with the final UF/DF step, hence the two tables below.)

Table 2: T7 RNA Polymerase and Proteinase K Results for clinical, initial emergency supply and process performance qualification drug substance batches [Andover]

Impurity	Safety Concern Threshold (ng Protein/dose)	ng Protein / dose[a]						
		20Y513C101	20Y513C201	20Y513C301	20Y513C401	20Y513C501	20Y513C601	20Y513C701
T7 RNA Polymerase	60	< 3.4 (LOQ)	< 3.4 (LOQ)	< 3.4 (LOQ)	< 3.4 (LOQ)	< 4.4 (LOQ)	< 4.4 (LOQ)	< 4.4 (LOQ)
Proteinase K	60	0.3	0.2	0.2	0.1	0.1	0.1	0.2

a. Converted from analytical method output of U/mL

Table 3: T7 RNA Polymerase and Proteinase K results for process performance qualification drug substance batches [BNT Mainz and Rentschler]

Impurity	Safety Concern Threshold (ng Protein/dose)	ng Protein / dose[a]		
		20E162001 (1071539)	20E162002 (1071542)	20E162003 (1071544)
T7 RNA Polymerase	60	< 4.0 (LOQ)	< 4.0 (LOQ)	< 4.0 (LOQ)
Proteinase K	60	0.1	0.2	0.1

a. Converted from analytical method output of U/mL

The results demonstrate that the drug substance manufacturing process (namely, digestion of residual enzymes by proteinase K, autolysis of proteinase K, and subsequent removal of residual proteinase K and polypeptides via UF/DF) consistently removes the levels of T7 RNA polymerase and proteinase K to below the safety concern threshold established using ovalbumin.

Request:
The question Medsafe has for the advisory group is whether ovalbumin is an appropriate substitute in the risk assessment for the safety of carryover enzymes into the drug substance

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for an mRNA vaccine? Although it seems a reasonable molecule to use with regard to protein immunogenicity, it is a relatively inert molecule when compared with the enzymes used in the drug substance manufacturing process.

If ovalbumin is not considered a suitable substitute for the risk assessment of residual enzymes, could the enzyme residual levels (taking into account those measured for T7 RNA polymerase and proteinase K) pose a safety risk for the vaccine?

Response:

Ovalbumin is not an optimal substitute for risk assessment and comparing the enzymes to ovalbumin tolerated doses is irrelevant as the issue with ovalbumin relates to egg sensitivity and anaphylaxis. Also was the 60 ng limit established with native or digested protein?

There appears to be no relevant safety data with the actual enzymes from pre-clinical animal studies. However obviously a wealth of safety data is being generated from ongoing phase III and IV studies. This means there is less concern for NZ regulators.

There are a couple of questions that could be asked – with the studies reported above how are the protein levels (ng Protein/dose) determined? Is this undigested active protein with enzymatic activity or does it include inactive digested fragments? Have they determined residual enzymatic activity?

The data provided is not optimal, but from the available literature it is likely the residual protein is not a safety issue.

Attached Documents:

Drug substance (mRNA) manufacturing process flow diagram.

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: [Name]

Date Completed: [Date]

Conflicts of interest declaration:

- *Declare any possible conflicts of interest relevant to this advice request, or*
- *Declare that no relevant conflicts exist*
- *Describe any actions taken to mitigate or manage any conflicts*

No conflicts exist

Advice:

Write report detailing advice in response to Medsafe request and include:

- *summary of supporting information, data, documents, guidelines referenced*
- *final opinion/recommendation regarding issues raised*
- *identification of any deficiencies in data and recommendations of any requests for information that may be made of the sponsor, including an indication of what would be an acceptable response.*

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii)

Date Completed: 19 January 2021

Advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).

With a two-month median follow-up the longevity of the protective effect cannot be ascertained; however, the benefit of vaccinating during a pandemic is likely to far outweigh the risk that the vaccine protection is short-lived. If the response is short-lived, it is likely that waning protective immunity could be enhanced by additional booster vaccinations if required (this may depend on the nature of the vaccine, since viral vectors may induce memory immunity to the vector itself, precluding multiple boosts with the same vector; however heterologous boosting should be possible in this case).

A further risk is the inability to determine whether the vaccine is efficacious against newly emerging strains of SARS-CoV-2, 3 of which have been described in recent weeks. This is likely to be an ongoing risk, and vaccine-driven viral evolution is possible.

