Study Data Reviewer's Guide

Nonclinical

(nSDRG)

24 Week Toxicity Study of Vector A and Vector B Following a Single Intravenous Injection in Adult Cynomolgus Macaques

(VECTORSTUDYU1)

Redacted Sponsor

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Abbreviations

Acronym	Translation
SDRG	Study Data Reviewer's Guide
SEND	Standard for Exchange of Nonclinical Data
LIMS	Laboratory Information Management System
CDISC	Clinical Data Interchange Standards Consortium

1 nSDRG Introduction

This document provides context for the SEND tabulation datasets and terminology for Study VECTORSTUDYU1, in addition to what is provided in the Data definitions (define.xml) file, to facilitate the FDA reviewer's and Data manager's use of the datasets. It also includes a summary of SEND dataset conformance findings.

1.1 Study Protocol Title, Number, and Report Version

Study Title	24 Week Toxicity Study of Vector A and Vector B Following a Single Intravenuous Injection in Adult Cynomogulus Macaques
Study Number	VECTORSTUDYU1
Study Version	1.0

1.2 Summary of SEND Dataset Creation Process

For study VECTORSTUDYU1, all in all in-life, clinical pathology, postmortem data were collected with LIMS 1 (Redacted Test Facility). Bioanalytical and Immunogenicity Assessments were captured by instrument software (Redacted Lab B).). Input (raw data extracted into Excel) from each of the LIMS and instrument software via LIMS-specific adaptors was processed by the Sponsor using Excel, R 3.4.2, Visual Define-XML Editor (v1.1) to produce one integrated SEND dataset with a define.xml, a validation report and LIMS terms mapped to controlled terminology.

1.3 SEND Dataset Verification

Data in the SEND datasets is a representative dataset of VECTORSTUDYU1 for the purposes of the SEND for CBER Proof of Concept Pilot; a nonclinical study report will not be submitted for this pilot. Verification procedures and documentation supporting this are available upon request.

2 Study Design

2.1 Study Design Summary

The following diagram illustrates the Experimental Design copied from the study plan:

Experimental Design

Group[a,b]	No. of Animals Males	Dose Level (vg/kg)	Dose Concentration (vg/mL)
1 (Vector A)	3	$1.024x10^{13}$	$1.28x10^{13}$
5 (Vector B)	3	$1.024x10^{13}$	$1.28x10^{13}$

vg = Vector genomes

2.2 Trial Design Domain Overview

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	**ARMCD**	**ARM**	**Acclimation**	**TREATMENT**	**Observation**	**SETCD**	**SET**
1	A1	1E13 vg/kg, Vector A, Single injection, intravenous bolus	Acclimation	1E13 vg/kg, Vector A	Postdose Observation	S1	1E13 GC/kg, Vector A, Single injection, intravenous bolus
5	A2	1E13 vg/kg, Vector B, Single injection, intravenous bolus	Acclimation	1E13 vg/kg, Vector B	Postdose Observation	S2	1E13 GC/kg, Vector B, Single injection, intravenous bolus

3 Standards, Formats, and Terminologies and their Versions

3.1 Standards Used

Dataset Component	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND Implementation Guide	SENDIG-3.1
Controlled Terminology	CDISC SEND Controlled Terminology	SEND Terminology 2019-03-29
Data Definition file	CDISC DEFINE	2.0.0
Validation Rules	FDA Business Rules	FDA Validator Rules 1.3

3.2 Rationale for Standards Selection

The standards and versions were selected on the basis of assessing the fitness of SENDIG 3.1 for the SEND for CBER proof of concept pilot.

3.3 Nonstandard Terminology

Nonstandard terminology is identified and mapped in table below:

DOMAIN	Variable	Codelist	Term	Decoded	Rationale
EX	EXDOSU	Units	10^13 vg/kg	10^13 vector genomes/kilogram	SEND CT does not have terminology for vector dosing
LB	LBORRESU	Units	E3/uL	10^9/L	As reported by Redacted Test Facility
LB	LBORRESU	Units	E6/uL	10^12/L	As reported by Redacted Test Facility

DOMAIN	Variable	Codelist	Term	Decoded	Rationale
LB	LBORRESU	Units	Ratio	RATIO	As reported by Redacted Test Facility
PC	PCORRESU	PK Units of Measure	% of normal	% of normal	Normalized data was reported by Test Site B
PC	PCORRESU	PK Units of Measure	copies/ug	copies/ug	SEND CT does not have terminology for DNA/RNA quantitation
PC	PCSTRESU	PK Units of Measure	DNA copies/ug	DNA copies/ug	SEND CT does not have terminology for DNA/RNA quantitation
PC	PCSTRESU	PK Units of Measure	RNA copies/ug	RNA copies/ug	SEND CT does not have terminology for DNA/RNA quantitation

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
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
DS	Disposition			Events
BW	Body Weights			Findings
CL	Clinical Observations			Findings
LB	Laboratory			Findings
MA	Macroscopic Findings	X	X	Findings
MI	Microscopic Findings	X	X	Findings
PC	Pharmacokinetics Concentrations			Findings

4.2 Dataset Explanation

Data collected during the acclimation/pretreatment period is contained in the SEND datasets, but not necessarily in the study report.

The SEND datasets may contain different significant digits and/or decimal places than what is presented in the report.

All explanations of abbreviations are included within the study report.

4.2.1 DM-Demographics

- AGETXT is an approximation from age range specified in the study plan.

4.2.2 TS-Trial Summary

- All variables are populated or derived as per the study plan and amendments, therefore they contain only planned information, not actual.
- AGE is an approximation because the study plan states “approximately” or “at least”.

