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 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: 2023.09.25 17:33:08 -04'00' |
| **Secondary Reviewer** | Paul Schuette Paul H. Schuette -S Digitally signed by Paul H. Schuette -S Date: 2023.09.26 08:56:54 -04'00' |
| **Supervisor** | Maria Matilde Kam Maria M. Kam -S Digitally signed by Maria M. Kam -S Date: 2023.09.27 12:07:27 -04'00' |
| **Date(s):** | August, 2023 |
| **Objective of the submission** | To test whether a Shiny application (app) created with the R-language can be successfully incorporated into a submission package and deployed to FDA reviewers. |
| **Location of datasets and programs** | BLA111111\0005 |
| **Reviewed tables and figures** | Demographic Table, Kaplan Meier (KM) plot for time to first dermatologic event (TTDE), Primary Table, Efficacy Table, and Visit Completion Table in the Shiny app |

## Pilot 2 R Shiny Application Review

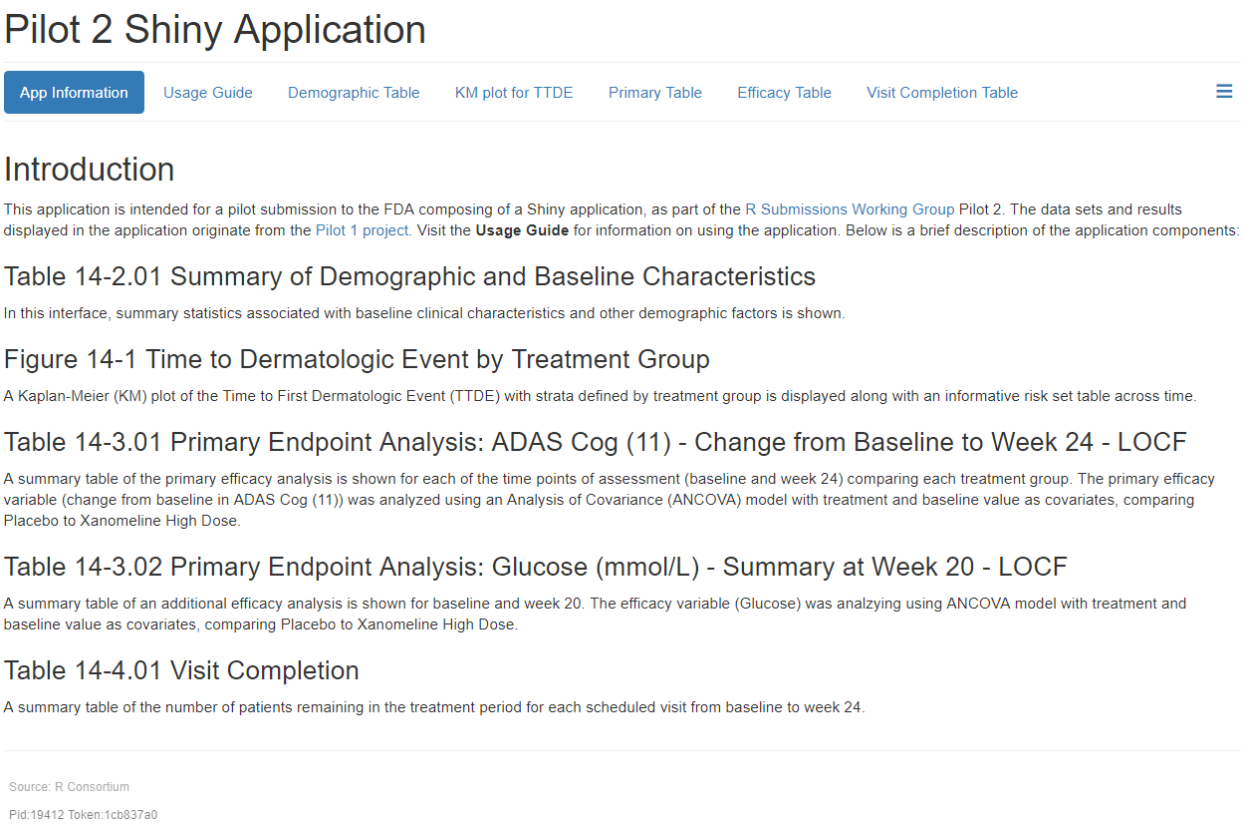
R Consortium's R Submission Working Group submitted the Pilot 2 R Shiny application (app) in November 2022. The objective of this pilot submission was to test whether a Shiny app created with the R-language could be successfully incorporated into a submission package and deployed to FDA reviewers. The app was built using the same source data sets and analyses contained in the Pilot 1 submission. This app is supplemental to the analysis programs and analyses submitted in Pilot 1. It is recommended that sponsors continue to follow the Study Data Technical Conformance Guide (SDTCG), and that any Shiny apps be provided as exploratory supplements rather than as replacements of required statistical programs, tables, listings, or figures. Note that the app is a supplementary material and does not replace any of R programs submitted in the Pilot 1. In future R based FDA submission, a Shiny app should be supplemental and should not replace any of analysis programs. Figures 1 - 7 show snapshots of each individual tab of the Pilot 2 Shiny App. Figure 1 illustrates the app information and provides a list of outputs with brief explanation. Figure 2 shows the relationship between each tab of Pilot 2 and previously submitted analysis from the Pilot 1 as well as a step-by-step example of how to use filters for the Kaplan