A final risk is that SARS-CoV-2 transmission by asymptomatic, vaccinated individuals is unlikely to have been determined in the two-month median follow up (although I am unaware if this will be measured in extended follow up studies). Asymptomatic viral shedding is known to occur in unvaccinated individuals[1]; however, these individuals had low virus-specific IgG, which is likely to differ from the vaccinated cohort.

Since vaccination can lead to behavioral changes, vaccinees should be made aware of this risk, as NZ vaccinees working in areas of higher risk should not relax their use of PPE as a result of being vaccinated, to avoid any possibility of community transmission; however, in my opinion the risk of viral shedding by exposed, asymptomatic, *vaccinated* individuals is likely very low.

2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).

Two-month median follow up is likely to be sufficient, in healthy adults, to detect serious adverse events, if sufficient severe cases of COVID-19 have been detected in the placebo group to rule out vaccine-associated enhanced respiratory disease (VAERD). It is notable that the adverse events reported

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after 2 month-follow up after dose 2 of BNT162b2 (Table 39, in the report0 were consistent with those reported after 1 month-follow up (Table 38) in a larger cohort, which implies that that extending the follow-up further is unlikely to reveal any additional adverse events.

Depending on the study site and age of the test cohort, there may be insufficient severe cases of COVID-19 in the study to detect VAERD in specific age groups (eg geriatric, pediatric) or in individuals with uncommon comorbidities after a two-month follow up, which may be important as the development of VAERD could differ by age or comorbidities (eg autoimmunity / immune deficiency).

Other risks, though very unlikely, include very late-onset serious adverse events (for example, Guillain Barre Syndrome may develop up to 42 days after influenza vaccination[2]).

3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

Although NZ does not presently have community transmission of SARS-CoV-2, there remains a reasonable risk that this could re-occur. **I consider two-month follow up sufficient for supporting emergency use in NZ in healthy adults.** Vaccinees working in higher-risk areas should be made aware that they could still be vehicles for disease transmission and must continue to be vigilant with PPE.

1. Long et al. Nat Med (2020) 26, 1200–1204

2. Wise et al American Journal of Epidemiology (2012) 175(11):1110-9

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Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii), Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	11 January 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: 10 working days

Request:
The US FDA recently granted Emergency Use Authorization for Pfizer's COVID-19 vaccine. FDA guidance is that a median of two-months clinical trial follow-up post immunization for emergency use authorization (refer page 10 of the link below).

https://www.fda.gov/media/142749/download

New Zealand currently has no community transmission of SARS-CoV-2, meaning that the benefits of an Emergency Use Authorization would not necessarily be sufficient to outweigh the risks of use based on review of limited data available. Recent research on FDA approval showed that the median follow-up was six months before approval for other vaccines.

In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

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relying on a shorter clinical trial follow-up period to make a decision regarding approval, and the risks associated with this. The supporting documents are provided to give context to this request, hence why they include summary overviews as opposed to more in-depth data and analysis.

Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii) [redacted]

Date Completed: 20 January 2021

Risks associated with shorter (i.e., 2 month) follow up

Efficacy

While the FDA guidelines are that a median 2-month follow is sufficient for emergency use authorization, information from the clinical overview shows that 25% of participants have been followed up for less than 6 weeks. Given that there are only 37,000 participants, I would like to see all participants followed up for at least 2 months before the question of efficacy at 2 vs 6 months is addressed. I am not a vaccine efficacy expert and I could not find studies reporting 2 vs 6 months efficacy data for other vaccines. But given the smaller cohort, the risk of relying on median 2-month follow up is that efficacy may be overestimated.

Safety

In France, a cohort of over 2 million young girls were vaccinated with HPV and the risk of autoimmune diseases was analyzed. The results showed that Guillain-Barre Syndrome (GBS) was the adverse event with the highest unadjusted hazard ratio. However, the adjusted HR decreased over time, 5.35 (0-2 months), 3.94 (2 months) and 2.43 (6 months). Additionally, the IRR also decreased over time 3.83 (42 days), 2.65 (2 months) and 2.39 (6 months) (Miranda et al., Vaccine 35:4761-4768, 2017). This study indicates that the data at 2 months is reliable for indicating the risk of autoimmune conditions.

In 1976 an increase in the incidence of GBS was observed during the swine flu vaccination program in the USA. A total of 532 patients received the vaccination prior to the onset of GBS. The estimated attributable risk of vaccine-related GBS in the adult population was just under one case per 100,000 vaccinations. The period of increased risk was concentrated primarily within the 5-week period after vaccination, although it lasted for approximately 9 or 10 weeks. The mean interval from vaccination to onset was 3.9 weeks (Israeli et al., Clinic Rev Allerg Immunol 42:121-30, 2012). While this is an older study, it does also indicate that when GBS occurs it happens earlier than 6 months.

