Study Data Reviewer's Guide Nonclinical

Study Title	Cardiovascular Safety Pharmacology Evaluation of LY3478045 (Compound 3478045) Administered by Oral Gavage to Male Telemetry-Instrumented Conscious Dogs
Study Number	8409511
Alternate Study ID	2302030
Sponsor	Eli Lilly and Company Lilly Corporate Center Indianapolis, Indiana 46285 UNITED STATES OF AMERICA
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1. SDRG INTRODUCTION

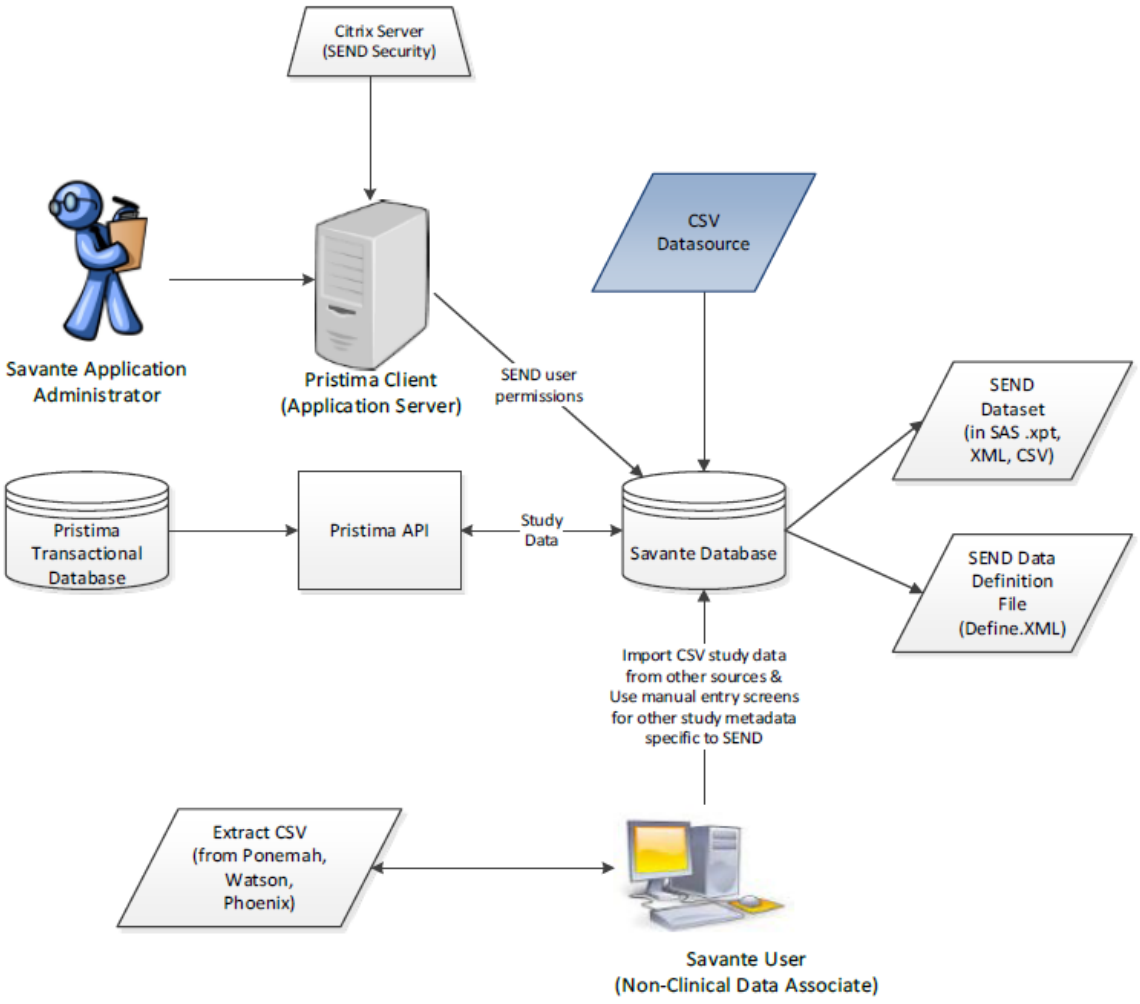
This document provides context for the SEND tabulation datasets and terminology for Study 8409511, in addition to what is provided in the define.xml file, to facilitate the FDA reviewer's and data manager's use of the datasets. It also includes a summary of SEND dataset conformance findings.

1.1 Study Title, Number, and Version

Study Title	Cardiovascular Safety Pharmacology Evaluation of LY3478045 (Compound 3478045) Administered by Oral Gavage to Male Telemetry-Instrumented Conscious Dogs
Study Number	8409511
Study Version	Draft

1.2 Summary of SEND Dataset Creation Process

All inlife, clinical pathology, and post-mortem data were collected with Pristima by Covance Inc. Bioanalytical, cardiovascular, and ECG data were collected externally from Pristima by Covance Inc or external contributors. The SEND module prepares a copy of the raw study data by using the Pristima Application Programming Interface (API) connector or CSV import functionality and produces an integrated SEND dataset with Controlled Terminology mapping applied and accompanying define.xml.



