STUDY DATA REVIEWER'S GUIDE

NON-CLINICAL

17-DAY INTRAMUSCULAR TOXICITY STUDY IN WISTAR HAN RATS WITH A 3-WEEK RECOVERY

STUDYID: 20GR142

Pfizer Inc.

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1. SDRG INTRODUCTION

1.1. Study Protocol Title, Number, and Version

STITLE	17-DAY INTRAMUSCULAR TOXICITY STUDY IN WISTAR HAN RATS WITH A 3-WEEK RECOVERY
Study Number	20GR142
Study Version	Final study report with protocol amendments.

1.2. Summary of SEND Dataset Creation Process

All in life, clinical pathology and post-mortem data were collected with Pristima by Pfizer Inc. The SEND (SAVANTE) module prepares a copy of the raw study data by using the Pristima Application Programming Interface (API) connector or CSV import functionality and produces an integrated SEND dataset with Controlled Terminology mapping applied and accompanying define.xml and nsdrg.

1.3. SEND Dataset Verification

Data in the SEND datasets are an accurate representation of data in the study report for Study No. 20GR142. Any differences between the datasets and the report are described in Section 6.2.

2. STUDY DESIGN

2.1. Study Design Summary

BNT162b2 (Version 9 [V9]) and BNT162b3c are candidate COVID-19 vaccines, which are based on an RNA platform and target the SARS-CoV-2 spike protein or its derivatives. The objectives of this study are 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 potential effects will be evaluated following a 3-week recovery phase.

2.2. Trial Design Domain Overview

The following diagram illustrates the trial design.

Study Group SPGRPCD	Trial Arms		Element in each Epoch			Trial Set	
	ARMCD	ARM	PID	Dosing	Recovery	SETCD	SET
1	1	Vehicle control1	PID	1D - BNT162b2(V9):0µg		1	Vehicle control: 0 µg/day1
1	1R	Vehicle control1R	PID	1D - BNT162b2(V9):0µg	Recovery	1R	Vehicle control: 0 µg/day1R
2	2	Dose2	PID	2D - BNT162b2(V9):30 µg		2	Dose:30 µg/day2
2	2R	Dose2R	PID	2D - BNT162b2(V9):30 µg	Recovery	2R	Dose:30 µg/day2R
3	3	Dose3	PID	3D - BNT162b3c:30µg		3	Dose:30 µg /day3
3	3R	Dose3R	PID	3D - BNT162b3c:30µg	Recovery	3R	Dose:30 µg /day3R

3. STANDARDS, FORMATS, AND TERMINOLOGIES AND THEIR VERSIONS

3.1. Standards Used

Standard or Dictionary	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND	SEND Implementation Guide Version 3.1
Controlled Terminology	CDISC SEND Controlled Terminology	SEND Terminology 2019-09-27
Data Definition file	CDISC DEFINE.XML	2.0

3.2. Rationale for Standards Selection

The standards versions used were the most current at the time of dataset creation. The CT version used is of 2019-09-27 as the data collection system is being updated with most recent version of CT i.e. November 2020.

3.3. Nonstandard Terminology

The following nonstandard terminology was used:

Dataset Name	Variable	Codelist	Term Used	Meaning
LB	LBTEST	LBTEST	Basophilia	Sponsor specific Laboratory test that are currently not modelled for SEND. Since this is an extensible list as a result this was populated as is in SEND LB domain.
LB	LBTEST	LBTEST	Hemoglobin Crystals	Sponsor specific Laboratory test that are currently not modelled for SEND. Since this is an extensible list as a result this was populated as is in SEND LB domain.
LB	LBTEST	LBTEST	Other Morphology	Urine microscopic that cannot be categorized as a cast, crystal, etc.
LB	LBTEST	LBTEST	Siderocyte-like Inclusions	Sponsor specific Laboratory test that are currently not modelled for SEND. Since this is an extensible list as a result this was populated as is in SEND LB domain.
LB	LBTESTCD	LBTESTCD	BASOPH	Sponsor specific Laboratory test code that are currently not