Meier (KM) plot. Figure 3 shows a summary of demographic and baseline characteristics table. Figure 4 shows a KM plot for time to first dermatologic event (TTDE) by treatment group. Figure 5 shows a summary table of the primary efficacy analysis for baseline and week 24. Figure 6 shows a summary table of an additional efficacy analysis for baseline and week 20. Figure 7 shows a summary table of the number of patients remaining in the treatment period for each visit. To evaluate the submission, the review team was able to complete the following tasks:

- Receive the electronic submission package in eCTD approved formats.
- Install and load open-source packages used in this submission and the submitted pilot2wrappers R package.
- Review Analysis Data Reviewer's Guide (ADRG) and execute a Shiny app.
- Identify issues and provide potential solutions.
- Review re-submissions.
- Share potential improvements to the submission deliverable and processes via a written communication.

The Pilot 2 submission materials and communication are publicly available.

[Figure 1] App Information



[Figure 2] Usage Guide

App Information | Usage Guide | Demographic Table | KM plot for TTDE | Primary Table | Efficacy Table | Visit Completion Table

# Application Guide

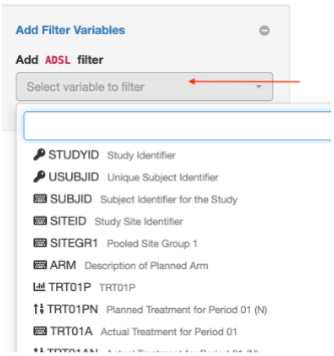
The Pilot 2 Shiny Application contains five distinct interfaces, each displaying a different analysis output as described in the App Information page.

| tab | output |
|---|---|
| Demographic Table | Table 14-2.01 Summary of Demographic and Baseline Characteristics |
| KM Plot for TTDE | Figure 14-1 Time to Dermatologic Event by Treatment Group |
| Primary Table | Table 14-3.01 Primary Endpoint Analysis: ADAS Cog(11) - Change from Baseline to Week 24 - LOCF |
| Efficacy Table | Table 14-3.02 Primary Endpoint Analysis: Glucose (mmol/L) - Summary at Week 20 - LOCF |
| Visit Completion Table | Not Applicable |

## Dynamic Filters

The **KM Plot for TTDE** module allows for filters to be applied based on variables in the **ADSL** and **ADTTE** data sets. Below is an example of performing subpopulation analysis for an age group within the module:

Step 1 | Step 2 | Step 3




Within the **Add Filter Variables** widget, click the box with the placeholder **Select variables to filter**

