U.S. FOOD & DRUG ADMINISTRATION

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH
OFFICE OF TRANSLATIONAL SCIENCES
OFFICE OF BIOSTATISTICS

STATISTICAL REVIEW AND EVALUATION

NDA/BLA #:	BLA 111111 (R pilot 3 submission)
Applicant:	R Consortium's R Submission Working Group
Statistical Analyst	Hye Soo Cho — Hye Soo Cho -S — Digitally signed by Hye Soo Cho -S Date: 2024.08.06 12:30:05 -04'00'
	Youn Kyeong Chang — Youn Kyeong Chang -S — Digitally signed by Youn Kyeong Chang -S Date: 2024.08.06 12:34:59 -04'00'
Secondary Reviewer	Paul Schuette — Paul H. Schuette -S — Digitally signed by Paul H. Schuette -S Date: 2024.08.08 11:29:59 -04'00'
Supervisor	Maria Matilde Kam — Maria M. Kam -S — Digitally signed by Maria M. Kam -S Date: 2024.08.08 12:14:05 -04'00'
Date(s):	August, 2024
Objective of the submission	Utilize R to produce Pilot 1 ADaM (Analysis Data Model) datasets from SDTM (Study Data Tabulation Model) datasets and generate Pilot 1 tables, listings, and figures (TLFs) using Pilot 3 R derived ADaM datasets
Location of datasets and programs	BLA111111\0006 and 0007
Reviewed tables and figures	Demographic Table, Primary Table, Efficacy Table, and Kaplan Meier (KM) Figure using R generated ADaM datasets

Pilot 3 Application Review

The R Consortium's R Submission Working Group submitted Pilot 3 (using R to derive Pilot 1 ADaM datasets from SDTM datasets) in August 2023. The objective of this pilot submission is to use R not only for analysis and visualization but also for data preparation in a regulatory submission to the FDA. The applicant used R to transform and manipulate SDTM datasets into ADaM datasets, and to produce the four analyses from Pilot 1. Note: in Pilot 1, the SDTM datasets were not included in the submission, and the applicant used the SAS derived ADaM datasets.

Pilot 3 was developed in R Posit Cloud using R version 4.2.3 on a Linux platform, and FDA reviewed it in RStudio Desktop using R version 4.2.3 on a Windows platform. The ADaM datasets as well as analysis results between Pilot 1 and Pilot 3 were expected to be identical, and no major discrepancies were observed. The analyses replicated by the FDA review team can be found in the Analysis Results Replication by FDA section below.

To evaluate the submission, the FDA review team completed the following tasks:

- Receive the electronic submission package in eCTD approved formats.
- Install and load open-source R packages used in the submission and the applicant developed pilot3utils package.
- Review Analysis Data Reviewer's Guide (ADRG).
- Run R code to derive five Pilot 1 ADaM datasets from SDTM datasets. The five ADaM datasets are the following:
    - ADSL: Subject-Level Analysis Dataset
    - ADADAS: Alzheimer's Disease Assessment Scale–Cognitive Subscale (ADAS-COG) Analysis Dataset
    - ADAE: Adverse Events Analysis Dataset
    - ADLBC: Analysis Dataset Lab Blood Chemistry
    - ADTTE: Adverse Event (AE) Time to 1st Dermatologic (Derm.) Event Analysis
- Compare the R derived ADaM datasets in Pilot 3 and the SAS derived ADaM datasets in Pilot 1.
- Run R code to produce four TLFs using the derived ADaM datasets in Pilot 3. The four TLFs are the following:
    - Table 14-2.01 - Demographic and Baseline Characteristics
    - Table 14-3.01 - Primary Endpoint Analysis: ADAS Cog (11)
    - Table 14-3.02 - Analysis of Covariance (ANCOVA) of Change from Baseline at Week 20
    - Figure 14-1 - KM plot for Time to First Dermatologic Event: Safety population
- Compare four TLFs from Pilot 3 and Pilot 1.
- Review re-submissions (exploring the zip file approach).
- Identify issues and provide potential solutions.
- Share potential improvements to the submission deliverables and processes via a written communication.

The Pilot 3 submission materials and communication are publicly available[1].

In contrast to the previous Pilot 2, two different approaches for loading R packages in the FDA computing environment were investigated in Pilot 3. First, the renv package was employed to create a reproducible environment for R package using renv.lock file directly. Second, the applicant explored delivering the applicant developed pilot3utils R package as a zip file through the eCTD gateway. The zip file approach was part of the resubmission from April 2024. These details and additional discussion points are summarized in the Issues and Implementation section below.

