Study Data Reviewer's Guide

Nonclinical

(nSDRG)

CARDIOVASCULAR SAFETY EVALUATION OF ORALLY ADMINISTERED DRUG-X FREE FORM IN BEAGLE DOGS

Testing Facility Study Number: 3-1-PILOT

Sponsor Study Number: 12345

Sponsor, Inc.

123 Main Street, USA

CONTENTS

1. NSDRG INTRODUCTION

1.1. Study Protocol Title, Number and Report Version

Study Title	Cardiovascular Safety Evaluation of Orally Administered Drug-X Free Form in Beagle Dogs
Testing Facility Study Number	3-1-PILOT
Sponsor Study Number	12345
Report Version	Audited Draft Report

1.2. Summary of SEND Dataset Creation Process

In life and clinical pathology data were collected using <system redacted>. Electrocardiograms, body temperatures, and blood pressure measurements were collected using <system redacted>. CV, EG, and VS domains were generated using <system redacted>. Plasma drug concentrations were determined by Sponsor, Inc. All data were processed by <system redacted> to produce one integrated SEND dataset package. The define.xml file was created using <system redacted>.

The <system redacted> is validated in accordance with FDA 21 CFR Part 11.

1.3. SEND Dataset Verification

Data in the SEND datasets are an accurate representation of the data for Testing Facility Study Number 3-1-PILOT. Any differences between the datasets and the study report are described in Section 6.2.

2. STUDY DESIGN

2.1. Study Design Summary

Treatment Number	Treatment	Dose Level (mg Drug-X/kg)	Dose Concentration (mg Drug-X/mL)	Dose Volume (mL/kg)	Number of Male Animals[a]
1	Vehicle	0	0	5	6
2	Drug-X	20	4	5	6
3	Drug-X	50	10	5	6
4	Drug-X	150	30	5	6

[a]The same 6 animals received all 4 treatments according to a Latin square design with at least a 10-day washout between treatments.
[b]Body temperature, blood pressure, heart rate, and the electrocardiogram (ECG) were monitored continuously for at least 2 hours prior to dosing and for at least 24 hours postdose.

Treatments were administered according to the following schedule:

Animal No.	Dose Level (mg Drug-X/kg)			
	0	20	50	150
1001	Day 1	Day 11	Day 22	Day 36
1002	Day 36	Day 22	Day 11	Day 1
1003	Day 1	Day 22	Day 11	Day 36
1004	Day 36	Day 11	Day 22	Day 1
1005	Day 11	Day 1	Day 36	Day 22
1006	Day 22	Day 36	Day 1	Day 11

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	WASHOUT	TREATMENT	WASHOUT	TREATMENT	WASHOUT	TREATMENT	WASHOUT	SETCD	SET
1	1	0/20/50/150 mg Drug-X/kg	Screening	0 mg Drug-X/kg	WO_10D	20 mg Drug-X/kg	WO_11D	50 mg Drug-X/kg	WO_14D	150 mg Drug-X/kg	WO_8D	1	0/20/50/150 mg Drug-X/kg
2	2	150/50/20/0 mg Drug-X/kg	Screening	150 mg Drug-X/kg	WO_10D	50 mg Drug-X/kg	WO_11D	20 mg Drug-X/kg	WO_14D	0 mg Drug-X/kg	WO_8D	2	150/50/20/0 mg Drug-X/kg
3	3	0/50/20/150 mg Drug-X/kg	Screening	0 mg Drug-X/kg	WO_10D	50 mg Drug-X/kg	WO_11D	20 mg Drug-X/kg	WO_14D	150 mg Drug-X/kg	WO_8D	3	0/50/20/150 mg Drug-X/kg
4	4	150/20/50/0 mg Drug-X/kg	Screening	150 mg Drug-X/kg	WO_10D	20 mg Drug-X/kg	WO_11D	50 mg Drug-X/kg	WO_14D	0 mg Drug-X/kg	WO_8D	4	150/20/50/0 mg Drug-X/kg
5	5	20/0/150/50 mg Drug-X/kg	Screening	20 mg Drug-X/kg	WO_10D	0 mg Drug-X/kg	WO_11D	150 mg Drug-X/kg	WO_14D	50 mg Drug-X/kg	WO_8D	5	20/0/150/50 mg Drug-X/kg
6	6	50/150/0/20 mg Drug-X/kg	Screening	50 mg Drug-X/kg	WO_10D	150 mg Drug-X/kg	WO_11D	0 mg Drug-X/kg	WO_14D	20 mg Drug-X/kg	WO_8D	6	50/150/0/20 mg Drug-X/kg