Source: R Consortium

[Figure 3] Demographic Table – Table 14-2.01 in Pilot 1

App Information | Usage Guide | Demographic Table | KM plot for TTDE | Primary Table | Efficacy Table | Visit Completion Table

Table 14-2.01

Summary of Demographic and Baseline Characteristics

| | Placebo (N=86) | Xanomeline Low Dose (N=84) | Xanomeline High Dose (N=84) |
|---|---|---|---|
| Age (year) | | | |
| Mean (SD) | 75.21 (8.59) | 75.67 (8.29) | 74.38 (7.89) |
| Median | 76.00 | 77.50 | 76.00 |
| Min - Max | 52.00 - 89.00 | 51.00 - 88.00 | 56.00 - 88.00 |
| Age group | | | |
| <65 | 14 | 8 | 11 |
| 65-80 | 42 | 47 | 55 |
| >80 | 30 | 29 | 18 |
| Race | | | |
| WHITE | 78 | 78 | 74 |
| BLACK OR AFRICAN AMERICAN | 8 | 6 | 9 |
| AMERICAN INDIAN OR ALASKA NATIVE | 0 | 0 | 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 | 137.20 - 185.40 | 135.90 - 195.60 | 146.10 - 190.50 |
| 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 | 34.00 - 86.20 | 45.40 - 106.10 | 41.70 - 108.00 |
| 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 | 15.10 - 33.30 | 17.70 - 40.10 | 13.70 - 34.50 |

Program: tm_t_demographic.R 2023-08-24 08:33:26

Source: R Consortium

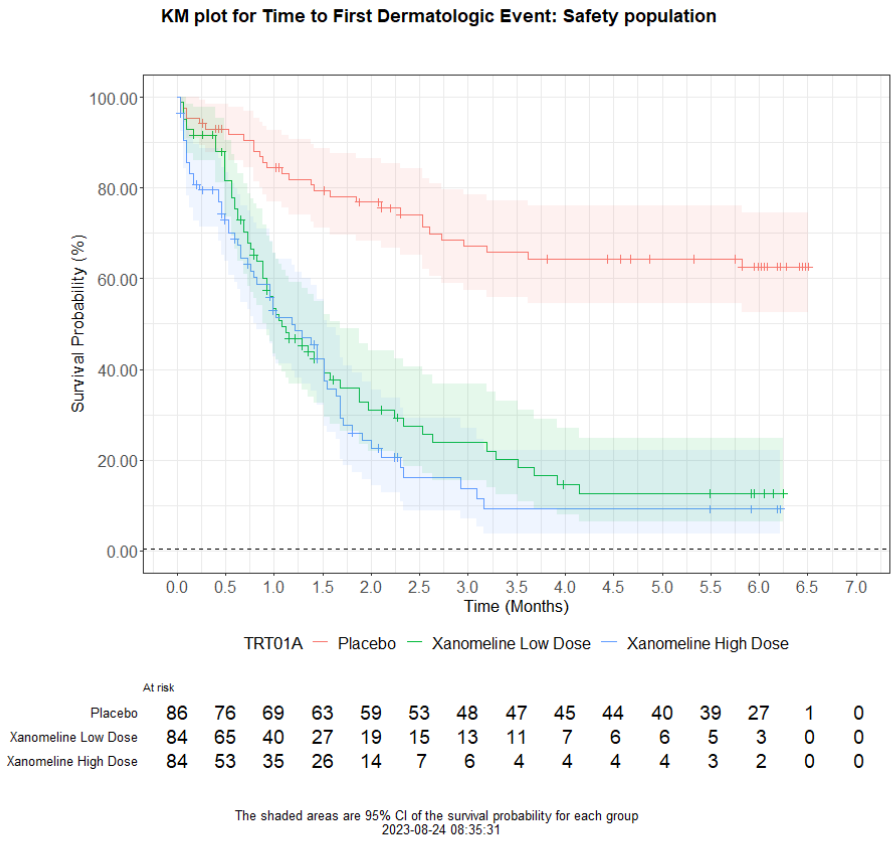
[Figure 4] KM plot for TTDE – Figure 14-1 in Pilot 1