[1] https://rconsortium.github.io/submissions-wg/pilot3.html

Analysis Results Replication by FDA (based on the resubmission)

- **R derived ADaM datasets from SDTM datasets**

During the implementation of Pilot 3, the applicant identified discrepancies between the ADaM datasets from Pilot 1 and ADaM datasets generated using R in Pilot 3, as noted in Appendix 2 of the ADRG. Although there were discrepancies, they did not affect the replication of the four TLFs.

Differences were also observed in attributes, data types (such as integer vs. double), and handling of missing values (such as NA vs. NULL). The applicant conducted a thorough investigation into these differences and confirmed that they did not impact the analysis.

- **Four Tables, Listing, and Figures**

The applicant produced the four TLFs using different file extensions (such as .out and .rtf) and formats to explore broader use-case scenarios and encompass different formatting options. FDA was able to replicate the results below without any discrepancies between Pilot 1 and Pilot 3. Below are the tables generated independently by the FDA review team using the ADaM datasets created using R in Pilot 3.

Table 14-2.01 Summary of Demographic and Baseline Characteristics

	Placebo N=86	Xanomeline Low Dose N=84	Xanomeline High Dose N=84
Age			
Mean (SD)	75.21 (8.59)	75.67 (8.29)	74.38 (7.89)
Median	76.00	77.50	76.00
Min, Max	52.0, 89.0	51.0, 88.0	56.0, 88.0
Pooled Age Group 1			
<65	14 (16)	8 (10)	11 (13)
65-80	42 (49)	47 (56)	55 (65)
>80	30 (35)	29 (35)	18 (21)
Race			
White	78 (91)	78 (93)	74 (88)
Black or African American	8 (9)	6 (7)	9 (11)
American Indian or Alaska Native	0 (0)	0 (0)	1 (1)
Baseline Height (cm)			
Mean (SD)	162.57 (11.52)	163.43 (10.42)	165.82 (10.13)
Median	162.60	162.60	165.10
Min, Max	137.2, 185.4	135.9, 195.6	146.1, 190.5
Baseline Weight (kg)			
Mean (SD)	62.76 (12.77)	67.28 (14.12)	70.00 (14.65)
Median	60.55	64.90	69.20
Min, Max	34.0, 86.2	45.4, 106.1	41.7, 108.0
Missing	0	1	0
Baseline BMI ($kg/m^{2)}$			
Mean (SD)	23.64 (3.67)	25.06 (4.27)	25.35 (4.16)
Median	23.40	24.30	24.80
Min, Max	15.1, 33.3	17.7, 40.1	13.7, 34.5
Missing	0	1	0
MMSE Total			
Mean (SD)	18.05 (4.27)	17.87 (4.22)	18.51 (4.16)
Median	19.50	18.00	20.00
Min, Max	10.0, 23.0	10.0, 24.0	10.0, 24.0