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	2019-06-28
Data Definition File	CDISC DEFINE.XML	2.0

3.2. Rationale for Standards Selection

SEND Implementation Guide (IG) v3.1 is the current version required by the FDA Study Data Standards Catalog for studies of this type and study start date. The version of Controlled Terminology (CT) selected was the most recent version available in <system redacted> as implemented at the CRO at the time of dataset generation. Define.xml v2.0 is the current specification for data definition files listed in the FDA Data Standards Catalog.

3.3. Nonstandard Terminology

For variables requiring the use of a CT codelist, the terminology used on study was mapped to a synonymous term in the codelist, to the greatest extent possible. When a synonymous term was not available in the extensible codelist, a nonstandard term was used. In these instances, the case-sensitivity and other characteristics of the codelist were followed as closely as possible when selecting extended terminology for use in the SEND dataset.

The following nonstandard terminology was used:

Dataset Name	Variable	Codelist	Extended Term	Term Definition
EG	EGTESTCD; EGTEST	ECG Test Code; ECG Test Name	QTCSAG; QTc Interval, Modified Spence, Aggregate	A QT aggregate interval corrected for heart rate using Spence's formula based on analysis of covariance and modified by Miyazaki and Tagawa's rate correction technique.
LB	LBTESTCD; LBTEST	Laboratory Test Code; Laboratory Test Name	WBCAGGLU; Leukocyte Agglutination	A measurement of leukocyte agglutination (small aggregates of 3-15 leukocytes) in a biological specimen.
LB	LBTESTCD; LBTEST	Laboratory Test Code; Laboratory Test Name	MONOAT; Monocytes Atypical	A measurement of atypical monocytes in a biological specimen.
LB	LBTESTCD; LBTEST	Laboratory Test Code; Laboratory Test Name	PYKNOTIC; Pyknotic Cells	A measurement of leukocytes with dense, rounded to fragmented nuclei in a biological specimen.
LB	LBTESTCD; LBTEST	Laboratory Test Code; Laboratory Test Name	UNPOIKIL; Unclassified Poikilocytosis	A measurement of unclassified poikilocytes (irregularly shaped erythrocytes not otherwise classified) in a biological specimen.

4. DESCRIPTION OF STUDY DATASETS

4.1. Dataset Summary

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
TS	Trial Summary			Trial Design
TE	Trial Elements			Trial Design
TA	Trial Arms			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			Events
BW	Body Weight			Findings
CL	Clinical Observations	X		Findings
CV	Cardiovascular Test Results			Findings
EG	ECG Test Results			Findings
LB	Laboratory Test Results			Findings
PC	Pharmacokinetic Concentrations			Findings
VS	Vital Signs			Findings

4.2. Dataset Explanation

4.2.1. Latin Square Study Design

ELEMENT is used to describe the treatment and SE contains the ELEMENT start and end timing for each subject. SESTDTC can be matched to --RFTDTC for each Finding domain to determine the treatment associated with each finding.

4.2.2. Nominal Label (--NOMLBL)

Due to the Latin Square study design, the Nominal Label (--NOMLBL) variable was populated for data collected during the treatment period of the study using the dose level and time point to allow for grouping by dose level rather than study day. This coincides with the report presentation and summarization of data by dose level.

On other occasions when data were included in the datasets but not the study report, --NOMLBL was populated according to the time period of the study (*i.e.*, per protocol physical examinations were performed pretest on Day -4; --NOMLBL was populated as Pretest).

4.2.3. Baseline Flags

Baseline flag (--BLFL) is populated with the last non-missing value prior to the first dose administration in the BW and LB domains.

Baseline flag (--BLFL) is populated with the last non-missing value prior to dose administration for each treatment for each animal in the CV, EG, and VS domains. This was done to accurately represent the Latin square study design as each treatment is considered a different analysis period with a separate baseline designation.

4.2.4. EX-Exposure

The EX domain contains the nominal dose administered. The EX domain contains one record per animal per dose.

