

State Board of Health: Nominating Committee
June 23, 2022 - 8:30am
Perimeter Center, Boardroom 2

Members Present: Jim Edmondson; Maribel Ramos.
VDH Staff Present: Alexandra Jansson, Senior Policy Analyst.

Call to Order

Ms. Ramos called the meeting to order at 8:31am.

Public Comment

There was no one signed up for the public comment period.

Nomination of Officers

Mr. Edmondson made a motion to nominate Gary Critzer as Chair, Dr. Wendy Klein as Vice Chair, and Dr. Anna Jeng and Dr. Jim Shuler as the two members of the Executive Committee. Ms. Ramos seconded the motion. The motion was carried by a unanimous roll call vote.

Other Business

There was no other business before the committee.

Adjourn

The meeting was adjourned at 8:36am.

State Board of Health
June 23, 2022 - 9:00am
Perimeter Center, Boardroom 2

Members Present: Gary Critzer;; Jim Edmondson; Melissa Green; Linda Hines; Anna Jeng; Patricia Kinser, PhD; Wendy Klein, MD, Vice Chair; Benita Miller, DDS; Faye Prichard, Chair; Holly Puritz, MD; Maribel Ramos; and Mary Margaret Whipple.

Members Absent: Stacey Swartz, PharmD; Elizabeth Harrison; Jim Shuler, DVM.

VDH Staff Present: Kathryn Crosby, Chief Diversity, Equity, and Inclusion Officer; Tiffany Ford, Deputy Commissioner for Administration; Dr. Colin Greene, State Health Commissioner; Joe Hilbert, Deputy Commissioner for Governmental and Regulatory Affairs; Parham Jaber, Deputy Commissioner for Community Health Services; Alexandra Jansson, Senior Policy Analyst; Maria Reppas, Director, Office of Communications; Whitney Rickman, Administrative Assistant for Governmental and Regulatory Affairs, Diversity, Equity and Inclusion, and Community Health Services; and Tammie Smith, Public Relations Coordinator.

Other Staff Present: Robin Kurz, JD, Senior Assistant Attorney General; Allyson Tysinger, JD, Senior Assistant Attorney General/Section Chief

Call to Order

Ms. Prichard called the meeting to order at 9:01am.

Introductions

Ms. Prichard welcomed those in attendance to the meeting. Ms. Prichard then started the introductions of the Board members and VDH staff present.

Review of Agenda

Ms. Jansson reviewed the agenda and the items contained in the Board's binder. Ms. Prichard suggested an amendment to the agenda by adding a Q&A section with Dr. Greene regarding a recent Washington Post article. Dr. Kinser made the motion to approve the amendment to the agenda with Dr. Puritz seconding the motion. The motion passed unanimously.

Approval of March 31, 2022 Minutes

Mr. Critzer made the motion to approve the minutes from the March 31, 2022 meeting with Dr. Puritz seconding the motion. The minutes were approved unanimously by voice vote.

Q&A Section with Dr. Greene

Dr. Kinser, Dr. Klein, Mr. Edmondson, Dr. Puritz, Ms. Ramos, Ms. Prichard, Ms. Hines, and Dr. Miller each posed questions to Dr. Greene regarding a recent article in the Washington Post.

Topics discussed included:

- Structural racism and health disparities;
- Board of Health as an apolitical entity;
- Removal of certain links from VDH website;
- Gun violence, including suicide, homicide, accidents, and active shooter incidents
- Regional and urban/rural health disparities;
- Extent to which Dr. Greene believes he was misquoted in the Washington Post article, and any efforts he made to request that corrections be made to the article;
- Dr. Greene's communications with his staff; and
- The importance of choosing the right words when delivering public health messages.

Mr. Edmondson presented, and read aloud to the Board, a resolution pertaining to Dr. Greene. Mr. Edmondson made the motion to approve the recommended resolution with Mr. Critzer seconding the motion. Ms. Tysinger stated the resolution can serve as a guide and recommendation to Dr. Greene but cannot be enforced by the Board. The resolution was approved unanimously by voice vote. The resolution is attached at the end of the minutes.

Commissioner's Report

Dr. Greene provided the Commissioner's Report to the Board. He updated the Board on key issues and projects VDH is engaged in including:

- Agency Stars
- Infant Formula Shortage
- COVID-19 Update
- Monkeypox Update
- Infant and Maternal Mortality
- Suicide and Substance Use Disorder
- ARPA Project: Drinking Water
- Lyme Disease
- Extreme Heat
- Hurricane Season

Non-Regulatory Item: EMS Regional Council Designation

Ron Passmore presented a memo regarding designation of regional emergency medical services councils. Mr. Critzer made the motion to approve the amendments with Ms. Hines seconding the motion. The designation of regional councils was approved unanimously by voice vote.

Public Comment Period

There were three persons who signed up for public comment at the meeting. Brent Rawlings recommended approval of the Fast Track Amendments for Hospitals. Doris Knick provided comment on her concerns about the COVID-19 vaccine and safety (see additional written comments at the end of the minutes document). Lindsey Lockwood provided comments regarding a recent Washington Post article pertaining to Dr. Greene. Additional public comment was received via email and is included at the end of the minutes.

Regulatory Action Update

Mr. Hilbert reviewed the summary of all pending VDH regulatory actions.

Since the March 2022 meeting, the Commissioner approved two regulatory actions on behalf of the Board while the Board was not in session. First, the NOIRA for the Regulations for Summer Camps (12VAC5-440) which followed a periodic review and will update the Regulations with modern standards for health and safety at summer camps. Second, the Commissioner approved a NOIRA for the Regulations Governing Virginia Newborn Screening Services (12VAC5-71). This regulatory action follows a periodic review and will update the Regulations to remove outdated information and reflect recommended national best practices.

Since the March 2022 meeting the Commissioner has taken no non-regulatory action on behalf of the Board while the Board was not in session.

Mr. Hilbert advised the Board that there are 20 periodic reviews in progress:

- 12 VAC 5-20 Regulations for the Conduct of Human Research
- 12 VAC 5-66 Regulations Governing Durable Do Not Resuscitate Orders
- 12 VAC 5-191 State plan for the Children with Special Health Care Needs Program
- 12 VAC 5-195 Virginia Women Infants and Children Program Regulations
- 12 VAC 5-200 Regulations Governing Eligibility Standards and Charges for Health Care Services to Individuals
- 12 VAC 5-215 Rules and Regulations Governing Health Data Reporting
- 12 VAC 5-216 Methodology to Measure Efficiency and Productivity of Health Care Institutions
- 12 VAC 5-217 Regulations of the Patient Level Data System
- 12 VAC 5-218 Rules and Regulations Governing Outpatient Data Reporting
- 12 VAC 5-220 Virginia Medical Care Facilities Certificate of Public Need Rules and Regulations
- 12 VAC 5-407 Regulations for the Submission of Health Maintenance Organization Quality of Care Performance Information
- 12 VAC 5-408 Regulation for the Certificate of Quality Assurance of Managed Care Health Insurance Plan (MCHIP) Licensees
- 12 VAC 5-410 Regulations for the Licensure of Hospitals in Virginia
- 12 VAC 5-431 Sanitary Regulations for Hotels
- 12 VAC 5-481 Virginia Radiation Protection Regulations
- 12 VAC 5-490 Virginia Radiation Protection Regulations: Fee Schedule
- 12 VAC 5-501 Rules and Regulations Governing the Construction of Migrant Labor Camps

- 12 VAC 5-508 Regulations Governing the Virginia Physician Loan Repayment Program
- 12 VAC 5-510 Guidelines for General Assembly Nursing Scholarships
- 12 VAC 5-540 Rules and Regulations for the Identification of Medically Underserved Areas in Virginia

Since the March 2022 meeting, the Executive Branch completed the review of two regulatory actions while the Board was not in session – a NOIRA for the Regulations Governing Virginia Newborn Screening Services (12 VAC 5-71) and a NOIRA for the Regulations for Summer Camps (12VAC 5-440).

Since the March 2022 meeting, there were two Fast Track items withdrawn that were previously approved by the Board – Virginia Medical Care Facilities Certificate of Public Need Rules and Regulations (12 VAC 5-220) and Regulations Governing Vital Records (12 VAC 5-550).

Public Health History in Virginia

Mr. Stover presented information on the Public Health History in Virginia.

Budget Update

Ms. Gilliam presented an update on the status of the budget from the 2022 General Assembly Session. The governor has now signed the biennial budget. The COVID-19 portion of the budget is still very large.

Amendments that the General Assembly made to the Budget Bill introduced by the Governor include:

- Drinking Water
 - Created a phase-in to implementation of the Water Sampling Verification Program
- Epidemiology
 - Level funded comprehensive harm reduction services
- Family Health Services
 - Reduced the amount of new funding for marijuana prevention and education
 - Maintained Temporary Assistance for Needy Families as a funding source for the Virginia Resource Mothers program
- Administration
 - Reduced the amount of funding for an integrated e-referral system
- Pass through payments
 - Increased funding for Pediatric Hospice and Palliative Care

Proposed Rainwater Harvesting Regulations

Julie Henderson presented the proposed Regulations to the Board. The proposed Regulations will promote the use of rainwater as means to reduce fresh water consumption, ease demands on public treatment works and water supply systems, and promote conservation. Mr. Critzer made the motion to approve the proposed regulations with Dr. Puritz seconding the motion. The proposed regulation was approved unanimously by voice vote.

Fast Track Amendments to Food Regulations

Ms. Henderson presented the Fast Track Amendments to the Board. The Fast Track Amendments conform the Food Regulations to the provisions of Chapter 853 of the 2020 General Assembly Session, which authorize any employee of a licensed restaurant to possess and administer epinephrine on the premises of a restaurant at which the employee is employed, provided that such employee is authorized by a prescriber, and is trained in the administration of

epinephrine. Trained employees who provide, administer, or assist in the administration of epinephrine to someone who, in good faith they believe is having an anaphylactic reaction, shall not be liable for certain civil damage. The proposed regulatory change will also allow for the storage of medications for use by children at a daycare center which contains a permitted food establishment.

Dr. Puritz made the motion to approve the proposed regulations with Dr. Jeng seconding the motion. There was discussion around the scope of the changes to the regulations and how training and administration of medications would be tracked. The Fast Track amendments were approved by voice vote, with Dr. Kinser voting no.

Fast Track Amendments to Regulations for the Licensure of Hospitals in Virginia

The Fast Track amendments were presented by Rebekah Allen. Chapters 712 and 722 of the 2022 Acts of Assembly require the State Board of Health to amend its hospital regulations to exempt from licensure temporary increase in the total number of beds in an existing hospital to include “a temporary increase in the total number of beds resulting from the addition of beds at a temporary structure or satellite location operated by the hospital..., provided that the ability remains to safely staff services across the existing hospital...” These acts also amended the exemption to now also be triggered by an emergency order entered pursuant to Va. Code section 32.1-13 or 32.1-20 for the purpose of suppressing a nuisance dangerous to public health or a communicable, contagious or infectious disease or other danger to the public life and health. The duration of this exemption has been amended to be either “a period of no more than the duration of the Commissioner’s determination plus 30 days...when the Commissioner has determined that a natural or man made disaster has caused the evacuation of a hospital or nursing home and that a public health and that a public health emergency exists due to a shortage of hospital or nursing home beds” or “ a period of no more than the duration of the emergency order entered pursuant to” section 32.1-13 or 32.1-20.

Ms. Whipple made the motion to approve the proposed regulations with Ms. Green seconding the motion. The Fast Track amendments were approved unanimously by voice vote.

Fast Track Amendments to the Virginia Medical Care Facilities Certificate of Public Need Rules and Regulations

The Fast Track amendments were presented by Ms. Allen. Chapters 712 and 722 of the 2022 Acts of Assembly require the State Board of Health to amend its regulation about exemptions for certificates of public need for projects that involve a temporary increase in the total number of beds in an existing hospital or nursing home to include “a temporary increase in the total number of beds resulting from the addition of beds at a temporary structure or satellite location operated by the hospital or nursing home, provided that the ability remains to safely staff services across the existing hospital or nursing home.” These acts also amended the exemption to now also be triggered by an emergency order entered pursuant to Va. Code section 32.1-13 or 32.1-20 for the purpose of suppressing a nuisance dangerous to public health or a communicable, contagious or infectious disease or other danger to the public life and health. The duration of this exemption has been amended to be either “a period of no more than the duration of the Commissioner’s determination plus 30 days...when the Commissioner has determined that a natural or man made disaster has caused the evacuation of a hospital or nursing home and that a public health and that a public health emergency exists due to a shortage of hospital or nursing home beds” or “ a period of no more than the duration of the emergency order entered pursuant to” section 32.1-13 or 32.1-20.

Dr. Kinser made the motion to approve the proposed regulations with Dr. Miller seconding the motion. The Fast Track amendments were approved unanimously by voice vote.

Fast Track Amendments to Regulations for Nursing Facilities

The Fast Track amendments were presented by Ms. Allen. Chapters 712 and 722 of the 2022 Acts of Assembly require the State Board of Health to amend its nursing home regulation to exempt from licensure a temporary increase in the total number of beds in an existing nursing home to include “a temporary increase in the total number of beds resulting from the addition of beds at a temporary structure or satellite location operated by the... nursing home, provided that the ability remains to safely staff services across the existing... nursing home.” These acts also amended the exemption to now also be triggered by an emergency order entered pursuant to Va. Code section 32.1-13 or 32.1-20 for the purpose of suppressing a nuisance dangerous to public health or a communicable, contagious or infectious disease or other danger to the public life and health. The duration of this exemption has been amended to be either “a period of no more than the duration of the Commissioner’s determination plus 30 days...when the Commissioner has determined that a natural or man made disaster has caused the evacuation of a hospital or nursing home and that a public health and that a public health emergency exists due to a shortage of hospital or nursing home beds” or “ a period of no more than the duration of the emergency order entered pursuant to” section 32.1-13 or 32.1-20.

Dr. Puritz made the motion to approve the proposed regulations with Mr. Critzer seconding the motion. The Fast Track amendments were approved unanimously by voice vote.

Fast Track Amendments to the Public Participation Guidelines

The Fast Track amendments were presented by Mr. Hilbert. The fast track amendments will conform the Guidelines to relevant statutes and regulations, as well as changes in style to conform to the Form, Style and Procedure Manual for Publication of Virginia Regulations.

Dr. Jeng made the motion to approve the proposed regulations with Ms. Green seconding the motion. The Fast Track amendments were approved unanimously by voice vote.

Report of the Nominating Committee

Ms. Ramos presented the report of the Nominating Committee. The recommended slate of officers for the year beginning July 1, 2022 is Chair - Gary Critzer, Vice Chair - Dr. Wendy Klein, Executive Committee Member - Dr. Jim Shuler, Executive Committee Member - Dr. Anna Jeng. Ms. Ramos made a motion to approve the nominations with Dr. Miller seconding the motion. The nominations were approved unanimously by voice vote.

Other Business

During other business, Ms. Prichard, Mr. Edmondson, and Dr. Miller noted that the June 2022 meeting was the last meeting of their terms, expressed their thanks for their time on the Board, and their appreciation for VDH staff.

Adjourn

The meeting adjourned at 2:49 pm

A RESOLUTION OF THE VIRGINIA BOARD OF HEALTH
ADOPTED AT ITS MEETING OF JUNE 23, 2022

WHEREAS, it has been the policy of the Board of Health and the Department of Health for many years to recognize that health care access and health outcomes have not been comparable across all demographic groups in the Commonwealth; and

WHEREAS, the truth of these observations has been proved by analysis of data over many years by medical scientists in the Commonwealth and across the country, and in particular by previous Commissioners of the Department and staff; and

WHEREAS, the disparities in health care outcomes between minority and low-income households and individuals and the population at large are particularly great, and greatest between African-Americans and the population at large; and

WHEREAS, the differences have been and continue to be most noticeable in maternal care and outcomes, but also in many other health categories; and

WHEREAS, the Commissioner has recently made public statements contrary to the position on these issues of the Board and its individual members to their and our embarrassment; now be it

RESOLVED BY THE BOARD OF HEALTH

That the Board directs the Commissioner and Department staff to acknowledge these differences as demonstrated by scientific and statistical evidence and to direct resources of the Department to the offices within the Department that focus on improving practices and delivery of care that will reduce these disparities over time. Improvements can and must be made in education of both the health care workforce and members of minority and lower-income groups; location of points of access to services; building of staff for new facilities; recruitment of voices within the communities to use such services confidently; continued gathering of statistics that demonstrate progress or lack of progress in achieving these goals.

FURTHER RESOLVED

That the Commissioner and other spokespeople of the Department will make no public statements contrary to the Board's policy or intentions regarding disparities in care and outcomes, nor make statements that carry a message of denial of basic scientific facts regarding disparities.

FURTHER RESOLVED

That the Commissioner and Department should advocate vigorously within the current and future administrations for additional resources to meet specific goals for the reduction and eventual elimination of the disparities.



State Board of Health, rr <boardofhealth@vdh.virginia.gov>

Public Comment - Commissioner Greene

1 message

Jessica Hunt <jessicah1228@gmail.com>

Wed, Jun 22, 2022 at 9:34 PM

To: boardofhealth@vdh.virginia.gov, faye.prichard@gmail.com, lisaruffinharrison@gmail.com, ramosmvaboh@gmail.com, lillian.peake@vdh.virginia.gov

To the Esteemed Members of the Virginia State Board of Health,

Unfortunately, I cannot be there to express my sentiments in person, but I hope that you will share this letter at your meeting tomorrow.

I implore you to remove Colin Greene from the position of State Health Commissioner. He has proven he is unfit for duty by denying, downplaying, and dismissing racism, gun violence, and scientific data. The mission of the Virginia Department of Health is "to protect the health and promote the well-being of all people in Virginia," yet he has hurt his colleagues without remorse. He does not represent the values of the Department of Health nor does he respect their work. Please remove him from this influential position before he causes further harm to the people of Virginia.

We deserve better.

We demand better.



Jansson, Alexandra <alexandra.jansson@vdh.virginia.gov>

Missing Data: Doris Knick's Public Comments at VDH BOH on June 23rd

1 message

Doris Knick <healersporch@yahoo.com>

Fri, Jun 24, 2022 at 8:34 PM

Reply-To: Doris Knick <healersporch@yahoo.com>

To: Alexandra Jansson <alexandra.jansson@vdh.virginia.gov>, "faye.prichard@gmail.com" <faye.prichard@gmail.com>, "critzergp@ci.waynesboro.va.us" <critzergp@ci.waynesboro.va.us>, "jedmondson@eandgggroup.com" <jedmondson@eandgggroup.com>, "Melissa.Green@NevaSeniorCare.com" <Melissa.Green@nevaseniorcare.com>, "lisaruffinharrison@gmail.com" <lisaruffinharrison@gmail.com>, "lhines@vapremier.com" <lhines@vapremier.com>, "hjeng@odu.edu" <hjeng@odu.edu>, "kinserpa.boh@gmail.com" <kinserpa.boh@gmail.com>, "wklein@healthbrigade.org" <wklein@healthbrigade.org>, "benitamiller58@gmail.com" <benitamiller58@gmail.com>, "h.puritz@tgfw.com" <h.puritz@tgfw.com>, "stacey.swartz@gmail.com" <stacey.swartz@gmail.com>, "mmwhipple@erols.com" <mmwhipple@erols.com>, "ramosmvaboh@gmail.com" <ramosmvaboh@gmail.com>, "Dr. Greene's Assistant" <maryanne.wollman@vdh.virginia.gov>

Ms. Jansson, VDH Board of Health Members, and Dr. Greene,

I spoke yesterday at the board of health meeting but forgot to give copies of what I spoke in regard to. I am emailing this to the board members listed on the website but if I missed anyone could you please forward to them?

Would you please add these documents attached to the public record?

One last comment for all members is that **these meetings should be recorded and posted** so the public whom you advocate for can be aware.

It would also be appreciated if there was a **virtual option to speak for those of us with children out of school for the summer**. There are many more parents with similar concerns to mine.

Since Mr. Edmondson alerted me to the fact that this has not been spoken about before it has assured me that only one narrative has primarily been shared with this board of health. I'm confident that he does not know anyone who is fully unvaccinated to be able to ask about their experiences.

As most physicians have only a half day of training on vaccines, none of which includes adverse events, it's not surprising that many physicians aren't aware of the dangers. Feel free to correct me if I am wrong.

The science is settled, and the evidence points to vaccine injury from this Covid "Vaccine" showing more deaths in the past 2 years than in all 30 years from VAERS combined, that cannot and should not be allowed to continue to be denied!

There has been far too much censorship surrounding this topic. I pray debates and open conversations continue to be welcomed and not discouraged by demeaning, gaslighting comments to the public from board members.

Sincerely,

Doris Knick
healersporch@yahoo.com

[VDH BOH 6/23/2022](#)



VDH BOH 6/23/2022

Board Members and fellow citizens. I know you can't answer questions during this time but I'd like to make this...

Your Advocate for Wellness,
"May your path to healing be natural, safe, pure and JOYfilled."

2 attachments



Pfizer Adverse Events Reported 5.3.6.pdf

984K



Pfizer NonClinical Overview 125742_S1_M2_24_.pdf

1650K

5.3.6 CUMULATIVE ANALYSIS OF POST-AUTHORIZATION ADVERSE EVENT REPORTS OF PF-07302048 (BNT162B2) RECEIVED THROUGH 28-FEB-2021

Report Prepared by:

Worldwide Safety

Pfizer

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APPENDICES

APPENDIX 1 LIST OF ADVERSE EVENTS OF SPECIAL INTEREST30

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LIST OF ABBREVIATIONS

Acronym	Term
AE	adverse event
AESI	adverse event of special interest
BC	Brighton Collaboration
CDC	Centers for Disease Control and Prevention
COVID-19	coronavirus disease 2019
DLP	data lock point
EUA	emergency use authorisation
HLGT	(MedDRA) High Group Level Term
HLT	(MedDRA) High Level Term
MAH	marketing authorisation holder
MedDRA	medical dictionary for regulatory activities
MHRA	Medicines and Healthcare products Regulatory Agency
PCR	Polymerase Chain Reaction
PT	(MedDRA) Preferred Term
PVP	pharmacovigilance plan
RT-PCR	Reverse Transcription-Polymerase Chain Reaction
RSI	reference safety information
TME	targeted medically event
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2
SMQ	standardised MedDRA query
SOC	(MedDRA) System Organ Class
UK	United Kingdom
US	United States
VAED	vaccine-associated enhanced disease
VAERD	vaccine-associated enhanced respiratory disease
VAERS	vaccine adverse event reporting system

1. INTRODUCTION

Reference is made to the Request for Comments and Advice submitted 04 February 2021 regarding Pfizer/BioNTech's proposal for the clinical and post-authorization safety data package for the Biologics License Application (BLA) for our investigational COVID-19 Vaccine (BNT162b2). Further reference is made to the Agency's 09 March 2021 response to this request, and specifically, the following request from the Agency.

“Monthly safety reports primarily focus on events that occurred during the reporting interval and include information not relevant to a BLA submission such as line lists of adverse events by country. We are most interested in a cumulative analysis of post-authorization safety data to support your future BLA submission. Please submit an integrated analysis of your cumulative post-authorization safety data, including U.S. and foreign post-authorization experience, in your upcoming BLA submission. Please include a cumulative analysis of the Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in your Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). Please also include distribution data and an analysis of the most common adverse events. In addition, please submit your updated Pharmacovigilance Plan with your BLA submission.”

This document provides an integrated analysis of the cumulative post-authorization safety data, including U.S. and foreign post-authorization adverse event reports received through 28 February 2021.

2. METHODOLOGY

Pfizer is responsible for the management post-authorization safety data on behalf of the MAH BioNTech according to the Pharmacovigilance Agreement in place. Data from BioNTech are included in the report when applicable.

Pfizer's safety database contains cases of AEs reported spontaneously to Pfizer, cases reported by the health authorities, cases published in the medical literature, cases from Pfizer-sponsored marketing programs, non-interventional studies, and cases of serious AEs reported from clinical studies regardless of causality assessment.

The limitations of post-marketing adverse drug event reporting should be considered when interpreting these data:

- Reports are submitted voluntarily, and the magnitude of underreporting is unknown. Some of the factors that may influence whether an event is reported include: length of time since marketing, market share of the drug, publicity about a drug or an AE, seriousness of the reaction, regulatory actions, awareness by health professionals and consumers of adverse drug event reporting, and litigation.
- Because many external factors influence whether or not an AE is reported, the spontaneous reporting system yields reporting proportions not incidence rates. As a result, it is generally not appropriate to make between-drug comparisons using these

proportions; the spontaneous reporting system should be used for signal detection rather than hypothesis testing.

