Analysis Data Reviewer's Guide

CDISC SDTM/ADaM Pilot Project

CDISCPilot01

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Contents

1. Introduction

1.1 Purpose

This document provides context for the analysis datasets and terminology that benefit from additional explanation beyond the Data Definitions document (define.xml). In addition, this document provides a summary of ADaM conformance findings.

1.2 Acronyms

Acronym	Translation
CRF	Case Report Form
IG	Implementation Guide

1.3 Study Data Standards and Dictionary Inventory

Standard or Dictionary	Versions Used
SDTM	SDTM v1.2/SDTM IG v3.1.2 (with amendment 1)
ADaM	ADaM Model Document 2.0 ADaM Implementation Guide v1.0 ADaM Data Structure for Adverse Event Analysis v1.0 ADAM Basic Data Structure for Time-to-Event Analysis v1.0
Data Definitions	define.xml v1.0

1.4 Source Data Used for Analysis Dataset Creation

The analysis files for this study were derived from the submitted SDTM files. SDTM files were prepared from CRF data according to version 3.1.2 of the SDTM IG (with amendment 1). No non-CRF or non-SDTM data were used to create the ADaM data

2. Protocol Description

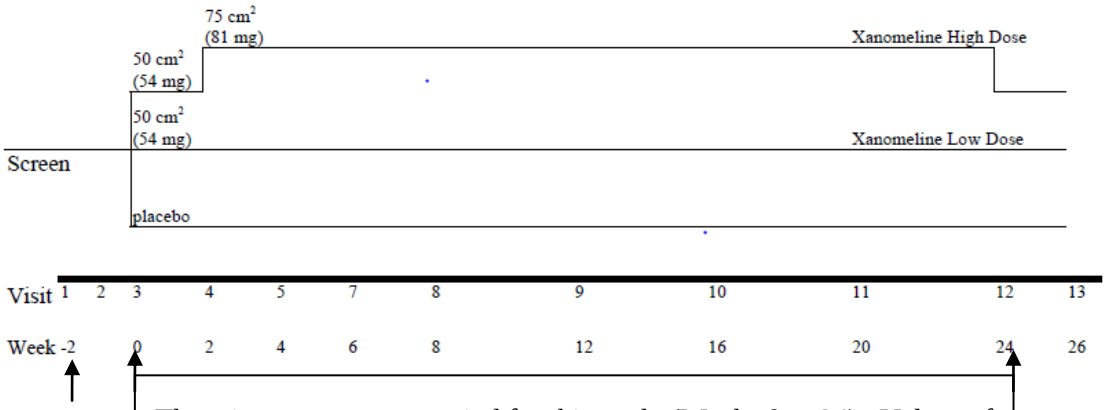
2.1 Protocol Number and Title

Protocol Number: CDISCPILOT01

Protocol Title: Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease

2.2 Protocol Design in Relation to ADaM Concepts

Figure 9-1. Study Schema



There is one treatment period for this study (Weeks 0 to 24). Values of TRT01P and TRT01PN are shown above. Data collected at Visit 1 (Screening) was used to define baseline but otherwise was not summarized for analysis. APERIOD was not used in any analysis

3. Analysis Considerations Related to Multiple Analysis Datasets

3.1 Comparison of SDTM and ADaM Content

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

  No data for screen failures are used for analysis. Therefore, there are no records for screen failures in any analysis dataset

- Are data taken from an ongoing study?

  Data are not taken from an ongoing study

Additional Content of Interest

- Values of baseline are identical between SDTM domains (xxSTRESN where xxBLFL='Y') and ADaM datasets (AVAL where ABLFL='Y')

- Population flags are included in both SDTM (SUPPDM) and in ADaM (ADSL) and have identical values

3.2 Core Variables

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

Variable Name	Variable Description
USUBJID	Unique subject identifier
STUDYID	Study identifier used for this protocol
SITEID	Study Site Identifier
TRTSDT	Date of First Exposure to Treatment
TRTEDT	Date of Last Exposure to Treatment
AGE	Age
AGEGR1	Pooled Age Group 1
AGEGRN1	Pooled Age Group 1 (N)
SEX	Sex
RACE	Race
RACEN	Race (N)

3.3 Treatment Variables

ARM versus TRTxxP

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

  Yes, for this study, the values of ARM and TRT01P are identical. Values of treatment variables are 'Placebo', 'Xanomeline Low Dose', 'Xanomeline High Dose'.

ACTARM versus TRTxxA

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

  The values of ACTARM in SDTM is identical the value of TRT01A. ACTARM is not included in ADSL. TRT01A is included in ADSL and is identical to TRT01P for all subjects.

Use of ADaM Treatment Variables in Analysis

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

  There are no differences between the planned and the actual arm. Therefore, the variables TRT01P, TRTP can be used for all analyses. TRT01A is present only in ADSL.

