CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761142Orig1s000

STATISTICAL REVIEW(S)

U.S. 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

CLINICAL STUDIES

BLA Number:	761142
Drug Name:	Uplizna (inebilizumab-cdon) injection
Indication:	Treatment of neuromyelitis optica spectrum disorders
Applicant:	Viela Bio
Dates:	Receipt date: June 11, 2019 PDUFA Goal Date: June 11, 2020
Review Priority:	Standard
Biometrics Division:	Division of Biometrics I
Statistical Reviewer:	Xiangmin Zhang, Ph.D.
Concurring Reviewers:	Kun Jin, Ph.D., Team Leader Hsien Ming Hung, Ph.D., Director
Medical Division:	Division of Neurology 2
Clinical Team:	Lawrence Rodichok, M.D., Clinical Reviewer Paul Lee, M.D., Ph.D., Team Leader
Project Manager:	Sandra Folkendt

Keywords: clinical study, BLA review

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

1 EXECUTIVE SUMMARY

On June 11, 2019, Viela Bio (the Applicant) submitted an original biologics license application (BLA) for Uplizna (inebilizumab, or MEDI-551 under the Applicant's clinical development plan). The application relies on clinical study CD-IA-MEDI-551-1155 to demonstrate the drug efficacy for the proposed indication "treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult patients". The study was a randomized, double-blind, placebo-controlled, parallel-group, clinical study that had two treatment groups (inebilizumab and placebo) and used the time (in days) from Day 1 to onset of an adjudication committee (AC)-determined NMO/NMOSD attack on or before the end of randomized-controlled period (Day 197/discontinuation visit) as the primary endpoint. The study showed that the estimated hazard ratio of inebilizumab group relative to placebo group was 0.227 (95% confidence interval = (0.1214, 0.4232), p-value < 0.0001) for the aquaporin-4-antibody (AQP4-IgG) seropostive subjects.

2 INTRODUCTION

2.1 Overview

This original BLA for Uplizna (inebilizumab, or MEDI-551 under the Applicant's clinical development plan) for the treatment of neuromyelitis optica spectrum disorders (NMOSD) in adult patients relies on one randomized, double-blind, placebo-controlled clinical study to demonstrate the drug efficacy. The clinical study is thereafter referred to as Study 1155. It is summarized below and reviewed in Section 3.

Table 1. Clinical study in this review

Study	**Design**	**Study Arm (Number of randomized subjects per arm)**	**Study Population**
CD-IA-MEDI-551-1155 (Study 1155)	Randomized, placebo-controlled, double-blind, parallel-group	Inebilizumab (174) Placebo (56)	Adult patients with NMO and NMOSD.

AQP4-IgG: autoantibodies against aquaporin-4; NMO: neuromyelitis optica; NMOSD: neuromyelitis optica spectrum disorders.
Source: statistical reviewer's summary

2.2 Data Sources

The electronic submission of the BLA are located at
\\CDSESUB1\evsprod\BLA761142\0001\
\\CDSESUB1\evsprod\BLA761142\0006\
\\CDSESUB1\evsprod\BLA761142\0007\

The study report is located at
\\CDSESUB1\evsprod\BLA761142\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\neuromyleitisopticaspectrumdisorder\5351-stud-rep-contr\cd-ia-medi-551-1155\

