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 |
| Page Number | 1 of 10 |

Table of Contents

[Table of Contents 2](#_Toc19704790)

[1. SDRG Introduction 3](#_Toc19704791)

[1.1 Study Title, Number, and Version 3](#_Toc19704792)

[1.2 Summary of SEND Dataset Creation Process 4](#_Toc19704793)

[1.3 SEND Dataset Verification 4](#_Toc19704794)

[2. Study Design 5](#_Toc19704795)

[2.1 Study Design Summary 5](#_Toc19704796)

[2.2 Trial Design Domain Overview 5](#_Toc19704797)

[3. Standards, Formats, and Terminologies and their Versions 6](#_Toc19704798)

[3.1 Standards Used 6](#_Toc19704799)

[3.2 Rationale for Standards Selection 6](#_Toc19704800)

[3.3 Nonstandard Terminology 6](#_Toc19704801)

[4. Description of Study Datasets 6](#_Toc19704802)

[4.1 Dataset Summary 6](#_Toc19704803)

[4.2 Dataset Explanation 6](#_Toc19704804)

[4.2.1 CL 6](#_Toc19704805)

[4.2.2 DS 7](#_Toc19704806)

[4.2.3 EX 7](#_Toc19704807)

[4.2.4 PC 7](#_Toc19704808)

[4.2.5 Define File 7](#_Toc19704809)

[4.3 Use of Supplemental Qualifiers 8](#_Toc19704810)

[5. Data Standards Validation Rules, Versions, and Conformance Issues 8](#_Toc19704811)

[5.1 Validation Outcome Summary 8](#_Toc19704812)

[5.2 FDA SEND Validation Rules Version 8](#_Toc19704813)

[5.3 Errors 8](#_Toc19704814)

[5.4 Warnings 8](#_Toc19704815)

[6. Sponsor Decisions Related to Data Standard Implementations 9](#_Toc19704816)

[6.1 Sponsor-Defined Standardization Descriptions 9](#_Toc19704817)

[6.2 Differences between SEND Datasets and Study Report 9](#_Toc19704818)

[6.3 Nonstandard Electronic Data Submitted 10](#_Toc19704819)

[6.4 Legacy Data Conversion 10](#_Toc19704820)

# SDRG Introduction

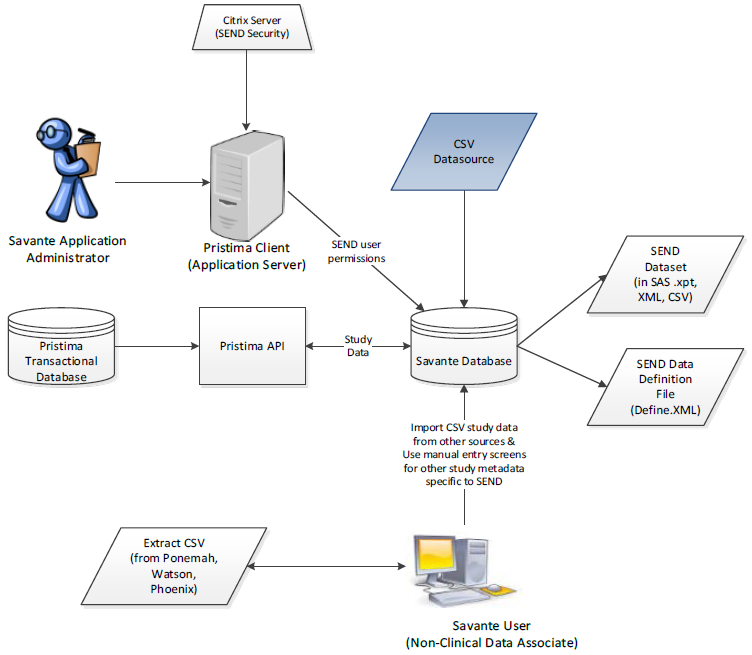
This document provides context for the SEND tabulation datasets and terminology for Study 8409511, in addition to what is provided in the define.xml file, to facilitate the FDA reviewer’s and data manager’s use of the datasets. It also includes a summary of SEND dataset conformance findings.

## 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 |

## 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.



## 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.

# Study Design

## Study Design Summary

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Malea | 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) | | |
| Controla | | 0 | | 5 | | 0 | | |
| Low | | 20 | | 5 | | 4 | | |
| Mid | | 75 | | 5 | | 15 | | |
| High | | 225 | | 5 | | 45 | | |
| a Control animals were administered vehicle control article. | | | | | | | | |

## 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 |

# Standards, Formats, and Terminologies and their Versions

## 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 |

## 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.

## Nonstandard Terminology

Nonstandard terminology was not used on this study.

# Description of Study Datasets

## 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](#_EX) | Exposure |  |  | Interventions |
| [DS](#_DS) | Disposition | X |  | Events |
| BW | Body Weight | X |  | Findings |
| BG | Body Weight Gain | X |  | Findings |
| [CL](#_CL) | Clinical Observations | X |  | Findings |
| CV | Cardiovascular Test Results |  |  | Findings |
| DD | Death Diagnosis |  |  | Findings |
| [EG](#_EG) | ECG Test Results |  |  | Findings |
| [PC](#_PC_1) | Pharmacokinetic Concentrations |  |  | Findings |

## Dataset Explanation

### 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.

### 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.

### EX

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

### PC

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

### 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.

## 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. |

# Data Standards Validation Rules, Versions, and Conformance Issues

## Validation Outcome Summary

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

## 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.

## 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. |

## 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. |

# Sponsor Decisions Related to Data Standard Implementations

## Sponsor-Defined Standardization Descriptions

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

## 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.

## Nonstandard Electronic Data Submitted

Nonstandard electronic data are not part of this submission.

## Legacy Data Conversion

Legacy data are not part of this submission.