Final Report Amendment 1

17-DAY INTRAMUSCULAR TOXICITY STUDY OF BNT162B2 (V9) AND [redacted] IN WISTAR HAN RATS WITH A 3-WEEK RECOVERY

Testing Facility Study Number: 20GR142

Alternative Test Article Identifier(s):

PF-07302048: Generic number for COVID-19 vaccine program

BNT162b2 (V9): BNT162b2 (Version 9); RBP020.2; PF-07305885

[redacted]

TESTING FACILITY:

[redacted]

SIGNATURES

The final report has been amended to clarify and correct the data and/or interpretation of the results following issuance on 13 Nov 2020.

Study Director

[redacted]

Quality Assurance Statement Signature

The signature for the following individual applies only to the [redacted] Quality Assurance Statement contained in this study report.

[redacted], Pfizer, [redacted]

For signatures see the Document Approval Record located on the last page of this report amendment.

1. AMENDED TEXT

Section: GLP Compliance Statement

Justification for revision(s): Text is being revised based on feedback from regulatory authorities to clarify that manufacturing of the test articles was conducted non-GMP but characterization of the test articles was conducted under GMP conditions, and that serology analysis was conducted under Good Clinical Laboratory Practice (GCLP).

Current:

This study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies regulations as set forth in the Code of Federal Regulations (21 CFR Part 58) with the exceptions of the analyses of alpha-1 acid glycoprotein (A1AGP) and alpha-2-macroglobulin (A2M), and testing performed on the test articles BNT162b2 (Version 9 [V9]) and [redacted] which were under non-GLP and non-GMP conditions, respectively. These parameters were conducted under non-GLP and non-GMP conditions and were performed according to fit-for-purpose methods. These exceptions did not have an impact on the integrity or data interpretation of the study.

Amended To:

This study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies regulations as set forth in the Code of Federal Regulations (21 CFR Part 58) with the exceptions of the analyses of alpha-1 acid glycoprotein (A1AGP) and alpha-2-macroglobulin (A2M) which were under non-GLP conditions. Manufacturing of the test articles BNT162b2 (Version 9 [V9]) and [redacted] was conducted under non-GMP conditions, while characterization of the test articles was conducted under GMP conditions. Serology analysis was performed in accordance with Good Clinical Laboratory Practice (GCLP). All parameters that were conducted under non-GLP and non-GMP conditions were performed according to fit-for-purpose methods. These exceptions did not have an impact on the integrity or data interpretation of the study.

Regulatory Quality Assurance

Quality Assurance Statement

Title: 17-DAY INTRAMUSCULAR TOXICITY STUDY OF BNT162B2 (V9) AND [redacted] IN WISTAR HAN RATS WITH A 3-WEEK RECOVERY

Study: 20GR142

In accordance with Pfizer policies and Regulatory Quality Assurance procedures for Good Laboratory Practice (GLP), the conduct of this study has been inspected and/or audited as follows. The Individual Quality Assurance Statement for study phase(s) conducted at other site(s) are contained within this report.

Phase Inspected	Audit/Inspection Date GMT	Reporting Date GMT
Report Amendment 1: Nonclinical Study	17-Dec-2020 to 17-Dec-2020	17-Dec-2020

In addition Routine Facility and Process audits are conducted in accordance with RQA SOPs and Site Monitoring Plans.

[redacted]

Pfizer Confidential

Document Approval Record

Document Name:	Report Amendment
Document Title:	Study 20GR142 Report Amendment 1

Signed By:	Date(GMT)	Signing Capacity
[redacted]	17-Dec-2020 21:25:01	Quality Assurance Approval
[redacted]	17-Dec-2020 21:28:51	Author Approval

17-DAY INTRAMUSCULAR TOXICITY STUDY OF BNT162B2 (V9) AND [redacted] IN WISTAR HAN RATS WITH A 3-WEEK RECOVERY

Testing Facility Study Number: 20GR142

Alternative Test Article Identifier(s):

PF-07302048: Generic number for COVID-19 vaccine program

BNT162b2 (V9): BNT162b2 (Version 9); RBP020.2; PF-07305885

[redacted]

TESTING FACILITY:

[redacted]

SIGNATURES

I approve the report and confirm that the study was conducted in compliance with GLP regulations with the exceptions noted (see GLP Compliance Statement). My interpretation and conclusion of the data accurately reflects the interpretation of the Contributing Scientists and Principal Investigators.

Study Director
[redacted]

Quality Assurance Statement Signature

The signature for the following individual applies only to the [redacted] Quality Assurance Statement contained in this study report.

[redacted], Pfizer, [redacted]

For signatures see the Document Approval Record located on the last page of this report.

OTHER STUDY PERSONNEL

The following personnel were involved in the conduct of this study:

Comparative Medicine Activities:	[redacted]
Ophthalmology Examinations:	
Study Technician(s):	
Study Scientist:	
Study Toxicologist:	
Test Formulations Coordinator: Formulator:	[redacted]
Clinical Pathology Coordinator:	
Necropsy/Histology Coordinator:	
Biostatistician:	
Safety Biomarkers and Translational Sciences Scientist: Principal Investigators: Serum Antibody Sample Analysis:	[redacted]
Clinical Pathologist:	
Anatomic Pathologist:	
Peer Review Pathologist	

GLP COMPLIANCE STATEMENT

This study was conducted in compliance with Good Laboratory Practice for Nonclinical Laboratory Studies regulations as set forth in the Code of Federal Regulations (21 CFR Part 58) with the exceptions of the analyses of alpha-1 acid glycoprotein (A1AGP) and alpha-2-macroglobulin (A2M), and testing performed on the test articles BNT162b2 (Version 9 [V9]) and [redacted] which were under non-GLP and non-GMP conditions, respectively. These parameters were conducted under non-GLP and non-GMP conditions and were performed according to fit-for-purpose methods. These exceptions did not have an impact on the integrity or data interpretation of the study.