- In some reports, clinical information (such as medical history, validation of diagnosis, time from drug use to onset of illness, dose, and use of concomitant drugs) is missing or incomplete, and follow-up information may not be available.
- An accumulation of adverse event reports (AERs) does not necessarily indicate that a particular AE was caused by the drug; rather, the event may be due to an underlying disease or some other factor(s) such as past medical history or concomitant medication.
- Among adverse event reports received into the Pfizer safety database during the cumulative period, only those having a complete workflow cycle in the safety database (meaning they progressed to Distribution or Closed workflow status) are included in the monthly SMSR. This approach prevents the inclusion of cases that are not fully processed hence not accurately reflecting final information. Due to the large numbers of spontaneous adverse event reports received for the product, the MAH has prioritised the processing of serious cases, in order to meet expedited regulatory reporting timelines and ensure these reports are available for signal detection and evaluation activity. The increased volume of reports has not impacted case processing for serious reports, and compliance metrics continue to be monitored weekly with prompt action taken as needed to maintain compliance with expedited reporting obligations. Non-serious cases are entered into the safety database no later than 4 calendar days from receipt. Entrance into the database includes the coding of all adverse events; this allow for a manual review of events being received but may not include immediate case processing to completion. Non-serious cases are processed as soon as possible and no later than 90 days from receipt. Pfizer has also taken a multiple actions to help alleviate the large increase of adverse event reports. This includes significant technology enhancements, and process and workflow solutions, as well as increasing the number of data entry and case processing colleagues. To date, Pfizer has onboarded approximately (b) (4) additional full-time employees (FTEs). More are joining each month with an expected total of more than (b) (4) additional resources by the end of June 2021.

3. RESULTS

3.1. Safety Database

3.1.1. General Overview

It is estimated that approximately (b) (4) doses of BNT162b2 were shipped worldwide from the receipt of the first temporary authorisation for emergency supply on 01 December 2020 through 28 February 2021.

Cumulatively, through 28 February 2021, there was a total of 42,086 case reports (25,379 medically confirmed and 16,707 non-medically confirmed) containing 158,893 events. Most cases (34,762) were received from United States (13,739), United Kingdom (13,404) Italy (2,578), Germany (1913), France (1506), Portugal (866) and Spain (756); the remaining 7,324 were distributed among 56 other countries.

Table 1 below presents the main characteristics of the overall cases.

Table 1. General Overview: Selected Characteristics of All Cases Received During the Reporting Interval

	Characteristics	Relevant cases (N=42086)
Gender:	Female	29914
	Male	9182
	No Data	2990
Age range (years): 0.01 -107 years Mean = 50.9 years n = 34952	≤ 17	175 ^a
	18-30	4953
	31-50	13886
	51-64	7884
	65-74	3098
	≥ 75	5214
	Unknown	6876
Case outcome:	Recovered/Recovering	19582
	Recovered with sequelae	520
	Not recovered at the time of report	11361
	Fatal	1223
	Unknown	9400

a. in 46 cases reported age was <16-year-old and in 34 cases <12-year-old.

As shown in [Figure 1](#), the System Organ Classes (SOCs) that contained the greatest number ($\geq 2\%$) of events, in the overall dataset, were General disorders and administration site conditions (51,335 AEs), Nervous system disorders (25,957), Musculoskeletal and connective tissue disorders (17,283), Gastrointestinal disorders (14,096), Skin and subcutaneous tissue disorders (8,476), Respiratory, thoracic and mediastinal disorders (8,848), Infections and infestations (4,610), Injury, poisoning and procedural complications (5,590), and Investigations (3,693).

Figure 1. Total Number of BNT162b2 AEs by System Organ Classes and Event Seriousness

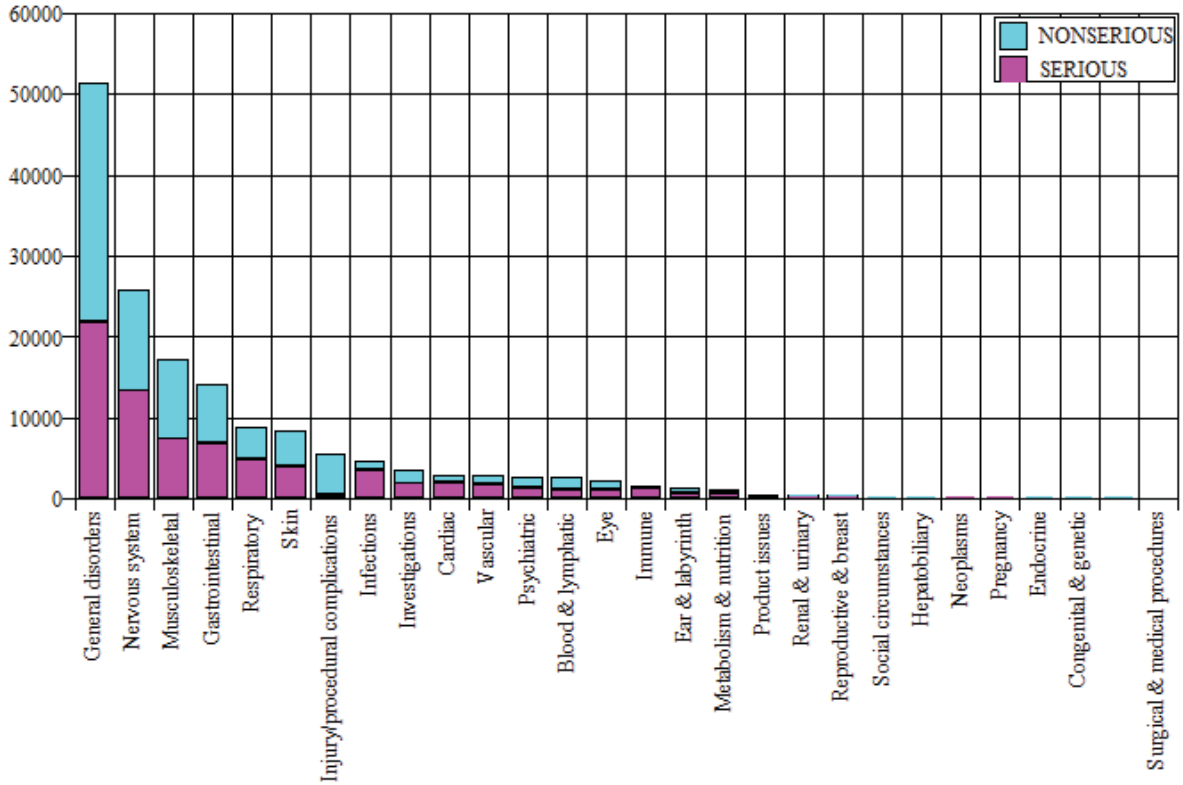


Table 2 shows the most commonly ($\geq 2\%$) reported MedDRA (v. 23.1) PTs in the overall dataset (through 28 February 2021),

Table 2. Events Reported in $\geq 2\%$ Cases

MedDRA SOC	MedDRA PT	Cumulatively Through 28 February 2021 AEs (AERP%) N = 42086
Blood and lymphatic system disorders		
	Lymphadenopathy	1972 (4.7%)
Cardiac disorders		
	Tachycardia	1098 (2.6%)
Gastrointestinal disorders		
	Nausea	5182 (12.3%)
	Diarrhoea	1880 (4.5%)
	Vomiting	1698 (4.0%)
General disorders and administration site conditions		
	Pyrexia	7666 (18.2%)
	Fatigue	7338 (17.4%)
	Chills	5514 (13.1%)
	Vaccination site pain	5181 (12.3%)

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Table 2. Events Reported in $\geq 2\%$ Cases

		Cumulatively Through 28 February 2021
MedDRA SOC	MedDRA PT	AEs (AERP%) N = 42086
	Pain	3691 (8.8%)
	Malaise	2897 (6.9%)
	Asthenia	2285 (5.4%)
	Drug ineffective	2201 (5.2%)
	Vaccination site erythema	930 (2.2%)
	Vaccination site swelling	913 (2.2%)
	Influenza like illness	835 (2%)
Infections and infestations		
	COVID-19	1927 (4.6%)
Injury, poisoning and procedural complications		
	Off label use	880 (2.1%)
	Product use issue	828 (2.0%)
Musculoskeletal and connective tissue disorders		
	Myalgia	4915 (11.7%)
	Pain in extremity	3959 (9.4%)
	Arthralgia	3525 (8.4%)
Nervous system disorders		
	Headache	10131 (24.1%)
	Dizziness	3720 (8.8%)
	Paraesthesia	1500 (3.6%)
	Hypoaesthesia	999 (2.4%)
Respiratory, thoracic and mediastinal disorders		
	Dyspnoea	2057 (4.9%)
	Cough	1146 (2.7%)
	Oropharyngeal pain	948 (2.3%)
Skin and subcutaneous tissue disorders		
	Pruritus	1447 (3.4%)
	Rash	1404 (3.3%)
	Erythema	1044 (2.5%)
	Hyperhidrosis	900 (2.1%)
	Urticaria	862 (2.1%)
Total number of events		93473

3.1.2. Summary of Safety Concerns in the US Pharmacovigilance Plan**Table 3. Safety concerns**

Important identified risks	Anaphylaxis
Important potential risks	Vaccine-Associated Enhanced Disease (VAED), Including Vaccine-associated Enhanced Respiratory Disease (VAERD)
Missing information	Use in Pregnancy and lactation Use in Paediatric Individuals <12 Years of Age Vaccine Effectiveness

Table 4. Important Identified Risk

Topic	Description														
Important Identified Risk	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)														
Anaphylaxis	<p>Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 1833 potentially relevant cases were retrieved from the Anaphylactic reaction SMQ (Narrow and Broad) search strategy, applying the MedDRA algorithm. These cases were individually reviewed and assessed according to Brighton Collaboration (BC) definition and level of diagnostic certainty as shown in the Table below:</p> <table border="1" data-bbox="423 562 1276 766"> <thead> <tr> <th>Brighton Collaboration Level</th> <th>Number of cases</th> </tr> </thead> <tbody> <tr> <td>BC 1</td> <td>290</td> </tr> <tr> <td>BC 2</td> <td>311</td> </tr> <tr> <td>BC 3</td> <td>10</td> </tr> <tr> <td>BC 4</td> <td>391</td> </tr> <tr> <td>BC 5</td> <td>831</td> </tr> <tr> <td><i>Total</i></td> <td>1833</td> </tr> </tbody> </table> <p>Level 1 indicates a case with the highest level of diagnostic certainty of anaphylaxis, whereas the diagnostic certainty is lowest for Level 3. Level 4 is defined as “reported event of anaphylaxis with insufficient evidence to meet the case definition” and Level 5 as not a case of anaphylaxis.</p> <p>There were 1002 cases (54.0% of the potentially relevant cases retrieved), 2958 potentially relevant events, from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy, meeting BC Level 1 to 4:</p> <p>Country of incidence: UK (261), US (184), Mexico (99), Italy (82), Germany (67), Spain (38), France (36), Portugal (22), Denmark (20), Finland, Greece (19 each), Sweden (17), Czech Republic , Netherlands (16 each), Belgium, Ireland (13 each), Poland (12), Austria (11); the remaining 57 cases originated from 15 different countries.</p> <p>Relevant event seriousness: Serious (2341), Non-Serious (617);</p> <p>Gender: Females (876), Males (106), Unknown (20);</p> <p>Age (n=961) ranged from 16 to 98 years (mean = 54.8 years, median = 42.5 years);</p> <p>Relevant even outcome^a: fatal (9)^b, resolved/resolving (1922), not resolved (229), resolved with sequelae (48), unknown (754);</p> <p>Most frequently reported relevant PTs (≥2%), from the Anaphylactic reaction SMQ (Broad and Narrow) search strategy: Anaphylactic reaction (435), Dyspnoea (356), Rash (190), Pruritus (175), Erythema (159), Urticaria (133), Cough (115), Respiratory distress, Throat tightness (97 each), Swollen tongue (93), Anaphylactic shock (80), Hypotension (72), Chest discomfort (71), Swelling face (70), Pharyngeal swelling (68), and Lip swelling (64).</p> <p>Conclusion: Evaluation of BC cases Level 1 - 4 did not reveal any significant new safety information. Anaphylaxis is appropriately described in the product labeling as are non-anaphylactic hypersensitivity events. Surveillance will continue.</p>	Brighton Collaboration Level	Number of cases	BC 1	290	BC 2	311	BC 3	10	BC 4	391	BC 5	831	<i>Total</i>	1833
Brighton Collaboration Level	Number of cases														
BC 1	290														
BC 2	311														
BC 3	10														
BC 4	391														
BC 5	831														
<i>Total</i>	1833														

a Different clinical outcome may be reported for an event that occurred more than once to the same individual.

b There were 4 individuals in the anaphylaxis evaluation who died on the same day they were vaccinated. Although these patients experienced adverse events (9) that are potential symptoms of anaphylaxis, they all had serious underlying medical conditions, and one individual appeared to also have COVID-19 pneumonia, that likely contributed to their deaths

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Table 5. Important Potential Risk

Topic	Description
Important Potential Risk	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
Vaccine-Associated Enhanced Disease (VAED), including Vaccine-Associated Respiratory Disease (VAERD)	<p>No post-authorized AE reports have been identified as cases of VAED/VAERD, therefore, there is no observed data at this time. An expected rate of VAED is difficult to establish so a meaningful observed/expected analysis cannot be conducted at this point based on available data. The feasibility of conducting such an analysis will be re-evaluated on an ongoing basis as data on the virus grows and the vaccine safety data continues to accrue.</p> <p>The search criteria utilised to identify potential cases of VAED for this report includes PTs indicating a lack of effect of the vaccine and PTs potentially indicative of severe or atypical COVID-19^a.</p> <p>Since the first temporary authorization for emergency supply under Regulation 174 in the UK (01 December 2020) and through 28 February 2021, 138 cases [0.33% of the total PM dataset], reporting 317 potentially relevant events were retrieved:</p> <p>Country of incidence: UK (71), US (25), Germany (14), France, Italy, Mexico, Spain, (4 each), Denmark (3); the remaining 9 cases originated from 9 different countries; Cases Seriousness: 138; Seriousness criteria for the total 138 cases: Medically significant (71, of which 8 also serious for disability), Hospitalization required (non-fatal/non-life threatening) (16, of which 1 also serious for disability), Life threatening (13, of which 7 were also serious for hospitalization), Death (38). Gender: Females (73), Males (57), Unknown (8); Age (n=132) ranged from 21 to 100 years (mean = 57.2 years, median = 59.5); Case outcome: fatal (38), resolved/resolving (26), not resolved (65), resolved with sequelae (1), unknown (8); Of the 317 relevant events, the most frequently reported PTs (≥2%) were: Drug ineffective (135), Dyspnoea (53), Diarrhoea (30), COVID-19 pneumonia (23), Vomiting (20), Respiratory failure (8), and Seizure (7).</p> <p>Conclusion: VAED may present as severe or unusual clinical manifestations of COVID-19. Overall, there were 37 subjects with suspected COVID-19 and 101 subjects with confirmed COVID-19 following one or both doses of the vaccine; 75 of the 101 cases were severe, resulting in hospitalisation, disability, life-threatening consequences or death. None of the 75 cases could be definitively considered as VAED/VAERD.</p> <p>In this review of subjects with COVID-19 following vaccination, based on the current evidence, VAED/VAERD remains a theoretical risk for the vaccine. Surveillance will continue.</p>

a. Search criteria: Standard Decreased Therapeutic Response Search AND PTs Dyspnoea; Tachypnoea; Hypoxia; COVID 19 pneumonia; Respiratory Failure; Acute Respiratory Distress Syndrome; Cardiac Failure; Cardiogenic shock; Acute myocardial infarction; Arrhythmia; Myocarditis; Vomiting; Diarrhoea; Abdominal pain; Jaundice; Acute hepatic failure; Deep vein thrombosis; Pulmonary embolism; Peripheral Ischaemia; Vasculitis; Shock; Acute kidney injury; Renal failure; Altered state of consciousness; Seizure; Encephalopathy; Meningitis; Cerebrovascular accident; Thrombocytopenia; Disseminated intravascular coagulation; Chillblains; Erythema multiforme; Multiple organ dysfunction syndrome; Multisystem inflammatory syndrome in children.

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Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
Use in Pregnancy and lactation	<ul style="list-style-type: none"> • Number of cases: 413^a (0.98% of the total PM dataset); 84 serious and 329 non-serious; • Country of incidence: US (205), UK (64), Canada (31), Germany (30), Poland (13), Israel (11); Italy (9), Portugal (8), Mexico (6), Estonia, Hungary and Ireland, (5 each), Romania (4), Spain (3), Czech Republic and France (2 each), the remaining 10 cases were distributed among 10 other countries. <p>Pregnancy cases: 274 cases including:</p> <ul style="list-style-type: none"> • 270 mother cases and 4 foetus/baby cases representing 270 unique pregnancies (the 4 foetus/baby cases were linked to 3 mother cases; 1 mother case involved twins). • Pregnancy outcomes for the 270 pregnancies were reported as spontaneous abortion (23), outcome pending (5), premature birth with neonatal death, spontaneous abortion with intrauterine death (2 each), spontaneous abortion with neonatal death, and normal outcome (1 each). No outcome was provided for 238 pregnancies (note that 2 different outcomes were reported for each twin, and both were counted). • 146 non-serious mother cases reported exposure to vaccine in utero without the occurrence of any clinical adverse event. The exposure PTs coded to the PTs Maternal exposure during pregnancy (111), Exposure during pregnancy (29) and Maternal exposure timing unspecified (6). Trimester of exposure was reported in 21 of these cases: 1st trimester (15 cases), 2nd trimester (7), and 3rd trimester (2). • 124 mother cases, 49 non-serious and 75 serious, reported clinical events, which occurred in the vaccinated mothers. Pregnancy related events reported in these cases coded to the PTs Abortion spontaneous (25), Uterine contraction during pregnancy, Premature rupture of membranes, Abortion, Abortion missed, and Foetal death (1 each). Other clinical events which occurred in more than 5 cases coded to the PTs Headache (33), Vaccination site pain (24), Pain in extremity and Fatigue (22 each), Myalgia and Pyrexia (16 each), Chills (13) Nausea (12), Pain (11), Arthralgia (9), Lymphadenopathy and Drug ineffective (7 each), Chest pain, Dizziness and Asthenia (6 each), Malaise and COVID-19 (5 each). Trimester of exposure was reported in 22 of these cases: 1st trimester (19 cases), 2nd trimester (1 case), 3rd trimester (2 cases). • 4 serious foetus/baby cases reported the PTs Exposure during pregnancy, Foetal growth restriction, Maternal exposure during pregnancy, Premature baby (2 each), and Death neonatal (1). Trimester of exposure was reported for 2 cases (twins) as occurring during the 1st trimester. <p>Breast feeding baby cases: 133, of which:</p> <ul style="list-style-type: none"> • 116 cases reported exposure to vaccine during breastfeeding (PT Exposure via breast milk) without the occurrence of any clinical adverse events; • 17 cases, 3 serious and 14 non-serious, reported the following clinical events that occurred in the infant/child exposed to vaccine via breastfeeding: Pyrexia (5), Rash (4), Infant irritability (3), Infantile vomiting, Diarrhoea, Insomnia, and Illness (2 each), Poor feeding infant, Lethargy, Abdominal discomfort, Vomiting, Allergy to vaccine, Increased appetite, Anxiety, Crying, Poor quality sleep, Eructation, Agitation, Pain and Urticaria (1 each). <p>Breast feeding mother cases (6):</p> <ul style="list-style-type: none"> • 1 serious case reported 3 clinical events that occurred in a mother during breast feeding (PT Maternal exposure during breast feeding); these events coded to the PTs Chills, Malaise, and Pyrexia • 1 non-serious case reported with very limited information and without associated AEs.

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Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
	<ul style="list-style-type: none"> • In 4 cases (3 non-serious; 1 serious) Suppressed lactation occurred in a breast feeding women with the following co-reported events: Pyrexia (2), Paresis, Headache, Chills, Vomiting, Pain in extremity, Arthralgia, Breast pain, Scar pain, Nausea, Migraine, Myalgia, Fatigue and Breast milk discolouration (1 each). <p>Conclusion: There were no safety signals that emerged from the review of these cases of use in pregnancy and while breast feeding.</p>
Use in Paediatric Individuals <12 Years of Age	<p style="text-align: center;"><u>Paediatric individuals <12 years of age</u></p> <ul style="list-style-type: none"> • Number of cases: 34^d (0.1% of the total PM dataset), indicative of administration in paediatric subjects <12 years of age; • Country of incidence: UK (29), US (3), Germany and Andorra (1 each); • Cases Seriousness: Serious (24), Non-Serious (10); • Gender: Females (25), Males (7), Unknown (2); • Age (n=34) ranged from 2 months to 9 years, mean = 3.7 years, median = 4.0; • Case outcome: resolved/resolving (16), not resolved (13), and unknown (5). • Of the 132 reported events, those reported more than once were as follows: Product administered to patient of inappropriate age (27, see Medication Error), Off label use (11), Pyrexia (6), Product use issue (5), Fatigue, Headache and Nausea (4 each), Vaccination site pain (3), Abdominal pain upper, COVID-19, Facial paralysis, Lymphadenopathy, Malaise, Pruritus and Swelling (2 each). <p>Conclusion: No new significant safety information was identified based on a review of these cases compared with the non-paediatric population.</p>
Vaccine Effectiveness	<p>Company conventions for coding cases indicative of lack of efficacy:</p> <p>The coding conventions for lack of efficacy in the context of administration of the COVID-19 vaccine were revised on 15 February 2021, as shown below:</p> <ul style="list-style-type: none"> • PT “Vaccination failure” is coded when ALL of the following criteria are met: <ul style="list-style-type: none"> ○ The subject has received the series of two doses per the dosing regimen in local labeling. ○ At least 7 days have elapsed since the second dose of vaccine has been administered. ○ The subject experiences SARS-CoV-2 infection (confirmed laboratory tests). • PT “Drug ineffective” is coded when either of the following applies: <ul style="list-style-type: none"> ○ The infection is not confirmed as SARS-CoV-2 through laboratory tests (irrespective of the vaccination schedule). This includes scenarios where LOE is stated or implied, e.g., “the vaccine did not work”, “I got COVID-19”. ○ It is unknown: <ul style="list-style-type: none"> ▪ Whether the subject has received the series of two doses per the dosing regimen in local labeling; ▪ How many days have passed since the first dose (including unspecified number of days like” a few days”, “some days”, etc.); ▪ If 7 days have passed since the second dose; ○ The subject experiences a vaccine preventable illness 14 days after receiving the first dose up to and through 6 days after receipt of the second dose. <p>Note: after the immune system as had sufficient time (14 days) to respond to the vaccine, a report of COVID-19 is considered a potential lack of efficacy even if the vaccination course is not complete.</p> <p>Summary of the coding conventions for onset of vaccine preventable disease versus the vaccination date:</p>

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Table 6. Description of Missing Information

Topic	Description		
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)		
	1st dose (day 1-13)	From day 14 post 1st dose to day 6 post 2nd dose	Day 7 post 2nd dose
	Code only the events describing the SARS-CoV-2 infection	Code “Drug ineffective”	Code “Vaccination failure”
	Scenario Not considered LOE	Scenario considered LOE as “Drug ineffective”	Scenario considered LOE as “Vaccination failure”
	<p>Lack of efficacy cases</p> <ul style="list-style-type: none"> • Number of cases: 1665^b (3.9 % of the total PM dataset) of which 1100 were medically confirmed and 565 non medically confirmed; • Number of lack of efficacy events: 1665 [PT: Drug ineffective (1646) and Vaccination failure (19)^f]. • Country of incidence: US (665), UK (405), Germany (181), France (85), Italy (58), Romania (47), Belgium (33), Israel (30), Poland (28), Spain (21), Austria (18), Portugal (17), Greece (15), Mexico (13), Denmark (8), Canada (7), Hungary, Sweden and United Arab Emirates (5 each), Czech Republic (4), Switzerland (3); the remaining 12 cases originated from 9 different countries. • COVID-19 infection was suspected in 155 cases, confirmed in 228 cases, in 1 case it was reported that the first dose was not effective (no other information). • COVID-19 infection (suspected or confirmed) outcome was reported as resolved/resolving (165), not resolved (205) or unknown (1230) at the time of the reporting; there were 65 cases where a fatal outcome was reported. <p>Drug ineffective cases (1649)</p> <ul style="list-style-type: none"> • Drug ineffective event seriousness: serious (1625), non-serious (21)^e; • Lack of efficacy term was reported: <ul style="list-style-type: none"> ○ after the 1st dose in 788 cases ○ after the 2nd dose in 139 cases ○ in 722 cases it was unknown after which dose the lack of efficacy occurred. • Latency of lack of efficacy term reported after the first dose was known for 176 cases: <ul style="list-style-type: none"> ○ Within 9 days: 2 subjects; ○ Within 14 and 21 days: 154 subjects; ○ Within 22 and 50 days: 20 subjects; • Latency of lack of efficacy term reported after the second dose was known for 69 cases: <ul style="list-style-type: none"> ○ Within 0 and 7 days: 42 subjects; ○ Within 8 and 21 days: 22 subjects; ○ Within 23 and 36 days: 5 subjects. • Latency of lack of efficacy term reported in cases where the number of doses administered was not provided, was known in 409 cases: <ul style="list-style-type: none"> ○ Within 0 and 7 days after vaccination: 281 subjects. ○ Within 8 and 14 days after vaccination: 89 subjects. ○ Within 15 and 44 days after vaccination: 39 subjects. <p>According to the RSI, individuals may not be fully protected until 7 days after their second dose of vaccine, therefore for the above 1649 cases where lack of efficacy was reported after the 1st dose or the</p>		

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Table 6. Description of Missing Information

Topic	Description
Missing Information	Post Authorization Cases Evaluation (cumulative to 28 Feb 2021) Total Number of Cases in the Reporting Period (N=42086)
	<p>2nd dose, the reported events may represent signs and symptoms of intercurrent or undiagnosed COVID-19 infection or infection in an individual who was not fully vaccinated, rather than vaccine ineffectiveness.</p> <p style="text-align: center;"><i>Vaccination failure cases (16)</i></p> <ul style="list-style-type: none"> • Vaccination failure seriousness: all serious; • Lack of efficacy term was reported in all cases after the 2nd dose; • Latency of lack of efficacy was known for 14 cases: <ul style="list-style-type: none"> ○ Within 7 and 13 days: 8 subjects; ○ Within 15 and 29 days: 6 subjects. <p>COVID-19 (10) and Asymptomatic COVID-19 (6) were the reported vaccine preventable infections that occurred in these 16 cases.</p> <p>Conclusion: No new safety signals of vaccine lack of efficacy have emerged based on a review of these cases.</p>

- a. From a total of 417 cases, 4 cases were excluded from the analysis. In 3 cases, the MAH was informed that a 33-year-old and two unspecified age pregnant female patients were scheduled to receive bnt162b2 (PT reported Off label use and Product use issue in 2 cases; Circumstance or information capable of leading to medication error in one case). One case reported the PT Morning sickness; however, pregnancy was not confirmed in this case.
- b. 558 additional cases retrieved in this dataset were excluded from the analysis; upon review, 546 cases cannot be considered true lack of efficacy cases because the PT Drug ineffective was coded but the subjects developed SARS-CoV-2 infection during the early days from the first dose (days 1 – 13); the vaccine has not had sufficient time to stimulate the immune system and, consequently, the development of a vaccine preventable disease during this time is not considered a potential lack of effect of the vaccine; in 5 cases the PT Drug ineffective was removed after data lock point (DLP) because the subjects did not develop COVID-19 infection; in 1 case, reporting Treatment failure and Transient ischaemic attack, the Lack of efficacy PT did not refer to BNT162b2 vaccine; 5 cases have been invalidated in the safety database after DLP; 1 case has been deleted from the discussion because the PTs reported Pathogen resistance and Product preparation issue were not indicative of a lack of efficacy. to be eliminated.
- c. Upon review, 31 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects
- d. Upon review, 28 additional cases were excluded from the analysis as the data reported (e.g. clinical details, height, weight, etc.) were not consistent with paediatric subjects.
- e. Different clinical outcomes may be reported for an event that occurred more than once to the same individual
- f. In 2 cases the PT Vaccination failure was replaced with Drug ineffective after DLP. Another case was not included in the discussion of the Vaccination failure cases because correct scheduling (21 days apart between the first and second dose) cannot be confirmed.

