Study Data Reviewer's Guide

Nonclinical

Compound A: Effects on the Heart Rate, Blood Pressure, and the Electrocardiogram by Oral Administration in Conscious Monkeys

<CJUGSEND00>

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1. SDRG Introduction

1.1 Study Title, Number, and Version

Study Title	Compound A: Effects on the Heart Rate, Blood Pressure, and the Electrocardiogram by Oral Administration in Conscious Monkeys
Study Number	CJUGSEND00
Study Version	Final Report

1.2 Summary of SEND Dataset Creation Process

The raw data and other information related to the study were put into Excel spreadsheet (Excel 2016, Microsoft Corp., Washington, USA), in compliant with the format of SEND Implementation Guide version 3.1 (IG3.1). Excel spreadsheets were converted to SAS Transport File V5 using SAS (Ver. 9.3, SAS Institute Inc., North Carolina, USA). Define.xml file was generated using Pinnacle21 Community Validator tool (Ver. 2.2.0, Pinnacle 21, Pennsylvania, USA), and the source code were edited further using Visual Studio Code (Ver. 1.18.0, Microsoft Corp.).

1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of the data for Study No. CJUGSEND00. 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

Compound A was administered orally by gavage as a single dose (5 mL/kg) to 4 male Cynomolgus monkeys in a dose escalation manner. Each monkey received doses of 0 (vehicle only), 10, 30, and 100 mg/kg with an interval of 6 days between each dose.

Dosing Schedule (Dosing Day)[a)]	Test and Control Articles	Dose Level (mg/kg)	Dosing Volume (mL/kg)	Concentration (mg/mL)	Number of male monkeys
First (Day 1)	Vehicle	–	5	–	4
Second (Day 8)	Compound A	10	5	2	
Third (Day 15)	Compound A	30	5	6	
Fourth (Day 22)	Compound A	100	5	20	

a) The first day of dosing was designated as Day 1.

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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				
SPGRPCD	ARMCD	ARM	Acclimation	Screen	Trt1	Rest1	Trt2
1	1	Compound A, PO, 0-10-30-100 mg/kg	Acclimation	Screen	Vehicle Control	Rest for 6 days	10 mg/kg Compound A

Element in each Epoch (continued)				Trial Set	
Rest2	Trt3	Rest3	Trt4	SETCD	SET
Rest for 6 days	30 mg/kg Compound A	Rest for 6 days	100 mg/kg Compound A	1	Compound A, 0-10-30-100 mg/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	3.1
Controlled Terminology	CDISC SEND Controlled Terminology	2017-09-29
Data Definition file	CDISC DEFINE.XML	2.0

3.2 Rationale for Standards Selection

The standards versions used were the most current ones listed in the FDA Study Data Standards Catalog that were compatible with the version of software used to generate the SEND data package at the time of dataset creation. The Technical Conformance Guide v 4.1 (March 2018) was used as a reference.

3.3 Nonstandard Terminology

Nonstandard terminology was not used in this study.

4. Description of Study Datasets

The submitted SEND datasets represent a finalized study. The datasets included in this package are listed below.

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

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Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
TX	Trial Sets			Trial Design
CO	Comments			Special Purpose
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
DS	Disposition			Events
CL	Clinical Observations	X		Findings
CV	Cardiovascular			Findings
EG	ECG Test Results			Findings
RE	Respiratory Test Results			Findings
VS	Vital Signs			Findings

4.2 Dataset Explanation

4.2.1 TS- Trial Summary

SEND IG3.1 states that the Codelist NULLFLAVOR should be used for the variable TSVALNF if applicable. However, the codelist NULLFLAVOR is not included in the CDISC SEND Controlled Terminology version 2017-09-29. We therefore prepared the codelist NULLFLAVOR according to the section 7.6.4 in SEND IG3.1, and several terms were used in TS domain as following table.

Variable Name	Codelist	Term Used	Meaning
TSVALNF	NULLFLAVOR	MSK	Masked: There is information on this item available, but it has not been provided by the sender due to security, privacy or other reasons. There may be an alternate mechanism for gaining access to this information.
TSVALNF	NULLFLAVOR	NA	Not applicable: No proper value is applicable in this context.
TSVALNF	NULLFLAVOR	NAV	Temporarily unavailable: Information is not available at this time, but it is expected that it will be available later.