ANIMAL WELFARE COMPLIANCE

This study was conducted in accordance with the current guidelines for animal welfare (National Research Council Guide for the Care and Use of Laboratory Animals, 2011). The procedures used in this study were reviewed and approved by the Institutional Animal Care and Use Committee.

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ABSTRACT

BNT162b2 (Version 9 [V9]) and [redacted] are candidate COVID-19 vaccines, which are based on a lipid nanoparticle (LNP)-RNA platform and express the SARS-CoV-2 spike protein or its derivatives. The objective of this study was to determine the toxicity and development of a specific immune response to the antigen in each of the vaccine candidates following intramuscular (IM) administration once weekly for a total of 3 doses to Wistar Han (Crl:WI[Han]) rats. The reversibility of effects was evaluated following a 3-week recovery phase.

IM administration [redacted] for a total of 3 doses to Wistar Han rats was tolerated without evidence of systemic toxicity and produced nonadverse inflammatory changes consistent with expected immune responses to vaccines.

At the conclusion of the dosing phase, test article-related immune responses to both vaccines were evident as transient edema and erythema at the injection site after each dose, transient higher mean body temperatures compared with controls after each dose, higher white blood cell count (primarily involving neutrophils, monocytes and large unstained cells), and changes in acute phase reactants (higher [alpha-1 acid glycoprotein and alpha-2-macroglobulin and fibrinogen] and lower [lower albumin and albumin:globulin (AG) ratios] acute phase proteins. These test article-related changes were fully reversed after the recovery phase, with the exception of higher red cell distribution width, higher globulins, and lower AG ratio.

Changes secondary to inflammation included lower mean body weight, lower mean food consumption, transiently lower reticulocyte counts, and minor lower red cell mass at the conclusion of the dosing phase. These changes fully resolved in the recovery phase.

At the conclusion of the dosing phase, nonadverse test article-related microscopic findings consistent with immune activation and an inflammatory response included mixed cell inflammation and edema of the injection sites (which correlated with macroscopic observations of abnormal color, dark/pale and abnormal consistency, firm), increased cellularity of plasma cells and germinal centers of the draining and inguinal lymph nodes (which correlated with macroscopic observation of abnormal size, enlarged), increased cellularity of hematopoietic cells and germinal centers of the spleen (which correlated with macroscopic observation of abnormal size, enlarged and increased spleen weights), and increased cellularity of hematopoietic cells in the bone marrow were noted. These test article-related changes fully recovered, except for partial recovery of enlarged draining and inguinal lymph nodes and microscopic findings of inflammation at the injection sites, 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.

In addition, test article-related vacuolation of the periportal hepatocytes in the liver was observed, in the absence of biochemical evidence of liver injury, and may be related to hepatic clearance of PEGylated lipids that are part of the LNP formulation. At the end of the 3-week recovery phase, this finding was completely recovered.

Administration of 3 once weekly doses of BNT162b2 (V9) or [redacted] elicited SARS-CoV-2 neutralizing antibody responses in both 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 conclusion, BNT162b2 (V9) and [redacted] administered via intramuscular injection once weekly for a total of 3 doses to Wistar Han (Crl:WI[Han]) rats was tolerated without evidence of systemic toxicity, generated a SARS-CoV-2 neutralizing antibody response, and produced nonadverse changes consistent with an immune or inflammatory response at the conclusion of the dosing phase. At the end of the 3-week recovery phase, full or partial recovery of all findings was observed. Other nonadverse findings included vacuolation in the liver which may be related to hepatic clearance of PEGylated lipids and was noted at the conclusion of the dosing phase and completely recovered. The findings in this study are consistent with those typically associated with the intramuscular administration of LNP-encapsulated mRNA vaccines. Animals administered BNT162b2 (V9) or [redacted] elicited SARS-CoV-2 neutralizing antibody responses at the end of the dosing and recovery phases of the study.

1. INTRODUCTION AND OBJECTIVE

BNT162b2 (Version 9 [V9]) and [redacted] are candidate COVID-19 vaccines, which consist of an LNP-encapsulated RNA encoding the SARS-CoV-2 spike protein or its derivatives. The objective of this study was to determine the toxicity and development of a specific immune response to the antigens in each of the vaccine candidates following administration of intramuscular (IM) doses once weekly for a total of 3 doses to Wistar Han (Crl:WI[Han]) rats. The reversibility of effects was evaluated following a 3-week recovery phase.

2. STUDY RATIONALE

BNT162b2 (V9) and [redacted] were evaluated at the highest intended dose ([redacted]) in clinical trials. Therefore, 3 IM administrations [redacted] for a total of 3 doses were evaluated in the current study in rats on a more accelerated schedule (once weekly) compared to the clinic. The IM route is the clinical route of administration. The rat is a standard rodent test species for use in toxicity studies and has been shown to generate an immune response to very similar types of RNA-based vaccines.

3. MULTI-SITE INFORMATION

Microscopic examination was conducted at Pfizer, [redacted] Evaluation of Clinical Laboratory parameters was conducted at Pfizer, [redacted] The analysis for detection of neutralizing antibody titers (serology) to wild type live SARS-CoV-2 virus was conducted at [redacted]

3.1. Communication Method

The Principal Investigator was responsible for informing the Study Director of any deviations to the protocol or Standard Operating Procedures (SOPs) and unexpected events as they occurred during the respective study phase. Other issues were communicated at the end of the respective study phase prior to the issuance of the report.