In the USA, autoimmune surveillance was conducted with 189,629 women of all ages who received at least one dose of HPV4 between 2006 and 008. Women were followed up for 180 days after each dose of HPV4 to identify new-onset autoimmune conditions. No cluster of disease onset in relation to vaccination timing, dose sequence (up to 3 doses were given) or age was found for any autoimmune condition. None of the estimated IRR were significantly elevated except Hashimoto's disease [IRR = 1.29, 95% confidence interval: 1.08–1.56]. The authors concluded that there

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were no autoimmune safety concerns in this study because further investigation of a temporal relationship and biological plausibility revealed no consistent evidence. (Chao et al., Journal of Internal Medicine 271:193-203, 2011). Even though the conclusion of the paper was no safety concerns, I looked further into the timing of disease onset. The median time of onset for all conditions was 36-56 days (i.e., within the 2-month window), except Rheumatoid arthritis (62 days), Multiple sclerosis (73 days) and Optic neuritis (65.5 days).

These 3 studies support the idea that autoimmune conditions are detected in the 2-month window.

However, in Finland there was a 12.7-fold increase in the development of narcolepsy in 4-19 year olds within 8 months of receiving the Pandemrix vaccine (H1N1) compared to those in the same age group that were unvaccinated. This was a vaccine attributable risk of 1:16,000 (Nohymek et al., PloS one 7:e33536, 2012). In a review article Partinen et.al., (2014) make the case for narcolepsy as an autoimmune disease (Lancet Neurology Volume 13). These findings make it possible that narcolepsy could be an adverse event that would not be identified until after 6 months.

Overall, it seems as though, the risk of detecting common autoimmune conditions is not increased by shortening the follow up window to 2 months. However, as stated in the efficacy section, all patients have yet to be followed up for 2 months.

Appropriate time frames for follow up given the current situation in NZ

Given the current situation in NZ, there is no hurry to vaccinate and thus no fundamental reason to adhere to the FDA guidelines for emergency use authorization. New Zealand has time to wait for at least the full 2-month follow up and potentially even a median 6-month follow up. It is better to have more certainty regarding efficacy than to use a vaccine that might not have a longer duration of response. Medsafe is in a unique position, as it can wait for more evidence regarding efficacy without increasing the risk of New Zealanders contracting COVID-19.

Regarding safety, I am not a specialist in autoimmune diseases. However, from the papers I have found it appears that these conditions usually manifest themselves earlier rather than later and are identified within 2 months following various vaccinations. The paper on narcolepsy would contrast this conclusion and would suggest that a follow up greater than 6 months would be required. I am not in a position to comment on whether or not narcolepsy should be classified as an autoimmune condition. Overall, given the evidence and the size of the cohort I would suggest reassessing the 2-month vs 6-month efficacy when all patients have reached the 2-month follow up stage.

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Document 12

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii) Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii), Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	11 January 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: 10 working days

Request:
The US FDA recently granted Emergency Use Authorization for Pfizer's COVID-19 vaccine. FDA guidance is that a median of two-months clinical trial follow-up post immunization for emergency use authorization (refer page 10 of the link below).

https://www.fda.gov/media/142749/download

New Zealand currently has no community transmission of SARS-CoV-2, meaning that the benefits of an Emergency Use Authorization would not necessarily be sufficient to outweigh the risks of use based on review of limited data available. Recent research on FDA approval showed that the median follow-up was six months before approval for other vaccines.

In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

Please note that the advice requested is not intended to be specifically informed by the data submitted to date to support the quality, safety and efficacy of this vaccine. Rather it is requested that advice be provided regarding the general limitations of

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relying on a shorter clinical trial follow-up period to make a decision regarding approval, and the risks associated with this. The supporting documents are provided to give context to this request, hence why they include summary overviews as opposed to more in-depth data and analysis.

Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
- Updated data is expected in March 2021, which will include six-month median follow-up data.
- Medsafe is currently reviewing the UK MHRA clinical evaluation report. The report's discussion on clinical efficacy notes the following on page 48.

  The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.
- The current follow-up is shown by the application's Clinical Overview person-years surveillance time in Table 8, the 'No. at risk' in Figure 1, and the safety data for having follow-up after dose two ≥2 months (eg Table 32).