4.2.5. CL-Clinical Observations

The CL domain includes clinical observations and physical examinations.

4.2.6. EG-ECG Test Results

The EG domain includes electrocardiographic measurements.

The Date/Time of ECG Collection (EGDTC) and End Date/Time of ECG Collection (EGENDTC) are presented to the second reflecting the raw data in the data collection system.

4.2.7. LB-Laboratory Test Results

As there is no CT codelist for LBMETHOD in SEND, this variable was populated using terms found in the SDTM Controlled Terminology list.

The date or date/time presented in LBDTC is the date or date/time the sample placeholder was created in the data collection system, and is not the date or date/time of sample collection.

Coded laboratory test values are decoded in LBORRES and LBSTRESC for ease of review.

4.2.8. PC-Pharmacokinetic Concentrations

PCTPTNUM is populated with a numeric representation of the nominal times for sample collection.

4.2.9. SE-Subject Elements

Only dates are provided in SESTDTC and SEENDTC due to default system functionality.

4.2.10. TS-Trial Summary

All TSPARMCDs are populated using planned information from the study protocol, with the exception of the TSPARMCDs representing dates. All dates are populated using actual dates from the study report.

TSPARMCD	TSPARM	Definition
EXPSTDTC	Experimental Start Date	Date of animal transfer to study
EXPENDTC	Experimental End Date	Date the last animal was removed from study
DOSENDTC	End Date/Time of Dose Interval	Last date an animal was dosed on study
DOSSTDTC	Start Date/Time of Dose Interval	First date an animal was dosed on study
STSTDTC	Study Start Date	Date on which the Study Director signed the protocol
STENDTC	Study End Date	Date on which the final study report was signed

4.2.11. VS-Vital Signs

The VS domain includes body temperature.

The Date/Time of Measurement (VSDTC) and End Date/Time of Measurement (VSENDTC) are presented to the second reflecting the raw data in the data collection system.

4.2.12. CV-Cardiovascular Test Results

The CV domain includes blood pressure and the blood pressure derived heart rate.

The Date/Time of Cardiovascular Test (CVDTC) and End Date/Time of Cardiovascular Test (CVENDTC) are presented to the second reflecting the raw data in the data collection system.

4.3. Use of Supplemental Qualifiers

Dataset Name	Variable Name (QNAM)	Variable Label (QLABEL)	Description
SUPPCL	CLRESMOD	Result Modifiers	CLRESMOD contains modifiers from CLORRES for which SEND variables have not yet been developed.

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

The SEND datasets were evaluated for conformance using the SEND Checker functionality within <system redacted>and the Pinnacle 21 Community dataset validation tool. The define.xml file was evaluated for conformance using the Pinnacle 21 Community dataset validation tool.

5.1. Validation Outcome Summary

Pinnacle 21 Community identified no errors in the SEND datasets, but an error in the define.xml file which is detailed in Section 5.3. Pinnacle 21 Community identified dataset warnings which are detailed in Section 5.4. No warnings were identified for the define.xml file.

5.2. FDA SEND Validation Rules Version

Rule conformance to SENDIG 3.1 was evaluated using Pinnacle 21 Community, Version 3.0, which includes checks for conformance against published FDA Business and Validator Rules.

5.3. Errors

Pinnacle 21 Community identified no errors in the SEND datasets.

Pinnacle 21 Community identified an error in the define.xml which is explained in the following table.

Define.xml Warnings		
Rule	**Message**	**Explanation**
DD0118	NCI Code 'C71620' for Codelist 'Unit' on Variable 'VSORRESU' and Variable 'VSTRESU' does not match NCI Code 'C66770' for Standard Codelist 'Units for Vital Signs Results' for Variable 'VSORRESU' and Variable 'VSSTRESU'	This is an invalid error. Pinnacle 21 checked the VSORRESU and VSSTRESU variables against the 'Unit for Vital Signs Results' codelist (NCI Code C66770) rather than 'Unit' codelist (NCI Code C71620) required by SENDIG v3.1.

5.4. Warnings

Pinnacle 21 Community identified warnings in the SEND datasets which are explained in the following table.