3.2. Reporting Method

Clinical Pathology and Anatomic Pathology Principal Investigator's reports are appended to the final study report. Data and interpretation are integrated into the final study report. The Serology Principal Investigator's report is integrated and appended to the final study report.

Methods for each phase are described in the SOP of the respective test site.

4. CONTACT INFORMATION

Pfizer Lead Quality Assurance (QA)[a]	[redacted]
Pfizer Test Site QA[a]	
CRO Test Site[b]	

CRO = Contract Research Organization.
a. The Pfizer lead and test site QA monitored applicable study phases, audited the final study or Principal Investigator (PI) report(s), and issued QA statement(s) for work conducted at their respective test sites according to RQA-GLP SOPs. Lead QA was responsible for coordination to ensure appropriate overall study monitoring.
b. The CRO test site QA monitored the phase, audited the CRO Principal Investigator's report, and issued a QA Statement according to CRO test site QA SOPs.

5. MATERIALS AND METHODS

For phases of the study conducted at Pfizer Worldwide Research & Development (Pfizer [redacted] details of methods described below are included in the Standard Operating Procedures of Pfizer [redacted] and in the SOPs of the respective Pfizer WRD facility conducting those activities.

Minor deviations from the protocol and/or current standard operating procedures occurred and did not affect the quality, integrity or interpretations of the data or the conclusions of the study. The deviations are documented in the study records and are discussed in the appropriate section of the report.

5.1. Study Schedule

Study Initiation Date (date protocol signed):	23 Jun 2020
Experimental Start Date (first day of study-specific data collection):	24 Jun 2020
First Day of Dosing (Day 1):	06 Jul 2020
First Day of Recovery Phase:	23 Jul 2020
Dosing Phase Necropsy (first 10 animals/sex/group):	22 Jul 2020
Recovery Phase Necropsy (remaining animals):	13 Aug 2020
Experimental Completion Date (last day of study-specific data collection):	13 Aug 2020

5.2. Test and Control Articles

5.2.1. Test Articles

5.2.1.1. BNT162b2 (V9)

Test Article Number:	BNT162b2 (V9)
Lot Number:	COVVAC/270320
Manufacturer:	[redacted]
Composition	0.5 mg/mL RNA encoding the full SARS-CoV-2 Spike (S) P2 variant protein
Expiration Date:	27 Sep 2020
Storage Conditions:	Frozen at -80°C, protected from light
Composition:	See Certificate of Analysis in Appendix C.

[redacted]

5.2.2. Control Article(s)

5.2.2.1. Vehicle

A solution of 0.9% sterile saline was used to dose the control animals (Group 1).

Excipient:	0.9% sterile saline
Lot Number:	J8L247
Expiration Date:	31 Mar 2021

5.2.3. Test Article Formulation and Analyses

Test Article Numbers: BNT162b2 (V9) and [redacted]

Type of Formulation:	Suspension
Method of Preparation:	Thawing of frozen formulation
Frequency of Preparation:	06 Jul 2020, 13 Jul 2020, and 20 Jul 2020
Storage:	Room temperature, protected from light
Formulation Handling at Time of Dispensing for Dosing:	Formulations were gently inverted to mix to ensure uniformity prior to dose administration
Stability:	2 hours from the time thaw was completed[a]
Concentration Analyses:	Not applicable; material was utilized as supplied

a. Reference: [redacted] NOTE: Although the information in this reference document is not specific to the test articles utilized in this study, it was for the same platform of vaccines and was deemed appropriate for use.

5.3. Test System

Species:	Rat
Strain/Breed/Origin:	Wistar Han (Crl:WI[Han])
Animal Use Protocol (AUP) Number:	GTN-2011-00314
Source:	[redacted]
Age at Dose Initiation:	9 weeks
Weight at Dose Initiation:	Males: 243.1 grams - 291.6 grams Females: 172.9 grams - 209.5 grams

5.3.1. Acclimation

Animals were acclimated to the laboratory environment for a minimum of 13 days prior to initiation of dosing.

5.3.2. Identification

Animals were identified by a radio frequency identification device (RFID) implanted by the vendor (subscapular region) that was associated with a unique identification number for each animal. Each cage was labeled with a cage card for each animal in the cage.

5.3.3. Allocation and Randomization

Clinically acceptable animals were allocated to study groups following the review of data collected prior to the initiation of dosing and using a computer-assisted randomization procedure based on body weights.

5.4. Housing and Environmental Conditions

Caging:	Housed individually in suspended cages
Bedding:	Enrich-n'Pure®, The Andersons, Inc.
Temperature:	68°F-79°F
Humidity:	30%-70%
Lighting:	Approximate 12-hour light, 12-hour dark cycle.
Water:	Municipal drinking water, further purified by reverse osmosis, was provided ad libitum.
Diet:	Certified Irradiated Rodent Diet 5002 (PMI Feeds Inc.) was provided ad libitum. Lot number(s) are included in the raw data.

There are no known contaminants in the food or water that interfered with the quality or integrity of the data.

5.5. Experimental Groups

Group Number	Test Article or Vehicle Dose (µg RNA/Dose Day)	Dose Volume (µL/injection site)[a]	Animal Numbers Males	Animal Numbers Females
1	0[b]	60	1-15	46-60
2	30[c]	60	16-30	61-75
3	[redacted]	[redacted]	31-45	76-90

a. Each animal received a single intramuscular injection on each dose day.
b. Sterile saline.
c. BNT162b2 (V9)
[redacted]

Doses were administered by a single intramuscular injection [redacted] on each dosing day (Days 1, 8, and 15) into the left hindlimb quadriceps muscle.

The first 10 animals/sex/group, by ascending animal order, were designated for necropsy at the end of the dosing phase. The remaining 5 animals were retained for the recovery phase.