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii)

Date Completed: [21/01/2021]

Advice:

Thank you for the opportunity to comment on the potential risks associated with licensing a COVID-19 vaccine with a shorter-than-usual period of safety and efficacy data.

I note that the advice requested pertains to the general limitations of this shorter clinical trial follow-up period, rather than a request to specifically review the two month follow-up data available for the BNT162b2 mRNA COVID-19 vaccine. Relying on a shorter period of follow-up trial data introduces potential risk but, given the novel vaccine target and relative novel vaccine technologies, the level of this risk is not possible to quantify. High-quality data on long-term effects of mRNA vaccines, particularly with novel excipients and when administered to healthy adults, are not yet available. Therefore, an accurate risk assessment is not possible. In an effort to be as transparent and helpful as possible, in the absence of directly relevant data, I make some general comments below but these must not be interpreted as advice that is based on robust evidence.

It is worth noting that the vaccine effectiveness and safety data for lead COVID-19 vaccine candidates, including BNT162b2, are drawn from clinical trials that enrolled a relatively large number of participants (although with key missing data in specific age groups, ethnic groups, etc). For example, in the ongoing phase 2/3 trial C4591001, more than 20,000 participants were randomised to receive the BNT162b2 vaccine. Rather than an insufficient number of trial participants, the question posed here pertains to the short duration of follow-up data. This risk could be broadly considered in terms of a) vaccine effectiveness and b) vaccine safety.

The likelihood of rapidly waning vaccine effectiveness, beyond the currently-available two months of follow-up data, is not known when considering a COVID-19 vaccine that uses novel vaccine technology. However, based on our understanding of the immunology of mRNA vaccines, waning immunity can likely be addressed with a subsequent booster dose (or doses), including with the same vaccine.† If subsequent booster doses of a mRNA COVID-19 vaccine were required, this would not be a minor undertaking, but it should be considered somewhat differently from the potential for the risk of unidentified safety concerns arising due to a shorter-than-usual period of clinical trial safety data.

From a safety perspective, a median of two months follow-up data creates the potential for as-yet-unrecognised late adverse effects. Significant delayed adverse consequences of vaccination, generally, are very uncommon. However, it is unclear how much reassurance can be drawn from longer-term follow-up data with vaccines for other infectious diseases, using other vaccine technologies, when considering whether to license a vaccine for a novel disease, using novel vaccine technologies.

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Medsafe will need to find the balance between the unquantifiable potential risks of licensing a COVID-19 vaccine based on shorter-than-usual effectiveness and safety follow-up data, without the ability to draw on empirical data from previous clinical research about the vaccine target and/or the vaccine technology, against the benefits of protecting our community against COVID-19 with vaccines that have been shown to provide a high level of short-term protection. Further, this will need to be done as information is rapidly generated on the use of these vaccines internationally. A balance must be found that suits the New Zealand context, acknowledging the current absence of community transmission but the ever-present risk of a COVID-19 border incursion and subsequent outbreak. The lack of community transmission may be viewed as a chance to wait for longer follow-up. Alternatively, the emergence of new SARS-CoV-2 variants and the concern that subsequent outbreaks could easily occur might mean Medsafe consider two months of follow-up data, with the knowledge more data will follow, sufficient to allow provisional consent. Certainly, groups such as The Australasian Society for Infectious Diseases have advocated that "the practical steps required in order for vaccination to start in NZ should occur quickly, including the Medsafe approval process" (https://www.asid.net.au/documents/item/1951).

Adding further complexity, Medsafe could consider the asymmetric risk:benefit profile of a COVID-19 vaccine when it is considered for staged rollout to different New Zealand population groups. SARS-CoV-2 is a pandemic infection currently being managed in border facilities by a relatively small number of healthcare and other personnel. COVID-19 poses a significant risk to specific populations, should community transmission of SARS-CoV-2 occur, whereas the risk of poor outcomes from COVID-19 is much lower in other population groups. This creates a challenge in that a median of two months of follow-up data demonstrating a high level of vaccine effectiveness and an acceptable safety profile may be considered entirely satisfactory, from the perspective of your average front-line Managed Isolation Facility worker, or from the perspective of a frail rest home resident with hypertension and type two diabetes, but unsatisfactory for a vaccine hesitant member of the population who perceives themselves to be at very low risk of COVID-19. It is likely that the greatest benefit will be obtained from those in the populations who access an approved vaccine early in the immunisation programme. It is also likely that further data will have emerged by the time the immunisation programme starts to vaccinate those outside of the population groups identified as being at higher risk.

