

Analysis Data Reviewer's Guide

Sample Drug Company, Inc.

Study AB1234

ADRG Template Version 2019-07-18

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1. Introduction

1.1 Purpose

This document provides context for the analysis datasets and terminology that benefit from additional explanation beyond the Data Definition document (define.xml). In addition, this document provides a summary of ADaM conformance findings. Also included are details regarding legacy tabulation data conversion to SDTM and then to ADaM.

1.2 Acronyms

Acronym	Translation
aCRF	Annotated Case Report Form
ADaM	Analysis Dataset Model
AED	Antiepileptic Drug
CSSRS	Columbia Suicide Severity Rating Scale
CSR	Clinical Study Report
DRM	Data Review Meeting
eCRF	Electronic Case Report Form
eDT	Electronic Data Transfer (e.g. central lab data, ECG vendor data, PK data, etc.)
EDV	Early Discontinuation Visit
IG	Implementation Guide
ILAE	International League Against Epilepsy
LTFU	long-term follow-up
NA	Not Applicable
PBO	Placebo
POS	partial onset seizure
SDTM	Study Data Tabulation Model
TAUG	Therapeutic Area User Guide

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	v1.2/IG 3.1.2 Amendment 1
SDTM Controlled Terminology	2016-09-30
ADaM	v2.1/IG 1.0
ADaM Controlled Terminology	2016-09-30
Data Definitions	define.xml v2.0
TAUG (if applicable)	NA
Medications Dictionary	WHO Drug 2017 Q2
Medical Events Dictionary	Initial: 20.1 Final: 21.0
Other standards (optional)	NA

1.4 Source Data Used for Analysis Dataset Creation

The ADaM datasets were derived from SDTM that was previously converted from legacy tabulation data. The datasets were derived from the final locked database. Please refer to the Legacy Data Conversion Plan and Report Appendix for additional details.

2. Protocol Description

2.1 Protocol Number and Title

Protocol Number: AB1234

Protocol Title: A Randomized, Double-blind, Placebo-controlled, Multicenter, Parallel-group Study to Evaluate the Efficacy and Safety of TEST DRUG in Subjects with Epilepsy

Protocol Versions: Amendment 1 and Amendment 2

Amendment 1

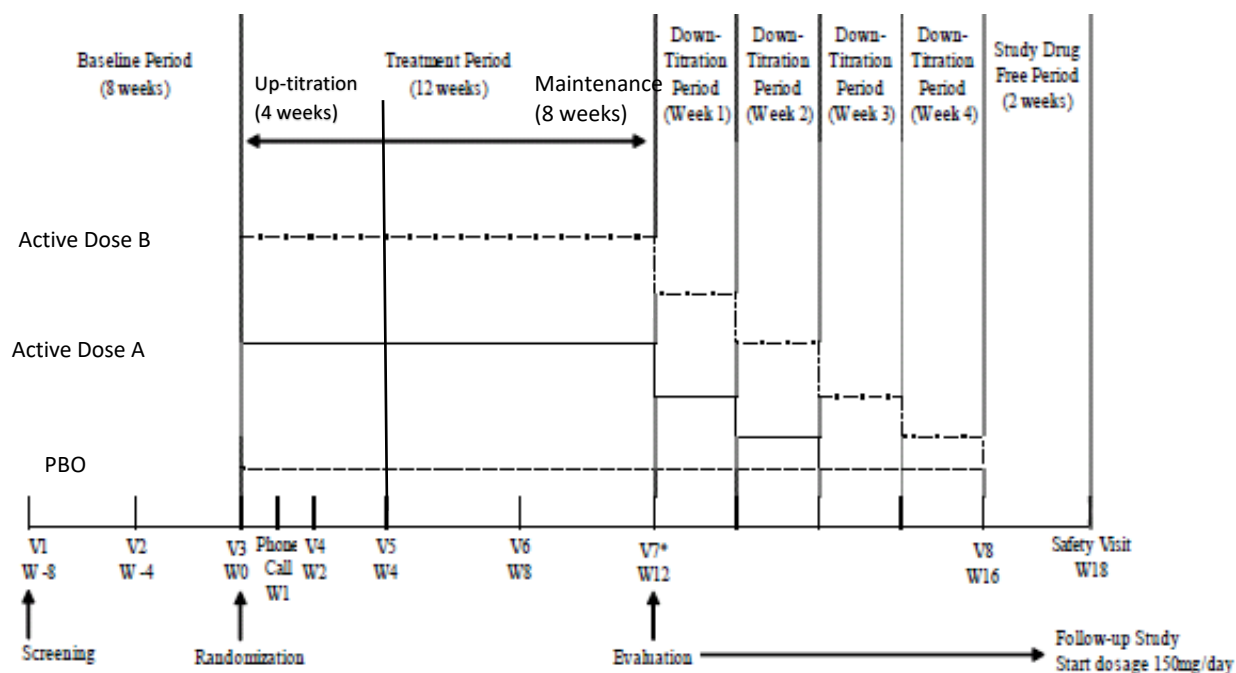
1. SAE procedures updated to implement FDA Final Rule requirements
2. CSSRS added to address FDA requirement that prospective assessments for suicidality should be included in clinical studies involving all drugs for neurological indicators