App Information | Usage Guide | Demographic Table | KM plot for TTDE | Primary Table | Efficacy Table | Visit Completion Table

**Important Information:**
The analyses performed when utilizing subgroups or other subsets of the source data sets are considered **exploratory.**

- Treatment information variables from the **ADTTE** data set are excluded from the variable list. Use the treatment variables present in the **ADSL** set to perform treatment-related filters.
- In rare situations, applying filters with variables from both **ADSL** and **ADTTE** that overlap in content could result in an invalid data subset. When possible, select variables with distinct content.

Figure 14-1
Time to Dermatologic Event by Treatment Group




**Active Filter Summary**

| | Obs | Subjects |
|---|---|---|
| ADSL | 254/254 | 254/254 |
| ADTTE | 254/254 | 254/254 |

**Active Filter Variables**

ADSL

ADTTE

**Add Filter Variables**

Add ADSL filter
Select variable to filter

Add ADTTE filter
Select variable to filter

Source: R Consortium

[Figure 5] Primary Table – Table 14-3.01 in Pilot 1

App Information | Usage Guide | Demographic Table | KM plot for TTDE | **Primary Table** | Efficacy Table | Visit Completion Table

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

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

Statistical model and comparison p-values removed when applying data filters. Refer to the application information for additional details.

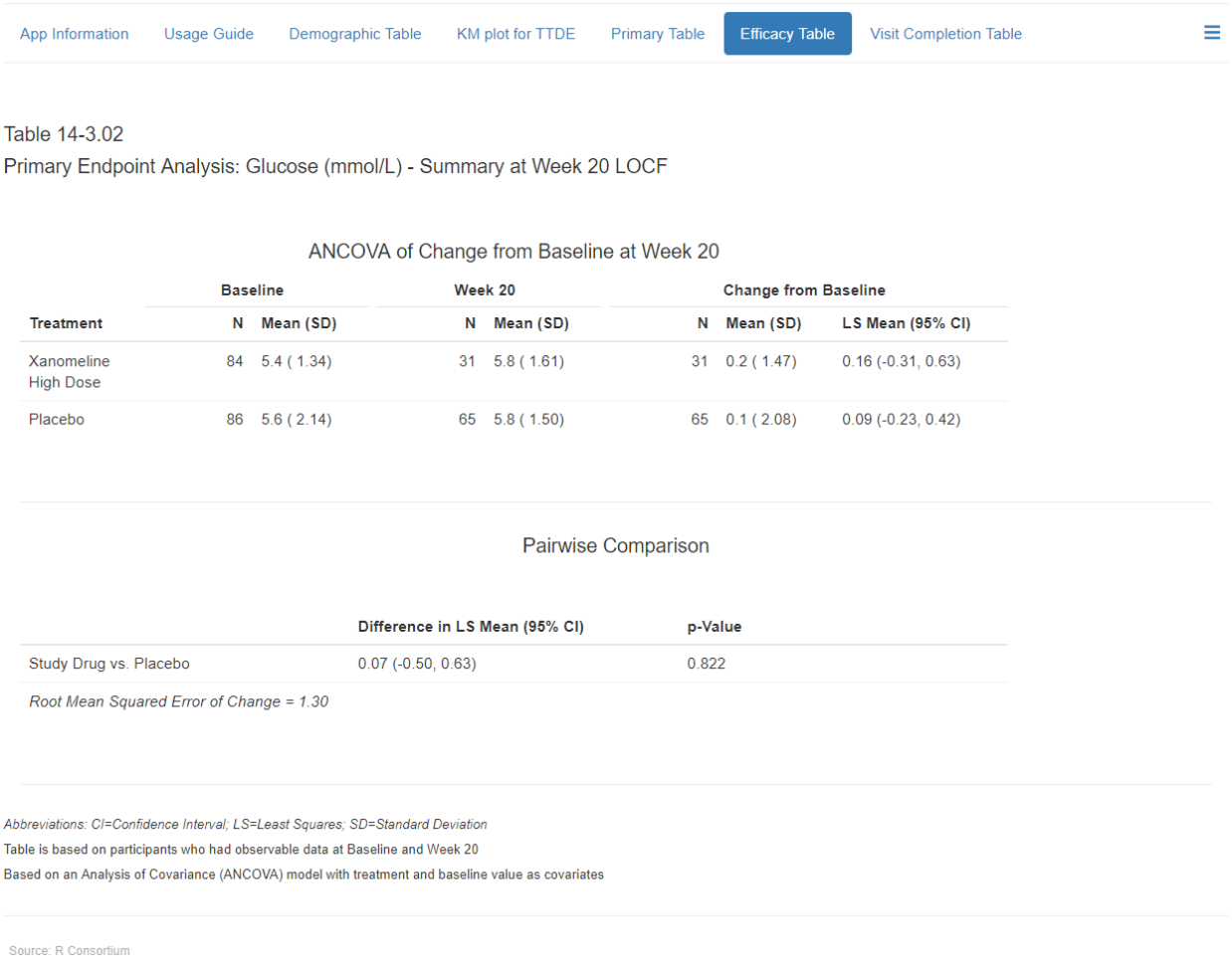
[1] Based on Analysis of covariance (ANCOVA) model with treatment and site group as factors and baseline value as a covariate.