The datasets are located at
\\CDSESUB1\evsprod\BLA761142\0001\m5\datasets\

3 STATISTICAL EVALUATION

3.1 Data and Analysis Quality

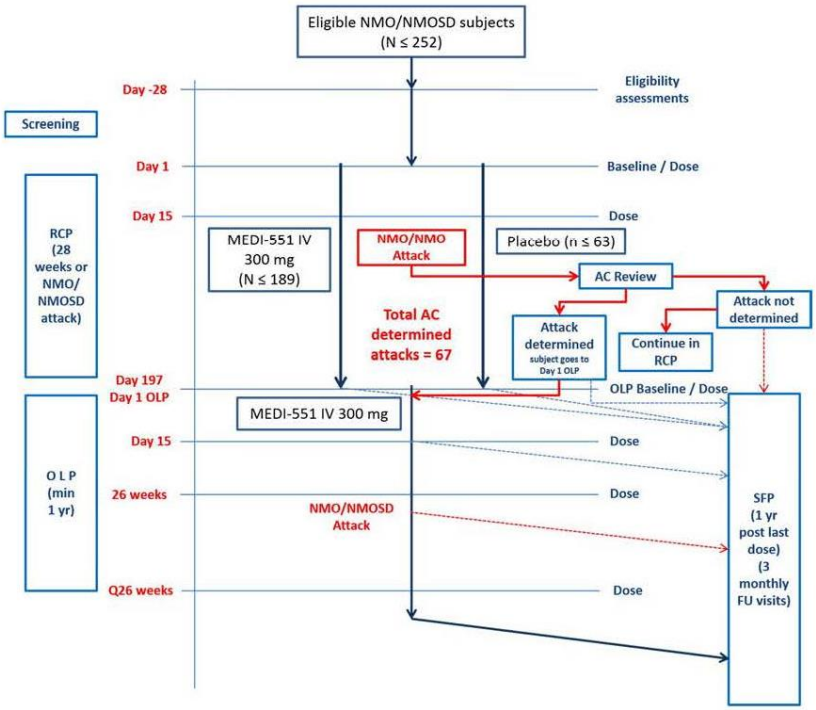
The statistical reviewer was able to perform independent review using the Applicant's submitted datasets and confirm the Applicant's analysis results.

3.2 Evaluation of Efficacy

3.2.1 Design and Endpoints

Study 1155 was a randomized, placebo-controlled, double-blind, parallel-group, 2-arm, multi-center, Phase 2/3 clinical study to evaluate the efficacy of inebilizumab in reducing the risk of an neuromyelitis optica/neuromyelitis optica spectrum disorders (NMO/NMOSD) attack in subjects with NMO/NMOSD. A maximum of 252 subjects aged 18 or above were planned to be randomized in a 3:1 ratio to receive inebilizumab (300 mg IV inebilizumab on Day 1 and 300 mg IV inebilizumab on Day 15) or placebo (IV Placebo on Day 1 and IV Placebo on Day 15).

Figure 1. Study 1155 design



AC = Adjudication Committee; AQP4-IgG = aquaporin-4 immunoglobulin G; FU = follow-up; IV = intravenous; max = maximum; min = minimum; NMO/NMOSD = neuromyelitis optica/neuromyelitis optica spectrum disorders; OLP = Open-label Period; RCP = Randomized-controlled Period; Q26W = every 26 weeks; SFP = Safety Follow-up Period; yr = year.

Source: Figure 1 in the porotocl amendment 6

Figure 1 depicts the design of Study 1155. The randomized-controlled period (RCP) of this study was 197 days. Subjects who completed the RCP without experiencing an NMO/NMOSD attack were given the option to enroll into an open label period.