5.6. Observations and Measurements

5.6.1. Clinical Observations/Measurements

General (Cageside) Clinical Observations:	**Days of Study**	**Time Points**
	Prior to the Initiation of Dosing (PID)	Once daily
	Nondosing Days (Dosing Phase)	Twice daily, except on days when detailed clinical observations were performed, then only once daily
	Dosing Days (Dosing Phase)	Predose, except on days that predose detailed clinical observations were performed, 4 hours after the last animal was dosed, and at the end of the workday. On 06 Jul 2020 (Day 1), clinical signs were not conducted at the end of the workday for Animals 001-090.
	Recovery Phase Days	Twice daily
Detailed Clinical Observations:	Detailed clinical observations were performed twice prior to the initiation of dosing, twice weekly at approximately the same time body weights were performed, and on the day(s) of necropsy.	
Body Weight:	All animals were weighed twice prior to the initiation of dosing on PID Phase Days 1 and 6, predose on Dosing Phase Days 1, 8, and 15; on Dosing Phase Days 4 and 11 (nondosing), and a fasted weight was collected just prior to scheduled necropsy. Body weights were collected on Recovery Phase Days 1, 4, 8, 11, 15, 18, and 21.	
Food Consumption:	Quantitative food consumption was recorded on Dosing Phase Days 4, 8, 11, and 15 and on Recovery Phase Days 4, 8, 11, 15, 18, and 21.	
Ophthalmology:	Ophthalmic examinations were performed once prior to the initiation of dosing (following randomization) on PID Phase Days 7/8 (males/females) and on Dosing Phase Days 15/16 (males/females). Recovery animals were not examined at the end of the recovery phase. See the Ophthalmology Report in Appendix B for complete materials and methods.	
Injection Site Scoring (Dermal Assessment):	Injection sites were observed during the dosing phase once predose and approximately 4 and 24 hours postdose on all animals. Animals with a score of 2 or greater at 24 hours postdose had additional evaluations at 48 and 72 hours postdose. Animals with a continued score of 2 or greater at 72 hours postdose had additional evaluations at 120 and 144 hours postdose. After dosing on Day 15, a 72-hour postdose evaluation was conducted on recovery animals only. Injection site score was recorded according to a standardized rating scale (Draize, 1959). On Dosing Phase Day 1 (06 Jul 2020), predose dermal assessments were collected on all animals for right-side injection sites (noninjection site), and at 4 hours postdose, dermal assessments were collected on Animals 1-7, 9 (Group 1, Males), and 46-58 (Group 1, Females) for right-side injection sites (noninjection site).	
Body Temperature:	Body temperature was collected on all animals once prior to the initiation of dosing on PID Phase Day 6, predose on Dosing Phase Days 1, 8, and 15, and at approximately 4 and 24 hours postdose from all animals.	

5.6.2. Clinical Laboratory Measurements

Schedule for Collection of Samples for Clinical Laboratory Measurements			
Parameter	**Day of Study**		
	Dosing Phase		**Recovery Phase**
	Day 4	Day 17[e]	Day 22
Hematology	X[a,c]	X[c]	X[c]
Coagulation	NA	X[c]	X[c]
Clinical Chemistry (Core Chemistry)	X[b,c]	X[c]	X[c]
Clinical Chemistry (Other Biomarkers – Acute Phase Proteins)/Serum[d]	X[b,c]	X[c]	X[c]
Urinalysis	NA	X	X

NA = Not applicable; X = Scheduled collection.
a. First 7 animals/sex/group.
b. Last 8 animals/sex/group.
c. Blood samples were collected from animals in a fasted state, with the exception of same day redraws.
d. Assay performed using shared clinical chemistry sample.
e. Evaluated on animals scheduled for necropsy.

See the Clinical Pathology Report in Appendix B for complete materials and methods.

5.6.3. Antibody (Serology) Response to Vaccine Components

Sample Collection and Storage Conditions	
Groups:	1-3
Collection Intervals:	PID Phase Day 8 and Dosing Phase Day 17[a], and Recovery Phase Day 21[a]
Collection Time Points:	PID Phase Day 8, Dosing Phase Day 17, and Recovery Phase Day 21: Once
Animals/Time Point:	All animals
Anticoagulant:	No anticoagulant
Collection Volume per Sample:	PID Phase Day 8: Approximately 0.7 mL Dosing Phase Day 17 and Recovery Phase Day 21: Approximately 1 mL
Sample Processing:	Samples were processed and stored as appropriate within 2 hours of collection
Sample Storage Conditions:	Approximately -60°C or lower

PID = Prior to initiation of dosing.
a. Samples collected prior to necropsy.

All samples collected were sent in one shipment after completion of the last blood sample collection.

Antibody Analysis	
Analysis of Samples from Control Animals (Group 1):	All samples were analyzed
Analysis of Samples from Animals Administered Test Article:	All samples were analyzed for a neutralizing antibody response to the antigens in BNT162b2 (V9) and [redacted]

Incurred Sample Reanalysis (ISR)/Project Numbers	
Antibody (Serology) Sample Analysis was conducted under the following Qualified Method ID:	PFZ_20GR142-WO4_MN SarsCov2_V2_20200924_GL

See the Serology Report in Appendix B for complete materials and methods.

5.7. Postmortem Observations

Animals (10/sex/group) were euthanized on Dosing Phase Day 17 (2 days after the last dose). Remaining animals were euthanized on Recovery Phase Day 22, the last day of the Recovery Phase (surviving animals).

Necropsy, tissue collection, organ weights, macroscopic tissue evaluation, and microscopic examination were performed.

Bone marrow smears were collected from all animals.

See the Anatomic Pathology Report in Appendix B for complete materials and methods.