1.3 SEND Dataset Verification

Data in the SEND datasets are an accurate representation of data in the study report for Study No. 8409511. Datasets were generated from a validated system with all manual modifications quality checked and documented per SOP. Any differences found by comparison between the datasets and the report are described in section 6.2. The content of the bioanalytical data generated by external vendors is the responsibility of the respective sites. The conformance to the SEND standard is checked by Covance, Inc. upon integration into the overall SEND datasets.

2. STUDY DESIGN

2.1 Study Design Summary

Male[a]	Day 1	Day 8	Day 15	Day 22
D0001	Low	Control	High	Mid
D0101	Mid	High	Control	Low
D0201	High	Low	Mid	Control
D0301	Control	Mid	Low	High
D0401	Control	High	Mid	Low
D0501	High	Low	Control	Mid
D0601	Mid	Control	Low	High
D0701	Low	Mid	High	Control

a Animals were dosed in ascending order based on dose level.

Dose Level Designation	Dose Level (mg LY3478045/kg)	Dose Volume (mL/kg)	Dose Concentration (mg LY3478045/mL)
Control[a]	0	5	0
Low	20	5	4
Mid	75	5	15
High	225	5	45

a Control animals were administered vehicle control article.

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	PREDOSE	DOSING	SETCD	SET
1	1	20-0-225-75	Predose	G1 - LY3478045: 20;0;225;75 mg/kg	1	20-0-225-75
2	2	75-225-0-20	Predose	G2 - LY3478045: 75;225;0;20 mg/kg	2	75-225-0-20
3	3	225-20-75-0	Predose	G3 - LY3478045: 225;20;75;0 mg/kg	3	225-20-75-0
4	4	0-75-20-225	Predose	G4 - LY3478045: 0;75;20;225 mg/kg	4	0-75-20-225
5	5	0-225-75-20	Predose	G5 - LY3478045: 0;225;75;20 mg/kg	5	0-225-75-20
6	6	225-20-0-75	Predose	G6 - LY3478045: 225;20;0;75 mg/kg	6	225-20-0-75
7	7	75-0-20-225	Predose	G7 - LY3478045: 75;0;20;225 mg/kg	7	75-0-20-225
8	8	20-75-225-0	Predose	G8 - LY3478045: 20;75;225;0 mg/kg	8	20-75-225-0

3. STANDARDS, FORMATS, AND TERMINOLOGIES AND THEIR VERSIONS

3.1 Standards Used

Standard or Dictionary	Standard or Dictionary	Versions Used
Tabulation Datasets	CDISC SEND IG	3.1
Tabulation Datasets	Technical Conformance Guide	4.0
Controlled Terminology	CDISC SEND Controlled Terminology	2019-03-29
Data Definition file	CDISC DEFINE.XML	2.0.0

3.2 Rationale for Standards Selection

The versions of the standards used were the most current ones listed in FDA's Study Data Standards Catalog or the most recent CT package available in our SEND system at the time of dataset creation.

3.3 Nonstandard Terminology

Nonstandard terminology was not used on this study.

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	X		Events
BW	Body Weight	X		Findings
BG	Body Weight Gain	X		Findings
CL	Clinical Observations	X		Findings
CV	Cardiovascular Test Results			Findings
DD	Death Diagnosis			Findings
EG	ECG Test Results			Findings
PC	Pharmacokinetic Concentrations			Findings

4.2 Dataset Explanation

4.2.1 CL

Incidence tables for clinical observations in the report use the values in CLORRES and not CLSTRESC.

Veterinary observations are presented in the CL under a CLTEST of Vet Assessment and CLCAT of PHYSICAL EXAM. CLORRES values for this measurement are reported as "SOAP:SOAP 1" or with a subsequent number if entries were made that exceeded

character limits in the collection system. SOAP is defined in the study report as Subjective Objective Assessment Plan. The actual original results as collected in free text form by the veterinarians are present in the CO domain with the IDVARVAL tying it to the SOAP record in the CL.

CLTPT is incorrectly populated with operational information of what type of collection is being done at that time and should be disregarded.

Observations observed in the pen of animals and cannot be attributed to a single individual are recorded under each animal in that given cage with a modifier of "group observation". These records are presented against each USUBJID as they were collected and reported and do not contain a POOLID.

4.2.2 DS

The DSSTDTC is the date and time a death status is assigned to a subject, not necessarily the time of removal from study alive.

For animals receiving no necropsy, a death status is assigned when the animals are removed from study alive.

4.2.3 EX

EXTPT and EXTPTNUM should be disregarded as they are populated with operational information.

4.2.4 PC

Values below the level of quantitation were treated as zero for normanalysis.

4.2.5 Define File

The domain sequence in the define file does not follow the sequence in the SENDIG, nor are the General Observation Class domains in alphabetical order.

Algorithms are presented using variable names and descriptions under comments instead of computational algorithms with variable codes.