Table 2. Protocol-defined criteria for an NMO/NMOSD attack

Example Symptoms of an NMO/NMOSD Attack [a]	Attack Type [b]	Protocol-defined Attack Criteria
Blurred vision Loss of vision Eye pain	ON	1. Greater than 15-character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in a previously affected eye and no other ophthalmological explanation 2. At least 2-step drop [c] in CF to NLP from last visit as measured in a previously affected eye and no other ophthalmological explanation 3. At least 7 or more character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye 4. At least 7 or more character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye 5. At least 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new RAPD in affected eye 6. At least 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND loss of a previously documented RAPD in fellow eye 7. At least 1-step drop [d] in CF to NLP from last visit as measured in a previously affected eye AND a new RAPD in affected eye 8. At least 1-step drop [d] in CF to NLP from last visit as measured in a previously affected eye AND loss of a previously documented RAPD in fellow eye 9. At least 7 or more character drop in low-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve [f] 10. At least 5 or more character drop in high-contrast Landolt C Broken Rings Chart from last visit as measured in either eye alone (monocular) AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve [f] 11. At least 1-step drop [d] in CF to NLP from last visit as measured in a previously affected eye **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the corresponding optic nerve [f]
Deep or radicular pain Extremity paraesthesia Weakness Sphincter dysfunction	Myelitis [e]	12. At least 2-point worsening in 1 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit 13. At least 1-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more
Lhermitte's sign (not in isolation)		14. At least 1-point worsening in 2 or more of the relevant (pyramidal, bladder/bowel, sensory) FSS compared to last visit when the last visit score was 1 or greater AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord 15. At least 0.5-point worsening in EDSS score compared to last visit if previous EDSS score is 5.5 or more **AND** a new GD-enhancing or new/enlarging T2 MRI lesion in the spinal cord
Nausea Intractable vomiting Intractable hiccups Other neurological signs (eg, double vision, dysarthria, dysphagia, vertigo, oculomotor palsy, weakness, nystagmus, other cranial nerve abnormality)	Brainstem	16. Isolated (not present at last visit) intractable nausea, vomiting, and/or hiccups lasting for greater than 48 hours AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem 17. At least 2-point worsening in 1 or more of the relevant (brainstem, cerebellar) FSS compared to last visit AND a new Gd-enhancing or new/enlarging T2 MRI lesion in the brainstem
Encephalopathy Hypothalamic dysfunction	Brain	18. At least 2-point worsening in 1 or more of the relevant (cerebral, sensory, pyramidal) FSS (with a score of 3 or more at the current visit) compared to last visit **AND** a new Gd-enhancing or new/enlarging T2 MRI lesion in the brain consistent with the clinical presentation

CF = counting fingers; EDSS = Expanded Disability Severity Score; FSS = Functional System Scores; Gd = gadolinium; HM = hand motion; LP = light perception; MRI = magnetic resonance imaging; NLP = no light perception; NMO/NMOSD = neuromyelitis optica/neuromyelitis optica spectrum disorders; ON = optic neuritis; RAPD = relative afferent pupillary defect.

[a] The symptoms listed are examples and are not inclusive of all NMO/NMOSD symptoms.

[b] Four major areas of the body may be affected by an attack: the optic nerve, resulting in ON; the spinal cord, resulting in myelitis; the brainstem, resulting in a number of outcomes; and the brain.

[c] At least 2-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to HM, LP, or NLP; CF to LP or NLP; HM to NLP.

[d] At least 1-step drop can be any of the following worsening: on Landolt C Broken Rings Chart to CF, HM, LP, or NLP; CF to HM or LP or NLP; HM to LP or NLP; LP to NLP.

[e] Note: A 1-point change in a single FSS without a change in the EDSS, with or without a new Gd-enhancing or new/enlarging T2 MRI lesion in the spinal cord, is not considered a clinically significant change and will not count as an attack per this protocol.

[f] Lesions seen in the optic chiasm also count towards these criteria.

Source: Table 11 in protocol amendment 6

The primary endpoint was the time (in days) from Day 1 to onset of an adjudication committee (AC)-determined NMO/NMOSD attack on or before the end of RCP (Day 197/discontinuation visit). The NMO/NMOSD attack is defined as a new symptom(s) or worsening of an existing symptom(s) related to NMO/NMOSD that meets at least one of the protocol-defined criteria, as shown in **Table 2**.

The secondary endpoints included:

1. Worsening from baseline in Kurtzke Expanded Disability Status Scale (EDSS) at last visit during the RCP. A subject were considered to have a worsening in overall EDSS score if one of the following criteria was met:
   a. Worsening of 2 points or more in EDSS score for subjects with baseline score of 0.
   b. Worsening of 1 point or more in EDSS score for subjects with baseline score of 1 to 5.
   c. Worsening of 0.5 point or more in EDSS score for subjects with baseline score of 5.5 or more.
2. Change from baseline in low-contrast visual acuity binocular score measured by low-contrast Landolt C Broken Rings Chart, at last visit during the RCP.
3. Cumulative total active magnetic resonance imagining (MRI) lesions (new Gadolinium[Gd]-enhancing or new/enlarging T2) during the RCP.
4. Number of NMO/NMOSD-related in-patient hospitalizations. In-patient hospitalization is defined as more than an overnight stay.