Dataset Name	Variable	Codelist	Term Used	Meaning
				modelled for SEND. Since this is an extensible list as a result this was populated as is in SEND LB domain.
LB	LBTESTCD	LBTESTCD	HGB_CRYS	Sponsor specific Laboratory test code that are currently not modelled for SEND. Since this is an extensible list as a result this was populated as is in SEND LB domain.
LB	LBTESTCD	LBTESTCD	OTHERM	Urine microscopic that cannot be categorized as a cast, crystal, etc.
LB	LBTESTCD	LBTESTCD	SIDERO	Sponsor specific Laboratory test code that are currently not modelled for SEND. Since this is an extensible list as a result this was populated as is in SEND LB domain.

4. DESCRIPTION OF STUDY DATASETS

4.1. Dataset Summary

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
TA	Trial Arms			TRIAL DESIGN
TE	Trial Elements			TRIAL DESIGN
TS	Trial Summary			TRIAL DESIGN
TX	Trial Sets			TRIAL DESIGN
CO	Comments			SPECIAL PURPOSE
DM	Demographics			SPECIAL PURPOSE
SE	Subject Elements			SPECIAL PURPOSE
EX	Exposure			INTERVENTIONS
DS	Disposition	X		EVENTS
BG	Body Weight Gains	X		FINDINGS
BW	Body Weights	X		FINDINGS
CL	Clinical Observations	X		FINDINGS
FW	Food and Water Consumption	X		FINDINGS
LB	Laboratory	X		FINDINGS
MA	Macroscopic Findings	X	X	FINDINGS
MI	Microscopic Findings	X	X	FINDINGS
OM	Organ Measurements			FINDINGS
VS	Vital Signs	X		FINDINGS
POOLDEF	Pool Definition			RELATIONSHIP

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
RELREC	Related Records			RELATIONSHIP

4.2. Dataset Explanation

All Domains
Baseline flag (--BLFL) is currently not populated in any of the domains with structure supporting BLFL. This will be incorporated in future release of the software.

4.2.2. CL - CLINICAL OBSERVATIONS

The SEND datasets include the NORMAL findings.

In the report, only animals with findings are presented. The NORMAL findings will not be presented in the report.

In addition to clinical observations, the CL domain also includes OPHTHALMOLOGY and DERMAL data.

4.2.3. DD- DEATH DIAGNOSIS

DD domain is not populated in this study as we do not collect cause of death in our data collection unless it is a Carci study.

4.2.4. EX-Exposure

The EX domain contains details of the planned dose administered at each dose event.

EXTRT for controlled group has been populated as “BNT162b2(V9)”. This study was set up in data collection system with the Control group in its own Dose Regimen. Our guidance for setting up control-only regimens in data collection system is to list the compound in the Test Material field (EXTRT in SEND EX domain). Then we put 0 in for the group dosage, so the dosing data essentially indicates that the animals received 0 units of the actual compound.

4.2.5. LB- Laboratory Test Results

“RATIO” has been populated as unit for Albumin/Globulin test.

LBMETHOD (expected variable) is not populated in LB domain due to system limitation. There is no information in the protocol or study report that provides methodology for tests in this domain.

Dashes (-, --, ---) has been populated in LB domain under LBTPT variable. These were multiple different types of collections on at least one day that needed multiple sessions. The current data collection system has limitation, if we use the same Session for all of those measurements, the system will only allow us to create one draw list on that day.

4.2.6. TS – TRIAL SUMMARY

All variables are populated or derived as per the study plan and amendments; therefore, they contain only actual information.

- STENDTC is populated as the date when study report is approved.
- DOSENDTC is populated with the date prior to necropsy.
- DOSSTDTC is populated with the first date of dosing.