Source: adsl.xpt

Table 14-3.01 Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

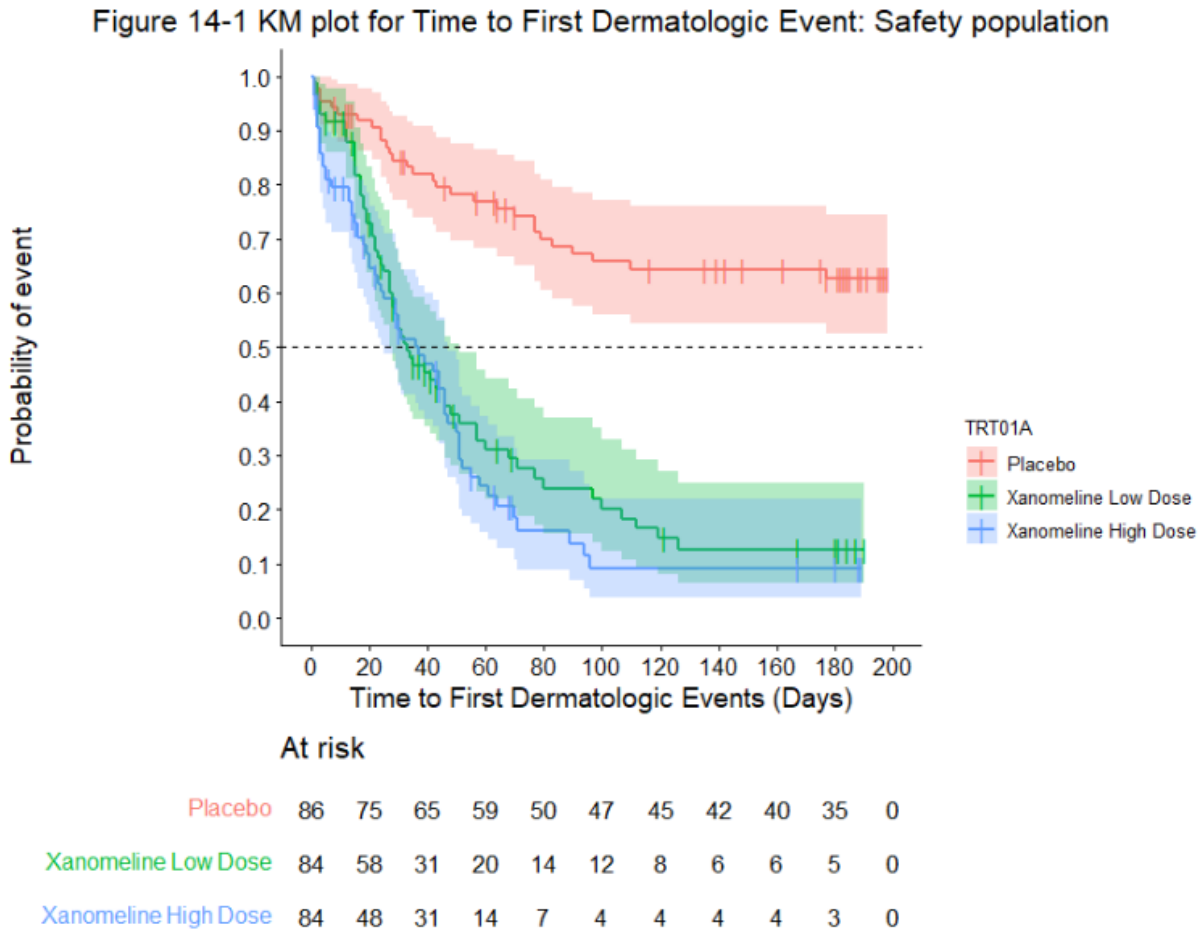
Parameter	Placebo	Xanomeline Low Dose	Xanomeline High Dose
Baseline			
n	79	81	74
Mean (SD)	24.1 (12.19)	24.4 (12.92)	21.3 (11.74)
Median (Range)	21.0 (5;61)	21.0 (5;57)	18.0 (3;57)
Week 24			
n	79	81	74
Mean (SD)	26.7 (13.79)	26.4 (13.18)	22.8 (12.48)
Median (Range)	24.0 (5;62)	25.0 (6;62)	20.0 (3;62)
Change from Baseline			
n	79	81	74
Mean (SD)	2.5 (5.80)	2.0 (5.55)	1.5 (4.26)
Median (Range)	2.0 (-11;16)	2.0 (-11;17)	1.0 (-7;13)
p-value (Dose Response) [1][2]			0.245
p-value (Xan - Placebo) [1][3]		0.569	0.233
Diff of LS Means (SE)		-0.5 (0.82)	-1.0 (0.84)
95% CI		(-2.1;1.1)	(-2.7;0.7)
p-value (Xan High - Xan Low) [1][3]			0.520
Diff of LS Means (SE)			-0.5 (0.84)
95% CI			(-2.2;1.1)

Source: adadas.xpt; Software: R version 4.2.3 (2023-03-15 ucrt)
[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.
[2] Test for a non-zero coefficient for treatment (dose) as a continuous variable
[3] Pairwise comparison with treatment as a categorical variable: p-values without adjustment for multiple comparisons.

Table 14-3.02 ANCOVA of Change from Baseline at Week 20

	Baseline[a]		Week 20		Change from Baseline		
Treatment	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)	LS Mean (95% CI)[b]
Xanomeline High Dose	84	5.4 (1.34)	31	5.8 (1.61)	31	0.2 (1.47)	0.16 (-0.31, 0.63)
Placebo	86	5.6 (2.14)	65	5.8 (1.50)	65	0.1 (2.08)	0.09 (-0.23, 0.42)
Pairwise Comparison				Difference in LS Mean(95% CI)[b]			p-Value
Xanomeline High Dose - Placebo				0.07 (-0.50,0.63)			0.822
Root Mean Squared Error of Change = 1.30							

[a] Table is based on participants who have observable data at Baseline and Week 20.
[b] Based on an Analysis of covariance (ANCOVA) model with treatment and baseline value as a covariate.
CI = Confidence Interval, LS = Least Squares, SD = Standard Deviation
Source: adlbc.xpt; Software: R version 4.2.3 (2023-03-15 ucrt)



Issues and Implementation

- **Controlling the R environment**

Controlling the R environment in a regulatory submission is essential to ensure reproducibility and maintain consistency in results because different versions of R and deployed packages can potentially produce different results due to updates, bug fixes, or changes in underlying algorithms. Pilots 1 and 2 were developed on a Linux platform using R version 4.1.2, whereas Pilot 3 was developed on a Linux platform with R version 4.2.3. Pilot 3 employed a more recent R version compared to Pilots 1 and 2 because R version 4.1.2 was not available in R Posit Cloud when the applicant started Pilot 3. During the FDA review, running the Pilot 3 R code with an R version older than 4.2.3 resulted in errors related to dynamic link libraries, likely due to compatibility issues with different R versions. Furthermore, switching between versions of R posed additional complications. As a best practice, it is recommended that sponsors engage the FDA review team early in the planning stages to agree upon specific versions of R along with compatible R package versions. The R Consortium's R Submission Working Group has discussed what a stable R version could be and how some pharmaceutical companies internally manage this challenge. More details can be found in this blog post[2].

