February 9, 2007

Food and Drug Administration
Center for Drug Evaluation and Research
5901-B Ammendale Road
Beltsville, MD 20705-1266

Re: CDISC Pilot Project, SDTM Sample Submission, Sample Number 900171

Dear Sir/Madam:

The objective of the CDISC SDTM/ADaM Pilot Project is to test the concept that data submitted to the FDA using CDISC standards will meet the needs and the expectations of the FDA reviewers, including assessing the data structure/architecture, resources and interoperability needed to transform data from legacy data sets into the SDTM and ADaM formats. The original submission was submitted in July, 2006. The comments made by reviewers regarding the original submission have been addressed. This revised submission is intended to allow the reviewers to evaluate the modifications. This submission includes one abbreviated study report, Study CDISCPILOT01, which documents the analysis results of the legacy data for this first pilot submission. The primary changes made to the submission are in the datasets and the data definition table.

In addition to the abbreviated study report, this revised submission contains the tabulation and analysis datasets associated with the study, as well as all necessary metadata documentation. This metadata documentation includes the annotated CRF, as well as the data definition table, in define.xml format. The tabulation data provided has been modeled to be in compliance with the SDTM Implementation Guide, Version 3.1.1 and SDTM, Version 1.1, the analysis data is in compliance with Analysis Data Model Version 2.0, and the define.xml is in compliance with CRT-DDS version 1.0 and ODM version 1.3**.** As this submission is intended only to be used for the purposes of a mock review, additional submission components beyond those provided for Study CDISCPILOT01 are not provided. An ASCII text file containing the patient narratives is also provided. This text file (named "narrative.txt") can be found in the same directory as the study report (900171/m5/53-clin-stud-rep/535-rep-effic-safety-stud/5351-stud-rep-contr/cdiscpilot01).

A Reviewers' Guide, included as an attachment to this cover letter, is provided to frame the review and assessment of the pilot submission by the FDA.

*[[NOTE: Text from the actual cover letter deemed not pertinent to the published example has been removed.]]*

# CDISC Pilot Project, Sample Number 900171
# Reviewers' Guide

## Purpose of the CDISC Pilot Project Submission

The objective of the CDISC SDTM/ADaM Pilot Project is to demonstrate the effective transformation of legacy data into CDISC SDTM domains and analysis datasets, as well as their associated metadata. This submission contains a "pilot submission" which is intended to be used by reviewers in a mock review, assessing whether data submitted to the FDA using the CDISC Standard will meet the needs and expectations of both medical and statistical FDA reviewers. The submission is not intended to prove or disprove efficacy and safety of a drug; therefore not all components of the legacy study, as discussed in the protocol, have been included in this submission package.

This submission includes one abbreviated study report, Study CDISCPILOT01, which documents the analysis results of the legacy data for this first pilot submission. The purpose of the study report is to test the summarizing of results and the linking to the metadata, as well as providing results or findings for the FDA reviewers to review and/or reproduce.

The legacy data being used in CDISCPILOT01 were provided by Eli Lilly and Company (Legacy Sponsor) for the purposes of this CDISC Pilot Project. The data were de-identified and documents were redacted prior to release to the CDISC Pilot Project team. De-identification included changing dates and shifting them into the future. All chronological relationships and sequences were maintained within the data elements for a subject (e.g., no change in the relationship of timing of adverse events with respect to dosing). This submission does not reproduce all of the Legacy Sponsor's analyses and reports, nor does it include all of the data from the legacy study. Instead only the more common elements of a submission are addressed. These included primary and some secondary safety data, the primary efficacy endpoints, a few secondary efficacy endpoints, and a representative set of analyses of these endpoints as specified in the protocol. The protocol provided is from the original study, though redacted. Deviations from the protocol-specified analyses are described in the statistical analysis plan created specifically for this study as part of the CDISC Pilot Project. The statistical analysis plan also describes some additional analyses included to test other aspects of the standards.

## Standards / Tools Used

The following standards and tools were used in creating this pilot submission:

- SDTM Implementation Guide Version 3.1.1
- SDTM Version 1.1
- Analysis Data Model Version 2.0 as issued for public comment in March, 2006
- CRT-DDS version 1.0
- ODM version 1.3 (public comment period closed on May 2, 2006)

- Consistent with CDISC's direction, CRTDDS were provided in XML for greatest flexibility (DEFINE.XML). The XML provided is an extension of ODM 1.3, with new elements added to support the ADaM Analysis Results Metadata. The underlying XML schema are illustrative of how Analysis Results Metadata could be implemented. The schema will likely change when formally vetted by CDISC ODM/DEFINE team. To be human readable, XML requires a stylesheet. The stylesheet used for the pilot submission was developed by members of the pilot team. It illustrates what the pilot team feels is a minimally-functional yet desirable rendering for the CRTDDS in a web browser. The present rendering is based on the traditional DEFINE.PDF, but the DEFINE.XML but could be rendered differently if desired.
- The datasets are in the version 5 SAS transport format.
- SAS version 9.1.3 was used to produce the final package.
- MedDRA version 8.0 was used to code the adverse events, with the higher level terms, the higher level group terms, and the verbatim terms masked. (The masking was necessary to meet licensing requirements for the use of MedDRA in this submission package because the package is intended to be made available to the public.)
- A sample of the WHO Drug Dictionary was downloaded for use in coding concomitant medications (http://www.umc-products.com/DynPage.aspx?id=2844) on 25 April 2006.

