Study Data Reviewer's Guide

Nonclinical

(nSDRG)

REPEAT-DOSE TOXICITY STUDY OF THREE LNP-FORMULATED RNA PLATFORMS ENCODING FOR VIRAL PROTEINS BY REPEATED INTRAMUSCULAR ADMINISTRATION TO WISTAR HAN RATS

Study ID: (b) (4) Study No. 38166

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1. nSDRG Introduction

This document provides context for the SEND tabulation dataset and terminology for (b) (4) Study 38166, in addition to what is provided in the define.xml file, to facilitate the FDA reviewer's and data manager's use of the dataset. It also includes a summary of SEND dataset conformance findings.

1.1 Study Protocol Title, Number and Report Version

Study Title	REPEAT-DOSE TOXICITY STUDY OF THREE LNP-FORMULATED RNA PLATFORMS ENCODING FOR VIRAL PROTEINS BY REPEATED INTRAMUSCULAR ADMINISTRATION TO WISTAR HAN RATS
Study Number	38166
Report Version	Final report and first amendment to final report

1.2 Summary of SEND Dataset Creation Process

In-life data, clinical pathology data and postmortem data were either directly collected using the Laboratory Information Management System (LIMS) Provantis 10.2.1 (Instem, Diamond Way Stone Business Park Stone, Staffordshire ST15 0SD, United Kingdom) or were retrospectively entered into Provantis or into excel spreadsheets (Microsoft, Redmond, WA, USA). Input from Provantis or excel spreadsheets via specific adapters was processed by Submit (Instem, Diamond Way Stone Business Park Stone, Staffordshire ST15 0SD, United Kingdom) to produce one integrated SEND dataset. Provantis, Submit and the specific adaptors are a validated system. All data that were retrospectively entered were QC checked. SENDView (Instem, Diamond Way Stone Business Park Stone, Staffordshire ST15 0SD, United Kingdom) was used to validate the SEND data.

1.3 SEND Dataset Verification

Data in the SEND dataset are an accurate representation of data in the study report for (b) (4) Study No. 38166. Any differences between the dataset and the report are described in section 6.2.

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2. Study Design

2.1 Study Design Summary

In (b) (4) study 38166, lipid nanoparticles-formulated RNA vaccines were given to male and female rats by intramuscular administration into the musculus biceps femoris at doses of 0 (buffer control), 10, 30 or 100 µg/animal on test days 1, 8 and 15 (groups 1, 2, 3, 4, 5 and 7) or on test days 1 and 8 (group 6). The recovery period was 3 weeks.

Group	Treatment	Dose Level µg/ animal	Number of administration sites	Dose Volume µL/ site	Dose Volume µL/ animal	Number of Animals					
						Main		Recovery		Satellite	
						Male	Female	Male	Female	Male	Female
1	(Buffer)	0	2	100	200	10	10	5	5	3	3
2	BNT162a1	30	1	60	60	10	10	5	5	3	3
3	BNT162a1	10	1	20	20	10	10	5	5	3	3
4	BNT162b1	30	1	60	60	10	10	5	5	3	3
5	BNT162b1	100	2	100	200	10	10	5	5	3	3
6	BNT162c1	30	1	70	70	10	10	5	5	3	3
7	BNT162b2	100	2	100	200	10	10	5	5	3	3

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2.2 Trial Design Domain Overview

The following diagram illustrates the trial design.

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	ARMCD	ARM	Screening	Treatment	Recovery	SETCD	SET
1	1	Group 1	Screening	Group 1:Control	-	1	Group 1
1	1R	Group 1R	Screening	Group 1:Control	Recovery	1R	Group 1R
1	1S	Group 1S	Screening	Group 1:Control	-	1S	Group 1S
2	2	Group 2	Screening	Group 2:30 µg/animalBNT162a1	-	2	Group 2
2	2R	Group 2R	Screening	Group 2:30 µg/animalBNT162a1	Recovery	2R	Group 2R
2	2S	Group 2S	Screening	Group 2:30 µg/animalBNT162a1	-	2S	Group 2S
3	3	Group 3	Screening	Group 3:10 µg/animalBNT162a1	-	3	Group 3
3	3R	Group 3R	Screening	Group 3:10 µg/animalBNT162a1	Recovery	3R	Group 3R
3	3S	Group 3S	Screening	Group 3:10 µg/animalBNT162a1	-	3S	Group 3S
4	4	Group 4	Screening	Group 4:30 µg/animalBNT162b1	-	4	Group 4
4	4R	Group 4R	Screening	Group 4:30 µg/animalBNT162b1	Recovery	4R	Group 4R
4	4S	Group 4S	Screening	Group 4:30 µg/animalBNT162b1	-	4S	Group 4S