SEND Dataset Warnings			
Rule	**Message**	**Domain(s)**	**Explanation**
CG0021	EGSTRESC value not found in 'ECG Result' extensible codelist	EG	Numeric results in EGSTRESC should not follow the 'ECG Result' extensible codelist; therefore, this warning is considered to be invalid.
CG0021	EGTEST value not found in 'ECG Test Name' extensible codelist	EG	EGTEST values were extended to include test names that are not currently available. See Section 3.3 for further details.
CG0021	EGTESTCD value not found in 'ECG Test Code' extensible codelist	EG	EGTESTCD values were extended to include test codes that are not currently available. See Section 3.3 for further details.
CG0021	LBTEST value not found in 'Laboratory Test Name' extensible codelist	LB	LBTEST values were extended to include test names that are not currently available. See Section 3.3 for further details.
CG0021	LBTESTCD value not found in 'Laboratory Test Code' extensible codelist	LB	LBTESTCD values were extended to include test codes that are not currently available. See Section 3.3 for further details.
FDAB046	No Trial Set with TCNTRL Parameter	TX	No TCNTRL parameter was assigned due to the Latin square study design and each SET containing a control treatment.

6. SPONSOR DECISIONS RELATED TO DATA STANDARDS IMPLEMENTATIONS

6.1. Sponsor Defined Standardization Descriptions

The SEND Datasets do not include permissible variables when all values for the variable are null.

The EX domain contains the nominal dose administered.

6.2. Differences between SEND Datasets and Study Report

Data in the SEND datasets are an accurate representation of data in the study report, with the exception of the differences noted in the following sections.

6.2.1. Controlled Terminology

Terminology used during data collection was used in the study report. The SEND datasets contain CT where CT codelists are applicable. The terminology is mapped to CT using <system redacted>.

6.2.2. BW-Body Weight

Pretest body weights not included in the study report tables are included in BW.

6.2.3. CL-Clinical Observations

Pretest physical pretest clinical signs, and Day 44 clinical signs data not included in the study report tables are presented in CL.

6.2.4. CO-Comments

Contains additional comments recorded during data collection, but not included in the study report.

6.2.5. EG-ECG Test Results

The software used to generate the EG domain displays results to a higher precision than presented on the study report tables.

6.2.6. LB-Laboratory Test Results

Pretest data not included in the study report tables are presented in LB.

6.2.7. VS-Vital Signs

Additional pretest data not included in the study report tables are presented in VS.

The software used to generate the VS domain displays results to a higher precision than presented on the study report tables.

6.2.8. CV-Cardiovascular Test Results

The software used to generate the CV domain displays results to a higher precision than presented on the study report tables.

6.2.9. TS-Trial Summary

The table below illustrates the differences between the terminology used in the SEND dataset and the study report.

Report Terminology	TSPARMCD	TSPARM
Experimental Termination Date	EXPENDTC	Experimental End Date
Experimental Start Date	DOSSTDTC	Start Date/Time of Dose Interval
Study Initiation Date	STSTDTC	Study Start Date

6.3. Nonstandard Electronic Data Submitted

There are no nonstandard electronic data included as part of the submission.

6.4. Legacy Data Conversion

No legacy data was converted as a part of the submission.

APPENDIX 1: SCORING SCALES

The following scoring scales were used for data collection and reporting of Blood Cell Morphology.

When LBTESTCD = ACANT, SPHERO, SCHISTO, KERAT, or HOWJOL:

0	Does Not Meet Reporting Criteria
1+	2-5 cells
2+	6-10 cells
3+	≥26 cells

When LBTESTCD = POLYCHR:

0	Does Not Meeting Reporting Criteria
1+	4-12 cells
2+	13-25 cells
3+	≥26 cells

When LBTESTCD = STIPBASO, PAPPEN, HEINZ, ECCENTCY, or RBCGHOST:

0	Does Not Meeting Reporting Criteria
1+	1-3 cells
2+	4-10 cells
3+	≥11 cells

When LBTESTCD = UNPOIKIL:

0	Does Not Meeting Reporting Criteria
1+	3-10 cells
2+	11-20 cells
3+	≥21 cells

The following scoring scales were used for data collection and reporting of Clinical Chemistry.

When LBTESTCD = HEMOLYSI

Hemolytic Index Result Reference Guide

0	No Hemolysis
1	Slight Hemolysis
2	Hemolyzed
3	Moderately Hemolyzed
4 or 6	Grossly Hemolyzed
L	Lipemic
I	Icteric