[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.

Source: R Consortium

[Figure 6] Efficacy Table – Table 14-3.02 in Pilot 1



App Information | Usage Guide | Demographic Table | KM plot for TTDE | Primary Table | Efficacy Table | Visit Completion Table

Table 14-3.02

Primary Endpoint Analysis: Glucose (mmol/L) - Summary at Week 20 LOCF

ANCOVA of Change from Baseline at Week 20

| | Baseline | | Week 20 | | Change from Baseline | | |
|---|---|---|---|---|---|---|---|
| **Treatment** | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **N** | **Mean (SD)** | **LS Mean (95% CI)** |
| 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) | p-Value |
|---|---|---|
| Study Drug vs. Placebo | 0.07 (-0.50, 0.63) | 0.822 |

*Root Mean Squared Error of Change = 1.30*

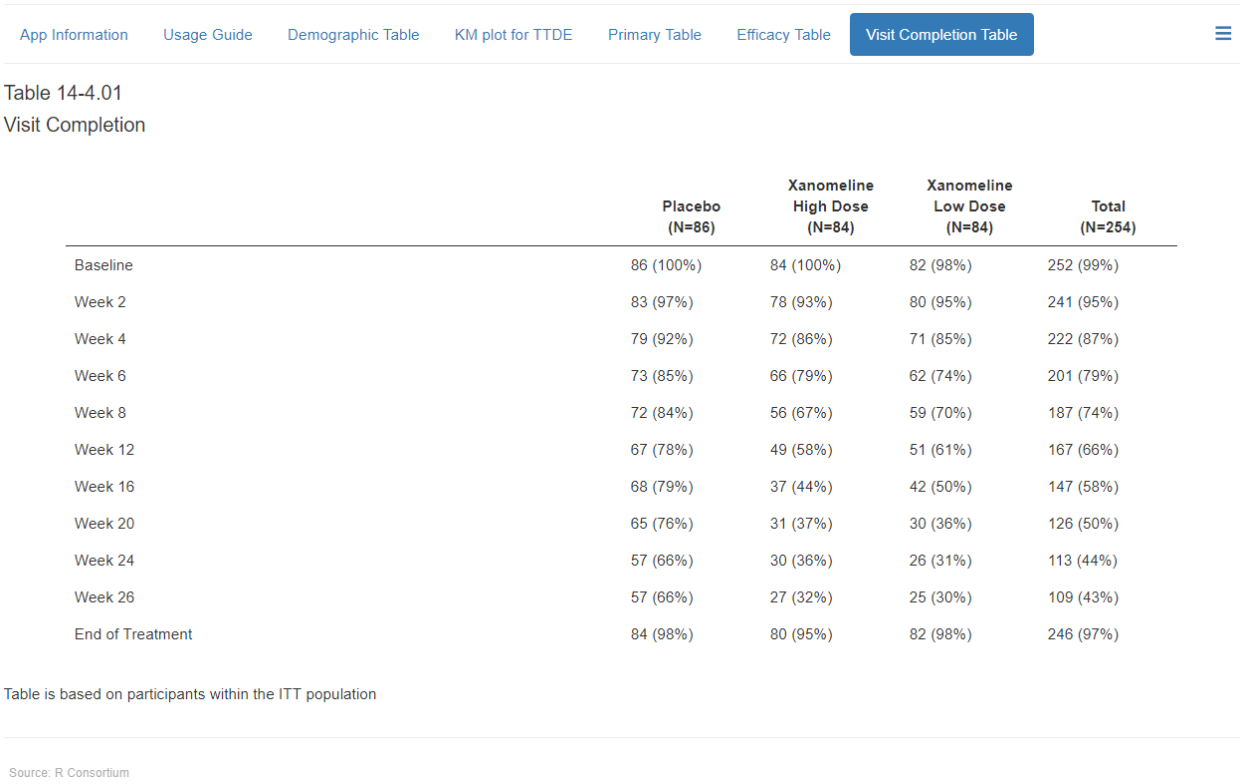
*Abbreviations: CI=Confidence Interval; LS=Least Squares; SD=Standard Deviation*

Table is based on participants who had observable data at Baseline and Week 20

Based on an Analysis of Covariance (ANCOVA) model with treatment and baseline value as covariates

Source: R Consortium

[Figure 7] Visit Completion Table



## Issues and Implementation

- The Shiny app's interactive features may be useful for visualization; however, the interactive features, including applying filters and dynamically displaying the generated outputs, could be inappropriately used to enable p-hacking and for cherry picking subgroups. The analyses performed when utilizing subsets of the source data sets should be considered exploratory, unless prespecified. Thus, FDA recommended displaying all tables in a static format (see Figures 3, 5, 6, and 7) and applying interactive features only for the KM plot (see Figure 4).

- It is possible to apply conflicting filters to source data sets, which produces a subset that is invalid. As a solution, the applicant provided guidance to handle these situations and added the following messages (see Figure 4):