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Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	ARMCD	ARM	Screening	Treatment	Recovery	SETCD	SET
5	5	Group 5	Screening	Group 5:100 µg/animalBNT162b1	-	5	Group 5
5	5R	Group 5R	Screening	Group 5:100 µg/animalBNT162b1	Recovery	5R	Group 5R
5	5S	Group 5S	Screening	Group 5:100 µg/animalBNT162b1	-	5S	Group 5S
6	6	Group 6	Screening	Group 6:30 µg/animalBNT162c1	-	6	Group 6
6	6R	Group 6R	Screening	Group 6:30 µg/animalBNT162c1	Recovery	6R	Group 6R
6	6S	Group 6S	Screening	Group 6:30 µg/animalBNT162c1	-	6S	Group 6S
7	7	Group 7	Screening	Group 7:100 µg/animalBNT162b2	-	7	Group 7
7	7R	Group 7R	Screening	Group 7:100 µg/animalBNT162b2	Recovery	7R	Group 7R
7	7S	Group 7S	Screening	Group 7:100 µg/animalBNT162b2	-	7S	Group 7S

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3. Standards, Formats, and Terminologies and their Versions

3.1 Standards Used

Standard or Dictionary	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND Implementation Guide	3.1
Controlled Terminology	CDISC SEND Controlled Terminology	2020-06-26
Data Definition file	CDISC DEFINE	2.0

3.2 Rationale for Standards Selection

The standards versions used were supported by FDA at the time of dataset creation.

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3.3 Nonstandard Terminology

The following nonstandard terminology was used:

Dataset Name	Variable	Codelist	Term Used	Meaning
LB	LBTEST	Laboratory Test Name	Standard Volume	additional variable for volume of urine (in the study report, 2 variables were used to report the volume of urine)
LB	LBTESTCD	Laboratory Test Code	STDUVOL	additional variable for volume of urine
LB	LBORRESU, LBSTRESU	Unit	mL/animal/16 h	additional unit for volume of urine
LB	LBTEST	Laboratory Test Name	Infectivity	Pseudovirus neutralization activity test, see 4.2 Dataset Explanation: LB
LB	LBTESTCD	Laboratory Test Code	INFECTIV	Pseudovirus neutralization activity test
MI	MISTRESC	NONNEO	PLASMACYTOSIS	a condition in which there is an unusually large proportion of plasma cells in tissues, exudates, or blood
MI	MISTRESC	NONNEO	Spermatid Giant Cells	round cells with multiple nuclei that appeare to arise by widening of narrow intercellular bridges that normally connect spermatogenic epithelial cells
MI	MISTRESC	NONNEO	Nematodiasis	infection with nematodes

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4. Description of Study Datasets

4.1 Dataset Summary

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
TS	Trial Summary			Special Purpose
TE	Trial Elements			Special Purpose
TA	Trial Arms			Special Purpose
TX	Trial Sets			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
CO	Comments			Special Purpose
EX	Exposure			Interventions
DS	Disposition			Events
BW	Body Weight			Findings
BG	Body Weight Gain			Findings
CL	Clinical Observations			Findings
FW	Food and Water Consumption			Findings
LB	Laboratory Test Results			Findings
MA	Macroscopic Findings	x	x	Findings
OM	Organ Measurements			Findings
MI	Microscopic Findings	x	x	Findings
VS	Vital Signs			Findings

4.2 Dataset Explanation

4.2.1 BG-Body Weight Gain

Due to technical reasons the data in the BG domain is in g, although the corresponding data in the report is in %. Additionally, cumulative weight gains are described in the report, whereas daily or weekly weight gains are described in the SEND dataset. The underlying data for study report and SEND dataset are the same, only the way of presentation differs.

4.2.2 CO-Comments

The expected variable CODTC is empty for all records because comments are related to a specific parent record or group of parent records in a domain.

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4.2.3 DS-Disposition

The expected variable DSUSCHFL is empty for all records because all dispositions based upon a schedule defined in the protocol.

4.2.4 LB-Laboratory Test Results

A Pseudovirus neutralization activity test was performed to functionally characterize the elicited SARS-CoV-2 spike protein specific antibody response. The neutralizing capacity of sera was assessed by measuring the percentage VSV/SARS-CoV-2-S pseudovirus infection in conjunction with Vero 76 cells as target (LBTEST: Infectivity).

The times presented in the LBDTC do not represent the times of specimen collection; instead, they represent the times when the LIMS was prepared for data collection.