Clearly, the decision regarding whether to license a vaccine based on shorter-than-usual follow-up period requires careful consideration by Medsafe. Unfortunately, the lack of scientific data on the vaccine target and technologies render it impossible to quantify the risk that this approach entails in a way that would allow me to provide specific and evidence-based advice. I would welcome the opportunity to review data, as it becomes available. Medsafe will undoubtedly be aware of logistics considerations, such as the exact dates New Zealand might reasonably expect to be shipped vaccine batches and the exact dates that longer follow-up data will be made available by the company; these practical considerations may or may not help guide decisions about how quickly an decision should be made.

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Footnote

† If a similar situation arose where only two months of follow-up data was available for a vaccine that employed a viral vector, the same reasoning could not be applied. Waning of protective immunity from viral vector vaccines e.g. a chimpanezee adenovirus (Oxford/AstraZeneca) or Ad26 (Janssen) may not be amenable to boosting with the same vaccine due to the development of neutralising immune responses against the viral vector which block the entry of the viral vector into cells and thus reduce expression of the target transgene, rendering booster doses less effective. Prior to COVID-19, this issue with viral vector vaccines gave rise to much pre-clinical and clinical research work to look at heterologous prime-boost regimens, using different viral vectors for 'prime' and 'boost' dosing. Data on whether heterologous prime boost regimens are useful with COVID-19 vaccines are awaited.

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Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii), Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii) Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	11 January 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: 10 working days

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1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).
2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).
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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: s 9(2)(g)(ii)

Date Completed: 21st January 2021

Advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response)

A two-month follow-up will identify short term immune response to the vaccine. From this it may be possible to extrapolate long-term immunity, but with a new infectious agent, such as COVID-19, it will not be possible to provide a confident prediction of long-term immunity from the short-term data. A vaccine that provides short-term protection would be useful in the context of a local outbreak or to provide a barrier to transmission at border, international transport and quarantine facilities. However, the data do not provide sufficient evidence of long-term protection to confidently predict community immunity.

2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).

A two-month follow-up would provide sufficient evidence of local (administration site) adverse reactions (such as pain, bruising, lumps, induration). A two-month follow-up would provide sufficient evidence of systemic side effects such as fever and malaise, indicative of activating an immune response. However, the time course of activation of autoimmune conditions, in my opinion, is over 6 weeks to 6 months. Hence a 2-month follow-up does not provide sufficient monitoring for autoimmune conditions.
The vaccines developed for COVID-19 involve the endogenous production of an exogenous protein (spike protein). The extent to which this might induce an autoimmune response is unpredictable as this is a new disease and new antigen. There have been reports of ongoing illnesses post-COVID which have not as yet been adequately characterized. It is unknown whether the vaccines could induce similar ongoing, related symptoms.

3. Do you have any additional comments that should be considered when determining what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand.

The COVID-19 pandemic situation in New Zealand is that there is currently no community transmission. Hence the current emphasis is to prevent COVID-19 establishing community transmission through transmission from returnees, and transportation, quarantine and border staff. Use of a vaccine with short-term efficacy and safety data should be considered in this population.
Should community transmission develop, widespread use of a vaccine with 2-month follow-up would be justifiable.

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There is an opportunity cost to using a vaccine with short-term follow-up. This is that should a better vaccine be available the opportunity to use it instead would be lost. The currently regulatory guidance for approval of vaccines is also appropriate for COVID-19 vaccines. In my view, there is no need for additional data to that required for standard vaccine applications.

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Medsafe COVID-19 Vaccine Advisory Group – Request for Advice

To: s 9(2)(g)(ii), Chair, Medsafe Vaccine Advisory Group, s 9(2)(g)(ii)

From: s 9(2)(g)(ii), Principal Technical Specialist, Product Regulation

Approving Manager: s 9(2)(g)(ii) Team Leader – Medicines Assessment, Product Regulation

Date: 18 January 2021

Product: Comirnaty (COVID-19 mRNA vaccine) (Pfizer-BioNTech)

Subject: Residual enzyme levels

Expertise Required: Biochemistry/pharmaceutics/immunology

Requested Urgency: **Urgent**: 3-5 working days

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Background:
Various enzymes (T7 RNA polymerase, RNase inhibitor, pyrophosphatase, DNase I, Proteinase K) are added during the drug substance (mRNA) manufacturing process.