Codelists are combined across variables that use the same codelists. Codelists decode all elements rather than enumerating elements that do not require decoding.

The keys for the PC domain should not include PCDTC as this variable is null for all records. The correct key structure is: STUDYID, USUBJID, PCTESTCD, PCSPEC, VISITDY, PCTPTNUM.

The following variables should have "date" listed as their Type instead of "datetime" as there is only a date present for all values: RFSTDTC; RFENDTC; BRTHDTC; SESTDTC.

4.3 Use of Supplemental Qualifiers

Dataset Name	Variable Name (QNAM)	Variable Label (QLABEL)	Description
SUPPDS	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPDS	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.
SUPPBW	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPBW	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.
SUPPBG	PHSNAME1	Start Phase name	The phase in which records began collected for traceability to raw data.
SUPPBG	PHSNAME2	End Phase name	The phase in which records ended collected for traceability to raw data.
SUPPBG	PHSEDAY1	Start Day of Phase	The first day of a record's collection interval for traceability to raw data.
SUPPBG	PHSEDAY2	End Day of Phase	The last day of a record's collection interval for traceability to raw data.
SUPPCL	PHSENAME	Phase name	The phase in which records were collected in for traceability to raw data.
SUPPCL	PHASEDAY	Day of Phase	The day records were collected on for traceability to raw data.

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

5.1 Validation Outcome Summary

1369 warnings and 26 errors were identified and are further explained in the following section.

5.2 FDA SEND Validation Rules Version

Rule conformance to SEND 3.1 was evaluated using Pinnacle 21 Community, version 3.0.1, which includes checks for conformance against the FDA Specific SEND Validation Rules Version 1.3, and Business Rules Version 1.4.

5.3 Errors

Rule	Message	Domain(s)	Count	Explanation
DD0042	Missing Method reference	Define	26	The Define-XML lacks a Method Definition for variable with an origin of DERIVED. Derivations are noted as comments to the appropriate variables.

5.4 Warnings

The following warnings were reported:

Rule	Message	Domain	Count	Explanation
CG0013	Model permissible variable added into standard domain	CO	1	COVAL1 was populated in the CO domain for comments longer than 200 characters.
FDAB013	No baseline flag record in EG for subject	DM	8	EGBLFL is an expected variable. However, all records are null as Covance does not collect or report baseline flag data.
CG0021	EGMETHOD value not found in 'ECG Test Method' extensible codelist	EG	640	User defined terms have been used for the method "CONTINUOUS ECG FOR NON-HUMAN SPECIES USING IMPLANTED LEADS" as the CT term this applies to exceeds the character limit in our software system.
CG0021	EGSTRESC value not found in 'ECG Result' extensible codelist	EG	640	Numeric results are not included in the ECG Result extensible codelist, however are acceptable results for EGSTRESC.
CG0303	SEND/dataset variable label mismatch	PC	1	The label for VISITDY is Visit Day in the pc.xpt, however this should be "Planned Study Day of Collection".
CG0007	PCDY variable value is imputed	PC	32	This warning states that PCDY should not be present when PCDTC is not populated however, as all records for PCDTC are null as the data were not available to the Principal Investigator, PCDY is populated in order to provide a timing variable.
FDAB011	Missing STENDTC Trial Summary Parameter	TS	1	The study end date is currently unknown and will be populated with the date the report is signed in the final dataset.

6. SPONSOR DECISIONS RELATED TO DATA STANDARD IMPLEMENTATIONS

6.1 Sponsor-Defined Standardization Descriptions

No custom domains or custom endpoints were prepared for this study.

6.2 Differences between SEND Datasets and Study Report

Data in the SEND datasets are an accurate representation of the data in the study report for Study 8409511, with the following differences noted:

- Dose administration data are included in the EX domain and not in the study report.
- Data collected in the predose phase are included in the dataset but may not all be included in the study report.
- Predose data in the study report are reported by phase days which differs from the VISITDY and the --DY in the datasets which are presented as study days. The phase days are provided in the supplemental domains.

- Age of the subjects is presented in the DM and TS domains.
  - DM: Each subject's actual age is presented in the DM domain, derived as Age = Subject Reference Start Date – Subject Date of Birth, rounded up to the nearest integer and presented in the age unit to match the age unit in the study report. The age range computed from the SEND dataset may differ from the age range presented in the study report, which is rounded down to the nearest whole number. Date of Birth is not presented in the study report.
  - TS: The planned age range of the test subjects [as a group] is presented using the Age Text and Age Unit Trial Summary Parameters (TSPARM) and matches the Age at Initiation of Dosing presented in the study protocol.
- Various models of calculators, computers, and computer programs were used to collect data in this study. Because different models round or truncate numbers differently, values in some report tables (e.g., means, standard deviations, or individual values) may differ slightly from those in SEND. Neither the integrity nor the interpretation of the data was affected by these differences.

6.3 Nonstandard Electronic Data Submitted

Nonstandard electronic data are not part of this submission.

6.4 Legacy Data Conversion

Legacy data are not part of this submission.