Amendment 2

1. Protocol amended to include an additional secondary efficacy analysis – time to achieving sustained 50% responder status

2.2 Protocol Design in Relation to ADaM Concepts

This is a randomized, double-blind, PBO-controlled, multicenter, therapeutic confirmatory study evaluating 2 active doses of TEST DRUG. The subject population will be adults (≥ 16 years to 80 years) with refractory epilepsy. Subjects will complete an 8-week prospective Baseline Period, followed by a 12-week Treatment Period. There is a 4-week Down-Titration Period followed by a 2-week Study Drug Free Period for subjects not entering the LTFU study.



D=dose, V=visit, W=week

* Subjects with an EDV at any time during the Treatment Period should proceed through the 4-week Down-Titration Period and 2-week Study Drug Free Period

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Core Variables

Core variables are those that are represented across all/most analysis datasets.

Variable Name	Variable Description
STUDYID	Study Identifier
USUBJID	Unique Subject Identifier
SITEID	Study Site Identifier
COUNTRY	Country

Variable Name	Variable Description
TRT01P	Planned Treatment for Period 01
SEX	Sex
AGE	Age
AGEU	Age Units
RACE	Race
SCRNFL	Screened Flag
RANDFL	Randomized Population Flag
SAFFL	Safety Population Flag
ITTFL	Intent-To-Treat Population Flag
PPROTFL	Per-Protocol Population Flag
DWNTITFL	Entered Down-Titration Period Flag
PSTTRTFL	Entered Post-Treatment Period Flag
RACEGR1	Pooled Race Group 1
AGEGR2	Age Group 2
REGION1	Geographic Region 1
REGION2	Geographic Region 2
SITEGR1	Pooled Site Group 1
WEIGHT	Weight

3.2 Treatment Variables

ARM versus TRTxxP

Are the values of ARM equivalent in meaning to values of TRTxxP?

Yes.

ACTARM versus TRTxxA

If TRTxxA is used, then are the values of ACTARM equivalent in meaning to values of TRTxxA?

Yes. TRT01A=TRT01P, the variable ACTARM is not kept in ADSL

Use of ADaM Treatment Variables in Analysis

Are both planned and actual treatment variables used in analyses?

No. Only planned treatment is used since all subjects were treatment as planned during the study, with the exception of one dose described below.

Use of ADaM Treatment Grouping Variables in Analysis

Are both planned and actual treatment grouping variables used in analyses?

No. The TR01PG1/TR01PG1N variables were used for all analyses that were broken out by treatment grouping.

3.3 Subject Issues that Require Special Analysis Rules

Subjects randomized in error – 001-00007, 013-00015, 024-00105, and 032-00214. These four subjects did not receive any doses of study medication and therefore are not included in the safety population.