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3.1.3. Review of Adverse Events of Special Interest (AESIs)

Please refer to [Appendix 1](#) for the list of the company's AESIs for BNT162b2.

The company's AESI list takes into consideration the lists of AESIs from the following expert groups and regulatory authorities: Brighton Collaboration (SPEAC), ACCESS protocol, US CDC (preliminary list of AESI for VAERS surveillance), MHRA (unpublished guideline).

The AESI terms are incorporated into a TME list and include events of interest due to their association with severe COVID-19 and events of interest for vaccines in general.

The AESI list is comprised of MedDRA PTs, HLTs, HLTs or MedDRA SMQs and can be changed as appropriate based on the evolving safety profile of the vaccine.

Table 7 provides a summary review of cumulative cases within AESI categories in the Pfizer safety database. This is distinct from safety signal evaluations which are conducted and included, as appropriate, in the Summary Monthly Safety Reports submitted regularly to the FDA and other Health Authorities.

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
Anaphylactic Reactions <i>Search criteria: Anaphylactic reaction SMQ (Narrow and Broad, with the algorithm applied), selecting relevant cases according to BC criteria</i>	Please refer to the Risk 'Anaphylaxis' included above in Table 4 .
Cardiovascular AESIs <i>Search criteria: PTs Acute myocardial infarction; Arrhythmia; Cardiac failure; Cardiac failure acute; Cardiogenic shock; Coronary artery disease; Myocardial infarction; Postural orthostatic tachycardia syndrome; Stress cardiomyopathy; Tachycardia</i>	<ul style="list-style-type: none"> • Number of cases: 1403 (3.3% of the total PM dataset), of which 241 are medically confirmed and 1162 are non-medically confirmed; • Country of incidence: UK (268), US (233), Mexico (196), Italy (141), France (128), Germany (102), Spain (46), Greece (45), Portugal (37), Sweden (20), Ireland (17), Poland (16), Israel (13), Austria, Romania and Finland (12 each), Netherlands (11), Belgium and Norway (10 each), Czech Republic (9), Hungary and Canada (8 each), Croatia and Denmark (7 each), Iceland (5); the remaining 30 cases were distributed among 13 other countries; • Subjects' gender: female (1076), male (291) and unknown (36); • Subjects' age group (n = 1346): Adult^c (1078), Elderly^d (266) Child^e and Adolescent^f (1 each); • Number of relevant events: 1441, of which 946 serious, 495 non-serious; in the cases reporting relevant serious events; • Reported relevant PTs: Tachycardia (1098), Arrhythmia (102), Myocardial infarction (89), Cardiac failure (80), Acute myocardial infarction (41), Cardiac failure acute (11), Cardiogenic shock and Postural orthostatic tachycardia syndrome (7 each) and Coronary artery disease (6); • Relevant event onset latency (n = 1209): Range from <24 hours to 21 days, median <24 hours;

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> • Relevant event outcome^g: fatal (136), resolved/resolving (767), resolved with sequelae (21), not resolved (140) and unknown (380); <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>COVID-19 AESIs <i>Search criteria: Covid-19 SMQ (Narrow and Broad) OR PTs Ageusia; Anosmia</i></p>	<ul style="list-style-type: none"> • Number of cases: 3067 (7.3% of the total PM dataset), of which 1013 are medically confirmed and 2054 are non-medically confirmed; • Country of incidence: US (1272), UK (609), Germany (360), France (161), Italy (94), Spain (69), Romania (62), Portugal (51), Poland (50), Mexico (43), Belgium (42), Israel (41), Sweden (30), Austria (27), Greece (24), Denmark (18), Czech Republic and Hungary (17 each), Canada (12), Ireland (11), Slovakia (9), Latvia and United Arab Emirates (6 each); the remaining 36 cases were distributed among 16 other different countries; • Subjects' gender: female (1650), male (844) and unknown (573); • Subjects' age group (n= 1880): Adult (1315), Elderly (560), Infant^h and Adolescent (2 each), Child (1); • Number of relevant events: 3359, of which 2585 serious, 774 non-serious; • Most frequently reported relevant PTs (>1 occurrence): COVID-19 (1927), SARS-CoV-2 test positive (415), Suspected COVID-19 (270), Ageusia (228), Anosmia (194), SARS-CoV-2 antibody test negative (83), Exposure to SARS-CoV-2 (62), SARS-CoV-2 antibody test positive (53), COVID-19 pneumonia (51), Asymptomatic COVID-19 (31), Coronavirus infection (13), Occupational exposure to SARS-CoV-2 (11), SARS-CoV-2 test false positive (7), Coronavirus test positive (6), SARS-CoV-2 test negative (3) SARS-CoV-2 antibody test (2); • Relevant event onset latency (n = 2070): Range from <24 hours to 374 days, median 5 days; • Relevant event outcome: fatal (136), not resolved (547), resolved/resolving (558), resolved with sequelae (9) and unknown (2110). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Dermatological AESIs <i>Search criteria: PT Chillblains; Erythema multiforme</i></p>	<ul style="list-style-type: none"> • Number of cases: 20 cases (0.05% of the total PM dataset), of which 15 are medically confirmed and 5 are non-medically confirmed; • Country of incidence: UK (8), France and Poland (2 each), and the remaining 8 cases were distributed among 8 other different countries; • Subjects' gender: female (17) male and unknown (1 each); • Subjects' age group (n=19): Adult (18), Elderly (1); • Number of relevant events: 20 events, 16 serious, 4 non-serious

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Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> • Reported relevant PTs: Erythema multiforme (13) and Chillblains (7) • Relevant event onset latency (n = 18): Range from <24 hours to 17 days, median 3 days; • Relevant event outcome: resolved/resolving (7), not resolved (8) and unknown (6). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Haematological AESIs <i>Search criteria: Leukopenias NEC (HLT) (Primary Path) OR Neutropenias (HLT) (Primary Path) OR PTs Immune thrombocytopenia, Thrombocytopenia OR SMQ Haemorrhage terms (excl laboratory terms</i></p>	<ul style="list-style-type: none"> • Number of cases: 932 (2.2 % of the total PM dataset), of which 524 medically confirmed and 408 non-medically confirmed; • Country of incidence: UK (343), US (308), France (50), Germany (43), Italy (37), Spain (27), Mexico and Poland (13 each), Sweden (10), Israel (9), Netherlands (8), Denmark, Finland, Portugal and Ireland (7 each), Austria and Norway (6 each), Croatia (4), Greece, Belgium, Hungary and Switzerland (3 each), Cyprus, Latvia and Serbia (2 each); the remaining 9 cases originated from 9 different countries; • Subjects' gender (n=898): female (676) and male (222); • Subjects' age group (n=837): Adult (543), Elderly (293), Infant (1); • Number of relevant events: 1080, of which 681 serious, 399 non-serious; • Most frequently reported relevant PTs (≥15 occurrences) include: Epistaxis (127), Contusion (112), Vaccination site bruising (96), Vaccination site haemorrhage (51), Petechiae (50), Haemorrhage (42), Haematochezia (34), Thrombocytopenia (33), Vaccination site haematoma (32), Conjunctival haemorrhage and Vaginal haemorrhage (29 each), Haematoma, Haemoptysis and Menorrhagia (27 each), Haematemesis (25), Eye haemorrhage (23), Rectal haemorrhage (22), Immune thrombocytopenia (20), Blood urine present (19), Haematuria, Neutropenia and Purpura (16 each) Diarrhoea haemorrhagic (15); • Relevant event onset latency (n = 787): Range from <24 hours to 33 days, median = 1 day; • Relevant event outcome: fatal (34), resolved/resolving (393), resolved with sequelae (17), not resolved (267) and unknown (371). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Hepatic AESIs <i>Search criteria: Liver related investigations, signs and symptoms (SMQ) (Narrow and Broad) OR PT Liver injury</i></p>	<ul style="list-style-type: none"> • Number of cases: 70 cases (0.2% of the total PM dataset), of which 54 medically confirmed and 16 non-medically confirmed; • Country of incidence: UK (19), US (14), France (7), Italy (5), Germany (4), Belgium, Mexico and Spain (3 each), Austria, and Iceland (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (43), male (26) and unknown (1); • Subjects' age group (n=64): Adult (37), Elderly (27);

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> • Number of relevant events: 94, of which 53 serious, 41 non-serious; • Most frequently reported relevant PTs (≥ 3 occurrences) include: Alanine aminotransferase increased (16), Transaminases increased and Hepatic pain (9 each), Liver function test increased (8), Aspartate aminotransferase increased and Liver function test abnormal (7 each), Gamma-glutamyltransferase increased and Hepatic enzyme increased (6 each), Blood alkaline phosphatase increased and Liver injury (5 each), Ascites, Blood bilirubin increased and Hypertransaminasaemia (3 each); • Relevant event onset latency (n = 57): Range from <24 hours to 20 days, median 3 days; • Relevant event outcome: fatal (5), resolved/resolving (27), resolved with sequelae (1), not resolved (14) and unknown (47). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Facial Paralysis <i>Search criteria: PTs Facial paralysis, Facial paresis</i></p>	<ul style="list-style-type: none"> • Number of cases: 449ⁱ (1.07% of the total PM dataset), 314 medically confirmed and 135 non-medically confirmed; • Country of incidence: US (124), UK (119), Italy (40), France (27), Israel (20), Spain (18), Germany (13), Sweden (11), Ireland (9), Cyprus (8), Austria (7), Finland and Portugal (6 each), Hungary and Romania (5 each), Croatia and Mexico (4 each), Canada (3), Czech Republic, Malta, Netherlands, Norway, Poland and Puerto Rico (2 each); the remaining 8 cases originated from 8 different countries; • Subjects' gender: female (295), male (133), unknown (21); • Subjects' age group (n=411): Adult (313), Elderly (96), Infant and Child (1 each); • Number of relevant events^k: 453, of which 399 serious, 54 non-serious; • Reported relevant PTs: Facial paralysis (401), Facial paresis (64); • Relevant event onset latency (n = 404): Range from <24 hours to 46 days, median 2 days; • Relevant event outcome: resolved/resolving (184), resolved with sequelae (3), not resolved (183) and unknown (97); <p>Overall Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue. Causality assessment will be further evaluated following availability of additional unblinded data from the clinical study C4591001, which will be unblinded for final analysis approximately mid-April 2021. Additionally, non-interventional post-authorisation safety studies, C4591011 and C4591012 are expected to capture data on a sufficiently large vaccinated population to detect an increased risk of Bell's palsy in vaccinated individuals. The timeline for conducting these analyses will be established based on the size of the vaccinated population captured in the study data sources by the first interim reports (due 30 June</p>

Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
<p>Immune-Mediated/Autoimmune AESIs</p> <p><i>Search criteria: Immune-mediated/autoimmune disorders (SMQ) (Broad and Narrow) OR Autoimmune disorders HLGT (Primary Path) OR PTs Cytokine release syndrome; Cytokine storm; Hypersensitivity</i></p>	<p>2021). Study C4591021, pending protocol endorsement by EMA, is also intended to inform this risk.</p> <ul style="list-style-type: none"> • Number of cases: 1050 (2.5 % of the total PM dataset), of which 760 medically confirmed and 290 non-medically confirmed; • Country of incidence (>10 cases): UK (267), US (257), Italy (70), France and Germany (69 each), Mexico (36), Sweden (35), Spain (32), Greece (31), Israel (21), Denmark (18), Portugal (17), Austria and Czech Republic (16 each), Canada (12), Finland (10). The remaining 74 cases were from 24 different countries. • Subjects' gender (n=682): female (526), male (156). • Subjects' age group (n=944): Adult (746), Elderly (196), Adolescent (2). • Number of relevant events: 1077, of which 780 serious, 297 non-serious. • Most frequently reported relevant PTs (>10 occurrences): Hypersensitivity (596), Neuropathy peripheral (49), Pericarditis (32), Myocarditis (25), Dermatitis (24), Diabetes mellitus and Encephalitis (16 each), Psoriasis (14), Dermatitis Bullous (13), Autoimmune disorder and Raynaud's phenomenon (11 each); • Relevant event onset latency (n = 807): Range from <24 hours to 30 days, median <24 hours. • Relevant event outcome¹: resolved/resolving (517), not resolved (215), fatal (12), resolved with sequelae (22) and unknown (312). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Musculoskeletal AESIs</p> <p><i>Search criteria: PTs Arthralgia; Arthritis; Arthritis bacterial¹; Chronic fatigue syndrome; Polyarthritits; Polyneuropathy; Post viral fatigue syndrome; Rheumatoid arthritis</i></p>	<ul style="list-style-type: none"> • Number of cases: 3600 (8.5% of the total PM dataset), of which 2045 medically confirmed and 1555 non-medically confirmed; • Country of incidence: UK (1406), US (1004), Italy (285), Mexico (236), Germany (72), Portugal (70), France (48), Greece and Poland (46), Latvia (33), Czech Republic (32), Israel and Spain (26), Sweden (25), Romania (24), Denmark (23), Finland and Ireland (19 each), Austria and Belgium (18 each), Canada (16), Netherlands (14), Bulgaria (12), Croatia and Serbia (9 each), Cyprus and Hungary (8 each), Norway (7), Estonia and Puerto Rico (6 each), Iceland and Lithuania (4 each); the remaining 21 cases originated from 11 different countries; • Subjects' gender (n=3471): female (2760), male (711); • Subjects' age group (n=3372): Adult (2850), Elderly (515), Child (4), Adolescent (2), Infant (1); • Number of relevant events: 3640, of which 1614 serious, 2026 non-serious; • Reported relevant PTs: Arthralgia (3525), Arthritis (70), Rheumatoid arthritis (26), Polyarthritits (5), Polyneuropathy, Post viral fatigue syndrome, Chronic fatigue syndrome (4 each), Arthritis bacterial (1); • Relevant event onset latency (n = 2968): Range from <24 hours to 32 days, median 1 day;

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
	<ul style="list-style-type: none"> Relevant event outcome: resolved/resolving (1801), not resolved (959), resolved with sequelae (49), and unknown (853). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Neurological AESIs (including demyelination)</p> <p><i>Search criteria: Convulsions (SMQ) (Broad and Narrow) OR Demyelination (SMQ) (Broad and Narrow) OR PTs Ataxia; Cataplexy; Encephalopathy; Fibromyalgia; Intracranial pressure increased; Meningitis; Meningitis aseptic; Narcolepsy</i></p>	<ul style="list-style-type: none"> Number of cases: 501 (1.2% of the total PM dataset), of which 365 medically confirmed and 136 non-medically confirmed. Country of incidence (≥9 cases): UK (157), US (68), Germany (49), Mexico (35), Italy (31), France (25), Spain (18), Poland (17), Netherlands and Israel (15 each), Sweden (9). The remaining 71 cases were from 22 different countries. Subjects' gender (n=478): female (328), male (150). Subjects' age group (n=478): Adult (329), Elderly (149); Number of relevant events: 542, of which 515 serious, 27 non-serious. Most frequently reported relevant PTs (>2 occurrences) included: Seizure (204), Epilepsy (83), Generalised tonic-clonic seizure (33), Guillain-Barre syndrome (24), Fibromyalgia and Trigeminal neuralgia (17 each), Febrile convulsion, (15), Status epilepticus (12), Aura and Myelitis transverse (11 each), Multiple sclerosis relapse and Optic neuritis (10 each), Petit mal epilepsy and Tonic convulsion (9 each), Ataxia (8), Encephalopathy and Tonic clonic movements (7 each), Foaming at mouth (5), Multiple sclerosis, Narcolepsy and Partial seizures (4 each), Bad sensation, Demyelination, Meningitis, Postictal state, Seizure like phenomena and Tongue biting (3 each); Relevant event onset latency (n = 423): Range from <24 hours to 48 days, median 1 day; Relevant events outcome: fatal (16), resolved/resolving (265), resolved with sequelae (13), not resolved (89) and unknown (161); <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
<p>Other AESIs</p> <p><i>Search criteria: Herpes viral infections (HLT) (Primary Path) OR PTs Adverse event following immunisation; Inflammation; Manufacturing laboratory analytical testing issue; Manufacturing materials issue; Manufacturing production issue; MERS-CoV test; MERS-CoV test negative; MERS-CoV test positive; Middle East respiratory syndrome; Multiple organ dysfunction syndrome; Occupational exposure to communicable disease; Patient</i></p>	<ul style="list-style-type: none"> Number of cases: 8152 (19.4% of the total PM dataset), of which 4977 were medically confirmed and 3175 non-medically confirmed; Country of incidence (> 20 occurrences): UK (2715), US (2421), Italy (710), Mexico (223), Portugal (210), Germany (207), France (186), Spain (183), Sweden (133), Denmark (127), Poland (120), Greece (95), Israel (79), Czech Republic (76), Romania (57), Hungary (53), Finland (52), Norway (51), Latvia (49), Austria (47), Croatia (42), Belgium (41), Canada (39), Ireland (34), Serbia (28), Iceland (25), Netherlands (22). The remaining 127 cases were from 21 different countries; Subjects' gender (n=7829): female (5969), male (1860); Subjects' age group (n=7479): Adult (6330), Elderly (1125), Adolescent, Child (9 each), Infant (6);

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Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<i>isolation; Product availability issue; Product distribution issue; Product supply issue; Pyrexia; Quarantine; SARS-CoV-1 test; SARS-CoV-1 test negative; SARS-CoV-1 test positive</i>	<ul style="list-style-type: none"> • Number of relevant events: 8241, of which 3674 serious, 4568 non-serious; • Most frequently reported relevant PTs (≥ 6 occurrences) included: Pyrexia (7666), Herpes zoster (259), Inflammation (132), Oral herpes (80), Multiple organ dysfunction syndrome (18), Herpes virus infection (17), Herpes simplex (13), Ophthalmic herpes zoster (10), Herpes ophthalmic and Herpes zoster reactivation (6 each); • Relevant event onset latency (n =6836): Range from <24 hours to 61 days, median 1 day; • Relevant events outcome: fatal (96), resolved/resolving (5008), resolved with sequelae (84), not resolved (1429) and unknown (1685). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>
Pregnancy Related AESIs <i>Search criteria: PTs Amniotic cavity infection; Caesarean section; Congenital anomaly; Death neonatal; Eclampsia; Foetal distress syndrome; Low birth weight baby; Maternal exposure during pregnancy; Placenta praevia; Pre-eclampsia; Premature labour; Stillbirth; Uterine rupture; Vasa praevia</i>	For relevant cases, please refer to Table 6 , Description of Missing Information, Use in Pregnancy and While Breast Feeding
Renal AESIs <i>Search criteria: PTs Acute kidney injury; Renal failure.</i>	<ul style="list-style-type: none"> • Number of cases: 69 cases (0.17% of the total PM dataset), of which 57 medically confirmed, 12 non-medically confirmed; • Country of incidence: Germany (17), France and UK (13 each), US (6), Belgium, Italy and Spain (4 each), Sweden (2), Austria, Canada, Denmark, Finland, Luxembourg and Norway (1 each); • Subjects' gender: female (46), male (23); • Subjects' age group (n=68): Adult (7), Elderly (60), Infant (1); • Number of relevant events: 70, all serious; • Reported relevant PTs: Acute kidney injury (40) and Renal failure (30); • Relevant event onset latency (n = 42): Range from <24 hours to 15 days, median 4 days; • Relevant event outcome: fatal (23), resolved/resolving (10), not resolved (15) and unknown (22). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
Respiratory AESIs <i>Search criteria: Lower respiratory tract infections NEC (HLT)</i>	<ul style="list-style-type: none"> • Number of cases: 130 cases (0.3% of the total PM dataset), of which 107 medically confirmed;

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<p><i>(Primary Path) OR Respiratory failures (excl neonatal) (HLT)</i> <i>(Primary Path) OR Viral lower respiratory tract infections (HLT)</i> <i>(Primary Path) OR PTs: Acute respiratory distress syndrome; Endotracheal intubation; Hypoxia; Pulmonary haemorrhage; Respiratory disorder; Severe acute respiratory syndrome</i></p>	<ul style="list-style-type: none"> • Countries of incidence: United Kingdom (20), France (18), United States (16), Germany (14), Spain (13), Belgium and Italy (9), Denmark (8), Norway (5), Czech Republic, Iceland (3 each); the remaining 12 cases originated from 8 different countries. • Subjects' gender (n=130): female (72), male (58). • Subjects's age group (n=126): Elderly (78), Adult (47), Adolescent (1). • Number of relevant events: 137, of which 126 serious, 11 non-serious; • Reported relevant PTs: Respiratory failure (44), Hypoxia (42), Respiratory disorder (36), Acute respiratory distress syndrome (10), Chronic respiratory syndrome (3), Severe acute respiratory syndrome (2). • Relevant event onset latency (n=102): range from < 24 hours to 18 days, median 1 day; • Relevant events outcome: fatal (41), Resolved/resolving (47), not recovered (18) and unknown (31). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Thromboembolic Events <i>Search criteria: Embolism and thrombosis (HLGT) (Primary Path), excluding PTs reviewed as Stroke AESIs, OR PTs Deep vein thrombosis; Disseminated intravascular coagulation; Embolism; Embolism venous; Pulmonary embolism</i></p>	<ul style="list-style-type: none"> • Number of cases: 151 (0.3% of the total PM dataset), of which 111 medically confirmed and 40 non-medically confirmed; • Country of incidence: UK (34), US (31), France (20), Germany (15), Italy and Spain (6 each), Denmark and Sweden (5 each), Austria, Belgium and Israel (3 each), Canada, Cyprus, Netherlands and Portugal (2 each); the remaining 12 cases originated from 12 different countries; • Subjects' gender (n= 144): female (89), male (55); • Subjects' age group (n=136): Adult (66), Elderly (70); • Number of relevant events: 168, of which 165 serious, 3 non-serious; • Most frequently reported relevant PTs (>1 occurrence) included: Pulmonary embolism (60), Thrombosis (39), Deep vein thrombosis (35), Thrombophlebitis superficial (6), Venous thrombosis limb (4), Embolism, Microembolism, Thrombophlebitis and Venous thrombosis (3 each) Blue toe syndrome (2); • Relevant event onset latency (n = 124): Range from <24 hours to 28 days, median 4 days; • Relevant event outcome: fatal (18), resolved/resolving (54), resolved with sequelae (6), not resolved (49) and unknown (42). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Stroke <i>Search criteria: HLT Central nervous system haemorrhages and cerebrovascular accidents</i></p>	<ul style="list-style-type: none"> • Number of cases: 275 (0.6% of the total PM dataset), of which 180 medically confirmed and 95 non-medically confirmed; • Country of incidence: UK (81), US (66), France (32), Germany (21), Norway (14), Netherlands and Spain (11 each), Sweden (9),