TRT for controlled group has not been populated. This study was set up in data collection system with the Control group in its own Dose Regimen. Our guidance for setting up control-only regimens in data collection system is to list the compound "BNT162b2(V9)" in the Test Material field (EXTRT in SEND EX domain and TRT in Trial Summary domain). Then we put 0 in for the group dosage, so the dosing data essentially indicates that the animals received 0 units of the actual compound. In this case, since group 2 animals were dosed with "BNT162b2(V9)" (TRT for group 2 was populated as "BNT162b2(V9)" in SEND TS domain) and again populating TRT for control group as "BNT162b2(V9)" would have resulted in duplicate records. Hence TRT for control group animals were not populated to avoid the duplicate records.

4.2.1. 4.2.8. Define File

User-defined nonstandard terminology test names not used on the study are present in the define file. All possible values present in the Controlled Terminology package are also present in the define file. Codelists are not included for terms that are not defined in Controlled Terminology.

Due to system limitation Define.xml file also contains codelists other than the one that are used for the study.

Define.xml may not have **structure** of the domains defined as per SENDIG 3.1 this is due to system limitation and will be corrected in next release. The pinnacle 21 validator reports however do not show any conformance issues with define.xml file.

TS domain origin is incorrectly populated as 'Assigned'. This does not follow the SENDIG 3.0 and has been identified as an error with the software and should be read as 'Other'.

Due to a software limitation, Value Level Metadata is missing Level data for QLABELs for all the QVALs presented. Value Level Metadata is also missing for the TX domain and incomplete for the TS domain.

The domain sequence in the define file does not follow the sequence in the SENDIG, nor are the General Observation Class domains in alphabetical order.

Algorithms are presented using variable names and descriptions under comments instead of computational algorithms with variable codes.

The following variables should have "date" listed as their Type instead of "datetime" as there is only a date present for all values: RFSTDTC; RFENDTC; BRTHDTC; SESTDTC.

4.3. Use of Supplemental Qualifiers

Dataset Name	Associated Dataset	QNAM	QLABEL	Qualifiers Used
SUPPDS	Disposition (DS)	PHSENAME	Phase Name	Phase of the study when the animal was disposed from the study for which SEND variables have not yet been developed.
		PHASEDAY	Day of Phase	Day of phase when the animal was disposed from the study for which SEND variables have not yet been developed.
SUPPBW	Body Weights (BW)	PHSENAME	Phase Name	Phase of the study when the body weights of the animals were taken for which SEND variables have not yet been developed.
		PHASEDAY	Day of Phase	Day of Phase of the study when the body weights of the animals were taken for which SEND variables have not yet been developed.
SUPPBG	Body Weight Gains (BG)	PHSNAME1	Start Phase Name	Starting phase of the study when change in body weight was measured.
		PHSNAME2	End Phase name	Ending phase of the study when change in body weight was measured.
		PHSEDAY1	Start Day of Phase	Starting day of phase of the study when change in body weight was measured.

Dataset Name	Associated Dataset	QNAM	QLABEL	Qualifiers Used
		PHSEDAY2	End Day of Phase	Ending day of phase of the study when change in body weight was measured.
SUPPMA	Macroscopic Findings (MA)	MARESMOD	Result Modifiers	Modifiers that were part of MAORRES for which SEND variables have not yet been developed
SUPPMI	Microscopic Findings (MI)	MIRESMOD	Result Modifiers	Modifiers that were part of MIORRES for which SEND variables have not yet been developed
SUPPLB	Laboratory Tests (LB)	PHSENAME	Phase Name	Phase of the study when the Laboratory evaluations were performed for which SEND variables have not yet been developed.
		PHASEDAY	Day of Phase	Day of phase of the study when the Laboratory evaluations were performed for which SEND variables have not yet been developed.
		LBCALCN	Numeric Interpretation for Calculations	When a value has a greater than (>) or less than (<) sign attached in --ORRES, the entire value with the greater than (>) or less than (<) sign is shown in --STRESC and --STRESN is Null. Assigning a numeric value to this result for the purpose of calculations is reflected by using the LBCALCN supplemental qualifier.