Proteinase K is added towards the end of the manufacturing process, with its primary objective to digest the proteins (i.e. enzymes) added throughout the manufacturing process to small polypeptides so that they can be removed in the following ultrafiltation/diafiltration step.

A copy of the manufacturing process is attached.

Enzyme removal from the drug substance has been evaluated as part of the process design and characterisation. Due to a lack of safety data on enzymes, the company has leveraged studies on ovalbumin (a common egg-derived protein impurity in commercialised vaccines) to assess the risk of the enzyme impurities. Studies have shown that ovalbumin was tolerated in patients with egg allergies up to a dose of 1.2 µg/mL with no significant allergic reactions. Assuming a typical vaccine dose of 0.5 mL, this equates to a 0.6 µg ovalbumin/dose, or 0.6 µg protein/dose. Applying a 10-fold uncertainty factor for the difference in ovalbumin versus the proteins used in the drug substance manufacturing process, the company has established a safety concern threshold of 0.06 µg/dose (60 ng/dose). The theoretical worst case of nanograms of enzyme per dose (assuming no removal) is shown in Table 1.

Table 1: Enzyme safety risk assessment (theoretical worst-case dose)

Impurity	ng Protein / Dose	Safety Concern Threshold (ng Protein/dose)
RNase Inhibitor	2.4	60
DNase I	39.4	60
T7 RNA Polymerase	140.8	60
Proteinase K	95.8	60
Pyrophosphatase	1.4	60

The safety risk assessment calculations identified that RNase inhibitor, DNase I, and pyrophosphatase are below the safety concern threshold of 60 ng/dose with no removal, and therefore do not pose a safety concern. T7 RNA Polymerase and Proteinase K levels with no removal would exceed the safety concern threshold of 60 ng/dose.

The levels of T7 RNA polymerase and Proteinase K that have been monitored in drug substance batches manufactured to date and are shown in Table 2 and 3 below. (Note there are two drug substance manufacturing sites associated with the final UF/DF step, hence the two tables below.)

Table 2: T7 RNA Polymerase and Proteinase K Results for clinical, initial emergency supply and process performance qualification drug substance batches [Andover]

Impurity	Safety Concern Threshold (ng Protein/dose)	ng Protein / dose[a]						
		20Y513C101	20Y513C201	20Y513C301	20Y513C401	20Y513C501	20Y513C601	20Y513C701
T7 RNA Polymerase	60	< 3.4 (LOQ)	< 3.4 (LOQ)	< 3.4 (LOQ)	< 3.4 (LOQ)	< 4.4 (LOQ)	< 4.4 (LOQ)	< 4.4 (LOQ)
Proteinase K	60	0.3	0.2	0.2	0.1	0.1	0.1	0.2

a. Converted from analytical method output of U/mL

Table 3: T7 RNA Polymerase and Proteinase K results for process performance qualification drug substance batches [BNT Mainz and Rentschler]

Impurity	Safety Concern Threshold (ng Protein/dose)	ng Protein / dose[a]		
		20E162001 (1071539)	20E162002 (1071542)	20E162003 (1071544)
T7 RNA Polymerase	60	< 4.0 (LOQ)	< 4.0 (LOQ)	< 4.0 (LOQ)
Proteinase K	60	0.1	0.2	0.1

a. Converted from analytical method output of U/mL

The results demonstrate that the drug substance manufacturing process (namely, digestion of residual enzymes by proteinase K, autolysis of proteinase K, and subsequent removal of residual proteinase K and polypeptides via UF/DF) consistently removes the levels of T7 RNA polymerase and proteinase K to below the safety concern threshold established using ovalbumin.

Request:
The question Medsafe has for the advisory group is whether ovalbumin is an appropriate

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substitute in the risk assessment for the safety of carryover enzymes into the drug substance for an mRNA vaccine? Although it seems a reasonable molecule to use with regard to protein immunogenicity, it is a relatively inert molecule when compared with the enzymes used in the drug substance manufacturing process.

If ovalbumin is not considered a suitable substitute for the risk assessment of residual enzymes, could the enzyme residual levels (taking into account those measured for T7 RNA polymerase and proteinase K) pose a safety risk for the vaccine?

Attached Documents:

Drug substance (mRNA) manufacturing process flow diagram.