Table 7. AESIs Evaluation for BNT162b2

AESIs^a Category	Post-Marketing Cases Evaluation^b Total Number of Cases (N=42086)
<p><i>(Primary Path) OR HLT Cerebrovascular venous and sinus thrombosis (Primary Path)</i></p>	<p>Israel (6), Italy (5), Belgium (3), Denmark, Finland, Poland and Switzerland (2 each); the remaining 8 cases originated from 8 different countries;</p> <ul style="list-style-type: none"> • Subjects' gender (n= 273): female (182), male (91); • Subjects' age group (n=265): Adult (59), Elderly (205), Child^m (1); • Number of relevant events: 300, all serious; • Most frequently reported relevant PTs (>1 occurrence) included: <ul style="list-style-type: none"> ○ PTs indicative of Ischaemic stroke: Cerebrovascular accident (160), Ischaemic stroke (41), Cerebral infarction (15), Cerebral ischaemia, Cerebral thrombosis, Cerebral venous sinus thrombosis, Ischaemic cerebral infarction and Lacunal infarction (3 each) Basal ganglia stroke, Cerebellar infarction and Thrombotic stroke (2 each); ○ PTs indicative of Haemorrhagic stroke: Cerebral haemorrhage (26), Haemorrhagic stroke (11), Haemorrhage intracranial and Subarachnoid haemorrhage (5 each), Cerebral haematoma (4), Basal ganglia haemorrhage and Cerebellar haemorrhage (2 each); • Relevant event onset latency (n = 241): Range from <24 hours to 41 days, median 2 days; • Relevant event outcome: fatal and resolved/resolving (61 each), resolved with sequelae (10), not resolved (85) and unknown (83). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue.</p>
<p>Vasculitic Events <i>Search criteria: Vasculitides HLT</i></p>	<ul style="list-style-type: none"> • Number of cases: 32 cases (0.08% of the total PM dataset), of which 26 medically confirmed and 6 non-medically confirmed; • Country of incidence: UK (13), France (4), Portugal, US and Spain (3 each), Cyprus, Germany, Hungary, Italy and Slovakia and Costa rica (1 each); • Subjects' gender: female (26), male (6); • Subjects' age group (n=31): Adult (15), Elderly (16); • Number of relevant events: 34, of which 25 serious, 9 non-serious; • Reported relevant PTs: Vasculitis (14), Cutaneous vasculitis and Vasculitic rash (4 each), (3), Giant cell arteritis and Peripheral ischaemia (3 each), Behcet's syndrome and Hypersensitivity vasculitis (2 each) Palpable purpura, and Takayasu's arteritis (1 each); • Relevant event onset latency (n = 25): Range from <24 hours to 19 days, median 3 days; • Relevant event outcome: fatal (1), resolved/resolving (13), not resolved (12) and unknown (8). <p>Conclusion: This cumulative case review does not raise new safety issues. Surveillance will continue</p>

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Table 7. AESIs Evaluation for BNT162b2

AESIs ^a Category	Post-Marketing Cases Evaluation ^b Total Number of Cases (N=42086)
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- a. For the complete list of the AESIs, please refer to Appendix 5;
- b. Please note that this corresponds to evidence from post-EUA/conditional marketing authorisation approval data sources;
- c. Subjects with age ranged between 18 and 64 years;
- d. Subjects with age equal to or above 65 years;
- e. Subjects with age ranged between 2 and 11 years;
- f. Subjects with age ranged between 12 and less than 18 years;
- g. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events;
- h. Subjects with age ranged between 1 (28 days) and 23 months;
- i. Twenty-four additional cases were excluded from the analysis as they were not cases of peripheral facial nerve palsy because they described other disorders (stroke, cerebral haemorrhage or transient ischaemic attack); 1 case was excluded from the analysis because it was invalid due to an unidentifiable reporter;
- j. This UK case report received from the UK MHRA described a 1-year-old subject who received the vaccine, and had left postauricular ear pain that progressed to left-sided Bell’s palsy 1 day following vaccination that had not resolved at the time of the report;
- k. If a case included both PT Facial paresis and PT Facial paralysis, only the PT Facial paralysis was considered in the descriptions of the events as it is most clinically important;
- l. Multiple episodes of the same PT event were reported with a different clinical outcome within some cases hence the sum of the events outcome exceeds the total number of PT events
- m. This UK case report received from the UK MHRA described a 7-year-old female subject who received the vaccine and had stroke (unknown outcome); no follow-up is possible for clarification.
- n. This PT not included in the AESIs/TME list was included in the review as relevant for ACCESS protocol criteria;

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3.1.4. Medication error

Cases potentially indicative of medication errors¹ that cumulatively occurred are summarized below.

- Number of relevant medication error cases: 2056² (4.9%) of which 1569 (3.7%) are medically confirmed.
- Number of relevant events: 2792
- Top 10 countries of incidence:
 - US (1201), France (171), UK (138), Germany (88), Czech Republic (87), Sweden (49), Israel (45), Italy (42), Canada (35), Romania (33), Finland (21), Portugal (20), Norway (14), Puerto Rico (13), Poland (12), Austria and Spain (10 each).

Medication error case outcomes:

- Fatal (7)³,
- Recovered/recovering (354, of which 4 are serious),
- Recovered with sequelae (8, of which 3 serious)

¹ MedDRA (version 23.1) Higher Level Terms: Accidental exposures to product; Product administration errors and issues; Product confusion errors and issues; Product dispensing errors and issues; Product label issues; Product monitoring errors and issues; Product preparation errors and issues; Product selection errors and issues; Product storage errors and issues in the product use system; Product transcribing errors and communication issues, OR Preferred Terms: Accidental poisoning; Circumstance or information capable of leading to device use error; Circumstance or information capable of leading to medication error; Contraindicated device used; Deprescribing error; Device use error; Dose calculation error; Drug titration error; Expired device used; Exposure via direct contact; Exposure via eye contact; Exposure via mucosa; Exposure via skin contact; Failure of child resistant product closure; Inadequate aseptic technique in use of product; Incorrect disposal of product; Intercepted medication error; Intercepted product prescribing error; Medication error; Multiple use of single-use product; Product advertising issue; Product distribution issue; Product prescribing error; Product prescribing issue; Product substitution error; Product temperature excursion issue; Product use in unapproved therapeutic environment; Radiation underdose; Underdose; Unintentional medical device removal; Unintentional use for unapproved indication; Vaccination error; Wrong device used; Wrong dosage form; Wrong dosage formulation; Wrong dose; Wrong drug; Wrong patient; Wrong product procured; Wrong product stored; Wrong rate; Wrong route; Wrong schedule; Wrong strength; Wrong technique in device usage process; Wrong technique in product usage process.

² Thirty-five (35) cases were excluded from the analysis because describing medication errors occurring in an unspecified number of individuals or describing medication errors occurring with co suspects were determined to be non-contributory.

³ All the medication errors reported in these cases were assessed as non-serious occurrences with an unknown outcome; based on the available information including the causes of death, the relationship between the medication error and the death is weak. .

- Not recovered (189, of which 84 are serious),
- Unknown (1498, of which 33 are serious).

1371 cases reported only MEs without any associated clinical adverse event. The PTs most frequently reported (≥ 12 occurrences) were: Poor quality product administered (539), Product temperature excursion issue (253), Inappropriate schedule of product administration (225), Product preparation error (206), Underdose (202), Circumstance or information capable of leading to medication error (120), Product preparation issue (119), Wrong technique in product usage process (76), Incorrect route of product administration (66), Accidental overdose (33), Product administered at inappropriate site (27), Incorrect dose administered and Accidental exposure to the product (25 each), Exposure via skin contact (22), Wrong product administered (17), Incomplete course of vaccination, and Product administration error (14 each) Product administered to patient of inappropriate age (12).

In 685 cases, there were co-reported AEs. The most frequently co-associated AEs (> 40 occurrences) were: Headache (187), Pyrexia (161), Fatigue (135), Chills (127), Pain (107), Vaccination site pain (100), Nausea (89), Myalgia (88), Pain in extremity (85) Arthralgia (68), Off label use (57), Dizziness (52), Lymphadenopathy (47), Asthenia (46) and Malaise (41). These cases are summarized in Table 8.

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

ME PTs	Serious		Non-Serious	
	With Harm	Without Harm	With Harm	Without Harm
Accidental exposure to product	0	0	0	5
Accidental overdose	4	1	9	6
Booster dose missed	0	0	0	1
Circumstance or information capable of leading to medication error	0	0	5	11
Contraindicated product administered	1	0	0	2
Expired product administered	0	0	0	2
Exposure via skin contact	0	0	0	5
Inappropriate schedule of product administration	0	2	8	264
Incorrect dose administered	1	1	0	0

Table 8. ME PTs by seriousness with or without harm co-association (Through 28 February 2021)

ME PTs	Serious		Non-Serious	
	With Harm	Without Harm	With Harm	Without Harm
Incorrect route of product administration	2	6	16	127
Lack of vaccination site rotation	1	0	0	0
Medication error	0	0	0	1
Poor quality product administered	1	0	0	34
Product administered at inappropriate site	2	1	13	29
Product administered to patient of inappropriate age	0	4	0	40
Product administration error	1	0	0	3
Product dose omission issue	0	1	0	3
Product preparation error	1	0	4	11
Product preparation issue	1	1	0	14

Overall, there were 68 cases with co-reported AEs reporting Harm and 599 cases with co-reported AEs without harm. Additionally, Intercepted medication errors was reported in 1 case (PTs Malaise, clinical outcome unknow) and Potential medication errors were reported in 17 cases.

4. DISCUSSION

Pfizer performs frequent and rigorous signal detection on BNT162b2 cases. The findings of these signal detection analyses are consistent with the known safety profile of the vaccine. This cumulative analysis to support the Biologics License Application for BNT162b2, is an integrated analysis of post-authorization safety data, from U.S. and foreign experience, focused on Important Identified Risks, Important Potential Risks, and areas of Important Missing Information identified in the Pharmacovigilance Plan, as well as adverse events of special interest and vaccine administration errors (whether or not associated with an adverse event). The data do not reveal any novel safety concerns or risks requiring label changes and support a favorable benefit risk profile of to the BNT162b2 vaccine.

5. SUMMARY AND CONCLUSION

Review of the available data for this cumulative PM experience, confirms a favorable benefit: risk balance for BNT162b2.

Pfizer will continue routine pharmacovigilance activities on behalf of BioNTech according to the Pharmacovigilance Agreement in place, in order to assure patient safety and will inform the Agency if an evaluation of the safety data yields significant new information for BNT162b2.

APPENDIX 1. LIST OF ADVERSE EVENTS OF SPECIAL INTEREST

1p36 deletion syndrome;2-Hydroxyglutaric aciduria;5'nucleotidase increased;Acoustic neuritis;Acquired C1 inhibitor deficiency;Acquired epidermolysis bullosa;Acquired epileptic aphasia;Acute cutaneous lupus erythematosus;Acute disseminated encephalomyelitis;Acute encephalitis with refractory, repetitive partial seizures;Acute febrile neutrophilic dermatosis;Acute flaccid myelitis;Acute haemorrhagic leukoencephalitis;Acute haemorrhagic oedema of infancy;Acute kidney injury;Acute macular outer retinopathy;Acute motor axonal neuropathy;Acute motor-sensory axonal neuropathy;Acute myocardial infarction;Acute respiratory distress syndrome;Acute respiratory failure;Addison's disease;Administration site thrombosis;Administration site vasculitis;Adrenal thrombosis;Adverse event following immunisation;Ageusia;Agranulocytosis;Air embolism;Alanine aminotransferase abnormal;Alanine aminotransferase increased;Alcoholic seizure;Allergic bronchopulmonary mycosis;Allergic oedema;Alloimmune hepatitis;Alopecia areata;Alpers disease;Alveolar proteinosis;Ammonia abnormal;Ammonia increased;Amniotic cavity infection;Amygdalohippocampectomy;Amyloid arthropathy;Amyloidosis;Amyloidosis senile;Anaphylactic reaction;Anaphylactic shock;Anaphylactic transfusion reaction;Anaphylactoid reaction;Anaphylactoid shock;Anaphylactoid syndrome of pregnancy;Angioedema;Angiopathic neuropathy;Ankylosing spondylitis;Anosmia;Anti-acetylcholine receptor antibody positive;Anti-actin antibody positive;Anti-aquaporin-4 antibody positive;Anti-basal ganglia antibody positive;Anti-cyclic citrullinated peptide antibody positive;Anti-epithelial antibody positive;Anti-erythrocyte antibody positive;Anti-exosome complex antibody positive;Anti-GAD antibody negative;Anti-GAD antibody positive;Anti-ganglioside antibody positive;Antigliadin antibody positive;Anti-glomerular basement membrane antibody positive;Anti-glomerular basement membrane disease;Anti-glycyl-tRNA synthetase antibody positive;Anti-HLA antibody test positive;Anti-IA2 antibody positive;Anti-insulin antibody increased;Anti-insulin antibody positive;Anti-insulin receptor antibody increased;Anti-insulin receptor antibody positive;Anti-interferon antibody negative;Anti-interferon antibody positive;Anti-islet cell antibody positive;Antimitochondrial antibody positive;Anti-muscle specific kinase antibody positive;Anti-myelin-associated glycoprotein antibodies positive;Anti-myelin-associated glycoprotein associated polyneuropathy;Antimyocardial antibody positive;Anti-neuronal antibody positive;Antineutrophil cytoplasmic antibody increased;Antineutrophil cytoplasmic antibody positive;Anti-neutrophil cytoplasmic antibody positive vasculitis;Anti-NMDA antibody positive;Antinuclear antibody increased;Antinuclear antibody positive;Antiphospholipid antibodies positive;Antiphospholipid syndrome;Anti-platelet antibody positive;Anti-prothrombin antibody positive;Antiribosomal P antibody positive;Anti-RNA polymerase III antibody positive;Anti-saccharomyces cerevisiae antibody test positive;Anti-sperm antibody positive;Anti-SRP antibody positive;Antisynthetase syndrome;Anti-thyroid antibody positive;Anti-transglutaminase antibody increased;Anti-VGCC antibody positive;Anti-VGKC antibody positive;Anti-vimentin antibody positive;Antiviral prophylaxis;Antiviral treatment;Anti-zinc transporter 8 antibody positive;Aortic embolus;Aortic thrombosis;Aortitis;Aplasia pure red cell;Aplastic anaemia;Application site thrombosis;Application site vasculitis;Arrhythmia;Arterial bypass occlusion;Arterial bypass thrombosis;Arterial thrombosis;Arteriovenous fistula thrombosis;Arteriovenous graft site stenosis;Arteriovenous graft thrombosis;Arteritis;Arteritis

coronary;Arthralgia;Arthritis;Arthritis enteropathic;Ascites;Aseptic cavernous sinus thrombosis;Aspartate aminotransferase abnormal;Aspartate aminotransferase increased;Aspartate-glutamate-transporter deficiency;AST to platelet ratio index increased;AST/ALT ratio abnormal;Asthma;Asymptomatic COVID-19;Ataxia;Atheroembolism;Atonic seizures;Atrial thrombosis;Atrophic thyroiditis;Atypical benign partial epilepsy;Atypical pneumonia;Aura;Autoantibody positive;Autoimmune anaemia;Autoimmune aplastic anaemia;Autoimmune arthritis;Autoimmune blistering disease;Autoimmune cholangitis;Autoimmune colitis;Autoimmune demyelinating disease;Autoimmune dermatitis;Autoimmune disorder;Autoimmune encephalopathy;Autoimmune endocrine disorder;Autoimmune enteropathy;Autoimmune eye disorder;Autoimmune haemolytic anaemia;Autoimmune heparin-induced thrombocytopenia;Autoimmune hepatitis;Autoimmune hyperlipidaemia;Autoimmune hypothyroidism;Autoimmune inner ear disease;Autoimmune lung disease;Autoimmune lymphoproliferative syndrome;Autoimmune myocarditis;Autoimmune myositis;Autoimmune nephritis;Autoimmune neuropathy;Autoimmune neutropenia;Autoimmune pancreatitis;Autoimmune pancytopenia;Autoimmune pericarditis;Autoimmune retinopathy;Autoimmune thyroid disorder;Autoimmune thyroiditis;Autoimmune uveitis;Autoinflammation with infantile enterocolitis;Autoinflammatory disease;Automatism epileptic;Autonomic nervous system imbalance;Autonomic seizure;Axial spondyloarthritis;Axillary vein thrombosis;Axonal and demyelinating polyneuropathy;Axonal neuropathy;Bacterascites;Baltic myoclonic epilepsy;Band sensation;Basedow's disease;Basilar artery thrombosis;Basophilopenia;B-cell aplasia;Behcet's syndrome;Benign ethnic neutropenia;Benign familial neonatal convulsions;Benign familial pemphigus;Benign rolandic epilepsy;Beta-2 glycoprotein antibody positive;Bickerstaff's encephalitis;Bile output abnormal;Bile output decreased;Biliary ascites;Bilirubin conjugated abnormal;Bilirubin conjugated increased;Bilirubin urine present;Biopsy liver abnormal;Biotinidase deficiency;Birdshot chorioretinopathy;Blood alkaline phosphatase abnormal;Blood alkaline phosphatase increased;Blood bilirubin abnormal;Blood bilirubin increased;Blood bilirubin unconjugated increased;Blood cholinesterase abnormal;Blood cholinesterase decreased;Blood pressure decreased;Blood pressure diastolic decreased;Blood pressure systolic decreased;Blue toe syndrome;Brachiocephalic vein thrombosis;Brain stem embolism;Brain stem thrombosis;Bromosulphthalein test abnormal;Bronchial oedema;Bronchitis;Bronchitis mycoplasmal;Bronchitis viral;Bronchopulmonary aspergillosis allergic;Bronchospasm;Budd-Chiari syndrome;Bulbar palsy;Butterfly rash;C1q nephropathy;Caesarean section;Calcium embolism;Capillaritis;Caplan's syndrome;Cardiac amyloidosis;Cardiac arrest;Cardiac failure;Cardiac failure acute;Cardiac sarcoidosis;Cardiac ventricular thrombosis;Cardiogenic shock;Cardiolipin antibody positive;Cardiopulmonary failure;Cardio-respiratory arrest;Cardio-respiratory distress;Cardiovascular insufficiency;Carotid arterial embolus;Carotid artery thrombosis;Cataplexy;Catheter site thrombosis;Catheter site vasculitis;Cavernous sinus thrombosis;CDKL5 deficiency disorder;CEC syndrome;Cement embolism;Central nervous system lupus;Central nervous system vasculitis;Cerebellar artery thrombosis;Cerebellar embolism;Cerebral amyloid angiopathy;Cerebral arteritis;Cerebral artery embolism;Cerebral artery thrombosis;Cerebral gas embolism;Cerebral microembolism;Cerebral septic infarct;Cerebral thrombosis;Cerebral venous sinus thrombosis;Cerebral venous thrombosis;Cerebrospinal thrombotic

tamponade;Cerebrovascular accident;Change in seizure presentation;Chest discomfort;Child-Pugh-Turcotte score abnormal;Child-Pugh-Turcotte score increased;Chillblains;Choking;Choking sensation;Cholangitis sclerosing;Chronic autoimmune glomerulonephritis;Chronic cutaneous lupus erythematosus;Chronic fatigue syndrome;Chronic gastritis;Chronic inflammatory demyelinating polyradiculoneuropathy;Chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids;Chronic recurrent multifocal osteomyelitis;Chronic respiratory failure;Chronic spontaneous urticaria;Circulatory collapse;Circumoral oedema;Circumoral swelling;Clinically isolated syndrome;Clonic convulsion;Coeliac disease;Cogan's syndrome;Cold agglutinins positive;Cold type haemolytic anaemia;Colitis;Colitis erosive;Colitis herpes;Colitis microscopic;Colitis ulcerative;Collagen disorder;Collagen-vascular disease;Complement factor abnormal;Complement factor C1 decreased;Complement factor C2 decreased;Complement factor C3 decreased;Complement factor C4 decreased;Complement factor decreased;Computerised tomogram liver abnormal;Concentric sclerosis;Congenital anomaly;Congenital bilateral perisylvian syndrome;Congenital herpes simplex infection;Congenital myasthenic syndrome;Congenital varicella infection;Congestive hepatopathy;Convulsion in childhood;Convulsions local;Convulsive threshold lowered;Coombs positive haemolytic anaemia;Coronary artery disease;Coronary artery embolism;Coronary artery thrombosis;Coronary bypass thrombosis;Coronavirus infection;Coronavirus test;Coronavirus test negative;Coronavirus test positive;Corpus callosotomy;Cough;Cough variant asthma;COVID-19;COVID-19 immunisation;COVID-19 pneumonia;COVID-19 prophylaxis;COVID-19 treatment;Cranial nerve disorder;Cranial nerve palsies multiple;Cranial nerve paralysis;CREST syndrome;Crohn's disease;Cryofibrinogenaemia;Cryoglobulinaemia;CSF oligoclonal band present;CSWS syndrome;Cutaneous amyloidosis;Cutaneous lupus erythematosus;Cutaneous sarcoidosis;Cutaneous vasculitis;Cyanosis;Cyclic neutropenia;Cystitis interstitial;Cytokine release syndrome;Cytokine storm;De novo purine synthesis inhibitors associated acute inflammatory syndrome;Death neonatal;Deep vein thrombosis;Deep vein thrombosis postoperative;Deficiency of bile secretion;Deja vu;Demyelinating polyneuropathy;Demyelination;Dermatitis;Dermatitis bullous;Dermatitis herpetiformis;Dermatomyositis;Device embolisation;Device related thrombosis;Diabetes mellitus;Diabetic ketoacidosis;Diabetic mastopathy;Dialysis amyloidosis;Dialysis membrane reaction;Diastolic hypotension;Diffuse vasculitis;Digital pitting scar;Disseminated intravascular coagulation;Disseminated intravascular coagulation in newborn;Disseminated neonatal herpes simplex;Disseminated varicella;Disseminated varicella zoster vaccine virus infection;Disseminated varicella zoster virus infection;DNA antibody positive;Double cortex syndrome;Double stranded DNA antibody positive;Dreamy state;Dressler's syndrome;Drop attacks;Drug withdrawal convulsions;Dyspnoea;Early infantile epileptic encephalopathy with burst-suppression;Eclampsia;Eczema herpeticum;Embolia cutis medicamentosa;Embolic cerebellar infarction;Embolic cerebral infarction;Embolic pneumonia;Embolic stroke;Embolism;Embolism arterial;Embolism venous;Encephalitis;Encephalitis allergic;Encephalitis autoimmune;Encephalitis brain stem;Encephalitis haemorrhagic;Encephalitis periaxialis diffusa;Encephalitis post immunisation;Encephalomyelitis;Encephalopathy;Endocrine disorder;Endocrine ophthalmopathy;Endotracheal intubation;Enteritis;Enteritis leukopenic;Enterobacter pneumonia;Enterocolitis;Enteropathic spondylitis;Eosinopenia;Eosinophilic

fasciitis;Eosinophilic granulomatosis with polyangiitis;Eosinophilic oesophagitis;Epidermolysis;Epilepsy;Epilepsy surgery;Epilepsy with myoclonic-atonic seizures;Epileptic aura;Epileptic psychosis;Erythema;Erythema induratum;Erythema multiforme;Erythema nodosum;Evans syndrome;Exanthema subitum;Expanded disability status scale score decreased;Expanded disability status scale score increased;Exposure to communicable disease;Exposure to SARS-CoV-2;Eye oedema;Eye pruritus;Eye swelling;Eyelid oedema;Face oedema;Facial paralysis;Facial paresis;Faciobrachial dystonic seizure;Fat embolism;Febrile convulsion;Febrile infection-related epilepsy syndrome;Febrile neutropenia;Felty's syndrome;Femoral artery embolism;Fibrillary glomerulonephritis;Fibromyalgia;Flushing;Foaming at mouth;Focal cortical resection;Focal dyscognitive seizures;Foetal distress syndrome;Foetal placental thrombosis;Foetor hepaticus;Foreign body embolism;Frontal lobe epilepsy;Fulminant type 1 diabetes mellitus;Galactose elimination capacity test abnormal;Galactose elimination capacity test decreased;Gamma-glutamyltransferase abnormal;Gamma-glutamyltransferase increased;Gastritis herpes;Gastrointestinal amyloidosis;Gelastic seizure;Generalised onset non-motor seizure;Generalised tonic-clonic seizure;Genital herpes;Genital herpes simplex;Genital herpes zoster;Giant cell arteritis;Glomerulonephritis;Glomerulonephritis membranoproliferative;Glomerulonephritis membranous;Glomerulonephritis rapidly progressive;Glossopharyngeal nerve paralysis;Glucose transporter type 1 deficiency syndrome;Glutamate dehydrogenase increased;Glycocholic acid increased;GM2 gangliosidosis;Goodpasture's syndrome;Graft thrombosis;Granulocytopenia;Granulocytopenia neonatal;Granulomatosis with polyangiitis;Granulomatous dermatitis;Grey matter heterotopia;Guanase increased;Guillain-Barre syndrome;Haemolytic anaemia;Haemophagocytic lymphohistiocytosis;Haemorrhage;Haemorrhagic ascites;Haemorrhagic disorder;Haemorrhagic pneumonia;Haemorrhagic varicella syndrome;Haemorrhagic vasculitis;Hantavirus pulmonary infection;Hashimoto's encephalopathy;Hashitoxicosis;Hemimegalencephaly;Henoch-Schonlein purpura;Henoch-Schonlein purpura nephritis;Hepaplastin abnormal;Hepaplastin decreased;Heparin-induced thrombocytopenia;Hepatic amyloidosis;Hepatic artery embolism;Hepatic artery flow decreased;Hepatic artery thrombosis;Hepatic enzyme abnormal;Hepatic enzyme decreased;Hepatic enzyme increased;Hepatic fibrosis marker abnormal;Hepatic fibrosis marker increased;Hepatic function abnormal;Hepatic hydrothorax;Hepatic hypertrophy;Hepatic hypoperfusion;Hepatic lymphocytic infiltration;Hepatic mass;Hepatic pain;Hepatic sequestration;Hepatic vascular resistance increased;Hepatic vascular thrombosis;Hepatic vein embolism;Hepatic vein thrombosis;Hepatic venous pressure gradient abnormal;Hepatic venous pressure gradient increased;Hepatitis;Hepatobiliary scan abnormal;Hepatomegaly;Hepatosplenomegaly;Hereditary angioedema with C1 esterase inhibitor deficiency;Herpes dermatitis;Herpes gestationis;Herpes oesophagitis;Herpes ophthalmic;Herpes pharyngitis;Herpes sepsis;Herpes simplex;Herpes simplex cervicitis;Herpes simplex colitis;Herpes simplex encephalitis;Herpes simplex gastritis;Herpes simplex hepatitis;Herpes simplex meningitis;Herpes simplex meningoencephalitis;Herpes simplex meningomyelitis;Herpes simplex necrotising retinopathy;Herpes simplex oesophagitis;Herpes simplex otitis externa;Herpes simplex pharyngitis;Herpes simplex pneumonia;Herpes simplex reactivation;Herpes simplex sepsis;Herpes simplex viraemia;Herpes simplex virus conjunctivitis neonatal;Herpes simplex visceral;Herpes virus