Variable Name	Codelist	Term Used	Meaning
TSVALNF	NULLFLAVOR	NI	No information: The value is exceptional (missing, omitted, incomplete, improper). No information as to the reason for being an exceptional value is provided. This is the most general exceptional value. It is also the default exceptional value.

4.2.2 EX-Exposure

The EX domain contains details of the intended dosing information.

4.3 Use of Supplemental Qualifiers

Dataset Name	Associated Dataset	Qualifiers Used
SUPPCL	Clinical Observations	Modifiers that were part of CLORRES for which SEND variables have not yet been developed.

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

5.1 Validation Outcome Summary

A total of 15 datasets with a total of 2561 records and one define file were validated. The validation found 23 errors and 992 warnings for datasets, and 304 errors for define.xml.

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

5.2 FDA SEND Validation Rules Version

The study dataset was verified against Version 2.1 of the FDA's validation rules for SEND formatted nonclinical studies using Pinnacle21 Community Validator tool version 2.2.0.

5.3 Errors

The following warnings were reported:

Rule	Message	Domain(s)	Count	Explanation
DD0022	Invalid Standard Version value '3.1' for 'SEND-IG'	Define.xml	1	Currently, SEND-IG 3.1 is not fully supported by Pinnacle validator.
DD0073	Invalid	Define.xml	303	Currently, SEND-IG 3.1 is not fully supported

Rule	Message	Domain(s)	Count	Explanation
	Origin Type value			by Pinnacle validator. In addition, the Pinnacle validator is using the STDM standard Origin type values. We consider this to be a false positive warning.
FDAN018, FDAN019	NULL value in TSVAL variable marked as Required	TS	6	TSVAL is marked as Expected in SEND IG3.1. TSVALNF is populated appropriately for the value is null in TSVAL. This error is not applicable.
FDAN027	Variable appears in dataset, but is not in SDTM model	CL	2	These variables (-NOMDY, -NOMLBL, -STINT, -ENINT, -USCHFL) are included in the current SDTM v1.5, but not in SDTM version 1.2 which is the reference of SEND IG3.0.
		CV	4	
		DS	3	
		EG	2	
		RE	4	
		VS	2	

5.4 Warnings

The following warnings were reported:

Rule	Message	Domain(s)	Count	Explanation
FDAN020	SEND Expected variable not found	SUPPCL	1	QVAL is marked as Permissible in SEND IG3.1. This warning is not applicable.
FDAN031	Model permissible variable added into standard domain	DM	2	This warning is for the variables added in SEND IG3.1. This warning is not applicable.
		TS	1	
FDAN033	SEND/dataset variable label mismatch '	CL	1	This warning was raised according to the rule in SEND IG3.0. The matching of valuables and labels are correct in the current dataset as per SEND IG3.1.
		CV	11	
		EG	4	
		RE	11	
FDAN334	Missing TCNTRL Trial Sets Parameter	TX	1	The dosing regimen of the study was dose escalation manner, and there was no control group.

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Rule	Message	Domain(s)	Count	Explanation
FDAN341	EGSTRESC value not found in 'ECG Result' extensible codelist	EG	960	These data are actually numeric, relevant terms are therefore not contained in Controlled Terminology. See Section 5.4.1.

5.4.1 EG Variables Not Associated with a –STRESN

The results of PRAG (C117773), QRSAG (C117779), QTAG (C117783), QTCBAG (C117784), and RRAG (C117791) are numeric values from the measurement equipment. The codelist ECG Result (C71150), designated to be used for EGSTRESC in SEND IG 3.1, is not including any numeric term.

6. Sponsor Decisions Related to Data Standard 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 datasets are an accurate representation of data in the study report for Study CJUGSEND00, 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. The translations are included in the DEFINE.XML.

6.3 Nonstandard Electronic Data Submitted

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

6.4 Legacy Data Conversion

Not performed.