Study Data Reviewer's Guide

Nonclinical

(nSDRG)

13-Week Repeat Dose Toxicity Study on PCDRUG in Rats

(PC201708)

PCLS Pharmaceuticals

CONTENTS

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 PC201708, 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	13-Week Repeat Dose Toxicity Study on PCDRUG in Rats
Study Number	PC201708
Study Version	1.0

1.2 Summary of SEND Dataset Creation Process

This is a synthetic dataset created based on published ranges for rat parameters, randomized data from public sources, and artificially adjusted to show signals as listed in Section 6.1. . Data was checked for SEND compliancy. Data were also validated against the FDA Specific SEND Validation Rules.

Domains from the SEND Submission template were converted to .csv files and uploaded into DSIMS, our commercial software solution that generates xpt files and define xml files. The standardized data were reviewed in ToxVision to ensure the datasets fit the needs of FDA nonclinical reviewers. SEND.xpt files were generated using an output function within DSIMS.

1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of the data for Study No. PC201708. Any differences between the data sets and the report are described in section 6.2. Verification procedures and documentation supporting this are available upon request.

2. Study Design

2.1 Study Design Summary

In study PC201708, PCDRUG was given to male and female rats by oral gavage at doses of 0 (vehicle), 2, 20, and 200 mg/kg/day for 13 weeks followed by a two week recovery period for all groups .Control group consisted of 15 subjects per sex and Treatment groups consisted of 15 subjects per sex. Following 13 weeks of treatment, all but 5 subjects per sex were euthanized. The remaining subjects continued onto a 2 week treatment-free recovery period, and were euthanized.

Group	Treatment	Dose Level	Dose Concentration	Dose Volume	Number of Animals					
					Main				TK	
					NonRecovery		Recovery			
					F	M	F	M	F	M
Group 1	Vehicle	0 mg/kg	0mg/kg		10	10	5	5	0	0
Group 2	PCDRUG	2 mg/kg	2mg/kg		10	10	5	5	5	5
Group 3	PCDRUG	20 mg/kg	20mg/kg		10	10	5	5	5	5
Group 4	PCDRUG	200 mg/kg	200mg/kg		10	10	5	5	5	5

2.2 Trial Design Domain Overview

Study Group	Trial Arms		Element in each Epoch			Trial Set	
SPGRPCD	**ARMCD**	**ARM**	**Prestudy**	**Treatment**	**Recovery**	**SETCD**	**SET**
Group 1	1	Vehicle Control	Acclimation	Vehicle Control		1	Group 1, Control, nonrecovery
	1R	Vehicle Control with recovery	Acclimation	Vehicle Control	Recovery	1R	Group 1, Control, recovery
Group 2	2	2 mg/kg PCDRUG	Acclimation	2 mg/kg PCDRUG, once daily		2	Group 2,2 mg/kg PCDRUG, nonrecovery
	2R	2 mg/kg PCDRUG with recovery	Acclimation	2 mg/kg PCDRUG, once daily	Recovery	2R	Group 2,2 mg/kg PCDRUG, recovery
	2	2 mg/kg PCDRUG	Acclimation	2 mg/kg PCDRUG, once daily		2TK	Group 2,2 mg/kg PCDRUG, TK
Group 3	3	20 mg/kg PCDRUG	Acclimation	20 mg/kg PCDRUG, once daily		3	Group 3,20 mg/kg PCDRUG, nonrecovery
	3R	20 mg/kg PCDRUG with recovery	Acclimation	20 mg/kg PCDRUG, once daily	Recovery	3R	Group 3,20 mg/kg PCDRUG, recovery
	3	20 mg/kg PCDRUG	Acclimation	20 mg/kg PCDRUG,		3TK	Group 3,20 mg/kg PCDRUG,

Study Group	Trial Arms		Element in each Epoch			Trial Set	
				once daily			TK
Group 4	4	200 mg/kg PCDRUG	Acclimation	200 mg/kg PCDRUG, once daily		4	Group 4,200 mg/kg PCDRUG, nonrecovery
	4R	200 mg/kg PCDRUG with recovery	Acclimation	200 mg/kg PCDRUG, once daily	Recovery	4R	Group 4,200 mg/kg PCDRUG, recovery
	4	200 mg/kg PCDRUG	Acclimation	200 mg/kg PCDRUG, once daily		4TK	Group 4,200 mg/kg PCDRUG, TK

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	SEND Implementation Guide Version 3.0
Controlled Terminology	CDISC SEND Controlled Terminology	SEND Terminology 2017-03-31
Data Definition file	CDISC DEFINE	2.0
Validation Rules	FDA Specific SEND Validation Rules	2.1

3.2 Rationale for Standards Selection

The standards and versions selected were the most current ones listed in FDA's Study Data Standards Catalog at the time of dataset creation.

