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, AIS Hye Soo Cho -S Digitally signed by Hye Soo Cho -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Hye Soo Cho -S, 0.9.2342.19200300.100.1.1=2003188359 Date: 2021.12.16 12:45:40 -05'00'
Supervisor	Maria Matilde Kam, AIS Maria Matilde S. Kam -S Digitally signed by Maria Matilde S. Kam -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=2002402795, cn=Maria Matilde S. Kam -S Date: 2021.12.16 17:23:18 -05'00'
Date(s):	November 22, 2021
Objectives of the submission	To test and support R-based clinical trial application submission
Location of datasets and programs	\\cdsesub3\evsprod\BLA111111\0001
Reviewed tables and figures	Table 14-2.01, Table 14-3.01, Table 14-3.02, Figure 14-1

Summary

- Using R version 4.1.1, FDA was able to run the submitted code and confirm the applicant's tables and the submitted figure in report-tlf pdf file.
- Using FDA developed code, a statistical analyst was able to independently generate tables using the submitted data. There are some minor issues with some of the tables that were submitted.
    - Minor issues:
        1) A few values are slightly off. This could potentially be a rounding issue.
        2) Column headers are switched in Table 14-3.01.
        3) Important information, such as a specification of the ANCOVA model, is not given for Table 14-3.02.

Table 14-2.01

[Issues]

- No discrepancies

[Table generated by FDA]

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)			
N	86	83	84
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$^{2)}$			
N	86	83	84
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
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Table 14-3.01

[Issues]

- Column headers of Xanomeline High Dose and Xanomeline Low Dose in Applicant's table are switched (Highlighted in the table below).

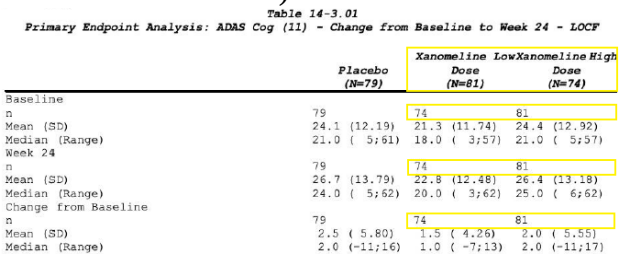

Table 14-3.01
Primary Endpoint Analysis: ADAS Cog (11) - Change from Baseline to Week 24 - LOCF

	Placebo (N=79)	Xanomeline Low Dose (N=81)	Xanomeline High Dose (N=74)
Baseline			
n	79	74	81
Mean (SD)	24.1 (12.19)	21.3 (11.74)	24.4 (12.92)
Median (Range)	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 (Range)	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 (Range)	2.0 (-11;16)	1.0 (-7;13)	2.0 (-11;17)

- The upper limit of 95% CI of difference of LS means between Xanomeline High Dose and placebo (Highlighted in the table below) is off by 0.1 in FDA's analysis. Potentially, this could be a rounding issue.

[Table generated by FDA]

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

Parameter	Placebo	Xanomeline High Dose	Xanomeline Low Dose
Baseline			
n	79	74	81
Mean (SD)	24.1 (12.19)	21.3 (11.74)	24.4 (12.92)
Median (Range)	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 (Range)	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 (Range)	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;0.6)	(-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)	

Source: adadas.xpt; Software: R version 4.1.1 (2021-08-10)
[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.
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Table 14-3.02

[Issues]

- In the Analysis Data Reviewer's Guide, adrg, the analysis dataset is incorrectly specified (ADLBC, not ADLB, in section 7.03 page 12).
- Tables should be able to stand alone.
    - Subtitles (LOCF, ITT population) are incorrectly included.
    - The sub-population should be specified for a table if the table is based on a subgroup. This table is based on participants who have observable data at baseline and Week 20. If the descriptive statistics were summarized based off each time point separately, the number of subjects, N, Mean, and SD at baseline would be different, as shown in the table below.

	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)

    - The ANCOVA model employed was not fully specified in either the applicant's table or adrg.

- Root mean squared error of change (Highlighted in the table below) differs by 0.01. This could potentially be a rounding issue.

[Table generated by FDA]

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	31	5.6 (1.44)	31	5.8 (1.61)	31	0.2 (1.47)	0.16 (-0.31, 0.63)
Placebo	65	5.7 (2.44)	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 4.1.1 (2021-08-10)
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Figure 14-1

[Issues]

- No discrepancies

[Figure generated by FDA]