Dataset Name	Associated Dataset	QNAM	QLABEL	Qualifiers Used
SUPPCL	Clinical Observations (CL)	PHSENAME	Phase Name	Phase of the study when the Clinical observations were performed for which SEND variables have not yet been developed.
		PHASEDAY	Day of Phase	Day of phase of the study when the Clinical observations were performed for which SEND variables have not yet been developed.
SUPPFW	Food and Water Consumption (FW)	PHSENAME	Phase name	Starting phase of the study when food consumption was measured.
		PHSEDAY1	Start Day of Phase	starting phase of the study when food consumption was measured.
		PHSEDAY2	End Day of Phase	Ending day of phase of the study when food consumption was measured.
SUPPVS	Vital Signs – VS	PHSENAME	Phase Name	Phase of the study when the Vital Signs were performed for which SEND variables have not yet been developed.
		PHASEDAY	Day of Phase	Day of phase of the study when the Vital Signs were performed for which SEND variables have not yet been developed.

5. DATA STANDARDS VALIDATION RULES, VERSIONS, AND CONFORMANCE ISSUES

5.1. Validation Outcome Summary

1150 warnings were reported for the study and are accurately explained within the nsdrg.

5.2. FDA SEND Validation Rules Version

Rule conformance to SEND 3.1 was evaluated using Pinnacle 21 Community version 3.0.2, which includes checks for conformance against the FDA Specific SEND Validation Rules, Version 2.1.

5.3. Errors

There were no errors reported.

5.4. Warnings

The following warnings were identified:

Pinnacle21 Rule	FDA Rule	Message	Domain(s)	Count	Explanation
SE2319	FDAB013	No baseline flag record in LB for subject	LB/DM	90	The current data generation system is not capable of generating Baseline flag in domains that has BLFL in structure. This will be corrected in upcoming version of the system.
SE2319	FDAB013	No baseline flag record in VS for subject	VS/DM	90	The current data generation system is not capable of generating Baseline flag in domains that has BLFL in structure. This will be corrected in upcoming version of the system.

SD1122	FDAB031	Missing value for LBSTRESN	LB	938	LBSTRESN is missing for records of Hematology and Coagulation. These parameters are not considered for summary values as they are in percentage (%) and not an actual numerical value.
CT2002	FDAB017	LBTEST value not found in 'Laboratory Test Name' extensible codelist	LB	16	There was some sponsor specific LBTEST used in this study that are yet to be mapped in NCI controlled Terminology. Since this is an extensible term, hence these values were added in LBTEST variable.
CT2002	FDAB017	LBTESTCD value not found in 'Laboratory Test Code' extensible codelist	LB	16	There was some sponsor specific LBTESTCD used in this study that are yet to be mapped in NCI controlled Terminology. Since this is an extensible term, hence these values were added in LBTESTCD variable.

6. SPONSOR DECISIONS RELATED TO DATA STANDARD IMPLEMENTATIONS

6.1. Sponsor Defined Standardization Descriptions

No baseline flag was assigned to any of the domains that support baseline flag in the structure.

6.2. Differences between SEND Datasets and Study Report

1. Exposure data are included in the SEND dataset and not in the study report.

2. Reporting units in the SEND datasets and study report may be different. Neither the integrity nor the interpretation was impacted by the differences.

3. Dose-normalized values manually calculated for the study report (if applicable); are not included in SEND datasets.

4. The BGDY-BGENDY intervals in the dataset reflect the actual collection interval. Intervals may be combined in the study report.

5. Standard Deviation (SD) in the Summary Table of the study report has been rounded off to the next value in the study report. The xpt value may show the SD up to 3-4 decimal places.

6. Due to system limitation BG and BW domain is not showing the range from Day 1 till Day last of dosing phase.

7. Subject numbers in the study report may include leading zeros or an “M” or “F” to differentiate between Male and Female, respectively. The subject numbers used in the SEND datasets are consistent with those listed in the Demographic domain.

6.3. Nonstandard Electronic Data Submitted

Nonstandard electronic data are not part of this submission.

6.4. Legacy Data Conversion

Legacy data are not part of this submission.