## Summary of Components of this Submission

This submission includes one abbreviated study report, Study CDISCPILOT01, documenting the analysis results of the legacy data for this first pilot submission.

The folder structure being used for the package is a hybrid eCTD/NDA table of contents. Module 1 contains the cover letter. Module 5 contains the clinical study report and the associated data and metadata. Both analysis datasets and tabulations datasets are included.

As requested by the FDA Review Team, sample patient narratives of the three deaths that occurred during the trial were included in the CSR. The patient narratives are also provided in this submission package as a separate ASCII text file ("narrative.txt") found in the same directory as the study report (900171/m5/53-clin-stud-rep/535-rep-effic-safety-stud/5351-stud-rep-contr/cdiscpilot01).

It was requested that a single DEFINE file be provided for the reviewers, to facilitate navigating among the information. However, it was also requested that two DEFINE files be provided to facilitate the storing of the DEFINE files in the folders with the datasets. The Pilot team decided to create a single DEFINE file that behaves in an identical fashion whether it is placed with the tabulations datasets, or the analysis datasets. In the CDISCPILOT01 submission, this DEFINE file is present in both the tabulations datasets folder and the analysis datasets folder.

Also, the DEFINE is included in the submission in a "framed" version – with a left-side navigation pane – but also as a "non-framed" version. The framed version is named "define.xml", and the non-framed version is "define_noframes.xml".

The framed version is specific to Internet Explorer, but offers much superior navigation capabilities. When the framed version is opened, Internet Explorer may warn that it has restricted a webpage from running scripts or ActiveX controls. To see the define.xml, the reader must right-click on the yellow warning bar and 'Allow Blocked Content'.

The non-framed version is not specific to Internet Explorer, and will open without warnings. However, in Internet Explorer 6, the non-framed version can be especially difficult to navigate due to a known bug with the 'Back' button in IE6.

### *Analysis datasets and metadata:*

- According to ADaM Version 2.0, analysis datasets only need to be provided for key analyses, as defined and agreed upon by the sponsor and reviewers. For the purposes of this mock submission, analysis datasets are provided for each analysis included in the package with the exception of the concurrent medication summary.
- No analysis dataset creation or analysis generating programs are included in the package because we expect the metadata to provide sufficient detail for the review. If this proves to not be true, we are prepared to revise the metadata or provide programs if necessary.
- The analysis results metadata could be used as a table of contents for the analyses, as links are included to the analysis datasets and to the sections of the SAP where the specified analysis is described. According to ADaM Version 2.0, analysis results metadata would be provided for key or difficult analyses. For the purpose of this mock submission, each analysis included in the abbreviated report is included in the analysis results metadata for illustrative purposes.

### *SDTM datasets and metadata:*

- The FDA reviewers requested that all five levels of MedDRA coding be included in the tabulation datasets. The three levels not currently included in the SDTM AE model (HLGT, HLT, LLT) were included in the supplemental qualifiers domain for AE (i.e. SUPPAE). The values of HLGT and HLT are masked by using non-informative terms (e.g. HLGT_0152) to protect the copyright and licensing agreement of MedDRA.
- Derived data (i.e., fields that involved calculations or manipulations of the CRF data, rather than simply all fields whose origin in the DDT is designated as "derived") are included in SDTM. These data include baseline and population flags, as described in the SDTM Implementation Guide. In addition, the following derived data are included in the tabulation datasets:
    - Adverse event treatment emergent flag (in SUPPAE)
    - ADAS-Cog(11) total (added as a record in QS)
    - NPIX Item Scores, computed from the CRF data (added as records in QS)
    - Endpoint flag for lab data (in SUPPLB)

- Derived value of LBTMSHI (defined as result/ULN) for lab data (in SUPPLB)

### *Naming Conventions:*

The following naming conventions were used as much as possible in the analysis datasets, given the restriction to 8 characters for variable names:

- If the variable came from SDTM with no changes, the name remained the same.
- Append an 'N' to the variable name for a numeric version of a variable (e.g., RACE and RACEN).
- In the analysis datasets, the treatment variables are TRTP (long description), TRTPCD (short description) and TRTPN (numeric version).

| Fragment | Indicates |
|---|---|
| GRP<br>GRPN | group variable |
| DT | date variables |
| ITM | item value |
| TOT | total value |
| BL | baseline value |
| CH | change from Baseline value |
| EN | value observed at Week 24 or Discontinuation visit |
| U | units |

### *Interesting Characteristics of the DEFINE file*

In the listing of the Variable Metadata, there is a column headed "COMMENT." The column is empty in the tabulations portion of the DEFINE file. In the DEFINE file provided with the submission, the Comment column for the analysis datasets lists the datasets that contribute to the identified variable, and provide active links to the DEFINE metadata for those datasets. For example, CUMDOSE in ADSL is computed using data from the SV domain and other data in ADSL.