Four subjects (004-00003, 019-00078, 045-00103, 048-00457) received an incorrect drug kit for the Treatment Period. The kit was the assigned treatment based on randomization. This was considered to be a conduct deviation.

Subject 025-00135 (randomized to PBO) received an incorrect drug kit (kit number 3021116) for the Treatment Period from 01Oct2013 through 29Oct2013. The kit was not of the assigned treatment; kit was for subjects randomized to ACTIVE DOSE B. This was considered to be an efficacy and conduct deviation. In dataset ADEX the dose for these days was identified as unknown.

3.4 Use of Visit Windowing, Unscheduled Visits, and Record Selection

Was windowing used in one or more analysis datasets?

Yes. Subjects with an EDV that corresponded to a scheduled visit had the assessments from the EDV slotted to the appropriate scheduled visit.

Were unscheduled visits used in any analyses?

Yes. Unscheduled visits were used for last value in ADLB, ADVS and ADEG. See section 3.2.4 of SAP for last value rules.

3.5 Imputation/Derivation Methods

If date imputation was performed, were there rules that were used in multiple analysis datasets?

No. Imputation rules were applied to individual domains. See individual datasets in section 5.2 for any date imputation rules.

APHASE values are one of the following: Baseline, Treatment, or Safety Follow-up. There is only one APERIOD/APERIODC of 1/Treatment. Treatment has 2 subperiods: Treatment or Down-Titration.

4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

No datasets were required to be split.

4.2 Data Dependencies

Analysis Dataset	Dependent on these other Analysis Datasets
ADSZP, ADSZFR and ADTTE	ADSZD
ADEXD and ADEXS	ADEX
ADAE	ADEXD

4.3 Intermediate Datasets

Intermediate datasets were not created.

4.4 Variable Conventions

APHASE values are one of the following: Baseline, Treatment, or Safety Follow-up. There is only one APERIOD/APERIODC of 1/Treatment. Treatment has 2 subperiods: Treatment or Down-Titration.

5. Analysis Dataset Descriptions

5.1 Overview

Are data for screen failures, including data for run-in screening (for example, SDTM values of ARMCD='SCRNFIL', or 'NOTASSGN') included in ADaM datasets?

Yes. Screen failure subjects are included in the following domains: ADSL, ADLB, and ADIE

Are data taken from an ongoing study?

No.

Do the analysis datasets support all protocol- and statistical analysis plan-specified objectives?

Yes.

5.2 Analysis Datasets

Dataset Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
<u>ADSL</u> Subject Level Analysis Dataset	ADSL			X			One observation per subject.
<u>ADAE</u> Adverse Events	OTHER		X				One record per subject per event
<u>ADCM</u> Concomitant Medications	OTHER		X				One record per medication occurrences or dosing interval per ATC code per subject
ADCO Comments	OTHER			X			One record per subject per comment
ADCSSRS CSSRS	BDS		X				One record per subject per parameter category per parameter per visit
ADDV Protocol Deviations	BDS		X				One record per subject per parameter category per parameter
ADEG Electrocardiogram	BDS		X				One record per subject per parameter category per parameter per visit

Dataset Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADEPHIS Epilepsy History	BDS			X			One record per subject per parameter category per parameter per visit
ADEX Exposure	BDS		X				One record per subject per visit
ADEXD Daily Exposure	BDS		X				One record per subject per exposure day
ADEXS Exposure Summary	OTHER		X				One record per subject
ADGES Global Evaluation Scale	OTHER	X					One record per subject per parameter category per parameter per visit
ADHADS HADS	OTHER	X					One record per subject per parameter category per parameter per visit
ADIE Inclusion / Exclusion Criteria Not Met	BDS			X			One record per subject