[2] https://www.r-consortium.org/blog/2024/06/24/the-crucial-role-of-release-control-in-r-for-healthcare-organizations

- **Submitting the renv.lock file**

According to the FDA Study Data Technical Conformance Guide – Technical Specifications Document[3] and Specifications for File Format Types Using eCTD Specifications[4], sponsors should provide the source code used to create all ADaM datasets, tables, and figures associated with primary and secondary efficacy analyses. Sponsors should submit source code in a text file, not an executable file (.cmd, .com, or .exe). In Pilots 1 and 2, the applicant utilized the pkglite package as a tool for packing multiple R packages into a single text file and transferring it to FDA. In Pilot 3, instead of using pkglite package, the applicant proceeded with the following approach.

1. Changing renv.lock to renv-lock.txt as .lock is not listed in the technical conformance guide
2. Submitting renv-lock.txt with instructions in the ADRG to change the extension to .lock when unpacking the Pilot 3 package (i.e. renaming renv-lock.txt to renv.lock)

FDA was able to install the R packages used in Pilot 3 without any issues.

- **Installing a R package from a zip file**

In Pilot 3, the pilot3utils package was initially included in the renv package. However, this approach failed to successfully install the pilot3utils package. Consequently, the applicant decided to proceed with separate steps: loading other R packages using renv and installing the pilot3utils package separately. Additionally, instructions were provided on how to install the pilot3utils package directly from its public GitHub repository. Moreover, the applicant explored delivering the pilot3utils package as a zip file through the eCTD gateway. For the resubmission, the applicant submitted the source file for the package as a zip file along with the renv package to manage dependencies from CRAN[5] (Comprehensive R Archive Network).

An issue arose regarding the filename of the zip file. Typically, R package zip files follow a naming convention that combines the package name with its version number. The package name and version are linked with an underscore ("_") and the version number itself includes major, minor, and patch numbers separated by dots (".”). For example, a standard R package zip file might be named as name_0.0.1.zip. The applicant adhered to this convention and submitted the zip file named pilot3utils_0.0.2.zip. However, according to an eCTD guidance[6], files and folder names must only contain letters, numbers, hyphens, or underscores; spaces or special characters such as periods (".”), are not permitted. Therefore, to comply with FDA requirements when submitting an R package zip file, it is necessary to rename it accordingly and provide instructions for renaming as part of the submission.

- **Formatting date and time variables**

Correctly formatting date and time variables ensure that the data is represented accurately and consistently across different programming language and analyses. When the derived ADaM datasets in Pilot 3 and ADaM datasets in Pilot 1 were compared, it was discovered that the date variables in the

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/study-data-technical-conformance-guide-technical-specifications-document
[4] Specifications for File Format Types Using eCTD Specifications
[5] https://cran.r-project.org/
[6] eCTD guidance

ADLBC dataset (i.e., variables for analysis date and date of first and last exposure to treatment) in Pilot 1 were numerically stored as days since time 0 (the reference point for time calculations), which is not CDISC compliant. This feature was not caught in the Pilot 1 review as an appropriately derived AVISIT variable was used in the analyses.

SAS and R apparently have different conventions for time 0. R often uses the Unix epoch (January 1, 1970, UTC) as time 0, while SAS can use a different starting point, namely January 1, 1960. Converting the numerically formatted variables into appropriate formatted date and time variables without detailed information can lead to discrepancies in calculation and analyses. Such discrepancies could potentially impact the interpretation and outcomes of clinical trials. Therefore, it is recommended to be consistent with CDISC guidelines and use the ISO 8601, which is an internationally recognized standard for accurately representing dates, times, and time intervals. If any, clear conversion procedures of date and time variables, such as specifying origin, should be provided.

- **Some additional recommendations**

The applicant submitted the Pilot 3 with relative file path for a directory location and incorrect names for a folder and package. It is recommended to specify full path and document accurate names to ensure that reviewers can easily follow the instructions without encountering any problems. As part of minor revisions, corrections were made to package names (i.e., changing 'pilot3' to 'pilot3utils'), and the applicant provided detailed steps to execute the analyses using R in their ADRG.