3.4 Subject Issues that Require Special Analysis Rules

There were no subjects who required any special analysis rules in this study.

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

- Was windowing used in one or more analysis datasets?

  Visit windowing was applied to the efficacy analysis. The same visit windowing rules were used in all analysis datasets where windowing was used. See below in sections 5.2.3 – 5.2.5 for more information.

- Were unscheduled visits used in any analyses?

  Unscheduled visits are present in SDTM but were not used for any analyses.

Additional Content of Interest

- Records that were used for analysis when windowing was present are identified with a value of ANL01FL='Y'
- The data associated with screening or follow up visits were not used for any analyses.

3.6 Imputation/Derivation Methods

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

  Date imputations were performed only for adverse event start dates and only when the day element was missing. In this event, a day value of '01' was used. If day and month were missing, no imputation was done.

Additional Content of Interest

- DTYPE was used in the efficacy analyses. Derivation methods relating to DTYPE='LOCF' and DTYPE='Average' were used. See section 5.2 for more information pertaining to specific analysis dataset where DTYPE is defined.

4. Analysis Data Creation and Processing Issues

4.1 Split Datasets

There were no datasets that were split at the time of submission due to size constraints.

4.2 Data Dependencies

ADSL was used in the creation of all other analysis datasets.

ADLBHY is derived from ADLBC

4.3 Intermediate Datasets

No intermediate analysis datasets were created in this trial.

4.4 Variable Conventions

For laboratory parameters for chemistry and hematology, the values of SDTM LBTESTCD are used for the value of PARAMCD while the text of PARAM indicates the units to the lab test description. For the analysis of chemistry and hematology measures, the parameters that correspond to the change from previous visit use the value of PARAMCD of the observed measured prefixed with an underscore '_'. For example PARAMCD='HGB' is for the observed value of hemoglobin while PARAMCD='_HGB' is used for the change from previous visit value.

5. Subject Data Description

5.2 Overview

- Do the analysis datasets support all protocol specified objectives?
  - Yes, all protocol specified objectives are supported by the analysis datasets.

5.2 Analysis Datasets

Dataset – Dataset Label	CLASS	Efficacy	Safety	Baseline or other subject characteristics	Primary Objective	Structure
ADSL Subject Level Analysis Dataset	ADSL			x		One observation per subject
ADAE Adverse Event Analysis Dataset	OTHER		x			One observation per subject per event
ADLBC Analysis Dataset Lab Blood Chemistry	BDS		x		x	One observation per subject per parameter per timepoint
ADLBH Analysis Dataset Lab Blood Hematology	BDS		x			One observation per subject per parameter per timepoint
ADLBHY Analysis Dataset Lab Hy's Law	BDS		x			One observation per subject per parameter per timepoint
ADVS Vital Signs Analysis Dataset	BDS		x			One observation per subject per parameter per visit
ADQSADAS ADAS-Cog Analysis	BDS	x			x	One observation per subject per visit

Dataset – Dataset Label	CLASS	Efficacy	Safety	Baseline or other subject characteristics	Primary Objective	Structure
ADQSCIBC CIBIC+ Analysis	BDS	x			x	One observation per subject per visit
ADQSNPIX NPI-X Item Analysis Data	BDS	x			x	One observation per subject per visit

5.2.1 ADSL – Subject Level Analysis Dataset

In addition to supporting all analyses, ADSL contains variables to also support baseline characteristics and disposition analyses. The population indicator variables are defined in ADSL and copied into other analysis datasets as needed. All subjects in DM, with the exception of screen failures (52 subjects), were included in ADSL.

5.2.2 ADLBC –Analysis Dataset Lab Blood Chemistry

ADLBC contain one record per lab analysis parameter, per time point, per subject. ADLBC contains lab chemistry parameters and these data are derived from the SDTM LB (Laboratory Tests) domain. Two sets of lab parameters exist in ADLBC. One set contains the standardized lab value from the LB domain and the second set contains change from previous visit relative to normal range values. In some of the summaries the derived end-of-treatment visit (AVISITN=99) is also presented.

5.2.3 ADQSADAS – ADAS-COG Analysis

ADQSADAS contains analysis data from the ADAS-Cog questionnaire, one of the primary efficacy endpoints. It contains one record per subject per parameter (ADAS-Cog questionnaire item) per visit. Visits are placed into analysis visits (represented by AVISIT and AVISITN) based on the date of the visit and the visit windows. If multiple visits fall into the same visit window, then the one closest to the target date is chosen for analysis. Records where ANL01FL='Y' are the ones that were used for analysis. The last observation carried forward (LOCF) algorithm only considered records used for analysis as candidates to carry forward. Records where DTYPE='LOCF' signify those where AVAL was imputed using the LOCF algorithm. Source data can be traced back to the SDTM.QS domain using USUBJID and QSSEQ. Details on how to derive the primary efficacy result based on ADAS-Cog data can be found in the analysis results metadata in the define.xml.