infection;Herpes zoster;Herpes zoster cutaneous disseminated;Herpes zoster infection neurological;Herpes zoster meningitis;Herpes zoster meningoencephalitis;Herpes zoster meningomyelitis;Herpes zoster meningoradiculitis;Herpes zoster necrotising retinopathy;Herpes zoster oticus;Herpes zoster pharyngitis;Herpes zoster reactivation;Herpetic radiculopathy;Histone antibody positive;Hoigne's syndrome;Human herpesvirus 6 encephalitis;Human herpesvirus 6 infection;Human herpesvirus 6 infection reactivation;Human herpesvirus 7 infection;Human herpesvirus 8 infection;Hyperammonaemia;Hyperbilirubinaemia;Hypercholia;Hypergammaglobulinaemia benign monoclonal;Hyperglycaemic seizure;Hypersensitivity;Hypersensitivity vasculitis;Hyperthyroidism;Hypertransaminaemia;Hyperventilation;Hypoalbuminaemia;Hypocalcaemic seizure;Hypogammaglobulinaemia;Hypoglossal nerve paralysis;Hypoglossal nerve paresis;Hypoglycaemic seizure;Hyponatraemic seizure;Hypotension;Hypotensive crisis;Hypothenar hammer syndrome;Hypothyroidism;Hypoxia;Idiopathic CD4 lymphocytopenia;Idiopathic generalised epilepsy;Idiopathic interstitial pneumonia;Idiopathic neutropenia;Idiopathic pulmonary fibrosis;IgA nephropathy;IgM nephropathy;IIIrd nerve paralysis;IIIrd nerve paresis;Iliac artery embolism;Immune thrombocytopenia;Immune-mediated adverse reaction;Immune-mediated cholangitis;Immune-mediated cholestasis;Immune-mediated cytopenia;Immune-mediated encephalitis;Immune-mediated encephalopathy;Immune-mediated endocrinopathy;Immune-mediated enterocolitis;Immune-mediated gastritis;Immune-mediated hepatic disorder;Immune-mediated hepatitis;Immune-mediated hyperthyroidism;Immune-mediated hypothyroidism;Immune-mediated myocarditis;Immune-mediated myositis;Immune-mediated nephritis;Immune-mediated neuropathy;Immune-mediated pancreatitis;Immune-mediated pneumonitis;Immune-mediated renal disorder;Immune-mediated thyroiditis;Immune-mediated uveitis;Immunoglobulin G4 related disease;Immunoglobulins abnormal;Implant site thrombosis;Inclusion body myositis;Infantile genetic agranulocytosis;Infantile spasms;Infected vasculitis;Infective thrombosis;Inflammation;Inflammatory bowel disease;Infusion site thrombosis;Infusion site vasculitis;Injection site thrombosis;Injection site urticaria;Injection site vasculitis;Instillation site thrombosis;Insulin autoimmune syndrome;Interstitial granulomatous dermatitis;Interstitial lung disease;Intracardiac mass;Intracardiac thrombus;Intracranial pressure increased;Intrapericardial thrombosis;Intrinsic factor antibody abnormal;Intrinsic factor antibody positive;IPEX syndrome;Irregular breathing;IRVAN syndrome;IVth nerve paralysis;IVth nerve paresis;JC polyomavirus test positive;JC virus CSF test positive;Jeavons syndrome;Jugular vein embolism;Jugular vein thrombosis;Juvenile idiopathic arthritis;Juvenile myoclonic epilepsy;Juvenile polymyositis;Juvenile psoriatic arthritis;Juvenile spondyloarthritis;Kaposi sarcoma inflammatory cytokine syndrome;Kawasaki's disease;Kayser-Fleischer ring;Keratoderma blenorrhagica;Ketosis-prone diabetes mellitus;Kounis syndrome;Lafora's myoclonic epilepsy;Lamb's excrescences;Laryngeal dyspnoea;Laryngeal oedema;Laryngeal rheumatoid arthritis;Laryngospasm;Laryngotracheal oedema;Latent autoimmune diabetes in adults;LE cells present;Lemierre syndrome;Lennox-Gastaut syndrome;Leucine aminopeptidase increased;Leukoencephalomyelitis;Leukoencephalopathy;Leukopenia;Leukopenia neonatal;Lewis-Sumner syndrome;Lhermitte's sign;Lichen planopilaris;Lichen planus;Lichen sclerosus;Limbic encephalitis;Linear IgA disease;Lip oedema;Lip swelling;Liver function test abnormal;Liver function test decreased;Liver function test increased;Liver induration;Liver injury;Liver iron concentration abnormal;Liver iron concentration

increased;Liver opacity;Liver palpable;Liver sarcoidosis;Liver scan abnormal;Liver tenderness;Low birth weight baby;Lower respiratory tract herpes infection;Lower respiratory tract infection;Lower respiratory tract infection viral;Lung abscess;Lupoid hepatic cirrhosis;Lupus cystitis;Lupus encephalitis;Lupus endocarditis;Lupus enteritis;Lupus hepatitis;Lupus myocarditis;Lupus myositis;Lupus nephritis;Lupus pancreatitis;Lupus pleurisy;Lupus pneumonitis;Lupus vasculitis;Lupus-like syndrome;Lymphocytic hypophysitis;Lymphocytopenia neonatal;Lymphopenia;MAGIC syndrome;Magnetic resonance imaging liver abnormal;Magnetic resonance proton density fat fraction measurement;Mahler sign;Manufacturing laboratory analytical testing issue;Manufacturing materials issue;Manufacturing production issue;Marburg's variant multiple sclerosis;Marchiafava-Bignami disease;Marine Lenhart syndrome;Mastocytic enterocolitis;Maternal exposure during pregnancy;Medical device site thrombosis;Medical device site vasculitis;MELAS syndrome;Meningitis;Meningitis aseptic;Meningitis herpes;Meningoencephalitis herpes simplex neonatal;Meningoencephalitis herpetic;Meningomyelitis herpes;MERS-CoV test;MERS-CoV test negative;MERS-CoV test positive;Mesangioproliferative glomerulonephritis;Mesenteric artery embolism;Mesenteric artery thrombosis;Mesenteric vein thrombosis;Metapneumovirus infection;Metastatic cutaneous Crohn's disease;Metastatic pulmonary embolism;Microangiopathy;Microembolism;Microscopic polyangiitis;Middle East respiratory syndrome;Migraine-triggered seizure;Miliary pneumonia;Miller Fisher syndrome;Mitochondrial aspartate aminotransferase increased;Mixed connective tissue disease;Model for end stage liver disease score abnormal;Model for end stage liver disease score increased;Molar ratio of total branched-chain amino acid to tyrosine;Molybdenum cofactor deficiency;Monocytopenia;Mononeuritis;Mononeuropathy multiplex;Morphoea;Morvan syndrome;Mouth swelling;Moyamoya disease;Multifocal motor neuropathy;Multiple organ dysfunction syndrome;Multiple sclerosis;Multiple sclerosis relapse;Multiple sclerosis relapse prophylaxis;Multiple subpial transection;Multisystem inflammatory syndrome in children;Muscular sarcoidosis;Myasthenia gravis;Myasthenia gravis crisis;Myasthenia gravis neonatal;Myasthenic syndrome;Myelitis;Myelitis transverse;Myocardial infarction;Myocarditis;Myocarditis post infection;Myoclonic epilepsy;Myoclonic epilepsy and ragged-red fibres;Myokymia;Myositis;Narcolepsy;Nasal herpes;Nasal obstruction;Necrotising herpetic retinopathy;Neonatal Crohn's disease;Neonatal epileptic seizure;Neonatal lupus erythematosus;Neonatal mucocutaneous herpes simplex;Neonatal pneumonia;Neonatal seizure;Nephritis;Nephrogenic systemic fibrosis;Neuralgic amyotrophy;Neuritis;Neuritis cranial;Neuromyelitis optica pseudo relapse;Neuromyelitis optica spectrum disorder;Neuromyotonia;Neuronal neuropathy;Neuropathy peripheral;Neuropathy, ataxia, retinitis pigmentosa syndrome;Neuropsychiatric lupus;Neurosarcoidosis;Neutropenia;Neutropenia neonatal;Neutropenic colitis;Neutropenic infection;Neutropenic sepsis;Nodular rash;Nodular vasculitis;Noninfectious myelitis;Noninfective encephalitis;Noninfective encephalomyelitis;Noninfective oophoritis;Obstetrical pulmonary embolism;Occupational exposure to communicable disease;Occupational exposure to SARS-CoV-2;Ocular hyperaemia;Ocular myasthenia;Ocular pemphigoid;Ocular sarcoidosis;Ocular vasculitis;Oculofacial paralysis;Oedema;Oedema blister;Oedema due to hepatic disease;Oedema mouth;Oesophageal achalasia;Ophthalmic artery thrombosis;Ophthalmic herpes simplex;Ophthalmic herpes zoster;Ophthalmic vein thrombosis;Optic neuritis;Optic

neuropathy;Optic perineuritis;Oral herpes;Oral lichen planus;Oropharyngeal oedema;Oropharyngeal spasm;Oropharyngeal swelling;Osmotic demyelination syndrome;Ovarian vein thrombosis;Overlap syndrome;Paediatric autoimmune neuropsychiatric disorders associated with streptococcal infection;Paget-Schroetter syndrome;Palindromic rheumatism;Palisaded neutrophilic granulomatous dermatitis;Palmoplantar keratoderma;Palpable purpura;Pancreatitis;Panencephalitis;Papillophlebitis;Paracancerous pneumonia;Paradoxical embolism;Parainfluenzae viral laryngotracheobronchitis;Paraneoplastic dermatomyositis;Paraneoplastic pemphigus;Paraneoplastic thrombosis;Paresis cranial nerve;Parietal cell antibody positive;Paroxysmal nocturnal haemoglobinuria;Partial seizures;Partial seizures with secondary generalisation;Patient isolation;Pelvic venous thrombosis;Pemphigoid;Pemphigus;Penile vein thrombosis;Pericarditis;Pericarditis lupus;Perihepatic discomfort;Periorbital oedema;Periorbital swelling;Peripheral artery thrombosis;Peripheral embolism;Peripheral ischaemia;Peripheral vein thrombus extension;Periportal oedema;Peritoneal fluid protein abnormal;Peritoneal fluid protein decreased;Peritoneal fluid protein increased;Peritonitis lupus;Pernicious anaemia;Petit mal epilepsy;Pharyngeal oedema;Pharyngeal swelling;Pityriasis lichenoides et varioliformis acuta;Placenta praevia;Pleuroparenchymal fibroelastosis;Pneumobilia;Pneumonia;Pneumonia adenoviral;Pneumonia cytomegaloviral;Pneumonia herpes viral;Pneumonia influenzal;Pneumonia measles;Pneumonia mycoplasmal;Pneumonia necrotising;Pneumonia parainfluenzae viral;Pneumonia respiratory syncytial viral;Pneumonia viral;POEMS syndrome;Polyarteritis nodosa;Polyarthritis;Polychondritis;Polyglandular autoimmune syndrome type I;Polyglandular autoimmune syndrome type II;Polyglandular autoimmune syndrome type III;Polyglandular disorder;Polymicrogyria;Polymyalgia rheumatica;Polymyositis;Polyneuropathy;Polyneuropathy idiopathic progressive;Portal pyaemia;Portal vein embolism;Portal vein flow decreased;Portal vein pressure increased;Portal vein thrombosis;Portosplenomesenteric venous thrombosis;Post procedural hypotension;Post procedural pneumonia;Post procedural pulmonary embolism;Post stroke epilepsy;Post stroke seizure;Post thrombotic retinopathy;Post thrombotic syndrome;Post viral fatigue syndrome;Postictal headache;Postictal paralysis;Postictal psychosis;Postictal state;Postoperative respiratory distress;Postoperative respiratory failure;Postoperative thrombosis;Postpartum thrombosis;Postpartum venous thrombosis;Postpericardiotomy syndrome;Post-traumatic epilepsy;Postural orthostatic tachycardia syndrome;Precerebral artery thrombosis;Pre-eclampsia;Preictal state;Premature labour;Premature menopause;Primary amyloidosis;Primary biliary cholangitis;Primary progressive multiple sclerosis;Procedural shock;Proctitis herpes;Proctitis ulcerative;Product availability issue;Product distribution issue;Product supply issue;Progressive facial hemiatrophy;Progressive multifocal leukoencephalopathy;Progressive multiple sclerosis;Progressive relapsing multiple sclerosis;Prosthetic cardiac valve thrombosis;Pruritus;Pruritus allergic;Pseudovasculitis;Psoriasis;Psoriatic arthropathy;Pulmonary amyloidosis;Pulmonary artery thrombosis;Pulmonary embolism;Pulmonary fibrosis;Pulmonary haemorrhage;Pulmonary microemboli;Pulmonary oil microembolism;Pulmonary renal syndrome;Pulmonary sarcoidosis;Pulmonary sepsis;Pulmonary thrombosis;Pulmonary tumour thrombotic microangiopathy;Pulmonary vasculitis;Pulmonary veno-occlusive disease;Pulmonary venous thrombosis;Pyoderma gangrenosum;Pyostomatitis vegetans;Pyrexia;Quarantine;Radiation leukopenia;Radiculitis

brachial;Radiologically isolated syndrome;Rash;Rash erythematous;Rash pruritic;Rasmussen encephalitis;Raynaud's phenomenon;Reactive capillary endothelial proliferation;Relapsing multiple sclerosis;Relapsing-remitting multiple sclerosis;Renal amyloidosis;Renal arteritis;Renal artery thrombosis;Renal embolism;Renal failure;Renal vascular thrombosis;Renal vasculitis;Renal vein embolism;Renal vein thrombosis;Respiratory arrest;Respiratory disorder;Respiratory distress;Respiratory failure;Respiratory paralysis;Respiratory syncytial virus bronchiolitis;Respiratory syncytial virus bronchitis;Retinal artery embolism;Retinal artery occlusion;Retinal artery thrombosis;Retinal vascular thrombosis;Retinal vasculitis;Retinal vein occlusion;Retinal vein thrombosis;Retinol binding protein decreased;Retinopathy;Retrograde portal vein flow;Retroperitoneal fibrosis;Reversible airways obstruction;Reynold's syndrome;Rheumatic brain disease;Rheumatic disorder;Rheumatoid arthritis;Rheumatoid factor increased;Rheumatoid factor positive;Rheumatoid factor quantitative increased;Rheumatoid lung;Rheumatoid neutrophilic dermatosis;Rheumatoid nodule;Rheumatoid nodule removal;Rheumatoid scleritis;Rheumatoid vasculitis;Saccadic eye movement;SAPHO syndrome;Sarcoidosis;SARS-CoV-1 test;SARS-CoV-1 test negative;SARS-CoV-1 test positive;SARS-CoV-2 antibody test;SARS-CoV-2 antibody test negative;SARS-CoV-2 antibody test positive;SARS-CoV-2 carrier;SARS-CoV-2 sepsis;SARS-CoV-2 test;SARS-CoV-2 test false negative;SARS-CoV-2 test false positive;SARS-CoV-2 test negative;SARS-CoV-2 test positive;SARS-CoV-2 viraemia;Satoyoshi syndrome;Schizencephaly;Scleritis;Sclerodactylia;Scleroderma;Scleroderma associated digital ulcer;Scleroderma renal crisis;Scleroderma-like reaction;Secondary amyloidosis;Secondary cerebellar degeneration;Secondary progressive multiple sclerosis;Segmented hyalinising vasculitis;Seizure;Seizure anoxic;Seizure cluster;Seizure like phenomena;Seizure prophylaxis;Sensation of foreign body;Septic embolus;Septic pulmonary embolism;Severe acute respiratory syndrome;Severe myoclonic epilepsy of infancy;Shock;Shock symptom;Shrinking lung syndrome;Shunt thrombosis;Silent thyroiditis;Simple partial seizures;Sjogren's syndrome;Skin swelling;SLE arthritis;Smooth muscle antibody positive;Sneezing;Spinal artery embolism;Spinal artery thrombosis;Splenic artery thrombosis;Splenic embolism;Splenic thrombosis;Splenic vein thrombosis;Spondylitis;Spondyloarthropathy;Spontaneous heparin-induced thrombocytopenia syndrome;Status epilepticus;Stevens-Johnson syndrome;Stiff leg syndrome;Stiff person syndrome;Stillbirth;Still's disease;Stoma site thrombosis;Stoma site vasculitis;Stress cardiomyopathy;Stridor;Subacute cutaneous lupus erythematosus;Subacute endocarditis;Subacute inflammatory demyelinating polyneuropathy;Subclavian artery embolism;Subclavian artery thrombosis;Subclavian vein thrombosis;Sudden unexplained death in epilepsy;Superior sagittal sinus thrombosis;Susac's syndrome;Suspected COVID-19;Swelling;Swelling face;Swelling of eyelid;Swollen tongue;Sympathetic ophthalmia;Systemic lupus erythematosus;Systemic lupus erythematosus disease activity index abnormal;Systemic lupus erythematosus disease activity index decreased;Systemic lupus erythematosus disease activity index increased;Systemic lupus erythematosus rash;Systemic scleroderma;Systemic sclerosis pulmonary;Tachycardia;Tachypnoea;Takayasu's arteritis;Temporal lobe epilepsy;Terminal ileitis;Testicular autoimmunity;Throat tightness;Thromboangiitis obliterans;Thrombocytopenia;Thrombocytopenic purpura;Thrombophlebitis;Thrombophlebitis migrans;Thrombophlebitis

neonatal;Thrombophlebitis septic;Thrombophlebitis superficial;Thromboplastin antibody positive;Thrombosis;Thrombosis corpora cavernosa;Thrombosis in device;Thrombosis mesenteric vessel;Thrombotic cerebral infarction;Thrombotic microangiopathy;Thrombotic stroke;Thrombotic thrombocytopenic purpura;Thyroid disorder;Thyroid stimulating immunoglobulin increased;Thyroiditis;Tongue amyloidosis;Tongue biting;Tongue oedema;Tonic clonic movements;Tonic convulsion;Tonic posturing;Topectomy;Total bile acids increased;Toxic epidermal necrolysis;Toxic leukoencephalopathy;Toxic oil syndrome;Tracheal obstruction;Tracheal oedema;Tracheobronchitis;Tracheobronchitis mycoplasmal;Tracheobronchitis viral;Transaminases abnormal;Transaminases increased;Transfusion-related alloimmune neutropenia;Transient epileptic amnesia;Transverse sinus thrombosis;Trigeminal nerve paresis;Trigeminal neuralgia;Trigeminal palsy;Truncus coeliacus thrombosis;Tuberous sclerosis complex;Tubulointerstitial nephritis and uveitis syndrome;Tumefactive multiple sclerosis;Tumour embolism;Tumour thrombosis;Type 1 diabetes mellitus;Type I hypersensitivity;Type III immune complex mediated reaction;Uhthoff's phenomenon;Ulcerative keratitis;Ultrasound liver abnormal;Umbilical cord thrombosis;Uncinate fits;Undifferentiated connective tissue disease;Upper airway obstruction;Urine bilirubin increased;Urobilinogen urine decreased;Urobilinogen urine increased;Urticaria;Urticaria papular;Urticular vasculitis;Uterine rupture;Uveitis;Vaccination site thrombosis;Vaccination site vasculitis;Vagus nerve paralysis;Varicella;Varicella keratitis;Varicella post vaccine;Varicella zoster gastritis;Varicella zoster oesophagitis;Varicella zoster pneumonia;Varicella zoster sepsis;Varicella zoster virus infection;Vasa praevia;Vascular graft thrombosis;Vascular pseudoaneurysm thrombosis;Vascular purpura;Vascular stent thrombosis;Vasculitic rash;Vasculitic ulcer;Vasculitis;Vasculitis gastrointestinal;Vasculitis necrotising;Vena cava embolism;Vena cava thrombosis;Venous intravasation;Venous recanalisation;Venous thrombosis;Venous thrombosis in pregnancy;Venous thrombosis limb;Venous thrombosis neonatal;Vertebral artery thrombosis;Vessel puncture site thrombosis;Visceral venous thrombosis;VIth nerve paralysis;VIth nerve paresis;Vitiligo;Vocal cord paralysis;Vocal cord paresis;Vogt-Koyanagi-Harada disease;Warm type haemolytic anaemia;Wheezing;White nipple sign;XIth nerve paralysis;X-ray hepatobiliary abnormal;Young's syndrome;Zika virus associated Guillain Barre syndrome.

2.4 NONCLINICAL OVERVIEW

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

A:G	Albumin:globulin ratio
ACE	Angiotension-converting enzyme
ADME	Absorption, distribution, metabolism, excretion
ALC-0159	Proprietary PEG-lipid included as an excipient in the LNP formulation used in BNT162b2
ALC-0315	Proprietary amino-lipid included as an excipient in the LNP formulation used in BNT162b2
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAL	Bronchoalveolar lavage
CAS	Chemical abstracts service
CBER	Center for Biologics Evaluation and Research
CD	Cluster of differentiation
COVID-19	Coronavirus Disease 2019
DART	Developmental and reproductive toxicity
DNA	Deoxyribonucleic acid
DSPC	1,2-distearoyl-sn-glycero-3-phosphocholine
ELISA	Enzyme-linked immunosorbent assay
EUA	Emergency Use Authorization
F0	Parental generation administered vaccine
F1	First generation offspring of F0 generation
GD	Gestation day
GGT	Gamma-glutamyl transferase
GLP	Good Laboratory Practice
H	Human (in metabolite scheme)
[³ H]-CHE	Radiolabeled [Cholesteryl-1,2- ³ H(N)]-Cholesteryl Hexadecyl Ether
HGB	Hemoglobin
IFN	Interferon
IgG	Immunoglobulin G
IL	Interleukin
IM	Intramuscular(ly)
IND	Investigational New Drug Application
IV	Intravenous(ly)
LC/MS	Liquid chromatography-tandem mass spectrometry
LD	Lactation day
LNP	Lipid-nanoparticle
Luc	Luciferase (from firefly <i>Pyroactomena lucifera</i>)
LUC	Large unstained cell
Mk	Monkey (in metabolite scheme)
Mo	Mouse (in metabolite scheme)
modRNA	Nucleoside-modified mRNA
mRNA	Messenger RNA
NA	Not applicable

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS - CONTINUED

NHP	Nonhuman primate
OECD	Organisation for Economic Co-operation and Development
P2 S	Spike protein P2 mutant
PEG	Polyethylene glycol
PK	Pharmacokinetics
PLT	Platelet
PND	Postnatal day
PT	Prothrombin time
QC	Quality control review
QW	Once weekly
R	Rat (in metabolite scheme)
RBC	Red blood cell
RBD	Receptor binding domain
RdRp	RNA-dependent RNA-polymerase
RDW	Red cell distribution width
RETIC	Reticulocyte
RNA	Ribonucleic acid
RT-PCR	Reverse transcription-polymerase chain reaction
S	SARS-CoV-2 spike glycoprotein
S1	S1 domain of the SARS-CoV-2 spike glycoprotein
S9	Supernatant fraction obtained from liver homogenate by centrifuging at 9000 g
SARS	Severe Acute Respiratory Syndrome
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2; coronavirus causing COVID-19
Tfh	T follicular helper cell
Th1	Type 1 T helper cells
TK	Toxicokinetic
TNF	Tumor necrosis factor
V8	Variant 8; P2 S
V9	Variant 9; P2 S
WBC	White blood cell
WHO	World Health Organization

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2.4.1. OVERVIEW OF NONCLINICAL TESTING STRATEGY

BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048) is an investigational vaccine intended to prevent COVID-19, which is caused by SARS-CoV-2. BNT162b2 is a nucleoside modified mRNA (modRNA) expressing full-length S with two proline mutations (P2) to lock the transmembrane protein in an antigenically optimal prefusion conformation (Pallesen et al, 2017; Wrapp et al, 2020). The vaccine is formulated in lipid nanoparticles (LNPs). The LNP is composed of 4 lipids: ALC-0315, ALC-0159, DSPC, and cholesterol. Other excipients in the formulation include sucrose, NaCl, KCl, Na₂HPO₄, and KH₂PO₄. The dose selected for BNT162b2, with efficacy demonstrated in Phase 2/3 clinical evaluation and intended for commercial use, is 30 µg administered IM as two doses given 21 days apart.