5.8. Statistical Analysis

Statistical analyses of body weight, body weight change, and food consumption data were conducted in Pristima and analyses of body temperature and injection site scores were conducted by DSRD Statistics using iStats v1.0 with the methods outlined below. All analyses were performed separately for each sex.

Descriptive statistics were generated for each parameter and group at each scheduled sampling time or each time interval. Statistical tests were conducted at the 5% and 1% significance levels.

Analyses of body weight and food consumption parameters were done on measurements collected for each animal at the scheduled sampling times or time intervals. In addition, body weight change at selected intervals was analyzed. Analysis of body temperature was based on the maximum body temperature after injection for each animal. Analysis of injection site score was based on the average irritation score after injection for each animal.

A nonparametric (rank-transform) one way analysis of variance (ANOVA) on all groups was conducted, with two-sided pairwise comparisons of Groups 2 and 3 to Group 1 using Dunnett's test. Average ranks were assigned to ties.

For statistical analysis performed for contributing scientist activities/measurements, see the corresponding report in Appendix B.

5.9. Data Acquisition

The following primary computer applications were used for the collection of data.

Computer Application	Data Collected/Usage
Pristima Preclinical Data Management Suite (Version 7.4.3)	In-life activities
DVMAX Research Version 3.1.2	Animal health records
Microsoft Excel	Sample tracking and antibody immunoassay result storage. Duplicate titration for each sample, provided two neutralization titers (MNt) for each sample. Information was documented according to [redacted] Standard Operating Procedures (WI-MNSARS-CoV-2) are stored in an Excel sheet (the basic format is provided in dedicated [redacted] procedure).
iStats Version 1.0	Statistical analysis

For data acquisition systems and version numbers of each of these systems used for contributing scientist/principal investigator activities/measurements, see the corresponding report in Appendix B.

5.10. Data Management and Archives

Data	Location of Archive
Raw data, documentation, protocol and amendments, final report, and any specimens generated at the Test Facility	Pfizer, [redacted]
Raw data and documents electronically archived	Pfizer OpenLab archive system or locked and retained in the source computerized system, as defined as per SOP.
Materials are retained in accordance with the Enterprise Records Retention Schedule.	
Raw data, working sheets and any template required by method procedure are archived as hard copies (original documents) in fireproof archives up to 25 years. Electronic format outputs are regularly backed up and archived in Microsoft cloud.	

6. RESULTS

6.1. Clinical Observations/Measurements

6.1.1. Mortality

Individual animal mortality data are included in Appendix 1.

There was no unscheduled euthanasia. All animals administered BNT162b2 (V9) or [redacted] survived to scheduled necropsy at the end of the dosing or recovery phase of the study.

6.1.2. Clinical Signs

An incidence summary of clinical signs is presented in Table 1. Individual animal clinical signs are included in Appendix 2.

There were no test article-related clinical signs noted for animals administered BNT162b2 (V9) or [redacted] during the dosing or recovery phase.

6.1.3. Body Weight

Group mean body weight data are presented in Table 3. Group mean body weight change during interval data are presented in Table 4. Individual animal body weight data are included in Appendix 4. Individual animal body weight change during interval data are included in Appendix 5.

Dosing Phase

No test article-related mean body weight changes were noted for animals administered BNT162b2 (V9) during the dosing phase.

[redacted]

Recovery Phase

Test article-related higher mean body weight (1.05-1.06x control) was noted in males only on Recovery Days 11, 15, 18 and 21 for animals administered BNT162b2 (V9).

[redacted]

Other differences between test article and control group were not test article-related due to the small magnitude of the change, inconsistent direction of the difference, and/or inconsistency of the response.

6.1.4. Food Consumption

Group mean food consumption data are presented in Table 5. Individual animal food consumption data are included in Appendix 6.

Dosing Phase

Test article-related lower mean food consumption (0.83x-0.87x control) was noted on Days 4 and 11 for animals administered BNT162b2 (V9) during the dosing phase.

[redacted]

Recovery Phase

Test article-related higher mean food consumption (1.08x-1.35x control) was noted throughout the recovery phase for male animals administered BNT162b2 (V9).

[redacted]

Other differences between test article and control group were not test article-related due to the small magnitude of the change, inconsistent direction of the difference, and/or inconsistency of the response.

6.1.5. Dermal Assessment

Group mean dermal assessment data are included in Table 12. Individual dermal assessment data are included in Appendix 12.

Dosing Phase

BNT162b2 (V9)-related injection site edema Grade 2 (slight, edges of area well defined by definite raising) or Grade 3 (moderate, raised approximately 1 mm) were noted in all animals (except Animal 17), and occurred following dosing on Days 1, 8 and/or 15 (see Text Table 1). The edema was generally observed up to 72 hours postdose, and fully resolved prior to dose administration on Days 8 and 15. Erythema was also observed at the injection site in all animals (except Animals 16-21 and 30), following each dose administration, however, it was only a Grade 1 (very slight, barely perceptible) and fully resolved prior to the next dose administration.