Dataset Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADLB Laboratory Test Results	BDS		X				One record per subject per parameter category per parameter per visit
ADMDRES Medical Resource	BDS	X					One record per subject per parameter category per parameter per visit
ADMH Medical History	OTHER			X			One record per subject per event
ADPC Pharmacokinetic Concentration	BDS				X		One record per subject per parameter category per parameter per visit
ADPE Physical Examination	BDS		X				One record per subject per parameter category per parameter per visit
ADQOLIE QOLIE-31-P	OTHER	X					One record per subject per parameter category per parameter per visit
ADSPS Socio-Professional	OTHER	X					One record per subject per parameter category per parameter per visit

Dataset Dataset Label	Class	Efficacy	Safety	Baseline or other subject characteristics	PK/PD	Primary Objective	Structure
ADSV Subject Visits	OTHER			X			One record per subject per visit
ADSZD Daily Seizure Records	BDS	X					One record per subject per parameter category per parameter per visit
ADSZFR Seizure Freedom	BDS	X				X	One record per subject per parameter category per study period
ADSZP Period Seizure	BDS	X				X	One record per subject per parameter per visit
ADTTE Time to nth Seizure	OTHER	X	X			X	One record per subject per parameter category per parameter per visit
ADVS Vital Signs	BDS		X				One record per subject per parameter category per parameter per visit

5.2.1 ADSL – Subject Level Analysis Dataset

Demographics information

In some countries, race is not allowed to be collected. In these instances, race is left missing and RACEGR1 is set to the category of MISSING.

In some countries only year can be collected for birth date. In these cases, January 1 is used as the month and year for these subjects. BRTHDTF is populated as 'M' for these cases.

5.2.2 ADAE – Adverse Events

Date Imputation Rules

Start Date:

If only the month and year are specified then:

1. Use the 1st of the month if the month and year are not the same as the month and year of the first dose of study medication.

OR

2. Use the date of first study medication if the month and year are the same as the first dose of study medications.

If only the year is specified then:

1. Use January 1 of that year if the year is not the same as the year of the first dose of study medication.

OR

2. Use the date of first study medication if the year is the same as the year of the first dose of study medication.

If the start date is completely missing, then set the start date to the subject's first dose date of study medication

Stop Date:

If only the month and year are specified, then use the last day of the month.

If only the year is specified, then use December 31 of that year.

If the stop date is missing (not ongoing), then set the resolution date to the latest of the following dates as long as the AE start date is \leq to the dates:

1. The date of the last dose of study medication.
2. The date of last contact from the termination CRF.
3. The date of last scheduled or unscheduled visit.

5.2.3 ADCM – Concomitant Medications

Date Imputation Rules:

Start Date:

If only the month and year are specified, then use the 1st of the month.

If only the year is specified, then use January 1 of that year.

If the start date is completely missing, then set the start date to the subject's birth date (after imputation for partial birth dates).

Stop Date:

If only the month and year are specified, then use the last day of the month.

If only the year is specified, then use December 31 of that year.

If the stop date is missing (not ongoing), then set the resolution date to the latest of the following dates, depending on what is available on the CRF: 1) the date of last contact from the termination CRF, 2) the date of last scheduled or unscheduled visit, and 3) the date of last phone contact.

6. Data Conformance Summary

6.1 Conformance Inputs

Specify the software name and version for the analysis datasets

Pinnacle 21 version 2.2.0

Specify the version of the validation rules (i.e. CDISC, FDA) for the analysis datasets

CDISC

Specify the software name and version for the define.xml

config-adam-1.0 xml

Specify the version of the validation rules (i.e. CDISC, FDA) for the define.xml

CDISC

6.2 Issues Summary

Dataset(s)	Diagnostic Message	Severity	Count	Explanation
ADAE	Neither AVAL nor AVALC are present in dataset	Error	1	Variables not needed for event analysis
ADPC	* TM is not a numeric variable	Error	1	LDOSETM is character variable
ADSL	TRT01P is present and TR01SDT is not present	Error	4	The 4 subjects randomized in error have TRT01P but no start date.
ADSL	TRT01P is present and TR01EDT is not present	Error	4	The 4 subjects randomized in error have TRT01P but no end date.