In nonclinical studies, two variants of BNT162b2 were tested; designated “variant 8” and “variant 9” (V8 and V9, respectively). The variants differ only in their codon optimization sequences which are designed to improve antigen expression, otherwise the amino acid sequences of the encoded antigens are identical. Only BNT162b2 (V9) has been evaluated in the clinic, is currently authorized under EUA, and is the subject of this BLA application. The characteristics of each variant are described in the table below (Table 2.4.1-1).

Table 2.4.1-1. Nomenclature of the Vaccine Candidates

Product Code	RNA Platform	Antigen Variant	Description/Translated Protein	Variant Code	GLP Tox Data	Clinical Candidate
BNT162b2	modRNA	V8 ^a	P2 S	RBP020.1	Yes	No
BNT162b2	modRNA	V9^a	P2 S	RBP020.2	Yes	Yes

a. The V8 and V9 variants of the P2 S antigen have the same amino acid sequence. Different codon optimizations were used for their ribonucleotide sequences.

Bold: BNT162b2 (V9) vaccine candidate submitted for licensure.

The primary pharmacology, distribution, metabolism, and safety of BNT162b2 were evaluated in nonclinical pharmacology, pharmacokinetic, and toxicity studies in vitro and in vivo (Table 2.4.1-2).

Immunogenicity of BNT162b2 was evaluated in mice (2.4.2.1.3), rats (2.4.2.1.5) and nonhuman primates (2.4.2.1.4). For assessment of serum antibody responses in mice and rats, S1 and RBD-binding IgG responses were tested by an ELISA. Functional antibody responses were tested by a SARS-CoV-2 pseudotype neutralization assay (pVNT). In nonhuman primate studies, S1-binding IgG responses were tested in a direct Luminex-based immunoassay (dLIA) and functional antibody responses were assessed in a SARS-CoV-2 neutralization assay. S-specific T cell responses were assessed in mouse and nonhuman primate studies in an IFNγ ELISpot and by intracellular cytokine staining flow cytometry-based analysis of the Th1/Th2 profile using splenocytes.

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A SARS-CoV-2 challenge study in BNT162b2 (V9)-immunized nonhuman primates was also conducted to assess protection against infection and to demonstrate lack of disease enhancement ([Section 2.4.2.1.4.2](#)).

Platform properties that support BNT162b2 were initially demonstrated with non-SARS-CoV-2 antigens. Non-GLP in vivo testing of an LNP-formulated modRNA encoding luciferase examined biodistribution in BALB/c mice and Wistar Han rats after IM injection ([Section 2.4.3.4](#)) and the PK of the two novel excipients in the LNP formulation, ALC-0315 and ALC-0159, in Wistar Han rats ([Section 2.4.3.3](#)). In addition, the metabolism of ALC-0315 and ALC-0159 was evaluated in mouse, rat, monkey, and human blood, liver microsomes, S9 fractions, and hepatocytes and in vivo in rat plasma, urine, feces, and liver samples from the PK study ([Table 2.4.1-2](#); [Section 2.4.3.5](#)).

BNT162b2 (V8) and (V9) have been studied in GLP-compliant repeat-dose toxicity studies in rats ([Table 2.4.1-2](#)). Two GLP repeat-dose toxicity studies for BNT162b2 (V8) and BNT162b2 (V9), one study for each variant, have been completed. The study designs are described in [Section 2.4.4](#) and are based on WHO guidelines for vaccine development ([WHO, 2005](#)). A DART study with BNT162b2 (V9) in rats has also been completed. No additional toxicity studies are planned for BNT162b2.

IM administration was chosen for the toxicity studies as this is the intended route of administration. Rats were chosen for toxicity assessments as they are a commonly used animal species for the evaluation of toxicity, and they mount an antigen-specific immune response to vaccination with BNT162b2.

The design of the nonclinical repeat-dose toxicity studies was consistent with the WHO Guidelines on Nonclinical Evaluation of Vaccines, the EMA Note for Guidance on Preclinical Pharmacological and Toxicological Testing of Vaccines, and Japan guidance on the nonclinical safety assessment of vaccines. In addition, the 2020 CBER guidance on “Development and Licensure of Vaccines to Prevent COVID-19” ([US FDA, 2020](#)) was considered when assembling the nonclinical safety licensure package as well as feedback from regulatory agencies. All GLP-compliant studies were conducted in accordance with Good Laboratory Practice for Nonclinical Laboratory Studies, Code of US Federal Regulations (21 CFR Part 58), in an OECD Mutual Acceptance of Data member state. All nonclinical studies described herein were conducted by or for Pfizer Inc or BioNTech RNA Pharmaceuticals GmbH. The location of records for inspection is included in each final study report.

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Table 2.4.1-2. Nonclinical Studies

Study Number	Study Type	Species / Test System	Test Item	Dose [RNA]	Cross reference
Pharmacology - BNT162b2 studies					
R-20-0085	In vivo immunogenicity	BALB/c mice	BNT162b2 (V9)	0.2, 1, 5 µg	Section 2.4.2.1.3
R-20-0112	In vivo immunogenicity	BALB/c mice	BNT162a1, BNT162b1, BNT162b2 (V9), BNT162c2	5 µg	Section 2.4.2.1.3
R-20-0211	In vitro protein expression	Cell culture	BNT162b2 (V9)	varied	Section 2.4.2.1.2
VR-VTR-10741	In vitro protein expression	Cell culture	BNT162b2 (V9)	varied	Section 2.4.2.1.2
VR-VTR-10671	In vivo immunogenicity and SARS-CoV-2 challenge	Rhesus macaques	BNT162b2 (V9)	30 and 100 µg	Section 2.4.2.1.4
ADME					
PF-07302048_06Jul20_072424	PK of ALC-0315 and ALC-0159	Wistar Han Rats	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	1 mg/kg	Section 2.4.3.3
R-20-0072	In vivo distribution	BALB/c mice	modRNA encoding luciferase formulated in LNP comparable to BNT162b2	2 µg	Section 2.4.3.4
185350	In vivo distribution	Wistar Han Rats	modRNA encoding luciferase formulated in LNP comparable to BNT162b2 with trace amounts of [³ H]-CHE as non-diffusible label	50 µg	Section 2.4.3.4
01049-20008	In vitro metabolism	CD-1/ICR mouse, Wistar Han and/or Sprague Dawley rat, cynomolgus monkey and human liver microsomes, S9 fraction, hepatocytes	ALC-0315	NA	Section 2.4.3.5
01049-20009					
01049-20010					
01049-20020			ALC-0159	NA	
01049-20021					
01049-20022					

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Table 2.4.1-2. Nonclinical Studies - Continued

Study Number	Study Type	Species / Test System	Test Item	Dose [RNA]	Cross reference
PF-07302048 _05Aug20_043725	In vitro and in vivo metabolism	Blood, liver S9 fractions and hepatocytes from CD-1 mouse, Wistar Han rat, cynomolgus monkey and human. In vivo samples from Wistar Han rat plasma, urine, feces, and liver	In vitro: ALC-0315 and ALC-0159 In vivo: modRNA encoding luciferase formulated in LNP comparable to BNT162b2	1 mg/kg modRNA (in vivo samples)	Section 2.4.3.5
Toxicology – Studies with BNT162b2 variants					
38166	Repeat-dose toxicity	Wistar Han Rats	BNT162b2 (V8)	100 µg	Section 2.4.4.3
20GR142	Repeat-dose toxicity	Wistar Han Rats	BNT162b2 (V9)	30 µg	Section 2.4.4.3
20256434	Development and Reproductive Toxicity	Wistar Han Rats	BNT162b2 (V9)	30 µg	Section 2.4.4.6

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2.4.2. PHARMACOLOGY

2.4.2.1. Primary Pharmacodynamics

2.4.2.1.1. Summary

BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048) is a nucleoside-modified mRNA (modRNA) vaccine that encodes the SARS-CoV-2 full-length spike glycoprotein (S). The glycoprotein encoded by both BNT162b2 variants includes two amino acid substitutions to proline (P2 S) locking the transmembrane protein in an antigenically optimal prefusion conformation (Wrapp et al, 2020; Pallesen et al, 2017). The RNA is formulated with functional and structural lipids, which protect the RNA from degradation and enable transfection of the RNA into host cells after IM injection. S is a major target of virus neutralizing antibodies and is a key antigen for vaccine development. The well-resolved trimeric prefusion structure and the high affinity binding to ACE2 and human neutralizing antibodies demonstrate that the recombinant P2 S authentically presents the ACE2 binding site and other epitopes targeted by many SARS-CoV-2 neutralizing antibodies.

In vitro studies and in vivo studies in mice and nonhuman primates demonstrate the mechanism of action for this RNA-based vaccine, which is to encode SARS-CoV-2 S that induces an immune response characterized by both a strong neutralizing antibody response and Th1-type CD4⁺ and an IFN γ ⁺ CD8⁺ T-cell response. BNT162b2 immunization protected rhesus macaques from infectious SARS-CoV-2 challenge, with reduced detection of viral RNA in vaccine-immunized animals compared to saline-immunized animals and with no evidence of clinical exacerbation.

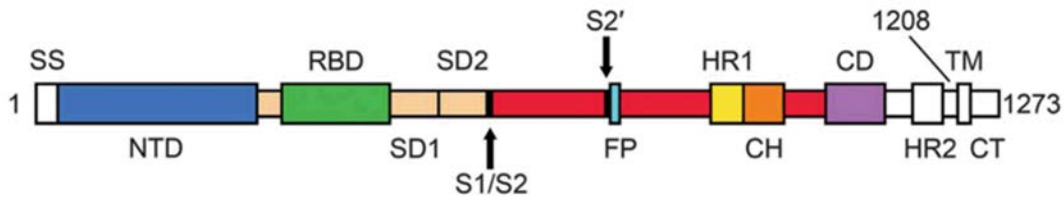
2.4.2.1.2. BNT162b2, A Lipid Nanoparticle Encapsulated RNA Vaccine Encoding the SARS-CoV-2 P2 S as a Vaccine Antigen

BNT162b2 is based on a nucleoside-modified mRNA (modRNA) platform technology. Vaccination with modRNA formulated in LNPs is characterized by strong expansion of Th1-skewed antigen-specific T follicular helper (Tfh) cells, which stimulate and expand germinal center B cells, thereby resulting in particularly strong, long lived, high-affinity antibody responses (Sahin et al, 2014; Pardi et al, 2018). ModRNA vaccine candidates against other infectious diseases induce strong antibody responses and prime and expand multifunctional CD4⁺ and CD8⁺ T cells (Pardi et al, 2017; Pardi et al, 2018).

SARS-CoV-2 S is a large, trimeric glycoprotein that exists predominantly in a prefusion conformation on the virion (Ke et al, 2020). It is cleaved by furin into an N-terminal S1 and a C-terminal S2 fragment. S attaches to the host cell receptor, ACE2, by its receptor binding domain which is contained in the S1 furin cleavage fragment. Spontaneously and during cell entry, the S1 fragment dissociates, and the S2 fragment undergoes a fold-back rearrangement to the post-fusion conformation in a process that facilitates fusion of viral and host cell membranes. S is the main target of virus neutralizing antibodies (Zakhartchouk et al, 2007; Yong et al, 2019). Most of the antibodies with SARS-CoV-2 neutralizing activity are directed against the RBD (Jiang et al, 2020; Zost et al, 2020).

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Figure 2.4.2-1. Schematic of the Organization of the SARS-CoV-2 S Glycoprotein



The S1 furin cleavage fragment includes the signal sequence (SS), the N terminal domain (NTD), the receptor binding domain (RBD, which binds the human cellular receptor, ACE-2), subdomain 1 (SD1), and subdomain 2 (SD2). The furin cleavage site (S1/S2) separates S1 from the S2 fragment, which contains the S2 protease cleavage site (S2') followed by a fusion peptide (FP), heptad repeats (HR1 and HR2), a central helix (CH) domain, the connector domain (CD), the transmembrane domain (TM) and a cytoplasmic tail (CT).
Source: modified from [Wrapp et al, 2020](#).

BNT162b2 (V9) encodes a full-length P2 S transmembrane protein that contains two consecutive prolines introduced at amino acid positions 986 and 987, between the central helix (CH) and heptad repeat 1 (HR1) (Figure 2.4.2-1) ([Wrapp et al, 2020](#); [Pallesen et al, 2017](#)). Two codon optimized forms of the coding sequence for this antigen were tested preclinically and were designated “variant 8” and “variant 9” (V8 and V9), with the vaccine candidate tested clinically and being proposed for licensure or authorization, V9, expressed from a codon optimized RNA gene with a higher content of cytosine ribonucleotides for increased protein expression. The RNA-expressed P2 S is membrane bound and elicits a potent humoral neutralizing antibody response and Th1-type CD4⁺ and CD8⁺ cellular response to block virus infection and kill virus infected cells, respectively.

Efficient in vitro expression of the P2 S protein was demonstrated following in vitro transfection of cells with BNT162b2 RNA drug substance and BNT162b2 drug product. Electron cryomicroscopy analysis of purified recombinant P2 S, expressed from DNA encoding the same S amino acid sequence as BNT162b2 RNA (except for the addition of a C-terminal tag for protein purification) revealed high similarity to previously reported structures ([Cai et al, 2020](#)). The well-resolved trimeric prefusion structure and the high affinity binding to ACE2 and human neutralizing antibodies demonstrate that the recombinant full-length P2 S protein authentically presents the ACE-2 binding site.

2.4.2.1.3. Immunogenicity of BNT162b2 (V9) in Mice

BNT162b2 was highly immunogenic in mice with strong antigen-binding IgG and high titer neutralizing antibody responses together with a Th1-phenotype CD4⁺ response as well as an IFN γ ⁺, IL-2⁺ CD8⁺ T-cell response after a single immunization. Total IgG ELISA showed that the vaccine induced a strong, dose-dependent IgG response that recognizes S1 and the RBD and elicited high neutralizing titers in a pseudotype neutralization assay.

Stimulation of fresh splenocytes, collected 28 days after immunization, with an S protein specific overlapping peptide pool demonstrated robust CD4⁺ and CD8⁺ T-cell IFN γ responses and a Th1-dominant profile was demonstrated in quantification of cytokines (IL-2 and IFN γ) in the corresponding culture supernatants.

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In summary, BNT162b2 induced a strong, neutralizing antibody response. CD4⁺ and CD8⁺ T-cell responses were detectable 12 and 28 days after one immunization and exhibited a Th1-dominant T cell response characteristic of RNA-based vaccines.

2.4.2.1.4. Evaluation of BNT162b2 (V9) Immunogenicity and Protection Against SARS-CoV-2 Challenge in Rhesus Macaques

BNT162b2 was assessed for immunogenicity and for protection against an infectious SARS-CoV-2 challenge in rhesus macaques. SARS-CoV-2 infection in humans manifests as both asymptomatic infection and as the disease COVID-19, with diverse signs, symptoms, and levels of severity. Based on published reports, SARS-CoV-2 challenged rhesus macaques develop an acute, transient infection in the upper and lower respiratory tract and have evidence of viral replication in the gastrointestinal tract, similar to humans (Zou et al, 2020; Kim et al, 2020). Varying degrees of pulmonary inflammation, primarily at the peak of infection at approximately Day 2 to 4 post-challenge, have been reported in the literature (Munster et al, 2020). The human and rhesus ACE-2 receptor have 100% amino acid identity at the critical binding residues, which may account for the fidelity of this SARS-CoV-2 animal model (Zhou et al, 2020).

2.4.2.1.4.1. Immunogenicity in Rhesus Macaques

Rhesus macaques immunized IM with 30 µg or 100 µg of BNT162b2 on Days 0 and 21 had readily detectable S1-binding IgG and SARS-CoV-2 neutralizing titers (NT50) as early as 14 days after a single immunization, with substantial increases following the second immunization. On Day 28, seven days after Dose 2 at the 30 µg dose level, the neutralizing geometric mean titer (GMT) reached 8-fold the GMT of a 38 member panel of human convalescent sera (HCS); at the 100 µg dose level, the neutralizing GMT was 18-fold the HCS GMT. The HCS sera were drawn from SARS-CoV-2 infected individuals 18 to 83 years of age, at least 14 days after PCR-confirmed diagnosis and at a time when individuals were asymptomatic. The HCS panel provides a currently accessible benchmark to judge the quality of the humoral immune response to the vaccine. A decline of both, S1-binding IgG levels and neutralizing titers, was observed out to the latest measured time point (Day 56) but remained above the neutralizing GMT and the S1-binding geometric mean concentration (GMC) of the HCS.

As seen following mouse immunization, strong S-specific Th1-dominant IFN γ ⁺ T-cell responses were detected in all immunized rhesus macaques. By intracellular cytokine staining analysis, there was a dose-dependent increase in S-specific CD4⁺ T cell responses with a strong Th1-bias evidenced by high frequency of IFN γ ⁺, IL-2⁺, or TNF- α ⁺ cells. Notably, CD8⁺ T-cell responses were also detectable in BNT162b2-immunized animals.

2.4.2.1.4.2. SARS-CoV-2 Challenge of BNT162b2 (V9)-Immunized Nonhuman Primates

Groups of 2-4 year old male rhesus macaques that had received two IM immunizations with 100 µg BNT162b2 V9 (n=6) or saline (Control; n=3) 21 days apart were challenged 55 days after the second immunization with 1.05×10^6 plaque forming units of SARS-CoV-2 (strain USA-WA1/2020), split equally between the intranasal (IN) and intratracheal (IT) routes, as

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previously described (Singh et al, 2020) (VR-VTR-10671). SARS-CoV-2 RNA was measured by reverse transcription- quantitative polymerase chain reaction (RT-qPCR) in bronchoalveolar lavage fluid, nasal swabs, and oropharyngeal swabs. The difference in viral RNA detection in BAL fluid between BNT162b2-immunised and control-immunised rhesus macaques after challenge is highly statistically significant (by a nonparametric test, $p=0.0014$). None of the challenged animals showed clinical signs of significant illness, indicating that the 2-4 years old male rhesus challenge model is primarily an infection model for SARS-CoV-2, not a COVID-19 disease model. No radiographic or histological evidence of vaccine-elicited enhanced disease was observed. In summary, BNT162b2 provided complete protection from the presence of detectable viral RNA in the lungs compared to the saline control with no evidence of vaccine-elicited disease enhancement.

2.4.2.1.5. Immunogenicity Testing After Weekly Immunization of Rats in GLP Compliant Repeat Dose Toxicology Studies and a Developmental and Reproductive Toxicity Study

The nonclinical safety data package consists of two GLP-compliant repeat-dose rat toxicity studies, in which both BNT162b2 variants (V8 and V9) were evaluated, and a DART study, in which BNT162b2 (V9) was evaluated (Section 2.4.4). In all studies, Study 38166 (evaluating V8) as well as Study 20GR142 and Study 20256434 (evaluating V9), the vaccine candidates were immunogenic.

In Study 38166, male and female rats received three weekly IM doses of BNT162b2 (V8). Serum samples were collected from main study animals on Day 17 (two days after the third dose) at the end of the dosing phase and on Day 38 at the end of a 3-week recovery phase. The sera were analyzed by ELISA for IgG that bound S1 and RBD as well as for SARS-CoV-2-S pseudovirus neutralizing antibodies. The vaccine candidates elicited IgG that recognized S1 and RBD. After immunization, animals developed high titers of antigen-specific antibodies as well as pseudovirus neutralization titers.

In Study 20GR142, male and female rats received three weekly IM doses of BNT162b2 (V9). Serum samples were collected from study animals prior to vaccine administration, at the end of the dosing phase on Day 17 (two days after the third dose), and at the end of the 3-week recovery phase on Recovery Phase Day 21. Sera were analyzed for SARS-CoV-2 neutralizing antibodies. After immunization, BNT162b2 (V9) elicited SARS-CoV-2 neutralizing antibody responses in males and females at the end of the dosing and recovery phases of the study. SARS-CoV-2 neutralizing antibody responses were not observed in animals prior to vaccine administration or in saline-administered control animals.

In Study 20256434, female rats were administered 4 total IM doses of BNT162b2 (V9) 21 and 14 days prior to mating and on GD9 and GD20. Serum samples were collected from females prior to vaccine administration, just prior to mating (M0), at the end of gestation (GD21), and at the end of lactation (LD21) and offspring (fetuses on GD21 and pups on PND21). Sera were analyzed for SARS-CoV-2 neutralizing antibodies. After immunization, SARS-CoV-2 neutralizing titers were detected in all maternal females as well as in their offspring (fetuses and pups). SARS-CoV-2 neutralizing antibody titers were not observed in animals prior to vaccine administration or in saline-administered control animals.

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2.4.2.2. Secondary Pharmacodynamics

No secondary pharmacodynamics studies were conducted with BNT162b2.

2.4.2.3. Safety Pharmacology

No safety pharmacology studies were conducted with BNT162b2 as they are not considered necessary for the development of vaccines according to the WHO guideline ([WHO, 2005](#)).

2.4.2.4. Pharmacodynamic Drug Interactions

Nonclinical studies evaluating pharmacodynamic drug interactions with BNT162b2 were not conducted as they are generally not considered necessary to support development and licensure of vaccine products for infectious diseases (WHO, 2005).

2.4.3. PHARMACOKINETICS

2.4.3.1. Brief Summary

Assessment of the ADME profile of BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048) included evaluating the PK and metabolism of two novel lipid excipients (ALC-0315 and ALC-0159) in the LNP and potential biodistribution of BNT162b2 using luciferase expression as a surrogate reporter. The luciferase reporter was used as it was a readily available reporter that has been widely used to develop an understanding of protein/organ expression (Chen et al, 2020; Elia et al, 2020; Fukuchi et al, 2020; Hassett et al, 2019; Truong et al, 2019; Barry et al, 2012; Jeon et al, 2006). An intravenous rat PK study, using LNPs with the identical lipid composition as BNT162b2, demonstrated that ALC-0315 and ALC-0159 distribute from the plasma to the liver. While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in feces was ~1% for ALC-0315 and ~50% for ALC-0159.

The biodistribution of BNT162b2 was evaluated using luciferase expression as a surrogate reporter in BALB/c mice. Mice were administered a luciferase expressing modRNA formulated like BNT162b2, with the identical lipid composition. Luciferase expression was measured in vivo following luciferin application. Luciferase expression was identified at the injection site at 6 hours after injection and was not detected after 9 days. Expression in the liver was also present to a lesser extent at 6 hours after injection and was not detected by 48 hours after injection. The distribution was also examined in male and female Wistar Han rats using LNPs with a comparable lipid composition to BNT162b2 but with a surrogate luciferase RNA and containing trace amounts of radiolabeled [³H]-CHE, a non-exchangeable, non-metabolizable lipid marker. The greatest mean concentration of LNP was found remaining in the injection site in both sexes. Total recovery (% of injected dose) of LNP outside the injection site was greatest in the liver and was much less in the spleen, adrenal glands, and ovaries.

The in vitro metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The in vivo metabolism was examined in rat plasma, urine, feces, and liver samples from the PK study. Metabolism of ALC-0315 and ALC-0159 appears to occur slowly in vitro and in vivo. ALC-0315 and ALC-0159 are metabolized by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

In summary, the nonclinical ADME studies indicate that the LNP distributes to the liver. Approximately 50% of ALC-0159 is excreted unchanged in feces, while metabolism played a role in the elimination of ALC-0315.

2.4.3.2. Methods of Analysis

No methods of analysis have been validated to support GLP TK studies of components of BNT162b2; however, a qualified LC/MS method was developed to support quantitation of the two novel LNP excipients for the non-GLP IV PK study in rats

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(Study PF-07302048_06Jul20_072424). Methods for immunogenicity and efficacy studies are described in Section 2.6.2.12.

2.4.3.3. Absorption

2.4.3.3.1. In Vitro Absorption

No absorption studies were conducted for BNT162b2, as the administration route is IM.