4.2.3 DS-Disposition

- Timing Variables:
  - This dataset populates the BWDTC with the of date data collection, not the date/time.
- VISITDY is being used in the following ways as per SENDIG v3.1:
  - To indicate the planned day of disposition. If the disposition was unplanned, VISITDY is blank.
- -NOMDY is being used in the following ways as per SENDIG v3.0:
  - To group observations that may occur on different days to a nominal study day for the purposes of tabulation.

4.2.4 BW-Body Weight

- Timing Variables:
  - This dataset populates the BWDTC with the of data collection, not the date/time.
- VISITDY is being used in the following ways as per SENDIG v3.1:

4.2.5 CL-Clinical Observations

- Timing Variables:
  - This dataset populates the CLDTC with the of date sample collection dates, not the date/time.
- The SEND datasets include the NORMAL findings.
- VISITDY is being used in the following ways as per SENDIG v3.1:
  - To indicate the planned day of collection. If the observation was unplanned, VISITDY is blank.
- -NOMDY is being used in the following ways as per SENDIG v3.0:
  - To group observations that may occur on different days to a nominal study day for the purposes of tabulation.

4.2.6 LB-Laboratory Test Results

- Timing Variables:
  - This dataset populates the LBDTC with the of date sample collection dates, not the date/time.
  - VISITDY is being used in the following ways as per SENDIG v3.1:
    - To indicate the planned day of collection. If the observation was unplanned, VISITDY is blank.

4.2.7 MA-Macroscopic Findings

- Timing Variables:
  - This dataset populates the MADTC with the of data collection dates, not the date/time.
- Tissue Comments:
  - Tissue comments in the microscopic pathology report which noted whether tissues were collected and did not addition interpretation, they were not included in the SEND dataset in the CO-Comments Domain
  - Measurements (dimensions) of lesions appear in –ORRES are not carried over to –STRESC or CO-Comments Domain

4.2.8 MI-Microscopic Findings

- Timing Variables:
  - This dataset populates the MIDTC with the of data collection dates, not the data/time.
- The SEND datasets include the UNREMARKABLE findings.

4.2.9 PC-Pharmacokinetics Concentrations

- The PC Domain is a representation individual animal concentration data for PROTEIN Expression and Biodistribution Data that is summarized report
  - VISITDY is being used in the following ways as per SENDIG v3.1:
    - VISITDY is the nominal day.

4.3 4.3 Use of Supplemental Qualifiers

No supplemental qualifiers are used.

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

5.1 5.1 Validation Outcome Summary

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

5.2 5.2 FDA SEND Validation Rules Version

Rule conformance to SENDIG-3.1 was evaluated using FDA Specific SEND Validation Rules, Version FDA Validator Rules 1.3

5.3 5.3 Errors

No errors in the standardized dataset were identified.

Seven warnings were identified using the Pinnacle 21 (v3.0.2) Community validator; four that we believe to be erroneous and three are related to modelling a custom IS Domain for the purposes of the SEND for CBER proof of concept pilot. Refer to the details below.

5.4 5.4 Warnings

The following warnings were identified:

Publisher Business Rule ID	FDA Validator Rule ID	Message	Domain	Explanation
CG0021	CT2002	EXDOSU value not found in 'Unit' extensible codelist	EX	Warning is not correct, "10^13 vg/kg" is in Extended Codelist outlined in Define.xml
CG0021	CT2002	DOMAIN value not found in 'SEND Domain Abbreviation' extensible codelist	IS	IS is being modelled as a custom domain for the purposes of the SEND for CBER proof of concept pilot. Domain was modelled after LB domain
CG0330	SD1079	Variable is in wrong order within domain	IS	IS is being modelled as a custom domain for the purposes of the SEND for CBER proof of concept pilot. Domain was modelled after LB domain
CG0303	SE0063	SEND/dataset variable label mismatch	IS	IS is being modelled as a custom domain for the purposes of the SEND for CBER proof of concept pilot. Domain was modelled after LB domain
CG0021	CT2002	LBORRESU value not found in 'Unit' extensible codelist	LB	Warning is not correct, "E3/uL", “E6/uL”, and “Ratio” are in Units Extended Codelist outlined in Define.xml
CG0021	CT2002	PCORRESU value not found in 'PK Units of Measure' extensible codelist	PC	Warning is not correct, "% of normal" and "copies/ug" are in PK Units of Measure Extended Codelist outlined in Define.xml
CG0021	CT2002	PCSTRESU value not found in 'PK Units of Measure' extensible codelist	PC	Warning is not correct, "DNA copies/ug" and "RNA copies/ug" are in PK Units of Measure Extended Codelist outlined in

				Define.xml

6 6. Sponsor Decisions Related to Data Standard Implementations

6.1 6.1 Sponsor-Defined Standardization Descriptions

- The SEND Datasets include Permissible variables when all values for the variable are null. The SEND Implementation Guide section 4.1.3 indicates this is acceptable.
- In the DM domain, RFSTDTC is the first day the animal was dosed.
- In the TS domain, the AGE variable is populated as per study plan.
- Baseline values are identified as Study Day 1 for BW and LB domains.
- IS Domain, which is currently not modelled in SENDIG 3.1, was modeled after SDTMIG v3.3
- No baseline flag was assigned to PC or IS domains

6.2 6.2 Differences between SEND Datasets and Study Report

For domain specific differences, see Section 4.2 Data Explanation.

6.3 6.3 Nonstandard Electronic Data Submitted

Not applicable.

6.4 6.4 Legacy Data Conversion

Not applicable.