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member: [Name] s 9(2)(g)(ii)

Date Completed: [Date] 21 January 2021

Conflicts of interest declaration:

- *Declare any possible conflicts of interest relevant to this advice request, or*
- *Declare that no relevant conflicts exist*
- *Describe any actions taken to mitigate or manage any conflicts*

No conflicts of interest declared

Advice:

Write report detailing advice in response to Medsafe request and include:

- *summary of supporting information, data, documents, guidelines referenced*
- *final opinion/recommendation regarding issues raised*
- *identification of any deficiencies in data and recommendations of any requests for information that may be made of the sponsor, including an indication of what would be an acceptable response.*

Comparing dose by weight, rather than by molarity

Ovalbumin from chicken egg has a molecular weight of ~44.3kDa[1]. The T7 RNA polymerase has a molecular weight of ~98.9kDa[2]. Proteinase K has a molecular weight of ~28.5kDa[3]. Therefore, when measuring by weight, there will be almost twice as many protein K molecules if measured by the equivalent weight of ovalbumin, and twice as few T7 RNA polymerase molecules. **Given that a 10-fold uncertainty factor has been allowed for, the differences in molecular weight between ovalbumin and proteinase K and T7 RNA polymerase are unlikely to be problematic.**

Measuring allergens

Biologic activity of allergens is challenging to measure, and there are various methods used to determine this eg the FDA-approved bioequivalent allergy unit (BAU), which is designed to compare the potency of allergen mixes from different commercial producers for allergy immunotherapy. Injected or ingested allergens can give rise to systemic responses, including anaphylaxis.

It is known that oral allergens vary in potency and this may also vary depending on the vehicle in which they are delivered and different manufacturing processes. Additionally, the dose required to elicit allergic responses in sensitized individuals can vary up to 1 million-fold. In a small study of oral allergens, individuals with hazelnut allergy (n=28) had the lowest objective eliciting dose $(ED)_5$, which was at 5-fold lower than the ED_5 in individuals with egg allergy (n=53)[4]; and 15-fold lower when the ED_5 included all symptoms (reported and objectively measured). Food allergies vary in the age groups in which they predominate, with egg and milk allergy occurring

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earlier in life and diminishing over time, and tree-nut, fruit and crustacea allergies developing with increasing age. This implies, at least for food allergens, there is a lot of heterogeneity between allergens and it is difficult to extrapolate the findings from one allergen to another.

Based on the knowledge that the potency of food allergens varies, and that allergy to egg (which includes ovalbumin as well as other protein allergens) is generally accepted to be less potent than other food allergens, I do not consider it scientifically reasonable to extrapolate the tolerable dose of one allergen type to another.

Residual enzymes

There is little data on the tolerable dose of vaccine-induced allergens beyond ovalbumin, the level of which has been monitored with influenza and yellow fever vaccines. Bovine gelatin is another protein vaccine component that has led to vaccine-induced allergy when administered at 13.5mg/vaccine dose[5], a far higher dose of than that of the enzymes being considered here.

The residual doses of the enzymes after removal (digestion and filtration) are extremely low or in the case of T7 RNA polymerase, undetectable by the assay, and are therefore more than 100-fold lower that the 600ng/dose that has been tolerated with ovalbumin. **Given there is marked variation in the doses of allergen that individuals can react to, a very small the risk of allergic reaction will remain if the contaminant is present at all. This risk is likely to be extremely low.**

1. https://www.sigmaaldrich.com/content/dam/sigma-aldrich/docs/Sigma/Product_Information_Sheet/a7641pis.pdf
2. Moffat *et al* JMB (1984) 173, 265-269
3. https://www.sigmaaldrich.com/life-science/metabolomics/enzyme-explorer/analytical-enzymes/proteinase-k.html
4. Blom *et al* J Allergy Clin Immunol (2013) 131, 172-179
5. Sakaguchi *et* al J Allergy Clin Immunol (1997) 99, 263-264

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Document 15

Medsafe COVID-19 Vaccine Advisory Committee – Request for Advice

To:	s 9(2)(g)(ii), Chair, Medsafe Vaccine Advisory Committee, s 9(2)(g)(ii)
From:	s 9(2)(g)(ii), Senior Medical Advisor
Approving Manager:	s 9(2)(g)(ii), Manager, Clinical Risk Management
Date:	21 December 2020
Product:	BNT162b2 30 µg mRNA COVID-19 Vaccine, TT50-10853
Subject:	Duration of vaccine protection and safety follow-up in clinical trials
Requested Urgency:	**Routine**: within 10 working days

Request:
FDA recently granted Emergency Use Authorization for Pfizer's COVID-19 vaccine. FDA guidance is that a median of two-months clinical trial follow-up post immunization for emergency use authorization (refer page 10 of the link below).

https://www.fda.gov/media/142749/download

New Zealand currently has no community transmission of SARS-CoV-2, meaning that the benefits of an Emergency Use Authorization would not necessarily be sufficient to outweigh the risks of use based on review of limited data available. Recent research on FDA approval showed that the median follow-up was six months before approval for other vaccines.