2.4.3.3.2. Single-Dose Pharmacokinetics

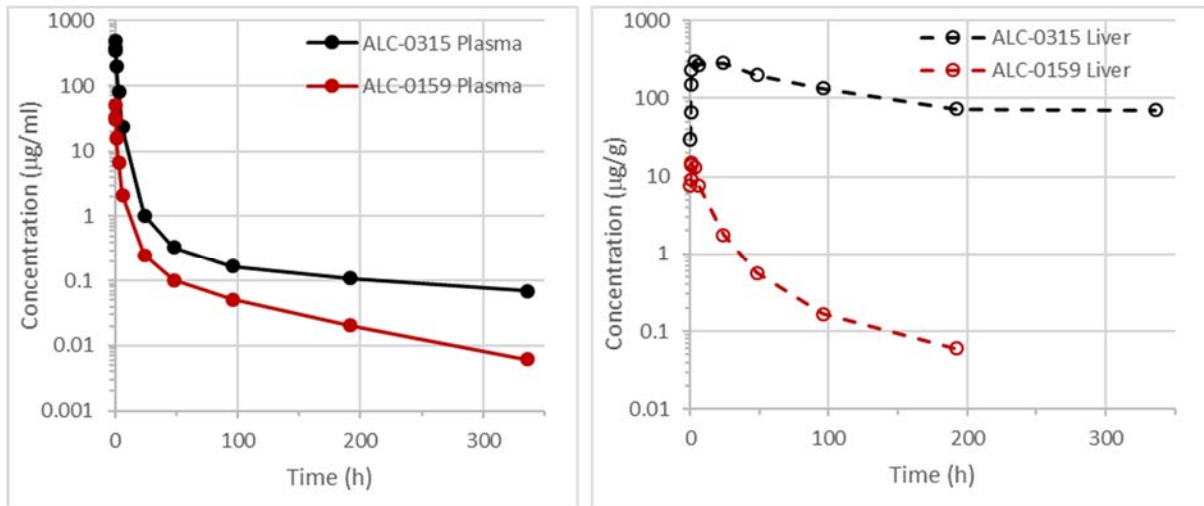
An intravenous rat PK study (PF-07302048_06Jul20_072424; Tabulated Summary 2.6.5.3) was performed using LNPs containing surrogate luciferase RNA, with the identical lipid composition as BNT162b2. This study was conducted to explore the disposition of ALC-0315 and ALC-0159 that had reached the systemic circulation following IM administration; thus, the IV route was felt to be appropriate. The findings are depicted in Table 2.4.3-1 and Figure 2.4.3-1.

Table 2.4.3-1. PK of ALC-0315 and ALC-0159 in Wistar Han Rats After IV Administration of LNPs Containing Surrogate Luciferase RNA at 1 mg/kg

Analyte	Dose of Analyte (mg/kg)	Gender /N	t _{1/2} (h)	AUC _{inf} (µg•h/mL)	AUC _{last} (µg•h/mL)	Estimated fraction of dose distributed to liver (%) ^a
ALC-0315	15.3	Male/3 ^b	139	1030	1020	60
ALC-0159	1.96	Male/3 ^b	72.7	99.2	98.6	20

a. Calculated as highest mean amount in the liver (µg)/total mean dose (µg) of ALC-0315 or ALC-0159.
 b. 3 animals per timepoint; non-serial sampling.

Figure 2.4.3-1. Plasma and Liver Concentrations of ALC-0315 and ALC-0159 in Wistar Han Rats After IV Administration of LNPs Containing Surrogate Luciferase RNA at 1 mg/kg



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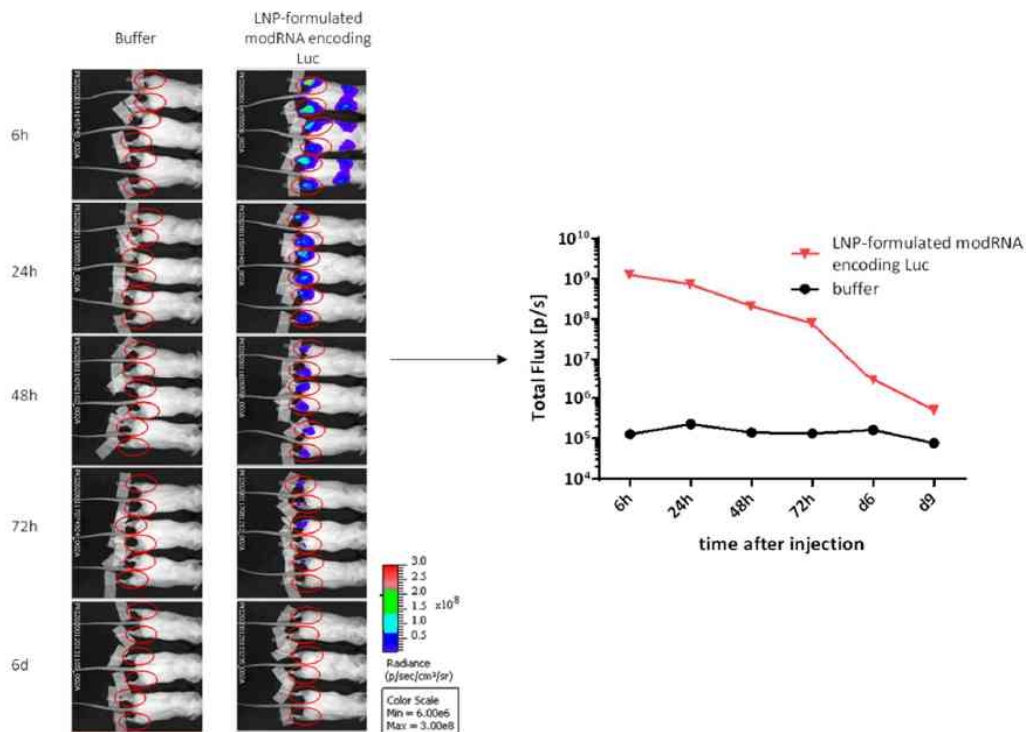
Pharmacokinetic studies have not been conducted with BNT162b2 and are generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005; WHO, 2014).

2.4.3.4. Distribution

In an in vivo study (R-20-0072; Tabulated Summary 2.6.5.5A), biodistribution was assessed using luciferase as a surrogate marker protein, with RNA encoding luciferase formulated like BNT162b2, with the identical lipid composition. The LNP-formulated luciferase-encoding modRNA was administered to BALB/c mice by IM injection of 1 µg each in the right and left hind leg (for a total of 2 µg). Using in vivo bioluminescence after injection of luciferin substrate, luciferase protein expression was detected at different timepoints at the site of injection and to a lesser extent, and more transiently, in the liver (Figure 2.4.3-2. Distribution to the liver is likely mediated by LNPs entering the blood stream. The luciferase expression at the injection sites dropped to background levels after 9 days. The repeat-dose toxicity study in rats showed no evidence of liver injury (Section 2.4.4.3).

The biodistribution of the antigen encoded by the RNA component of BNT162b2 is expected to be dependent on the LNP distribution and the results presented should be representative for the vaccine RNA platform, as the LNP-formulated luciferase-encoding modRNA had the same lipid composition.

Figure 2.4.3-2. Bioluminescence Emission in BALB/c Mice after IM Injection of an LNP Formulation of modRNA Encoding Luciferase



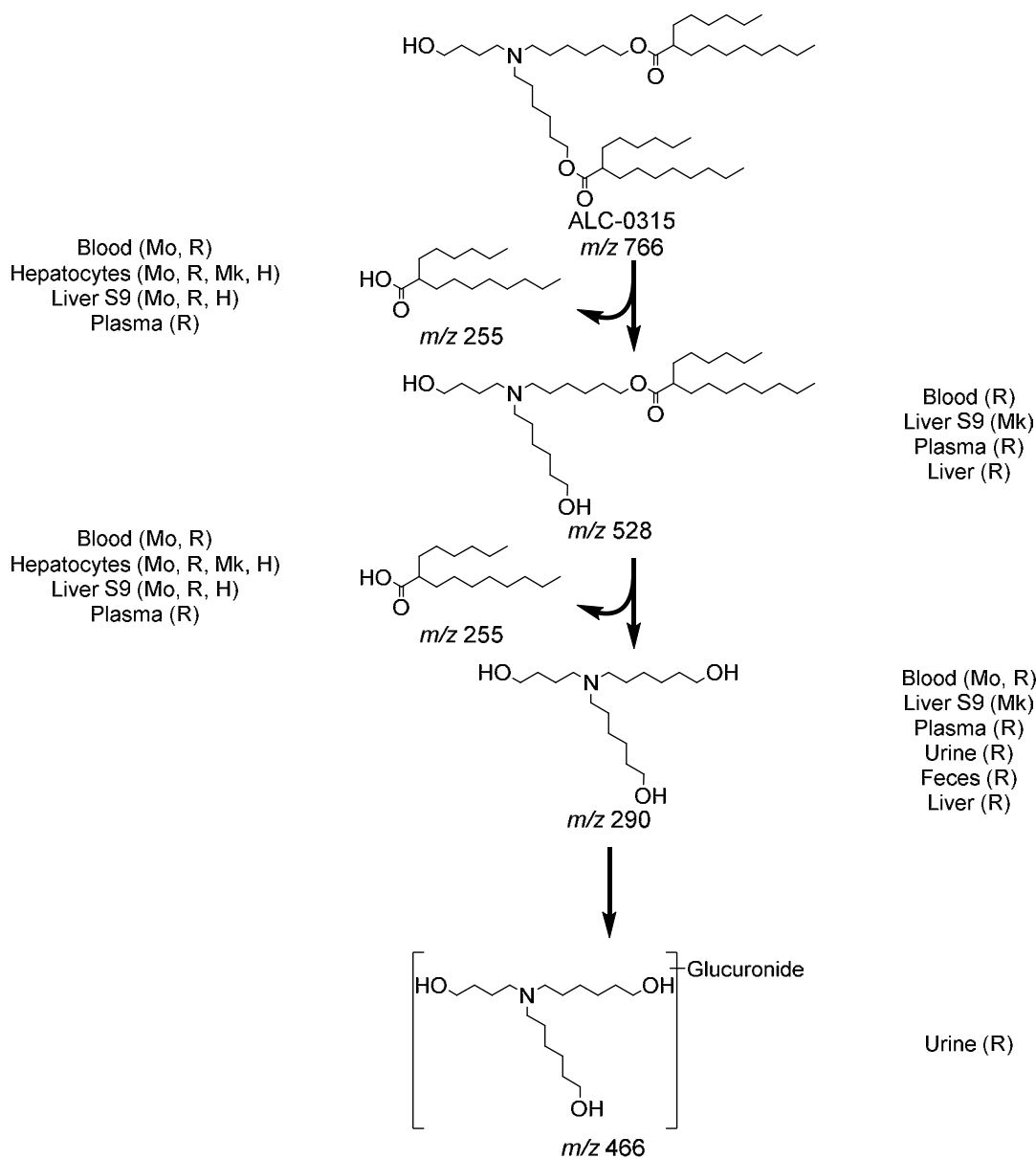
The distribution of a LNP with a comparable lipid composition to BNT162b2 but with a surrogate luciferase RNA (monitoring the ³H-CHE lipid label), was investigated in blood, plasma and selected tissues in male and female Wistar Han rats over 48 hours after a single IM injection at 50 µg mRNA/animal (Study 185350; Tabulated Summary 2.6.5.5B). The greatest mean concentration of LNP was found remaining in the injection site at each time point in both sexes. Outside the injection site, low levels of radioactivity were detected in most tissues, with the greatest levels in plasma observed 1-4 hours post-dose. Over 48 hours, the LNP distributed mainly to liver, adrenal glands, spleen and ovaries, with maximum concentrations observed at 8-48 hours post-dose. Total recovery (% of injected dose) of LNP, for combined male and female animals, outside of the injection site was greatest in the liver (up to 18%) and was much less in the spleen (≤1.0%), adrenal glands (≤0.11%) and ovaries (≤0.095%). The mean concentrations and tissue distribution pattern were broadly similar between the sexes.

2.4.3.5. Metabolism

Of the four lipids used as excipients in the LNP formulation, two are naturally occurring (cholesterol and DSPC) and will be metabolized and excreted like their endogenous counterparts. The in vitro metabolic stability of the two novel lipids, ALC-0315 (aminolipid) and ALC-0159 (PEG-lipid), were evaluated in mouse, rat, monkey, and human liver microsomes, S9 fractions, and hepatocytes. ALC-0315 and ALC-0159 were stable (>82% remaining) over 120 min in liver microsomes and S9 fractions and over 240 min in hepatocytes in all species and test systems (Studies 01049-20008, 01049-20009, 01049-20010, 01049-20020, 01049-20021, and 01049-20022; Tabulated Summaries 2.6.5.10A and 2.6.5.10B).

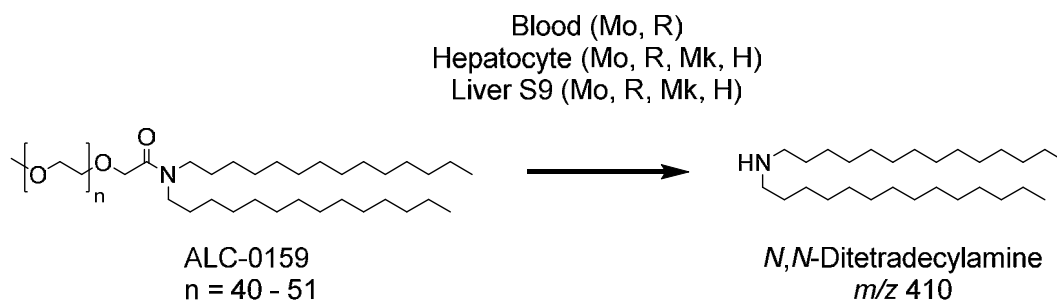
Further study of the metabolism of ALC-0315 and ALC-0159 in vitro and in vivo evaluating the plasma, urine, feces, and liver from the rat PK study (Section 2.4.3.3.2) determined ALC-0315 and ALC-0159 are metabolized slowly (Study PF-07302048_05Aug20_043725; Tabulated Summaries 2.6.5.9, 2.6.5.10C, and 2.6.5.10D). ALC-0315 and ALC-0159 underwent hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism was observed across the species evaluated (Figure 2.4.3-3 and Figure 2.4.3-4).

Figure 2.4.3-3. Proposed Biotransformation Pathway of ALC-0315 in Various Species



Metabolism of ALC-0315 occurs via two sequential ester hydrolysis reactions, first yielding the monoester metabolite (m/z 528) followed by the doubly deesterified metabolite (m/z 290). Subsequent metabolism of the doubly deesterified metabolite resulted in a glucuronide metabolite (m/z 466), which was only observed in urine from the rat PK study. Additionally, 6-hexyldecanoic acid (m/z 255), the acid product of both hydrolysis reactions of ALC-0315, was identified.

Figure 2.4.3-4. Proposed Biotransformation Pathway of ALC-0159 in Various Species



The primary route of metabolism identified for ALC-0159 involves amide bond hydrolysis yielding *N,N*-ditetradecylamine (*m/z* 410).

The protein encoded by the RNA in BNT162b2 is expected to be proteolytically degraded like other endogenous proteins. RNA is degraded by cellular RNases and subjected to nucleic acid metabolism. Nucleotide metabolism occurs continuously within the cell, with the nucleoside being degraded to waste products and excreted or recycled for nucleotide synthesis. Therefore, no RNA or protein metabolism or excretion studies will be conducted.

2.4.3.6. Excretion

In the rat PK study ([Section 2.4.3.3.2](#)), there was no detectable excretion of ALC-0315 and ALC-0159 in urine after IV administration of LNPs containing surrogate luciferase RNA at 1 mg/kg. The percent excreted unchanged in feces was ~1% for ALC-0315 and ~50% for ALC-0159. Metabolites of ALC-0315 were detected in the urine of rats ([Figure 2.4.3-3](#)). No excretion studies have been conducted with BNT162b2 for the reasons described in [Section 2.4.3.5](#).

2.4.3.7. Pharmacokinetic Drug Interactions

No PK drug interaction studies have been conducted with BNT162b2.

2.4.4. TOXICOLOGY

2.4.4.1. Brief Summary

The nonclinical toxicity assessment of BNT162b2 (BioNTech code number BNT162, Pfizer code number PF-07302048) includes 2 GLP-compliant repeat-dose toxicity studies and a developmental and reproductive toxicity (DART) study in Wistar Han rats, outlined below in [Table 2.4.4-1](#). The nonclinical safety evaluation included 2 variants of BNT162b2: V8 and V9. BNT162b2 (V9), the candidate submitted for licensure, differs from BNT162b2 (V8) only in the presence of optimized codons to improve antigen expression, but the amino acid sequences of the encoded antigens are identical. Two GLP repeat-dose toxicity studies for BNT162b2 (V8) and BNT162b2 (V9), one study for each variant, have been completed. In both studies, the nonclinical toxicology findings were similar between BNT162b2 (V9) and BNT162b2 (V8). BNT162b2 (V9) was assessed for development and reproductive toxicity in rats.

The IM route of exposure was selected as it is the intended route of clinical administration. The selection of rats as the toxicology test species is consistent with the WHO guidance documents on nonclinical evaluation of vaccines ([WHO, 2005](#)), which recommend that vaccine toxicity studies be conducted in a species in which an immune response is induced by the vaccine. Generation of an immune response to BNT162b2 has been confirmed in rats in both repeat-dose toxicity studies and the DART study. The Wistar Han rat is used routinely for regulatory toxicity studies, and there is an extensive historical safety database on this strain of rat.

Table 2.4.4-1. Overview of Toxicity Testing Program

Study ^a	Study (Sponsor) No.	Group/ Dose, µg RNA	Total Volume (µL) ^b	No. of Animals/ Group	Study Status
Repeat-Dose Toxicity					
17-Day, 2 or 3 Dose (1 Dose/Week) IM Toxicity With a 3 Week Recovery Phase in Rats ^{c,d}	38166	Control ^e , 0	200 ^f	15/sex	Completed
		BNT162b2 (V8) ⁱ , 100	200 ^f	15/sex	
17-Day, 3 Dose (1 Dose/Week) IM Toxicity With a 3 Week Recovery Phase in Rats ^g	20GR142	Saline ^h , 0	60	15/sex	Completed
		BNT162b2 (V9) ⁱ , 30	60	15/sex	
Developmental and Reproductive Toxicity					
Combined Fertility and Developmental Study (Including Teratogenicity and Postnatal Investigations) by the IM route in Rats ^j	20256434 (RN9391 R58)	Saline ^h , 0	60	44 F	Completed
		BNT162b2 (V9) ⁱ , 30	60	44 F	

- a. All studies are GLP-compliant and were conducted in an OECD mutual acceptance of data-compliant member state.
- b. Doses were administered as 1 application at 1 site unless otherwise indicated.
- c. Study also evaluated the BNT162a1, BNT162b1, and BNT162c1 vaccine candidates.
- d. QW x 3 (Days 1, 8, 15) for BNT162a1, BNT162b1, and BNT162b2 (V8); QW x 2 (Days 1, 8) for BNT162c1.
- e. Phosphate buffered saline, 300 mM sucrose.
- f. One application (100 µL) at 2 sites for a total dose volume of 200 µL.
- g. Study also evaluated BNT162b3.
- h. Sterile saline (0.9% NaCl).
- i. BNT162b2 (V8) and BNT162b2 (V9) both encode the same amino acid sequence of the spike protein antigen with two prefusion conformation-stabilizing amino acids in the stalk.
- j. Study also evaluated BNT162b1 and BNT162b3.

Administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week for a total of 3 weekly cycles of dosing was tolerated without evidence of systemic toxicity in GLP-compliant repeat-dose toxicity studies. Expected inflammatory responses to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBCs and acute phase reactants, and lower A:G ratios. A transient elevation in GGT was noted in animals vaccinated with BNT162b2 (V8) in Study 38166 without evidence of microscopic changes in the biliary system or other hepatobiliary biomarkers but was not recapitulated in Study 20GR142. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reduction in body weights and transient reductions in RETIC, PLT, and RBC mass parameters. All changes in clinical pathology parameters and acute phase proteins were reversed at the end of

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the recovery phase for BNT162b2 with the exception of higher RDW, higher globulins, and lower A:G ratios in animals administered BNT162b2 (V9). The higher RDW reflects prior RETIC increases. The higher A:G is due to low magnitude increases in globulins, which is an expected immune response to vaccine administration (Sellers et al, 2020).

Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size of draining iliac lymph nodes and increased size and weight of spleen. Vaccine-related microscopic findings at the end of the dosing phase consisted of edema and inflammation in injection sites and surrounding tissues; increased cellularity in the draining (iliac) lymph nodes, bone marrow, and spleen; and hepatocyte vacuolation in the liver. Periportal vacuolation of hepatocytes was not associated with any microscopic evidence of hepatic injury or alterations in liver function tests and is interpreted to reflect hepatocyte uptake of the LNP lipids (Sedic et al, 2018). Microscopic findings at the end of the dosing phase were partially or completely recovered in all animals at the end of the recovery phase for BNT162b2. A robust immune response was elicited to the BNT162b2 antigen.

In the DART study, administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day) was associated with nonadverse effects (body weight, food consumption, and localized effects in the injection site) after each dose administration. There were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring through the end of lactation. A SARS-CoV-2 neutralizing antibody response to the vaccine was confirmed in F0 female rats prior to mating, at the end of gestation, and at the end of lactation and these neutralizing antibodies were also detectable in the F1 offspring (fetuses and pups).

2.4.4.2. Single-Dose Toxicity

A separate single-dose toxicity study with BNT162b2 has not been conducted.

2.4.4.3. Repeat-Dose Toxicity

2.4.4.3.1. Repeat-Dose Toxicity Study of Three LNP-Formulated RNA Platforms Encoding for Viral Proteins by Repeated Intramuscular Administration to Wistar Han Rats

The vaccine candidate BNT162b2 (V8), an LNP-formulated modified RNA vaccine expressing SARS-CoV-2 P2 S, was assessed in a GLP-compliant repeat-dose toxicity study in Wistar Han rats (Study 38166). This study also included assessment of 3 other LNP-formulated RNA vaccines, encoding either the SARS-CoV-2 P2 S or RBD antigens, which were not selected for licensure. For the purpose of this submission, only the study findings from the 100 µg BNT162b2 (V8) vaccine group are summarized; findings from the other vaccine candidates were generally similar.

Administration of BNT162b2 (V8) via IM injections once weekly for 3 administrations to male and female Wistar Han rats was tolerated without evidence of systemic toxicity. The

vaccine elicited a robust antigen-specific immune response and produced nonadverse macroscopic changes at the injection sites, spleen, and the draining lymph nodes; increased hematopoiesis in the bone marrow and spleen; periportal hepatocyte vacuolation; and clinical pathology changes consistent with an immune response. The findings in this study were fully recovered or showed evidence of ongoing recovery at the end of the 3-week recovery phase, and were consistent with those typically associated with the IM administration of LNP-encapsulated mRNA vaccines (Hassett et al, 2019).

Body weights were lower 24 hours after each BNT162b2 (V8) vaccine administration compared with predose values (down to 0.92x versus baseline) with evidence of weight gain (1.22x to 1.37x versus baseline) by the end of recovery. Body weight gain between the administrations was comparable to the buffer control group. There were no noteworthy effects on body weight at the end of the recovery phase. There were no effects on food consumption.

BNT162b2 (V8)-administered animals generally had higher body temperatures compared with buffer control animals at 4 and 24 hours postdose. Group mean temperatures in rats administered the BNT162b2 (V8) vaccine were higher, but within approximately 1°C of the group mean body temperature of buffer-administered animals. Individual rats administered BNT162b2 (V8) did not have body temperatures >40.0°C after administration.

Local reactions were observed in male and female animals dosed IM with BNT162b2 (V8). The incidence and severity of the reactions were higher after the second or third injections compared with the first injection. The majority of animals had very slight edema or rarely slight erythema after the first dose. After the second or third dose, the severity of edema and erythema increased up to moderate or rarely, severe grades. These observations resolved prior to the next injection or for recovery animals resolved during the 3-week recovery phase.

Most BNT162b2 (V8)-related changes in clinical pathology were consistent with an acute phase response and anticipated inflammation. Minor and variable alterations in other clinical pathology parameters were considered secondary effects of vaccination.

Expected immune responses to BNT162b2 (V8) were evident in hematology, such as elevations in mean neutrophil (up to 7.8x) eosinophil (up to 5.1x controls), basophil (1.47x controls), and LUC counts (up to 7.7x controls) and were highest on Day 17, 48 hours after the last injection. WBCs were higher (up to 2.2x controls) in the BNT162b2 (V8) vaccinated group on Day 17. PLT counts were slightly decreased on Day 17 (down to 0.66x controls). A transient reduction in RETIC counts (down to 0.28x controls) was only observed after the administration of the first dose on Day 4. Decreased RETICs were similarly observed in rats treated with the licensed LNP-siRNA pharmaceutical Onpattro™ (NDA # 210922) but have not been observed in humans treated with this biotherapeutic (Kozauer et al, 2018), suggesting this is a species-specific effect. A slight reduction in red blood cell mass (HGB down to 0.87x controls) was observed on Day 17. RETIC and RBC mass parameter decreases were likely secondary to the inflammation.

BNT162b2 (V8)-related changes in clinical chemistry included slightly higher GGT (a biomarker of biliary and not hepatocellular injury [Boone et al, 2005]) on Days 4 (up to 4.6x

controls) and 17 (up to 4.2x controls) without evidence of microscopic changes in the biliary system or other hepatobiliary biomarkers. Additionally, higher GGT was not observed in the second repeat-dose toxicity study (20GR142), conducted with the clinical candidate submitted for licensure. Albumin was slightly lower on Days 4 (down to 0.87x controls) and 17 (down to 0.89x controls) and globulin slightly higher on Day 17 (up to 1.2x controls). This resulted in the A:G ratio being slightly lower on Days 4 (down to 0.84x controls) and 17 (down to 0.76x controls). The effect on albumin and globulin were related to the vaccine-mediated inflammatory response as part of the negative and positive acute phase response, respectively (Sellers et al, 2020).

