Study Data Reviewer's Guide

Nonclinical

Effects of Compound A on Respiratory Function in Rats
<CJ16050>

Kaku Pharmaceuticals Co., Ltd., Japan

1-1-1, Dokoka-cho, Chiyoda-ku, Tokyo, Japan

CONTENTS

1. SDRG Introduction

1.1 Study Title, Number, and Version

Study Title	Effects of Compound A on Respiratory Function in Rats
Study Number	CJ16050
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. 9.4, 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 text editor.

1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of the data for Study No. CJ16050. 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 (10 mL/kg) to 6 male Sprague-Dawley rats. The respiratory function was measured before and 1, 2, 4, and 8 hours after administration using the whole body plethysmography.

Test and Control Articles	Dose Level (mg/kg)	Dosing Volume (mL/kg)	Concentration (mg/mL)	Number of male rats
Vehicle*	–	10	–	6
Compound A	100	10	10	6
Compound A	1000	10	100	6

* Given 0.5% methylcellulose solution

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	Acclimation	Treatment	SETCD	SET
00	00	Control	Acclimation	Control	00	Control
01	01	Compound A 100 mg/kg	Acclimation	Compound A 100 mg/kg	01	Compound A 100 mg/kg
02	02	Compound A 1000 mg/kg	Acclimation	Compound A 1000 mg/kg	02	Compound A 1000 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	2017-12-22
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 4.2 (October 2018) was used as a reference.

3.3 Nonstandard Terminology

None

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
TX	Trial Sets			Trial Design

Dataset Name	Dataset Label	Supplemental Qualifiers?	Related Records?	Observation Class
DM	Demographics			Special Purpose
SE	Subject Elements			Special Purpose
EX	Exposure			Interventions
DS	Disposition			Events
CL	Clinical Observations			Findings
RE	Respiratory Test Results			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 2017-12-22. 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	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.

4.2.2 EX-Exposure

The EX domain contains details of the intended dosing information.

4.2.3 RE-Respiratory Test Results

The respiratory test results baseline values are identified as the data collected before dosing.

4.3 Use of Supplemental Qualifiers

None

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

5.1 Validation Outcome Summary

A total of 10 datasets with a total of 551 records and one define file were validated. The validation found 28 errors and 13 warnings for datasets, and 212 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 errors 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 Origin Type value	Define.xml	211	Currently, SEND-IG 3.1 is not fully supported 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	19	TSVAL is marked as Expected in SEND IG3.1. TSVALNF is populated appropriately for the value is null in TSVAL (see section 4.2.1). 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.
		DS	3	
		RE	4	

5.4 Warnings

The following warnings were reported:

Rule	Message	Domain(s)	Count	Explanation
FDAN031	Model permissible variable added into standard domain	TS	1	This warning is for the variables added in SEND IG3.1. This warning is not applicable.
FDAN033	SEND/dataset variable label	CL	1	This warning was raised according to the rule in SEND IG3.0. The matching

Rule	Message	Domain(s)	Count	Explanation
	mismatch	RE	11	of valuables and labels are correct in the current dataset as per SEND IG3.1.

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 CJ16050, with the following differences noted.

1. The study report stated that December 07, 2016 was defined as Day 1 (the study day 1) for all animals although that day was the dosing day only for animal numbers 00M01, 00M02, 01M01, 01M02, 02M01, and 02M02. Dosing day for animal numbers 00M03, 00M04, 01M03, 01M04, 02M03, 02M04 and that for 00M05, 00M06, 01M05, 01M06, 02M05, 02M06 were December 08 and 09, 2016, respectively. In this SEND dataset, Day 1 was defined as the day of dosing for each animal, which was populated as REFSTDTC value in DM domain and used for the calculation of values of --DY variables.
2. 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.