[redacted]

Text Table 1. BNT162b2 (V9) Animals with Injection Site Edema Score ≥ 2

Animal	Clinical Sign	Total Number of Days (Dosing Phase Study Day of Occurrence)
16 M	Edema, Grade 2	1 (D16: 24 HPD)
18 M	Edema, Grade 2	4 (D9: 24 HPD; D10: 48 HPD; D16: 24 HPD; D17: 48 HPD)
19 M	Edema, Grade 2	4 (D9: 24 HPD; D10: 48 HPD; D16: 24 HPD; D17: 48 HPD)
20 M	Edema, Grade 2	5 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
21 M	Edema, Grade 2	6 (D2: 24 HPD; D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
22 M	Edema, Grade 2	5 (D2: 24 HPD; D3: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	2 (D9: 24 HPD; D10: 48 HPD)
23 M	Edema, Grade 2	5 (D2: 24 HPD; D3: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	2 (D9: 24 HPD; D10: 48 HPD)
24 M	Edema, Grade 2	3 (D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	2 (D9: 24 HPD; D10: 48 HPD)
25 M	Edema, Grade 2	3 (D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	2 (D9: 24 HPD; D10: 48 HPD)

Text Table 1. BNT162b2 (V9) Animals with Injection Site Edema Score ≥ 2 - Cont'd

Animal	Clinical Sign	Total Number of Days (Dosing Phase Study Day of Occurrence)
26 M	Edema, Grade 2	5 (D2: 24 HPD; D3: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	2 (D9: 24 HPD; D10: 48 HPD)
27 M	Edema, Grade 2	5 (D2: 24 HPD; D3: 48 HPD; D9: 24 HPD; D10: 48 HPD; D11: 72 HPD)
	Edema, Grade 3	2 (D16: 24 HPD; D17: 48 HPD)
28 M	Edema, Grade 2	3 (D2: 24 HPD; D3: 48 HPD; D11: 72 HPD)
	Edema, Grade 3	4 (D9: 24 HPD; D10: 48 HPD; D16: 24 HPD; D17: 48 HPD)
29 M	Edema, Grade 2	1 (D11: 72 HPD)
	Edema, Grade 3	2 (D 9: 24 HPD; D10: 48 HPD)
30 M	Edema, Grade 2	5 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
61 F	Edema, Grade 2	5 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
62 F	Edema, Grade 2	5 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD)
	Edema, Grade 3	5 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
63 F	Edema, Grade 2	8 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D9: 24 HPD; D10: 48 HPD; D11: 72 HPD)
	Edema, Grade 3	2 (D16: 24 HPD; D17: 48 HPD)
64 F	Edema, Grade 2	9 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D17: 48 HPD)
	Edema, Grade 3	1 (D16: 24 HPD)
65 F	Edema, Grade 2	2 (D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	3 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD)
66 F	Edema, Grade 2	6 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D11: 72 HPD)
	Edema, Grade 3	4 (D9: 24 HPD; D10: 48 HPD; D16: 24 HPD; D17: 48 HPD)
67 F	Edema, Grade 2	6 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120, D7: 144; D17: 48 HPD)
	Edema, Grade 3	4 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD)
68 F	Edema, Grade 2	2 (D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	3 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD)
69 F	Edema, Grade 2	8 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D9: 24 HPD; D10: 48 HPD; D17: 48 HPD)
	Edema, Grade 3	1 (D16: 24 HPD)
70 F	Edema, Grade 2	2 (D16: 24 HPD; D17: 48 HPD)
	Edema, Grade 3	3 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD)
71 F	Edema, Grade 3	5 (D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
72 F	Edema, Grade 2	6 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D11: 72 HPD)
	Edema, Grade 3	4 (D9: 24 HPD; D10: 48 HPD; D16: 24 HPD; D17: 48 HPD)
73 F	Edema, Grade 2	10 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D9: 24 HPD; D10: 48 HPD; D11: 72 HPD; D16: 24 HPD; D17: 48 HPD)
74 F	Edema, Grade 2	7 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D11: 72 HPD; D16: 24 HPD)
	Edema, Grade 3	2 (D9: 24 HPD; D10: 48 HPD)

Text Table 1. BNT162b2 (V9) Animals with Injection Site Edema Score ≥ 2 - Cont'd

Animal	Clinical Sign	Total Number of Days (Dosing Phase Study Day of Occurrence)
75 F	Edema, Grade 2	8 (D2: 24 HPD; D3: 48 HPD; D4: 72 HPD; D6: 120 HPD; D7: 144 HPD; D9: 24 HPD; D10: 48 HPD; D11: 72 HPD)
	Edema, Grade 3	2 (D16: 24 HPD; D17: 48 HPD)

Note: Dosing Days = 1, 8, and 15.
D = Dosing Phase Day; F = Female; HPD = Hours postdose M = Male.
Grade 0 = No edema; 1 = Very slight edema (barely perceptible); 2 = Slight edema (edges of area well defined by definite raising); 3 = Moderate edema (raised approximately 1 millimeter); 4 = Severe edema (raised more than 1 millimeter and extends beyond the area of exposure).

Recovery Phase

BNT162b2 (V9)-related injection site edema Grade 2 (slight, edges of area well defined by definite raising) or Grade 3 (moderate, raised approximately 1 mm) was noted in 2/5 males and 5/5 females following dosing on Day 15 (see Text Table 3). The edema was generally observed up to 72 hours postdose, and fully resolved. Erythema was also observed at the injection site in 2/5 females after the final dose administration, however, it was only Grade 1 (very slight, barely perceptible) and fully resolved.

[redacted]

Text Table 3. BNT162b2 (V9) Animals with Injection Site Edema Score ≥ 2

Animal	Clinical Sign	Total Number of Days (Recovery Study Day of Occurrence)
26 M	Edema, Grade 2	1 (RPD1; 72 HPD)
30 M	Edema, Grade 2	1 (RPD1; 72 HPD)
71 F	Edema, Grade 2	1 (RPD1; 72 HPD)
72 F	Edema, Grade 3	1 (RPD1; 72 HPD)
73 F	Edema, Grade 2	1 (RPD1; 72 HPD)
74 F	Edema, Grade 2	1 (RPD1; 72 HPD)
75 F	Edema, Grade 3	1 (RPD1; 72 HPD)

F = Female; HPD = Hours post dose; M = Male; RPD = Recovery Phase Day
Grade 0 = No edema; 1 = Very slight edema (barely perceptible); 2 = Slight edema (edges of area well defined by definite raising); 3 = Moderate edema (raised approximately 1 millimeter); 4 = Severe edema (raised more than 1 millimeter and extends beyond the area of exposure).