The acute phase proteins alpha-1-acid glycoprotein (up to 21x controls on Day 17) and alpha-2-macroglobulin (up to 217x controls on Day 17) were elevated in both males and females in the BNT162b2 (V8)-administered group on Days 4 and 17. Fibrinogen was higher in the vaccine-administered group (up to 3.1x controls), consistent with an acute phase response. Higher concentrations of acute phase proteins are an anticipated response to vaccination.

All changes in clinical pathology parameters and acute phase proteins were reversed at the end of the recovery phase.

Compared with the buffer control, there were no test-article related differences in the concentration of serum cytokines evaluated, in urinalysis parameters, or in ophthalmoscopic or auditory parameters.

BNT162b2 (V8)-related higher absolute and relative (to body) spleen weights (up to 1.62x controls) were evident and correlated with the macroscopic observation of increased spleen size and the increased hematopoiesis. This is likely secondary to immune responses induced by the BNT162b2 (V8) vaccine.

The most common macroscopic observation in the BNT162b2 (V8) group was a thickened injection site and/or induration noted for nearly all animals (16/20) at necropsy. This finding correlated with microscopic inflammation at the injection site. Macroscopic findings at the injection site were resolved at the end of the recovery phase. Enlarged spleen and iliac lymph nodes were noted in several animals in the BNT162b2 (V8)-administered group, which correlated microscopically to expansion of lymphoid and/or hematopoietic cells. The effects on the lymphoid organs are consistent with immune responses to the BNT162b2 (V8).

Vaccine-related microscopic findings at the end of dosing were evident in injection sites and surrounding tissues, in the draining (iliac) lymph nodes, bone marrow, spleen, and liver.

The inflammation at the injection site was characterized by infiltrates of macrophages, granulocytes, and lymphocytes into the muscle, and variably into the dermis and subcutis. Injection site inflammation was associated with moderate edema, mild myofiber degeneration, occasional muscle necrosis, and mild fibrosis. Injection site findings were consistent with an immune/inflammatory response to an IM vaccine administration.

In the draining (iliac) lymph node, increased cellularity of the follicular germinal centers and increased plasma cells (plasmacytosis) were variably present for all BNT162b2 (V8)-dosed animals. In addition, minimal to mild increases in the cellularity of bone marrow and

hematopoiesis in the spleen likely related to increased granulopoiesis and correlated with increased circulating neutrophils (which correlated with increased spleen size and weight) were present in BNT162b2 (V8)-dosed animals.

Vacuolation of hepatocytes (minimal to mild) in the portal regions of the liver were present for all BNT162b2 (V8)-dosed animals. The liver findings were not associated with changes in markers of hepatocyte injury (eg, AST or ALT). While GGT was elevated in vaccine-administered animals, it was not considered to be associated with the vacuolation of hepatocytes (Enmulat et al, 2010). The microscopic observation of liver vacuolation is believed to be associated with hepatocyte uptake of the LNP lipids (Section 2.4.3.4; Sedic et al, 2018).

Microscopic findings at the end of the dosing phase were partially or completely resolved in all animals at the end of the recovery phase. Inflammation at the injection site and surrounding tissues was less severe (minimal to mild) in animals administered BNT162b2 (V8) at the end of the 3-week recovery phase, indicating partial recovery. In the iliac lymph node, plasmacytosis was less severe, and macrophage infiltrates were present at the end of the 3-week recovery phase and reflect resolution of the inflammation noted at the end of the dosing phase.

All other observations in the bone marrow, spleen, and liver were fully resolved at the end of the 3-week recovery phase.

The immune response to the vaccine antigen was evaluated by S1-binding IgG and RBD-binding IgG ELISAs, and a SARS-CoV-2 S pseudotype neutralization (pVNT) assay on Days 17 and 38 (Section 2.4.2.1.4). The data demonstrate that BNT162b2 (V8) elicited a SARS-CoV-2 S-specific antibody response with high neutralizing activity.

In conclusion, administration of BNT162b2 (V8) by IM injection to male and female Wistar Han rats once every week for 3 doses, was tolerated at 100 µg RNA/dosing day without evidence of systemic toxicity.

2.4.4.3.2. 17-Day Intramuscular Toxicity Study of BNT162b2 (V9) in Wistar Han Rats with a 3-week Recovery

The vaccine candidate BNT162b2 (V9), an LNP-formulated modified RNA vaccine expressing SARS-CoV-2 P2 S, was assessed in a GLP-compliant repeat-dose toxicity study in Wistar Han rats (Study 20GR142). This study also included assessment of another LNP-formulated RNA vaccine candidate (BNT162b3) that will not be included in the licensure application. For the purpose of this submission, the study findings from the BNT162b2 (V9) vaccine are summarized; findings from the BNT162b3 vaccine candidate also tested in this study were generally similar. BNT162b2 (V9) was administered at 30 µg once weekly for 3 doses (Days 1, 8, and 15) followed by a 3-week recovery phase.

Administration of BNT162b2 (V9) via IM injections once weekly for 3 administrations to male and female Wistar Han rats was tolerated without evidence of systemic toxicity. The vaccine elicited a robust antigen-specific immune response and produced nonadverse macroscopic changes at the injection sites, spleen, and the draining lymph nodes; increased

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hematopoiesis in the bone marrow and spleen; liver vacuolation; and clinical pathology changes consistent with an immune response. The findings in this study were either fully recovered or showed evidence of ongoing recovery at the end of the 3-week recovery phase, and were consistent with those typically associated with the IM administration of LNP-encapsulated mRNA vaccines ([Hassett et al, 2019](#)).

All animals administered BNT162b2 (V9) survived to scheduled necropsy. There were no test article-related clinical signs or body weight changes noted. Test article-related reduced mean food consumption was noted on Days 4 and 11 (down to 0.83x controls). Test article-related higher mean body temperature (maximum increase post each dose) compared with control animals was noted on Day 1 (up to 0.54°C), Day 8 (up to 0.98°C), and Day 15 (up to 1.03°C) postdose.

BNT162b2 (V9)-related injection site edema and erythema were noted on Days 1 (up to slight edema and very slight erythema), 8 (up to moderate edema and very slight erythema), and 15 (up to moderate edema and very slight erythema). The incidence and severity of the reactions were higher after the second or third injections compared with the first injection. Test article-related erythema and edema fully resolved prior to dose administration on Days 8 and 15. Injection site erythema and edema were fully resolved at the end of the recovery phase.

All clinical pathology changes (type and magnitude) were generally consistent with expected immune responses to the vaccine or secondary to inflammation.

There were higher WBCs (up to 2.95x controls), primarily involving neutrophils (up to 6.60x controls), monocytes (up to 3.30x controls), and LUC (up to 13.2x controls) and slightly higher eosinophils and basophils on Days 4 and 17. WBCs were higher on Day 17 as compared with Day 4. There were transiently lower RETICs on Day 4 (down to 0.27x controls) in both sexes and higher RETICs on Day 17 (up to 1.31x controls) in females only. Lower RBC mass parameters (down to 0.90x controls) were present on Days 4 and 17. All test article-related hematology and coagulation changes noted in the dosing phase were fully reversed after a 3-week recovery phase, with the exception of higher red cell distribution width (up to 1.21x controls) in animals administered BNT162b2 (V9). The higher RDW reflects prior reticulocyte increases.

There were lower A:G ratios (down to 0.82x) on Days 4 and 17. Higher fibrinogen levels were observed on Day 17 (up to 2.49x) when compared with control animals, consistent with an acute phase response. The acute phase proteins alpha-1-acid glycoprotein (up to 39x on Day 17) and alpha-2-macroglobulin (up to 71x on Day 17) were elevated in both males and females in the BNT162b2 (V9)-administered group on Days 4 and 17 with higher concentrations generally observed in males. All other changes in clinical pathology parameters were considered incidental. All test article-related clinical chemistry changes noted in the dosing phase were fully reversed after a 3-week recovery phase, except higher globulins (up to 1.08x controls) in animals administered BNT162b2 (V9) and lower A:G ratio (down to 0.91x controls) in females administered BNT162b2 (V9), reflecting vaccine-related immune response.

Test article-related higher group mean absolute and relative spleen weights (compared to body weight) were noted in males that had received BNT162b2 (V9) (up to 1.42x) and females (up to 1.59x) relative to control group means. There were no other test article-related changes in organ weights. At the end of the recovery phase, spleen weights were within normal limits.

Test article-related macroscopic findings included the observation of enlarged draining lymph nodes (2/20 animals) and pale/dark (5/20 animals) or firm (6/20 animals) injection sites in animals administered BNT162b2 (V9). These changes fully recovered, except for partial recovery of enlarged draining nodes, suggesting recovery in progress.

Test article-related microscopic pathology findings were observed at the injection site and in the draining (iliac) and inguinal lymph nodes, spleen, bone marrow, and liver for both vaccine candidates. All microscopic findings were nonadverse, as there was no evidence of systemic toxicity or clinical signs of illness or lameness.

At the end of the dosing phase, test article-related mixed cell inflammation (mild to moderate) and edema (mild to moderate) at the injection site were consistent with findings typically associated with the IM administration of LNP-encapsulated mRNA vaccines (Hassett et al, 2019). These findings correlated with macroscopic observations of abnormal color (dark/pale) and consistency (firm). At the end of the 3-week recovery phase, there was full recovery for injection site edema and partial recovery for injection site inflammation, suggesting recovery in progress.

At the end of the dosing phase, test article-related findings in the draining (iliac) and inguinal lymph nodes (up to moderately increased cellularity of plasma cells and germinal centers), spleen (minimally increased cellularity of hematopoietic cells and germinal centers), and the bone marrow (minimal increased cellularity of hematopoietic cells) were present. These changes are secondary to immune activation and/or inflammation at the injection site. The presence of plasma cells (interpreted as plasmablasts) in the draining (iliac) and inguinal lymph nodes is consistent with a robust immunological response to the vaccines. These observations correlated with macroscopic observations of abnormal size (enlarged) in the lymph nodes and spleen and increased spleen weights. At the end of the 3-week recovery phase, full recovery of increased cellularity of hematopoietic cells in the spleen and bone marrow, with partial recovery (recovery in progress) of increased cellularity of plasma cells and germinal centers in the draining and inguinal lymph nodes, and increased cellularity of the germinal centers in the spleen.

At the end of the dosing phase, the test article-related microscopic finding of minimal periportal hepatocyte vacuolation was not associated with hepatocellular damage or alterations in liver function tests. The liver vacuolation is believed to be associated with hepatocyte uptake of the LNP lipids (Section 2.4.3.4; Sedic et al, 2018). At the end of 3-week recovery phase, this finding was completely recovered.

Administration of 3 once weekly doses of BNT162b2 (V9) elicited SARS-CoV-2 neutralizing antibody responses in males and females at the end of the dosing (Day 17) and recovery phases (Day 21) of the study. SARS-CoV-2 neutralizing antibody responses were

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not observed in animals prior to vaccine administration or in saline-administered control animals.

In conclusion, administration of BNT162b2 (V9) at 30 µg RNA/dosing day via IM injections weekly for 3 administrations to male and female Wistar Han rats was tolerated without evidence of systemic toxicity. Dosing of BNT162b2 (V9) produced changes consistent with an inflammatory response and immune activation. The findings in this study are consistent with those typically associated with the IM administration of LNP-encapsulated mRNA vaccines.

2.4.4.4. Genotoxicity

No genotoxicity studies are planned for BNT162b2 as the components of the vaccine construct are lipids and RNA and are not expected to have genotoxic potential (WHO, 2005).

2.4.4.5. Carcinogenicity

Carcinogenicity studies with BNT162b2 have not been conducted as the components of the vaccine construct are lipids and RNA and are not expected to have carcinogenic or tumorigenic potential. Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005).

2.4.4.6. Reproductive and Developmental Toxicity

Reproductive and developmental toxicity assessments were made with BNT162b2 (V9) (Study 20256434). BNT162b2 was administered by IM injection at the human clinical dose (30 µg RNA/dosing day) to 44 female Wistar Han rats (F0) 21 and 14 days prior to mating with untreated males and on GD 9 and 20, for a total of 4 dosing days. A separate control group of 44 F0 females received saline by the same route and regimen.

Following completion of a mating phase with untreated males, 22 rats/group underwent caesarean-section on GD 21 and were submitted to routine embryo-fetal development evaluations. The remaining 22 rats/group were allowed to litter and development of the offspring was observed until PND 21.

There were no BNT162b2-related deaths during the study. IM administration of BNT162b2 before and during gestation to female Wistar rats resulted in nonadverse clinical signs and macroscopic findings localized to the injection site as well as transient, nonadverse body weight and food consumption effects after each dose administration. These maternal findings are all consistent with administration of a vaccine and an inflammatory/immune response.

There were no BNT162b2-related effects on any mating or fertility parameters. There were no BNT162b2-related effects on any ovarian, uterine, or litter parameters, including embryo-fetal survival, growth, or external, visceral, or skeletal malformations, anomalies, or variations. There were no effects of BNT162b2 administration on postnatal offspring (F1) development, including postnatal growth, physical development (pinna unfolding and eye

opening), reflex ontogeny (pre-weaning auditory and visual function tests), macroscopic observations, and survival.

All F0 females administered BNT162b2 developed SARS-CoV-2 neutralizing antibodies and these antibodies were also detectable in all fetuses and pups from the caesarean and littering groups, respectively. The animals in the saline control group did not exhibit an immune response to BNT162b2.

In conclusion, administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose was associated with nonadverse effects (body weight, food consumption, and effects localized to the injection site) after each dose administration. However, there were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of each vaccine candidate and these responses were also detectable in the F1 offspring (fetuses and pups).

Macroscopic and microscopic evaluation of male and female reproductive tissues from the repeat-dose toxicity studies with BNT162b2 showed no evidence of toxicity.

2.4.4.7. Local Tolerance

Local tolerance of IM administration of BNT162b2 was evaluated by injection site observations and macroscopic and microscopic examination of injection sites in the repeat-dose toxicity studies and is described in [Section 2.4.4.3](#).

2.4.4.8. Other Toxicity Studies

2.4.4.8.1. Phototoxicity

Phototoxicity studies with BNT162b2 have not been conducted.

2.4.4.8.2. Antigenicity

Immunogenicity was evaluated as part of the primary pharmacodynamic studies ([Section 2.4.2.1](#)). Serology data from the repeat-dose toxicity studies shows a robust antigen-specific immune response to BNT162b2.

2.4.4.8.3. Immunotoxicity

Stand-alone immunotoxicity studies with BNT162b2 have not been conducted. However, immunotoxicological endpoints were collected as part of the repeat-dose toxicity studies; there were no adverse effects observed and no significant effects on measured cytokines.

2.4.4.8.4. Mechanistic Studies

Mechanistic studies with BNT162b2 have not been conducted.

2.4.4.8.5. Dependence

Dependence studies with BNT162b2 have not been conducted.

2.4.4.8.6. Studies on Metabolites

Stand-alone studies with administration of metabolites of BNT162b2 have not been conducted.

2.4.4.8.7. Studies on Impurities

Stand-alone studies with administration of impurities of BNT162b2 have not been conducted.

2.4.4.8.8. Other Studies

No other studies with BNT162b2 evaluated in this submission have been conducted.

2.4.4.9. Target Organ Toxicity

Based on data from the GLP repeat-dose toxicity studies ([Section 2.4.4.3](#)), administration of BNT162b2 was well tolerated without any evidence of systemic toxicity. BNT162b2 administration was associated with local reactogenicity at the injection site and expected inflammatory responses, including increases in lymphoid cells in draining lymph nodes and spleen. Microscopic findings within injection sites, which were partially reversed by the end of recovery, support this conclusion. The liver finding was reversible, not associated with changes in markers of hepatocyte injury and not considered adverse. The elevated levels of GGT in [Study 38166](#) were not recapitulated in [Study 20GR142](#) and were not associated with hepatobiliary changes microscopically. Elevated GGT was not attributed to the hepatocyte vacuolation ([Enmulat et al, 2010](#)).

2.4.5. INTEGRATED OVERVIEW AND CONCLUSIONS

The nonclinical program demonstrates that BNT162b2 is immunogenic in mice, rats, and nonhuman primates, and the toxicity studies support the licensure of this vaccine. Preclinical assessments in mice and nonhuman primates demonstrate that BNT162b2 elicits a rapid antibody response with measurable SARS-CoV-2 neutralizing titers after a single dose and substantial increases in titers after a second dose that exceed titers in sera from SARS-CoV-2/COVID-19-recovered patients. A Th1-dominant T cell response was evident in both mice and nonhuman primates. In a SARS-CoV-2 rhesus challenge model, BNT162b2 provided complete protection in the lungs, as determined by lack of detectable viral RNA, and there was no evidence of vaccine-elicited disease enhancement.

An IV rat PK study, using an LNP with the identical lipid composition as BNT162b2, demonstrated that the novel lipid excipients in the LNP formulation, ALC-0315 and ALC-0159, distribute from the plasma to the liver. While there was no detectable excretion of either lipid in the urine, the percent of dose excreted unchanged in feces was ~1% for ALC-0315 and ~50% for ALC-0159. Further studies indicated metabolism played a role in the elimination of ALC-0315. Biodistribution was assessed using luciferase expression as a surrogate reporter formulated like BNT162b2, with the identical lipid composition. After IM injection of the LNP-formulated RNA encoding luciferase in BALB/c mice, luciferase protein expression was demonstrated at the site of injection 6 hours post dose and was not detected after 9 days. Luciferase was detected to a lesser extent in the liver; expression was present at 6 hours after injection and was not detected by 48 hours after injection. After IM administration of a radiolabeled LNP-mRNA formulation containing ALC-0315 and ALC-0159 to rats, the percent of administered dose was also greatest at the injection site. Outside of the injection site, total recovery of radioactivity was greatest in the liver and much lower in the spleen, with very little recovery in the adrenal glands and ovaries. The metabolism of ALC-0315 and ALC-0159 was evaluated in blood, liver microsomes, S9 fractions, and hepatocytes from mice, rats, monkeys, and humans. The *in vivo* metabolism was examined in rat plasma, urine, feces, and liver samples from the PK study. Metabolism of ALC-0315 and ALC-0159 appears to occur slowly *in vitro* and *in vivo*. ALC-0315 and ALC-0159 are metabolized by hydrolytic metabolism of the ester and amide functionalities, respectively, and this hydrolytic metabolism is observed across the species evaluated.

Administration of BNT162b2 by IM injection to male and female Wistar Han rats once every week for a total of 3 weekly cycles of dosing was tolerated without evidence of systemic toxicity in GLP-compliant repeat-dose toxicity studies. Expected immune responses to the vaccine were evident such as edema and erythema at the injection sites, transient elevation in body temperature, elevations in WBCs and acute phase reactants, and decreased A:G ratios. Injection site reactions were common in all vaccine-administered animals and were greater after boost immunizations. Changes secondary to inflammation included slight and transient reductions in body weights and transient reductions in RETIC, PLT, and RBC mass parameters. All changes in hematology parameters and acute phase proteins were similar to control at the end of the recovery phase for BNT162b2 with the exception of higher RDW and lower A:G ratios in animals administered BNT162b2 (V9). Macroscopic pathology and organ weight changes were also consistent with immune activation and inflammatory response and included increased size of draining iliac lymph nodes and increased size and

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weight of spleen. Vaccine-related microscopic findings at the end of dosing for BNT162b2 were evident in injection sites and surrounding tissues, in the draining iliac lymph nodes, bone marrow, spleen, and liver. Microscopic findings at the end of the dosing phase were partially (recovery in progress) or completely recovered in all animals at the end of the recovery phase for BNT162b2. A robust immune response was elicited to the BNT162b2 vaccine antigen.

Administration of BNT162b2 to female rats twice before the start of mating and twice during gestation at the human clinical dose (30 µg RNA/dosing day) was associated with nonadverse effects (body weight, food consumption and effects localized to the injection site) after each dose administration. There were no effects of BNT162b2 administration on mating performance, fertility, or any ovarian or uterine parameters in the F0 female rats nor on embryo-fetal or postnatal survival, growth, or development in the F1 offspring. An immune response was confirmed in F0 female rats following administration of BNT162b2 and this response was also detectable in the F1 offspring (fetuses and pups).

In summary, the nonclinical package summarized above supports the BLA of BNT162b2 administered twice by IM injection at a dose of 30 µg RNA.

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Board Members and fellow citizens.

I know you can't answer questions during this time but I'd like to make this more interactive. I have been here in December, March and this is my third time speaking at these meetings.

By a show of hands how many of you looked at the ¹[11,000 pages of evidence](#) I shared last time I was here?

Only one of you... Chairman of the board said we are not doing this.

I'd like to remind you that in the ²[mission statement for this board](#) that states: "In addition, the Board serves as the primary advocate and representative of the citizens of the Commonwealth..." So essentially you are the people's advocates.

I want to speak on another topic today and that is the lack of data on vaccine injuries and deaths.

Are you aware that since ³[1986 Vaccine Manufacturers](#) are not liable for injury or death? (This does not incentivize them to make vaccines safer.)

It's time Vaccine Manufacturers become liable again.

Have any of you examined ⁴[vaccine safety](#)?

Have you seen the studies that compare the health of the vaccinated to the unvaccinated?

⁵[National Health Federation Study](#)

⁶[Children's Health Defense Study Slides](#)

Are you aware of what ⁷[VAERS](#) is? The vaccine adverse events reporting system.

How is that the deaths and injuries have been ignored? There are an enormous amount of deaths. (This system is underreported and is estimated to be only 10% of the actual injuries and deaths)

¹ [11,000 Pages of Evidence Filed in Landmark 5G Case Against the FCC, Hearing Set for Jan. 25 • Children's Health Defense \(childrenshealthdefense.org\)](#)

² [Mission, Roles, Priorities and Functions - Commissioner \(virginia.gov\)](#)

³ [H.R.5546 - 99th Congress \(1985-1986\): National Childhood Vaccine Injury Act of 1986 | Congress.gov | Library of Congress](#)

⁴ [VaccineSafety-Version-1.0-October-2-2017-1.pdf \(icandecide.org\)](#)

⁵ [National Health Federation \(rallycongress.net\)](#)

⁶ [Fully Vaccinated vs. Unvaccinated — Part 1 • Children's Health Defense \(childrenshealthdefense.org\)](#)

⁷ [Vaccine Adverse Events Reporting System \(VAERS\) – MCH Data Connect \(harvard.edu\)](#)

I have made copies of the ⁸[VAERS data](#) so that you all can have it. (I would like this entered into public record)

Are you aware that Cancer is NEVER looked at and long-term studies are never done on Vaccines aka Biologics?

(Attached document 2.4 Nonclinical Overview Pfizer Document on page 29 look at 2.4.4.5. Carcinogenicity, you'll see it clearly states, "Carcinogenicity testing is generally not considered necessary to support the development and licensure of vaccine products for infectious diseases (WHO, 2005)

Have you seen the side effects from the [Pfizer data](#) that's been released?

(From this there are two in particular that I will attach to the email for ease of finding as there are now over 300 uploaded documents, 5.3.6 Adverse Events Reports beginning on page 30 through page 38 lists 8 pages of adverse events single spaced!)

Have you heard of SADS; ⁹[Sudden Adult Death Syndrome](#)?

Have any of you watched the ¹⁰[film Vaxxed](#)?

(Have you heard of William Thompson the whistleblower from the CDC?)

What about the docu-series ¹¹[The Truth about Vaccines](#)?

(Dr. Stanley Plotkin is the "godfather" of Vaccines, in his 9 hour [Deposition](#) in court he admits he is agnostic and the number of aborted fetal cells used to make vaccines astonished me as a Christian)

How about ¹²[Senator Johnson and the Covid 19 public hearings](#) that took place in Washington, DC?

What about the ¹³[Global Covid Summit](#) with incredible doctors like Peter McCullough, Dr. Robert Malone (inventor of the MRNA technology) and many more. ¹⁴[Letter for Doctors](#)

⁸ [COVID Vaccine Data \(openvaers.com\)](#)

⁹ [The Latest Tragedy: Sudden Adult Death Syndrome - The Post & Email \(thepostemail.com\)](#)

¹⁰ [Vaxxed: From Cover-Up to Catastrophe \(2016\) - IMDb](#)

¹¹ [The Truth About Vaccines 10-Day Docu-Series](#)

¹² [LIVE: Sen. Ron Johnson holds forum with people who claim 'adverse' reactions to COVID-19 vaccine - YouTube](#)

¹³ [EPISODE 267: THE REAL GLOBAL COVID SUMMIT - The HighWire](#)

¹⁴ [Letter to take to your doctor - Global Covid Summit](#)

Before you allow the VA school immunization lists to mimic the CDC schedule isn't it time vaccine manufacturers are liable again and we examine ¹⁵[vaccine safety](#)?

Thanks for your time.

I was not able in 2 minutes to remark on the fact that the majority of people who have taken this Covid 19 “vaccine” have done so without fully informed consent. Informed consent includes showing the vaccine insert and being made aware of all ingredients and potential side effects. I hope we can all agree that this one being under the [Emergency Use Authorization](#) (EUA) has made it different from any other in history. As the data shows in VAERS as well.

Sincerely,

Doris Knick

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¹⁵ [1-PAGE-INTRO-VAX-SAFETY.pdf \(icandecide.org\)](#)