Dataset(s)	Diagnostic Message	Severity	Count	Explanation
ADSL	Null value in variable marked as Required	Error	2	For variables AGE, AGEU and RACE - 2 subjects randomized in error are missing informed consent date so AGE cannot be calculated, RACE cannot be collected from subjects in France
ADSL	Expected variable is not present within dataset	Warning	4	TRTSEQP, TR01EDT, TRTSEQA, and TR01SDT variables not needed

7. Submission of Programs

All SAS programs for analysis datasets and primary and secondary efficacy results are submitted. They were all created on a SAS platform using version 9.3. The internal reference date used to create dates in ADaM datasets is January 1, 1960.

7.1 ADaM Programs

Program Name	Output	Macro Used
adsl.txt	adsl	attrib
adae.txt	adae	attrib, partdate
adcm.txt	adcm	attrib, partdate
adco.txt	adco	attrib
adcssrs.txt	adcssrs	attrib
addv.txt	addv	attrib
adeg.txt	adeg	attrib
adephis.txt	adephis	attrib
adex.txt	adex	attrib
adexd.txt	adexd	attrib
adexs.txt	adexs	attrib
adges.txt	adges	attrib
adhads.txt	adhads	attrib

Program Name	Output	Macro Used
adie.txt.	adie.	attrib
adlb.txt	adlb	attrib
admdres.txt	admdres	attrib
admh.txt	admh	attrib, partdate
adpc.txt	adpc	attrib
adpe.txt	adpe	attrib
adqolie.txt	adqolie	attrib
adsps.txt	adsps	attrib
adsv.txt	adsv	attrib
adszd.txt	adszd	attrib
adszfr.txt	adszfr	attrib
adszp.txt	adszp	attrib
adtte.txt	adtte	attrib
advs.txt	advs	attrib

7.2 Analysis Output Programs

Program Name	Output Number	Title	Input
t_predopbo.txt	7.1.1	Percent Reduction Over Placebo for – 28-Day Adjusted POS Frequency - ITT	ADSZP
t_predopbo.txt	7.1.2	Percent Reduction Over Placebo for 28-Day Adjusted POS Frequency - PP	ADSZP
t_resp.txt	7.2.1	Fifty Percent Responder Outcome for POS Frequency – ITT	ADSZP
t_resp.txt	7.2.2	Fifty Percent Responder Outcome for POS Frequency – PP	ADSZP
t_szfr.txt	7.3.1	Seizure Freedom for All Seizure Types - ITT	ADSZFR
t_nthseiz.txt	7.4	Time to nth Partial Onset Seizure – ITT	ADTTE
t_50resp.txt	7.6	Fifty Percent Responder Outcome for POS Frequency By Monthly Periods – ITT	ADTTE

7.3 Macro Programs

Program Name	Purpose
attrib.txt	Automatically set variable attributes based on specifications
partdate.txt	Creates full analysis dates from partial start or stop dates based on imputation rules.