The expected variable LBUSCHFL is empty for all records because all specimen collections based upon a schedule defined in the protocol.

pH, qualitative measurements (Urinalysis: Epithelial Cells, Leukocytes, Color, Crystals, Further constituents, Occult Blood and Organisms) and some semi-quantitative measurements (Urinalysis: Bilirubin, Ketones and Nitrite) have no unit. The following semi-quantitative determination levels were used:

neg = negative

pos = positive

+ = 'small amount' of analyte

++ = 'moderate amount' of analyte

+++ = 'large amount' of analyte

For microscopic examinations of urine samples, the semi-quantitative determination levels were:

0 = None found in any field examined

+ = Few found in some fields examined

++ = Few in all fields examined

+++ = Many in all fields examined

The meaning of abbreviations in LBORRES is:

LC = lemon -coloured

SC = straw-coloured

Some test names in study report are different from test names in SEND dataset because CDISC terminology is used in SEND dataset. Most of these relationships are evident. Some

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relationships between the test names of study report and SEND dataset are explained in the following table:

study report	SEND dataset
Haemoglobin (Urinalysis)	Occult Blood

Some units in study report are different from units in SEND dataset because CDISC terminology is used in SEND dataset. The following relationships exist between the units of study report and SEND dataset:

study report	SEND dataset	conversion
µmol/L	umol/L	1:1
x10E3/µL	10^9/L	1:1
x10E6/µL	10^12/L	1:1

4.2.5 OM-Organ Measurements

The times presented in the OMDTC do not represent the times of specimen collection; instead, they represent the times when the LIMS was prepared for data collection.

4.2.6 MA-Macroscopic Findings

Laterality for bilateral organs is only mapped if the report contains proper information.

4.2.7 MI-Microscopic Findings

Laterality for bilateral organs is only mapped if the report contains proper information.

4.3 Use of Supplemental Qualifiers

Dataset Name	Associated Dataset	Qualifiers Used
SUPPMA	MA Macroscopic Findings	Modifiers that were part of MAORRES for which SEND variables have not yet been developed.
SUPPMI	MI Microscopic Findings	Modifiers that were part of MIORRES for which SEND variables have not yet been developed.

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5. Data Standards Validation Rules, Versions, and Conformance Issues

5.1 Validation Outcome Summary

There were no conformance errors or issues that impacted the quality of these SEND datasets.

5.2 FDA SEND Validation Rules Version

Rule conformance to SEND 3.1 was evaluated using SENDView (Instem, Diamond Way Stone Business Park Stone, Staffordshire ST15 0SD, United Kingdom) version 4.0.1.1, which includes checks for conformance against the FDA Specific SEND Validation Rules, Version 2.1.

5.3 Errors

No errors with respect to FDA relevant rules were reported in SENDView.

5.4 Warnings

The following warnings with respect to FDA relevant rules were reported in SENDView:

Rule	Message	Domain(s)	Count	Explanation
CG0021	LBTESTCD entry is not a controlled term in the codelist 'LBTESTCD'	LB	770	The LBTESTCD list was extended, see 3.3.
CG0021	LBTEST entry is not a controlled term in the codelist 'LBTEST'	LB	770	The LBTEST list was extended, see 3.3.
CG0021	LBSTRESU value not found in 'Unit' extensible codelist	LB	210	The Unit list was extended, see 3.3.
CG0021	LBORRESU value not found in 'Unit' extensible codelist	LB	210	The Unit list was extended, see 3.3.
FDAB012	Original Units (LBORRESU) should not be NULL, when Result or Finding in Original Units (LBORRES) is provided	LB	1291	Qualitative measurements and some semi-quantitative measurements have no unit, see 4.2.2.
FDAB013	No baseline flag record.	VS	Entire domain	No predose values were collected for body temperature.

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6. Sponsor Decisions Related to Data Standards Implementations

6.1 Sponsor Defined Standardization Descriptions

There were no custom domains or custom endpoints for this study.

6.2 Differences between SEND Datasets and Study Report

Data in the SEND dataset are an accurate representation of data in the study report, with the following differences noted:

1) Terminology used during data collection is used in the study report. That terminology was converted to SEND Controlled Terminology during SEND dataset creation.

2) Derived group-related mean values (for example mean body weight) were not included in the SEND dataset because this information can be derived from individual data in the SEND dataset.

3) Ratios (for example Albumin/Globulin ratio) that can be derived from other data in the SEND dataset were not included in the SEND dataset.

4) The report is not always using the same units as the dataset. For the BG domain, the units were converted from % to g. For the FW domain, the units were converted from (g/kg b.w./day) to (g/animal/day). For all other domains, the units were merely 1:1 mapped to CDISC submission terminology without unit conversions.

There are no other differences between the SEND Dataset and the Study Report

6.3 Nonstandard Electronic Data Submitted

There were no nonstandard electronic data that were part of this submission.

6.4 Legacy Data Conversion

No legacy data conversion was performed.

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