The table below provides information regarding parameters in ADASCOG

PARAMCD	PARAM	Description	Usage

ACITM01-ACITM14	Textual description of each questionnaire item.	Individual item scores for the ADAS-Cog questionnaire	These are supportive parameters
ATOT	ADAS-Cog(11) Subscore	Derived parameter that reflects the total subscore based on the individual item scores	This is the co-primary efficacy parameter where AVISIT='Week 24'

5.2.4 ADQSCIBC – CIBIC+ Analysis

ADQSCIBC contains analysis data from the from CIBIC+ questionnaire, one of the co-primary efficacy endpoints. It contains one record per subject per visit. Note that there is just one parameter in this analysis dataset which represents the score from the CIBIC+ questionnaire and thus all records have PARAM='CIBIC Score' and PARAMCD='CIBICVAL'.

Visits are placed into analysis visits (represented by AVISIT and AVISITN) based on the date of the visit and the visit windows. If multiple visits fall into the same visit window, then the one closest to the target date is chosen for analysis. Records where ANL01FL='Y' are the ones that were used for analysis. The last observation carried forward (LOCF) algorithm only considered records used for analysis as candidates to carry forward.

Records where DTYPE='LOCF' signify those where AVAL was imputed using the LOCF algorithm. Source data can be traced back to the SDTM.QS domain using USUBJID and QSSEQ. Details on how to derive the primary efficacy result based on CIBIC+ data can be found in the analysis results metadata in the define.xml.

5.2.5 ADQSNPIX – NPI-X Item Analysis Data

ADQSNPIX contains one record per subject per parameter (NPI-X questionnaire item, total score, and mean total score from Week 4 through Week 24) per analysis visit (AVISIT). The analysis visits (represented by AVISIT and AVISITN) are derived from days between assessment date and randomization date and based on the visit windows that were specified in the statistical analysis plan (SAP). If multiple assessments fall into the same visit window, then the one closest to the target day is chosen for analysis. Records where analysis flag (ANL01FL) = 'Y' are the ones that were used for analysis. The last observation carried forward (LOCF) algorithm was not used for these data. Source data can be traced back to the SDTM.QS domain using USUBJID and QSSEQ. All the NPI-X parameters, except for the mean total score from Week 4 through Week 24 (NPTOTMN), are from SDTM.QS domain. The value of parameter, NPTOTMN, contains the mean total score for each patient who had any assessments from Week 4 through Week 24. The baseline value of the parameter, NPTOTMN, is the same as the baseline value of total score. The baseline value is a covariate in the analysis of covariance (ANCOVA) model.

The table below provides information regarding parameters in ADQSNPIX

PARAMCD	PARAM	Description	Usage
NPIX01S – NPIX12S	Text description of the individual NPIX questions.	Individual item scores for each NPIX question.	These are the 'data as observed' parameters and reflect the subject's response to each question. No imputation is done. These parameters are included for support.
NPTOT	NPI-X (9) Total Score	Total score for the NPI-X questionnaire	This total score is calculated and available in QS domain. This is included as a secondary efficacy parameter. No imputation was performed if there were missing item scores.
NPTOTMN	Mean NPI-X (9) Total (Week 4 to 24)	Derived parameter that is the average of all available NPTOT scores within the weeks of 4-24.	This is included as a secondary efficacy parameter. The baseline value of this parameter is used as a covariate in the ANCOVA

6. Data Conformance Summary

6.1 Conformance Inputs

- Were the analysis datasets evaluated for conformance with CDISC ADaM Validation Checks?
  - No, only manual checks of ADaM structure to ensure compliance with ADaM IG
- Were the ADaM datasets evaluated in relation to define.xml?
  - Yes
- Was define.xml evaluated?
  - Yes

6.2 Issues Summary

Not applicable

7. Submission of Programs

Only a few programs, which are considered as providing additional value for traceability, are included in the submission. These are all referred to in the define.xml.

Analysis results metadata are provided for all tables in this submission. This analysis results metadata can be found in the define.xml. This results metadata provides all of the necessary information to recreate a given analysis results. The analysis dataset, selection criteria, primary variable, and model statements are provided in a standard format. Because of the volume of analysis results metadata that is provided, only a few actual programs are included as indicated below:

Program name	Output	Inputs	Macros used
adae.sas	adae	ae, adsl,	Flagfrst (internal)
at14-5-02.sas	Table 14-5.02	adtte	none

- Submitted programs will execute on a PC environment running Windows and SAS version 9.2. Library definitions will need to be modified to reflect the actual environment where run.
- Only one SAS Macro is used and it is locally defined within the program. (adae.sas).