# Analysis Data Reviewer's Guide

## CDISC SDTM/ADaM Pilot Project

## CDISCPilot01

ADRG Template Version 2019-07-18

# Analysis Data Reviewer's Guide

## 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 |
|---|---|
| ADaM | Analysis Dataset Model |
| ADRG | Analysis Data Reviewer's Guide |
| CRF | Case Report Form |
| IG | Implementation Guide |
| NA | Not Applicable |
| 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 (with amendment 1) |
| SDTM Controlled Terminology | 2016-09-30 |
| ADaM | V2.0/ IG 1.0 |
| ADaM Controlled Terminology | 2016-09-30 |
| Data Definitions | define.xml v1.0 |
| TAUG (if applicable) | Alzheimer's Disease v2.0 |
| Medications Dictionary | WHO Drug Enhanced B2 Format 01Mar2016 |
| Medical Events Dictionary | Initial: 18.0<br>Final: 18.0 |
| Other standards (optional) | ADaM Data Structure for Adverse Event Analysis v1.0<br>ADAM Basic Data Structure for Time-to-Event Analysis 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

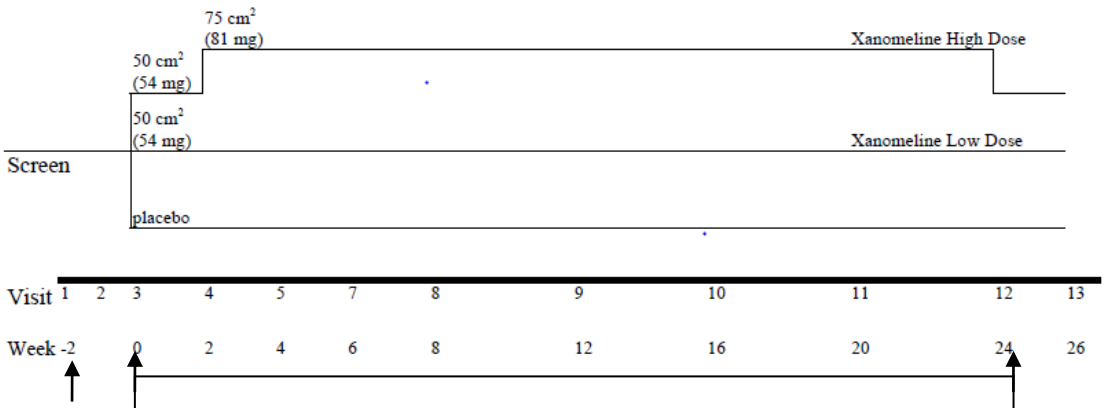
Protocol Number: CDISCPILOT01

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

Protocol Versions: Amendment 1

### 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 Core Variables

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

| Variable Name | Variable Description |
|---|---|
| STUDYID | Study identifier used for this protocol |

| | |
|---|---|
| USUBJID | Unique subject identifier |
| 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) |

## 3.2 Treatment Variables

ARM versus TRTxxP

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

Yes. 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?

Yes. The values of ACTARM in SDTM is identical to 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?

No. 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.

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

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

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

Was windowing used in one or more analysis datasets?

Yes. 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?

No. 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.

### 3.5 Imputation/Derivation Methods

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

Yes. 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.
- 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.

## 4. Analysis Data Creation and Processing Issues

### 4.1 Split Datasets

There are no datasets that required splitting 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.

## 5. Subject Data Description

### 5.2 Overview

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 not used for analysis. Therefore, there are no records for screen failures in any analysis dataset.

Are data taken from an ongoing study?

No. Data are not taken from an ongoing study.

Do the analysis datasets support all protocol specified objectives?

Yes. All protocol specified objectives are supported by the analysis datasets.

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

### 5.2 Analysis Datasets

| Dataset – Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADSL<br>Subject Level Analysis Dataset | ADSL | | | X | | | One observation per subject |
| ADAE<br>Adverse Event Analysis Dataset | OTHER | | X | | | | One observation per subject per event |

| Dataset – Dataset Label | Class | Efficacy | Safety | Baseline or other subject characteristics | PK/PD | Primary Objective | Structure |
|---|---|---|---|---|---|---|---|
| ADLBC<br>Analysis Dataset Lab Blood Chemistry | BDS | | X | | | X | One observation per subject per parameter per timepoint |
| ADLBH<br>Analysis Dataset Lab Blood Hematology | BDS | | X | | | | One observation per subject per parameter per timepoint |
| ADLBHY<br>Analysis Dataset Lab Hy's Law | BDS | | X | | | | One observation per subject per parameter per timepoint |
| ADVS<br>Vital Signs Analysis Dataset | BDS | | X | | | | One observation per subject per parameter per visit |
| ADQSADAS<br>ADAS-Cog Analysis | BDS | X | | | | X | One observation per subject per visit |
| ADQSCIBC<br>CIBIC+ Analysis | BDS | X | | | | X | One observation per subject per visit |
| ADQSNPIX<br>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

Specify the software name and version for the analysis datasets

NA. Only manual checks of ADaM structure to ensure compliance with ADaM IG.

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

NA

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

NA

# 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 datesets is January 1, 1960.

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.

## 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 |

| Program Name | Output | Macro Used |
|---|---|---|
| adexd.txt | adexd | attrib |
| adexs.txt | adexs | attrib |
| adges.txt | adges | attrib |
| adhads.txt | adhads | attrib |
| 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 Frequencycacy - ITT | ADSZP |
| t_predopbo.txt | 7.1.2 | Percent Reduction Over Placebo for 28-Day Adjusted POS Frequencycacy - 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 |

| Program Name | Output Number | Title | Input |
|---|---|---|---|
| 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. |