In light of the above, Medsafe is requesting the following advice:

1. What risks can be identified of a two-month follow-up relating to efficacy (for example duration of response).

There are 2 efficacy studies – the phase 1 study directly assessing immunogenicity on a small number of participants (antibody titres and neutralization assays from the phase I study) and the phase 2/3 study assessing confirmed COVID-19 and severe COVID-19. At the 2-month timepoint the vaccine appears effective in both these measures.

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The main risk of approving based on 2-months follow up, relating to efficacy, is of course that antibody titres may be short lived and any protection from the vaccine will be of short duration. Worst case scenario is that then the vaccination program is essentially a waste of resources, however it is likely that there will be at least some lower level of residual protection which would mean infection was less severe, allowing many individuals to mount their own protective response without getting severe disease. This would hopefully also lessen the impact on health care resources.

An added complication is obviously that while there is a large amount of disease and viral replication internationally, viral mutations are also likely to occur that will also reduce vaccine efficacy. This would mean we should use the vaccine as soon as possible before the virus mutates too far from the vaccine strain.

2. What risks can be identified of a two-month follow-up relating to safety (for example detection of autoimmune conditions).

The vaccine appears safe at present but it is correct there has been little time for follow up for immunological adverse events. The added complication here that this is the first time an mRNA vaccine has been used so widely so data from other similar vaccines is not available. So far there does not appear to be any risk associated with vaccine-associated antibody-dependent enhancement of disease or autoimmunity.

3. Do you have any additional comments on what time frames for follow-up would be appropriate given the current COVID-19 pandemic situation in New Zealand?

It is very difficult but on balance I believe the risks of waiting (circulating virus mutates too far from vaccine strain decreasing efficacy and/or outbreak in NZ) are <u>not</u> out-weighed by the benefits (longer follow up for safety and efficacy). Indeed efficacy in a few months may be irrelevant as the vaccine continues to mutate. In that situation we would then need to wait for a new vaccine which could cover the original virus plus any new dominant circulating strains.

As regards safety – although mRNA vaccines are new, a huge number of doses have been i given over the past weeks and any major safety concerns would have been apparent.

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Background:

- The data in the Pfizer application regarding the BNT162b2 mRNA COVID-19 Vaccine has the same 14 November 2020 cut-off as that supporting emergency use internationally, this is two-month median follow up data.
- Updated data is expected in March 2021, which will have six-month median follow-up data.

- Medsafe is currently reviewing the MHRA clinical evaluation report. The report's discussion on clinical efficacy notes the following on page 48.

  The final efficacy analyses demonstrate a very high level of short-term efficacy. The median duration of follow-up after the second vaccine dose is estimated to be a little shorter than 2 months, which is considered the shortest follow-up period required to achieve some confidence that any protection is likely to be more than very short-lived. Indeed, in the Phase 1/2 trials, neutralising antibody levels have been shown to peak 1-2 weeks after the second dose and, therefore, the VE estimated at the final analysis after a median follow-up of almost 2 months (95%) is reassuring.

- The current follow-up is shown by the application's Clinical Overview person-years surveillance time in Table 8, the 'No. at risk' in Figure 1, and the safety data for having follow-up after dose two ≥2 months (eg Table 32).

Attached Documents:

- FDA VRBPAC Briefing Document 'Vaccines and Related Biological Products Advisory Committee Meeting December 10, 2020' (53 pages)
- MHRA Public Assessment Report COVID-19 mRNA vaccine BNT162 (51 pages).
- CTD Module 2 document: Clinical Overview (257 pages)

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FOR ADVISORY GROUP MEMBER(S) TO COMPLETE

Advising Member(s): [Name]

Reviewing Member(s): [Name]

Date Completed: [Date]

Advice:
Write report detailing advice in response to Medsafe request and include:
- summary of supporting information, data, documents, guidelines referenced
- final opinion/recommendation regarding issues raised
- identification of any deficiencies in data and recommendations of any requests for information that may be made of the sponsor, including an indication of what would be an acceptable response.

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