## Navigation Tips

Basic PDF navigation, using hyperlinks from blue or boxed text or via bookmarks will be the primary method of navigating the PDF. As mentioned above, this submission does contain a DEFINE.XML file instead of a DEFINE.PDF, so we have provided some tips for navigating this, as well as describing some helpful advanced PDF navigation which might help in the review process.

### *DEFINE.XML*

As mentioned above, the DEFINE.XML file and the DEFINE_NOFRAMES.XML file are included in both the analysis data folder and in the tabulations folder. Both copies are identical and include references to all data. Both copies also include the same stylesheets, so they render (in Internet Explorer 6) identically. Because the DEFINE file has information describing 1) the Analysis Results metadata, 2) the Analysis datasets, 2) and 3) the SDTM datasets, the DEFINE file starts with a "mini-TOC" to help navigation links to one of these three major sections of the DEFINE.XML file, as well as to the

Reviewer's Guide. The Analysis Results table is new with ADaM 2.0, and is described below. The two sections concerning datasets correspond to the high-level tables that typically start every DEFINE.PDF file. Each of these tables contains information about their data and links to more detailed Data Description Tables (DDT's) of information, very similar to traditional DEFINE.PDF files.

The Analysis Results Metadata Summary table provides links to Analysis Results Metadata Detail tables. The latter tables provide information related to each table or figure in the study report, including links to the study report, to relevant sections of the protocol or analysis plan, and to the detail tables (DDT) for the Analysis Dataset(s) used to create the table.

In addition to the mini-TOC, the three high-level tables, and the DDT's, there are additionally the Computational Methods section and a Controlled Terminology (Code Lists) section which are linked to from various places within the DDT's.

The framed version of DEFINE.XML provides a left-side navigation pane that allows the reader to easily find a desired section of the document, as well as individual detail tables.

As noted earlier, there is a known problem relating to the use of the Internet Explorer 6 "BACK" button, when navigating the non-framed version DEFINE_NOFRAMES.XML. This issue can make navigation very difficult in IE6. Internet Explorer 7 and Firefox browser do not exhibit this difficulty.

The Analysis Results Metadata and the DDT tables for the SDTM have links to portions of PDF documents, such as the study report and annotated CRF, that are external to the DEFINE file. Depending on a setting in the Adobe Reader (not in the browser), those links behave differently. The following procedure describes the setting that has worked optimally for Pilot team members:

1. Open Adobe Reader, select 'Edit > Preferences' to produce a dialog with a pane labeled 'Categories'.
2. Select 'Internet' in the pane, and make sure that the option 'Display PDF in Browser' is checked.
3. Click OK.