3.3 Nonstandard Terminology

The following nonstandard terminology was used:

Dataset Name	Variable	Codelist	Term Used	Meaning
TS	TSPARM	STSPRM	Quality Assurance type	Type of quality assurance used in the study
TS	TSPARM	STSPRM	Lot Number	Lot number of the test article
TS	TSPARM	STSPRM	Percent Purity of Compound	Percent purity of the test article

4. Description of Study Datasets

The submitted SEND datasets represent a completed study. LIMS reports and not SEND datasets were used for data analysis. All data in the study report are included In the SEND dataset.

4.1 Dataset Summary

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
DS	Disposition			Events
BG	Body Weight Gains			Findings
BW	Body Weights			Findings
CL	Clinical Observations			Findings
DD	Death Diagnosis			Findings
EG	ECG Test Results			Findings
FW	Food and Water Consumption			Findings
LB	Laboratory Test Results			Findings
MA	Macroscopic Findings	X	X	Findings
MI	Microscopic Findings	X	X	Findings
OM	Organ Measurements			Findings
PC	Pharmacokinetics Concentrations			Findings
PM	Palpable Masses			Findings
PP	Pharmacokinetics Parameters			Findings
SC	Subject Characteristics			Findings
TF	Tumor Findings			Findings
VS	Vital Signs			Findings
EX	Exposure			Interventions
RELREC	Related Records			Relationship
CO	Comments			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
TA	Trial Arms			Trial Design
TE	Trial Elements			Trial Design
TS	Trial Summary			Trial Design
TX	Trial Sets			Trial Design

4.2 Dataset Explanation

4.3 Use of Supplemental Qualifiers

Dataset Name	Associated Dataset	Qualifiers Used
SUPPMA	Macroscopic Findings	Result Modifiers that were part of MAORRES
SUPPMI	Microscopic Findings	Result Modifiers that were part of MIORRES

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

5.1 Validation Outcome Summary

No errors in the standardized dataset were identified. A total of 942 warnings were identified by the Pinnacle 21 Community 2.2.1 Validator (formerly OpenCDISC). A total of 367 errors and 5 warnings were identified by the Pinnacle 21 Community 2.2.1 Validator against define file rules.

A total of 2436 warnings were identified by the FDA Nonclinical Validator Specifications version 2.1.

5.2 FDA SEND Validation Rules Version

Rule conformance to SEND 3.0 was evaluated using FDA Specific SEND Validation Rules, Version 2.1

5.3 Errors

5.3.1 Pinnacle21 Validator

The following errors were reported by the Pinnacle 21 Validator for the define file.

Rule	Message	Domain(s)	Count	Explanation
DD0038 (Define.xml)	Missing Value Level metadata for QVAL in Dataset 'SUPPMA' Missing Value Level metadata for QVAL in Dataset 'SUPPMI'	SUPPMA, SUPPMI	2	Pinnacle rule based on the PMDA published define rules for clinical studies. We therefore do not consider these errors to be applicable
DD0034 (Define.xml)	Unknown NCI Code value for Term in Codelist 'Specimen' Unknown NCI Code value for Term in Codelist 'SEND Trial Summary Parameter Test Name'	MA/MI/OM/TS	95	The NCI Code value present in the define file for each specimen or TSPARM are correct according to the Controlled Terminology list used in the study.
DD0073 (Define.xml)	Invalid Origin Type value	All	247	Pinnacle validator is using the PMDA defined rules that are not applicable for SEND. As per SEND IG 3.0, the allowed Origin values are “COLLECTED”, “DERIVED”, “OTHER” and “NOT AVAILABLE” (Section 3.2.2.1, page 19).

5.4 Warnings

5.4.1 Pinnacle21 Validator

The following warnings were reported by the Pinnacle 21 Validator:

Rule	Message	Domain(s)	Count	Explanation
FDAN212	Duplicate Records	FW, MA, MI	242	This Rule does not include a sufficient number of variables to determine uniqueness. For example, neither –ORRES nor –DY, nor other timing variables other than --DTC were included. We therefore do not consider these warnings to be applicable.
FDAN341	TSPARMCD value not found in 'SEND Trial Summary Parameter Test Code' extensible codelist TSPARM value not found in 'SEND Trial Summary Parameter Test Name' extensible codelist	TS	6	TSPARM and TSPARMCD are extensible variables, and in order to capture study information not included in the codelist, the parameter test names Lot Number, Percent Purity of Compound, Quality Assurance type, LOT, QATYPE, TRTPUR
FDAN341	EGSTRESC value not found in 'ECG Result' extensible codelist	EG	354	The values flagged are all numeric values which would not be included in a codelist. This is a bug in the Pinnacle 21 validator.
FDAN154	Missing value for LBORRESU, when LBORRES is provided	LB	120	Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in ORRESU for these measurements.
FDAN169	Missing value for LBSTRESU, when LBSTRESC is provided	LB	120	Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in STRESU for these measurements.
FDAN232	No result modifier (--RESMOD) qualifier for MA domain No result modifier (--	MA, MI	99	Not all Findings in MA or MI have modifiers in the original results, such as those listed as a single word or all text