[redacted]

6.1.6. Body Temperature

Group mean body temperature data are included in Table 13. Individual body temperature data are included in Appendix 13.

Test article-related higher mean body temperature differences from control were noted on Days 1 (+0.42°C-0.54°C), 8 (+0.66°C-0.98°C), and 15 (+0.13°C-1.03°C) following dose administration of BNT162b2 (V9).

[redacted]

Additional body temperature evaluations were not needed at 48 and 72 hours postdose as individual animal body temperatures were ≤40°C at 24 hours postdose.

6.1.7. Ophthalmology

The complete Ophthalmology Report is included in Appendix B and a summary of the results is included below.

There were no test article-related ophthalmic findings noted at the conclusion of the dosing phase. Recovery phase examinations were not performed due to no findings observed at the conclusion of the dosing phase.

6.2. Clinical Laboratory Measurements

The complete Clinical Pathology Report is included in Appendix B and a summary of the results is included below.

Dosing Phase

Test article-related hematology and coagulation findings were similar in rats administered either BNT162b2(V9) or [redacted] and included higher mean white blood cell (WBC) counts and fibrinogen concentrations, lower (Day 4) and higher (Day 17) reticulocyte counts, and lower red blood cell mass (red blood cell count, hemoglobin and hematocrit) as compared with controls.

Higher WBC primarily involved higher neutrophils, monocytes and large unstained cells , but also eosinophils and basophils. They were present on Days 4 and 17, with higher counts on Day 17 than Day 4. On Day 17, there were also test article-related higher fibrinogen concentrations in both sexes. Hypersegmented neutrophils were present on peripheral blood smears of test article-dosed animals.

In addition, there were test article-related transiently lower reticulocyte counts on Day 4, and higher reticulocytes on Day 17 (females only) with attendant expected changes in RBC indices (higher mean cell hemoglobin concentration; males on Day 4; lower mean cell hemoglobin [MCH] and higher red cell distribution width on Day 17; both sexes). These

were associated with lower RBC mass on Days 4 and 17 (comparable on both days or slightly lower on Day 17).

Test article-related clinical chemistry findings were similar in rats administered either BNT162b2(V9) or [redacted] and included higher mean alpha-1 acid glycoprotein and alpha-2-macroglobulin and lower AG ratios (primarily due to lower albumin with slight contribution from higher globulins) on Days 4 and 17 in both sexes.

Recovery Phase

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.

All test article-related clinical chemistry changes noted in the dosing phase were fully reversed after a 3-week recovery phase, with the exception of higher globulins in males administered BNT162b2(V9) and females administered BNT162b2(V9) and [redacted] and lower AG ratio in females administered BNT162b2(V9).

There were no test article-related findings noted in urinalysis parameters in the dosing or recovery phase.

6.2.1. Bone Marrow Assessment

The complete Clinical Pathology Report is included in Appendix B and a summary of the results is included below.

Bone marrow smears were prepared for all animals and were not examined.

6.3. Antibody (Serology) Analysis

The complete Serology Report is included in Appendix B and a summary of the results is included below.

Administration of 3 once weekly doses of BNT162b2 (V9) or [redacted] 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 not observed in animals prior to vaccine administration or in saline-administered control animals.

6.4. Postmortem Observations

The complete Anatomic Pathology Report is included in Appendix B and a summary of the results is included below.

Dosing Phase

Test article-related organ weight differences included higher absolute and relative (to body and brain weight) spleen weights in males and females administered BNT162b2 (V9) or [redacted]

Test article-related macroscopic findings included large draining lymph nodes (abnormal size, enlarged) and dark/pale and/or firm injection sites (abnormal color, dark/pale and/or abnormal consistency, firm) in animals administered BNT162b2 (V9) or [redacted]

Organs with test article-related microscopic findings included the injection site (mixed cell inflammation and edema), draining and inguinal lymph nodes (increased cellularity, plasma cells and germinal centers), liver (hepatocellular vacuolation), spleen (increased cellularity, hematopoietic cells and germinal centers), and bone marrow (increased cellularity, hematopoietic cells) in both males and females administered BNT162b2 (V9) or [redacted]

Recovery Phase

No test article-related organ weight changes were noted at the end of the recovery phase.

Test article-related macroscopic findings observed at the end of the recovery phase were limited to large draining lymph nodes (abnormal size, enlarged) in 1 male administered BNT162b2 (V9) an [redacted] Pale/dark and/or firm injection sites and enlarged spleen were not observed at the end of recovery phase in BNT162b2 (V9) or [redacted]

Test article-related microscopic findings noted at the end of the dosing phase including edema at the injection site, hepatocellular vacuolation in the liver, and increased cellularity of hematopoietic cells in the spleen and bone marrow were not observed at the end of recovery phase in BNT162b2 (V9) or [redacted]. Inflammation at the injection site was characterized by mostly lymphocytes and plasma cells with few neutrophils (indicating partial recovery) and no edema (full recovery). However, increased cellularity of the germinal centers in the spleen partially recovered, as the incidence and/or severity of these findings were lower in recovery phase animals as compared with dosing phase animals in both males and females administered BNT162b2 (V9) [redacted] At the end of recovery phase, mature plasma cells had replaced the plasmablasts identified in the inguinal and draining lymph nodes in the dosing phase animals. In recovery phase animals, infiltration of macrophages was observed in the draining lymph nodes (minimal to mild) in both sexes administered BNT162b2 (V9) or [redacted] and in the inguinal lymph nodes (minimal) in both sexes administered BNT162b2 (V9). This finding was considered indicative of a reparative process (consequence of phagocytosis), which can be seen following inflammatory reactions at the injection sites.