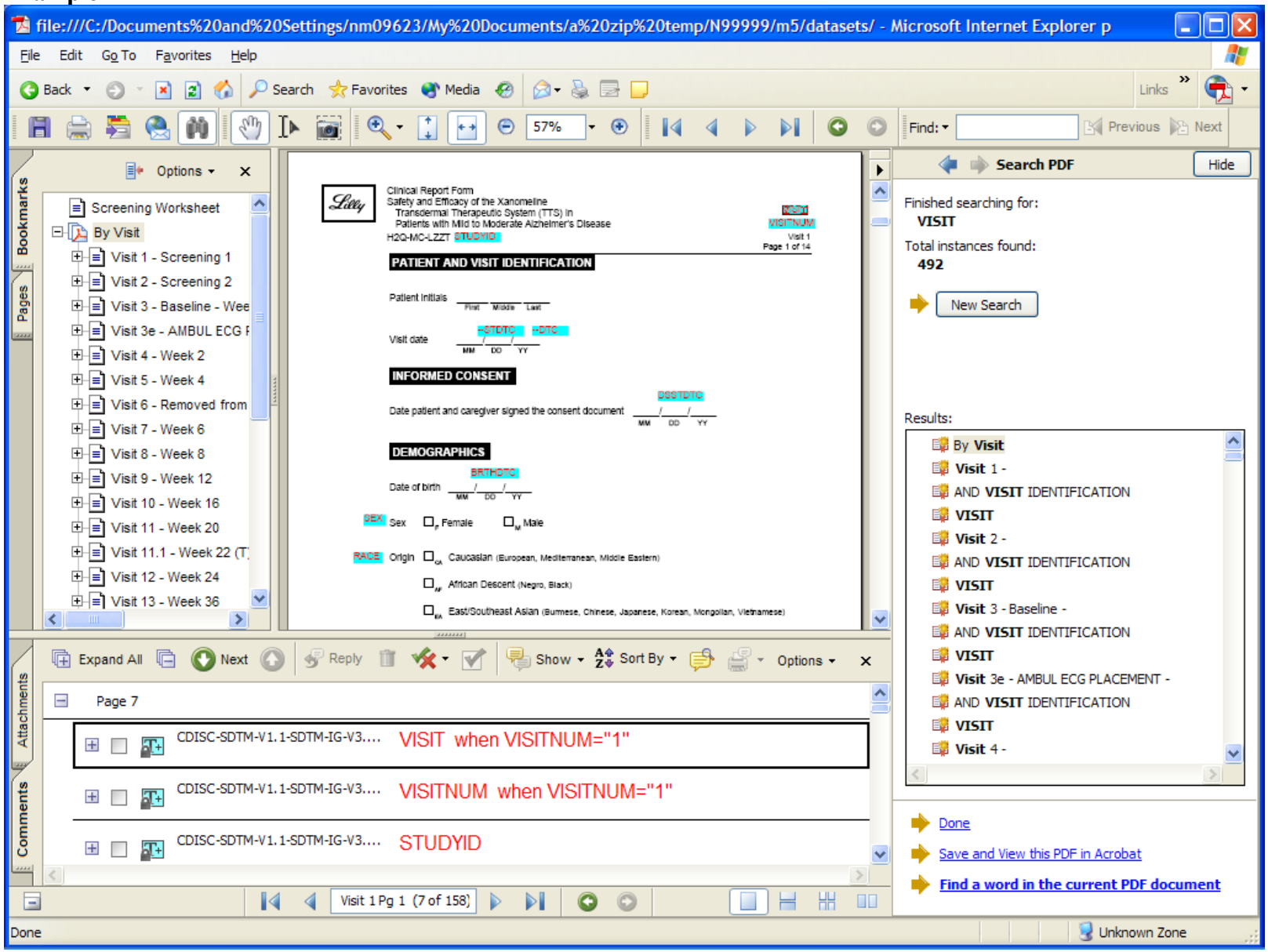
The DEFINE.XML DDT tables for the SDTM data have links to data annotated in the BLANKCRF.PDF. This PDF file was annotated using the Adobe Acrobat 7 commenting tool. You will see that this annotated CRF was created to provide a "clean" look for the reviewer, making sure that the annotations did not obscure the CRF data. As you may see in the screen image on Example 1 , many annotations contain more information than what is displayed on the screen (such as the example of "VISIT" which is highlighted). The "visible" information is the variable name, as is traditionally annotated, but the additional information in the comment pane may provide more detail about the variable. This is particularly helpful in the SDTM datasets when many tests use the same variable name (example QSTESTCD) but each test as a different value. The complete annotation

information may help understand the origin of discrete values, particularly when variables are recorded on multiple pages.

### *STUDY REPORT*

The study report is navigated as any standard PDF. The original submission included PDF links from the tables and figures in the study report to the DDT within the DEFINE.XML file where the table or figure is explained. These links no longer seem to work with the changes made to the package, so have been removed in the revised package. This issue will go on our list of outstanding issues to be addressed in future iterations of the pilot project.

**Example 1**


file:///C:/Documents%20and%20Settings/nm09623/My%20Documents/a%20zip%20temp/N99999/m5/datasets/ - Microsoft Internet Explorer p
Clinical Report Form
Safety and Efficacy of the Xanomeline Transdermal Therapeutic System (TTS) in Patients with Mild to Moderate Alzheimer's Disease
PATIENT AND VISIT IDENTIFICATION
INFORMED CONSENT
DEMOGRAPHICS
Search PDF
Finished searching for:
VISIT
Total instances found:
492
New Search
Results:
By Visit
Visit 1 -
AND VISIT IDENTIFICATION
VISIT
Visit 2 -
AND VISIT IDENTIFICATION
VISIT
Visit 3 - Baseline -
AND VISIT IDENTIFICATION
VISIT
Visit 3e - AMBUL ECG PLACEMENT -
AND VISIT IDENTIFICATION
VISIT
Visit 4 -
CDISC-SDTM-V1.1-SDTM-IG-V3.... VISIT when VISITNUM="1"
CDISC-SDTM-V1.1-SDTM-IG-V3.... VISITNUM when VISITNUM="1"
CDISC-SDTM-V1.1-SDTM-IG-V3.... STUDYID
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