Legacy Data Conversion Plan and Report Appendix

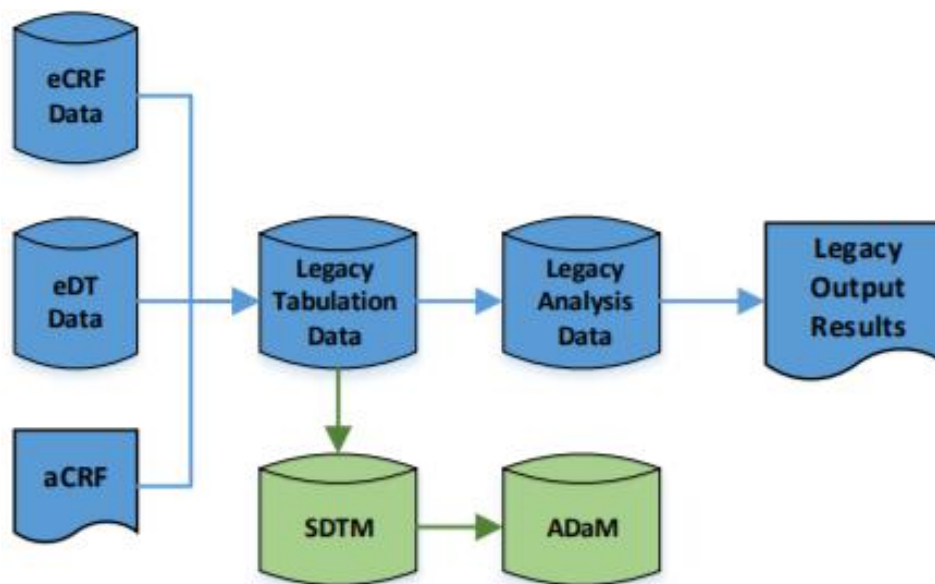
1. Purpose

The purpose of this appendix is to document the traceability of key output analysis results with ADaM when the analysis results were generated using a legacy process.

Because of transformations required during ADaM conversion, some of the terms, categories and data formats used in the tabulation data have been translated into CDISC standard formats in the ADaM data. This appendix identifies differences between the legacy analysis and ADaM data, and explains how ADaM represents the equivalent data.

2. Conversion Data Flow

The SDTM (converted from legacy tabulation data) was used to create ADaM as described in the following data flow diagram.



Rationale:

The study started before December 17, 2016. Therefore, standard data is not required. The legacy tabulation data was used to create SDTM which was then used to create ADaM. The Legacy Analysis Data was used for creating analysis results for the appendix of the CSR.

For this submission,

- Legacy tabulation data was converted to SDTM to assist FDA reviewers.
- SDTM was used to create ADaM to facilitate ISS/ISE ADaM data pools.

3. Converted Data Summary

During authoring of the mapping specification from SDTM to ADaM, CDISC Controlled Terminology was applied where applicable. After authoring of a mapping specification and programming of the ADaM SAS datasets, the Pinnacle21 validator was run to check compliance to ADaM IG 1.0 as Pinnacle 21 did not have compliance checks available for ADaM IG 1.1. Checks that signified a programming issue were addressed and the relevant ADaM datasets were updated when possible.

3.1 Issues Encountered and Resolved

A comparison between newly created key ADaM datasets and their corresponding legacy analysis data, SDTM and CSR analysis results was completed to ensure traceability. See below for a description of issues encountered and their resolutions:

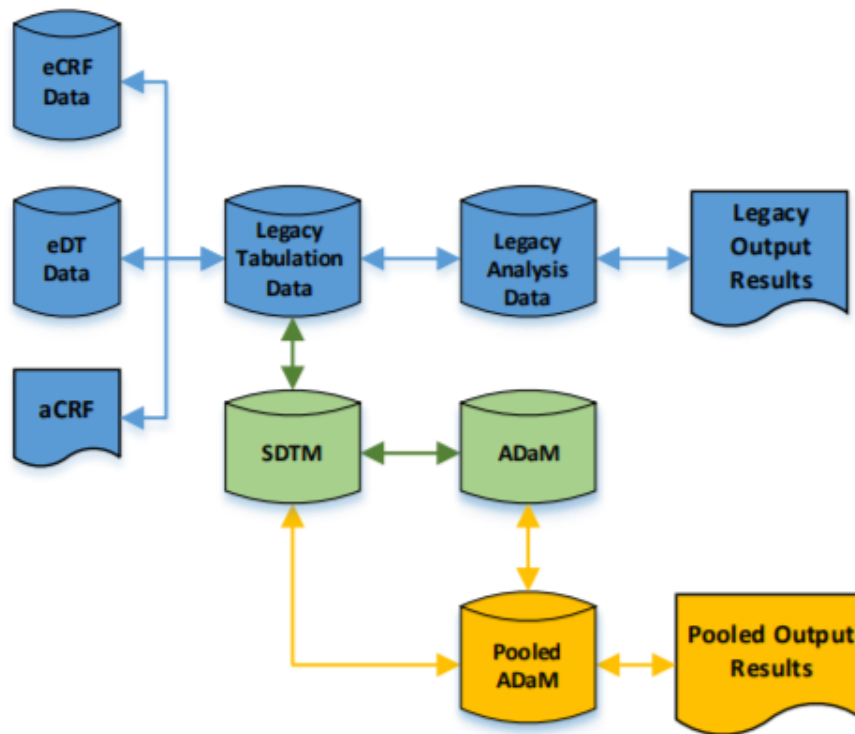
- Creation of ADSL: We have followed ADaM model v2.1 and ADaMIG v1.1 to create ADSL. Here is a summary of the variable changes based on the SDTMs:
 - Originally phases were referred to as periods in the legacy analysis data but in order to be ADaM compliant they were mapped from SDTM as follows:
 - Baseline Phase is PH1SDT and PH1EDT
 - Treatment Phase is PH2SDT and PH2EDT. This phase contains Up-titration (APERIOD = 1, AP01SDT, AP01EDT), Maintenance (APERIOD=2, AP02SDT, AP02EDT), and Down-titration (APERIOD= 3, AP03SDT, AP03EDT) periods.
 - Safety Follow-up Phase is PH3SDT and PH3EDT.
 - DCSREAS is mapped from the SDTM, and compared to original values and CDISC controlled terminology as follows:

SDTM DS.DSTERM/ ADSL.DCSREAS	SDTM/ ADAM Count	Legacy Analysis Data Value	Legacy Analysis Count	CSR Reported Value	CSR Count
OTHER	9	termination due to other reasons	9	Other	9
NON-COMPLIANCE WITH STUDY DRUG	3	termination due to unsatisfactory compliance of subject	3	Non-Compliance	3
WITHDRAWAL BY SUBJECT	15	termination because subject withdrew consent	15	Subject Withdrew Consent	15

SDTM DS.DSTERM/ ADSL.DCSREAS	SDTM/ ADAM Count	Legacy Analysis Data Value	Legacy Analysis Count	CSR Reported Value	CSR Count
PROTOCOL DEVIATION	7	termination with major protocol violation per investigator	7	Physician Discontinued Subject Due to Protocol Violation	7
LACK OF EFFICACY	22	termination with lack of efficacy	22	Lack of Efficacy	22
ADVERSE EVENT	61	termination due to adverse event	61	Adverse Event	61
LOST TO FOLLOW- UP	6	lost to follow up, reason for termination unknow	6	Lost to Follow-Up	6

4. Traceability Data Flow

The legacy data traceability from collection to submission is described in the following data flow diagram.



5. Outstanding Issues

ADSL

The PK population flag did not exist in the legacy analysis data. The flag was derived and assigned in the output programs. There is one more subject counted in the PK population represented in the CSR output than the number flagged in the ADSL. This subject, 007-00201, is not included in the ADSL PK population because their first PK draw was after first dose.

Adverse Events

Not all legacy analysis adverse event variable values are traceable to the CSR tables as only subjects with treatment emergent AEs were counted. The treatment emergent flag was programmed directly into the adverse event table programs. The ADaM ADAE domain includes the treatment emergent flag based on SAP rules.

There were two data issues with relation to start and end dates being switched in the legacy tabulation and analysis data. This was originally corrected exclusively in the table and listing programs. This has been corrected in the SDTM AE and ADaM ADAE domains. See the table below for detail concerning the discrepancy:

SUBJECT AETERM	Legacy Analysis Data Value	CSR Reported Value	AE and ADAE
SUBJECT=007-00103 AETERM=DIARRHEA	AESTDT=03OCT2013 AEENDT=02OCT2013	AESTDT=02OCT2013 AEENDT=03OCT2013	AESTDT=02OCT2013 AEENDT=03OCT2013
SUBJECT=007-04102 AETERM=EARACHE	AESTDT=15OCT2013 AEENDT=10OCT2013	AESTDT=10OCT2013 AEENDT=15OCT2013	AESTDT=10OCT2013 AEENDT=15OCT2013