7. INTEGRATED SUMMARY AND DISCUSSION OF RESULTS

Intramuscular administration [redacted] once weekly for a total of 3 doses to Wistar Han rats was tolerated during the dosing phase without evidence of systemic toxicity, generated a SARS-CoV-2 neutralizing antibody

response, and produced nonadverse changes consistent with inflammatory and immune responses to vaccine administration.

At the conclusion of the dosing phase, test article-related responses to both vaccines were evident as transient edema (very slight to moderate) and erythema (very slight) at the injection site after each dose of BNT162b2 (V9) and [redacted] Test article-related erythema and edema fully resolved prior to subsequent dose administration on Days 8 and 15 with findings generally resolved by 72 hours after the final dose administration (Recovery Phase Day 1). Transiently higher body temperature differences compared with concurrent controls were noted [redacted] on Days 1 (up to +0.54°C), 8 (up to +0.98°C), and 15 (up to +1.03°C) after administration of BNT162b2 (V9). Additional body temperature evaluations were not needed at 48 and 72 hours postdose as individual animal body temperatures were ≤40°C at 24 hours postdose.

[redacted]

At the conclusion of the dosing phase, all clinical pathology findings (type and magnitude) were generally similar between rats administered BNT162b2 (V9) or [redacted] and consistent with expected immune responses to vaccines or secondary to inflammation. The main findings were present in both sexes on Days 4 and/or 17 and included higher acute phase proteins (alpha-1 acid glycoprotein; 7.0x-42x controls], alpha-2-macroglobulin (3.3x-128x] and fibrinogen [2.4x-2.6x]) and white blood cell count (1.28x-2.95x; primarily involving neutrophils, monocytes and large unstained cells, which typically represent large mononuclear cells) and lower albumin:globulin (0.90x-0.82x). Hypersegmented neutrophils present on peripheral blood smears were considered to be secondary to the robust increases in neutrophil counts and likely related to mobilization of bone marrow storage neutrophils and prolonged neutrophil lifespan in circulation (Ulich et al, 1988). Collectively, these findings were consistent with immune responses to vaccines. Microscopic correlates included minimally increased cellularity of hematopoietic cells (primarily myeloid) in the bone marrow and the spleen, minimal to moderate mixed cell inflammation at the injection site and increased cellularity in germinal centers of lymphoid organs. In addition, there were transiently lower reticulocyte counts on Day 4 (0.44x-0.27x), and higher reticulocytes on Day 17 (1.20x-1.31x; females only), with minor lower red cell mass on Days 4 and 17 (HCT; 0.93x-0.89x). Lower reticulocytes were interpreted to be a transient effect of innate immune responses (Abreu et al, 2018; Brooks et al, 2017; Kim et al, 2014; Wrighting & Andrews, 2006).

All test article-related clinical pathology parameter changes were fully reversed after a 3-week recovery phase, with the exception of higher red cell distribution width in males and

females administered BNT162b2(V9) (1.13x and 1.21x, respectively) and [redacted] higher globulins in males administered BNT162b2(V9) (1.08x) and females administered BNT162b2(V9) (1.06x) and [redacted] and lower AG ratio in females administered BNT162b2(V9) (0.91x).

Test article-related microscopic pathology findings were observed at the injection site and in the 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 lipid nanoparticle (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, full recovery occurred for macroscopic findings of pale/dark and firm injection sites and the microscopic finding of edema, whereas partial recovery occurred for inflammation at the injection sites.

At the end of the dosing phase, test article-related findings in the lymph nodes (increased cellularity of plasma cells [minimal to moderate] and germinal centers [minimal to mild]), spleen (increased cellularity of hematopoietic cells [minimal] and germinal centers [minimal]), and the bone marrow (minimal increased cellularity of hematopoietic cells) were secondary to immune activation and/or inflammation at the injection site. The presence of plasma cells (interpreted as plasmablasts) in the draining and inguinal lymph nodes was interpreted to reflect 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 occurred for higher spleen weights, macroscopic finding of enlarged spleen, and microscopic findings of increased cellularity of hematopoietic cells in the spleen and bone marrow, whereas partial recovery occurred for macroscopic findings of enlarged draining and inguinal lymph nodes, microscopic findings 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, test article-related microscopic finding of minimal portal hepatocyte vacuolation was not associated with hepatic tissue damage or liver enzyme alterations. This change may be related to hepatic clearance of the pegylated lipid in the LNP (Ivens et al, 2015). At the end of 3-week recovery phase, this finding was completely recovered.

Administration of 3 once weekly doses of BNT162b2 (V9) or [redacted] elicited SARS-CoV-2 neutralizing antibody responses in both 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 not observed in animals prior to vaccine administration or in saline-administered control animals.

There were no other test article-related effects in the study.

8. CONCLUSIONS

In conclusion, BNT162b2 (V9) and [redacted] administered via intramuscular injection once weekly for a total of 3 doses to Wistar Han (Crl:WI[Han]) rats was tolerated without evidence of systemic toxicity, generated a SARS-CoV-2 neutralizing antibody response, and produced nonadverse changes consistent with an immune or inflammatory response at the conclusion of the dosing phase. At the end of the 3-week recovery phase, full or partial recovery of all findings was observed. Other nonadverse findings included vacuolation in the liver which may be related to hepatic clearance of PEGylated lipids and was noted at the conclusion of the dosing phase and completely recovered. The findings in this study are consistent with those typically associated with the intramuscular administration of LNP-encapsulated mRNA vaccines. Animals administered BNT162b2 (V9) [redacted] elicited SARS-CoV-2 neutralizing antibody responses at the end of the dosing and recovery phases of the study.

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