  - Treatment information variables from the ADTTE data set are excluded from the variable list. Use the treatment variables present in the ADSL set to perform treatment-related filters.
  - In rare situations, applying filters with variables from both ADSL and ADTTE that overlap in content could result in an invalid data subset. When possible, select variables with distinct content.

- FDA recommended that the Shiny app and its outputs should be stand-alone. The applicant added 'App Information' (see Figure 1) and 'Usage Guide' (see Figure 2) tabs and proper titles, footnotes, and footnote reference numbers for tables to provide the necessary documentation.

- There was one warning message below in retrieving one package when running the Shiny app. We recommended using CRAN or a curated repository for sourcing packages. We also recommended providing a list of potential warning messages that may be expected to occur. The applicant explained that 'teal' and 'teal.data' packages were not available on CRAN at the time of completing the Pilot 2 and included potential warning messages in the ADRG.

```
Warning message:
could not retrieve available packages for url "https://insightsengineering.github.io/depository/2022_06_09/bin/windows/contrib/4.1"
```

## Comments and Potential Improvements

- Validation of the R packages used in the app is outside of the scope of this pilot.

- In this pilot, 'renv' is used for R package management. Alternative ways to handle R packages are still being discussed.

- The applicant used 'pkglite' package to convert the Shiny app into a .txt format for Pilot 1 and Pilot 2 submission. FDA provided a list of acceptable file formats for use in eCTD, which might give other alternatives and simplify the flow of the work for the applicant.