Rule	Message	Domain(s)	Count	Explanation
	RESMOD) qualifier for MI domain			incorporated into the Standardized Result.
FDAN035	Variable is in wrong order within domain	EG	1	Pinnacle is expecting EGMETHOD before EGLEAD; but SEND IG 3.0 has EGLEAD before EGMETHOD. This order is wrong in SENDIG 3.0, but corrected in SENDIG 3.1. This does not affect reviewability of the EG data.
DD0059 (Define.xml)	Define.xml/CDISC dataset Description mismatch	PP, PC, MA	3	Issue with Pinnacle 21 validator where domain description is wrong. We therefore do not consider these warnings to be applicable
DD0024 (Define.xml)	Invalid Term in Codelist 'No Yes Response'	N/A	1	'N' is a correct term in Codelist 'No Yes Response', therefore this is a false positive
DD0039 (Define.xml)	Variable is in wrong order within Dataset 'EG'	EG	1	Pinnacle is expecting EGMETHOD before EGLEAD; but SEND IG 3.0 has EGLEAD before EGMETHOD. This order is wrong in SENDIG 3.0, but corrected in SENDIG 3.1. This does not affect reviewability of the EG data.

The following warnings were reported by the FDA Nonclinical rules Validator:

Rule	Message	Domain(s)	Count	Explanation
FDAN154	Missing value for LBORRESU, when LBORRES is provided	LB	1099	Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in ORRESU for these measurements.
FDAN169	Missing value for LBSTRESU, when LBSTRESC is provided	LB	1099	Certain LB parameters had qualitative results (Clarity, Color, etc.) or do not have associated units (pH, etc.). Thus, no unit was populated in STRESU for these measurements.

Rule	Message	Domain(s)	Count	Explanation
FDAN232	No result modifier (MARESMOD) qualifier for domain	MA	72	Not all Findings in MA have modifiers in the original results, such as those listed as a single word or all text incorporated into the Standardized Result.
FDAN232	No result modifier (MIRESMOD) qualifier for domain	MI	27	Not all Findings in MI have modifiers in the original results, such as those listed as a single word or all text incorporated into the Standardized Result.
FDAN212	Duplicate records	PC	120	This Rule does not include a sufficient number of variables to determine uniqueness. For example, neither –ORRES nor –DY, nor other timing variables other than --DTC were included. We therefore do not consider these warnings to be applicable.
FDAN154	Missing value for PMORRESU, when PMORRES is provided	PM	3	The PMORRES values were qualitative and did not have associated units.
FDAN169	Missing value for PMSTRESU, when PMSTRESC is provided	PM	3	The PMSTRESC values were qualitative and did not have associated units.
FDAN341	Value for TSPARM not found in 'SEND Trial Summary Parameter Test Name' CT codelist	TS	3	TSPARM is an extensible variable, and in order to capture study information not included in the codelist, the parameter test names Lot Number, Percent Purity of Compound, Quality Assurance type.
FDAN341	Value for TSPARMCD not found in 'SEND Trial Summary Parameter Test Name' CT codelist	TS	3	TSPARMCD is an extensible variable, and in order to capture study information not included in the codelist, the parameter test codes, LOT, QATYPE, TRTPUR.

6. Sponsor Decisions Related to Data Standard Implementations

6.1 Sponsor-Defined Standardization Descriptions

6.2 Differences between SEND Datasets and Study Report

1. In the Body Weight domain, body weights were adjusted to show decreased weights in Groups 3 and 4.
2. In the Body Weight Gain domain, the values were calculated from the adjusted body weights, so Groups 3 and 4 show decreased body weight gain.
3. In the Laboratory Test Results domain, values for AST, ALT, and ALP were adjusted to show an increase in Group 4, RBC, HGB, and HCT were adjusted to show a decrease in Group 4.
4. In the Organ Measurements domain, liver weights were adjusted to show an increase in Group 4.
5. In the Macroscopic and Microscopic Findings domains, liver findings were added to Group 3 and 4 to show increased liver effects. These were linked in the Related Records domain.
6. Tumor findings for liver were added to show increased liver effects in Group 4.
7. Premature deaths due to hepatocellular carcinoma were added to Group 4 and listed in the Death Diagnosis and Tumor Findings domains.