3.2.2 Statistical Methodologies

The efficacy analysis population was the intention-to-treat (ITT) population, defined as all subjects who are randomized and receive any investigational product.

For the aquaporin-4-antibody (AQP4-IgG) seropostive cohort, the primary endpoint was analyzed using a Cox proportional hazards model with treatment as an exploratory factor; for the ITT population, the Cox model also included the AQP4-IgG serostatus. Subjects who completed the Day 197 visit of the RCP or discontinued the study before Day 197 for reasons other than an AC-determined NMO/NMOSD attack were censored in the Cox model at the time of the Day 197/discontinuation visit. Only AC-determined attacks with an assessment visit scheduled within 120 hours (5 days) of reporting symptoms AND all necessary assessments done within 10 days of an assessment visit were included in the primary analysis.

For the AQP4-IgG seropositive cohort, analyses for the secondary endpoints were planned as follows:

- The worsening in EDSS was analyzed by a logistic regression model that included treatment and baseline EDSS score.
- The change from baseline in low-ctontrast Landolt C Broken Rings Chart binocular score was analyzed by an analysis of covariance model that included treatment and baseline Landolt C Broken Rings Chart binocular score.

- The cumulative number of active MRI leisions was analyzed by a negative binomial regression model that included treatment.
- The number of NMO/NMOSD-related hospitalizations was analyzed by a negative binomial regression model that included treatment.

For the ITT population, the analysis models for the secondary endpoints also included the AQP4-IgG serostatus.

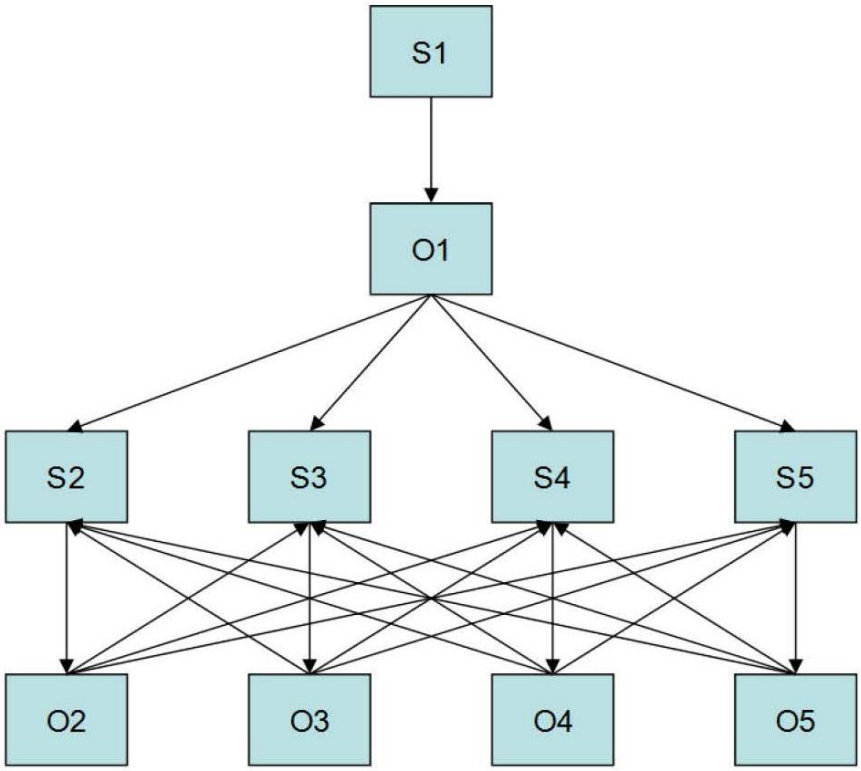
Table 3. List of null hypotheses

Hypothesis	Test
S1	Test E1 in seropositive subjects
S2	Test E2 in seropositive subjects
S3	Test E3 in seropositive subjects
S4	Test E4 in seropositive subjects
S5	Test E5 in seropositive subjects
O1	Test E1 in ITT population
O2	Test E2 in ITT population
O3	Test E3 in ITT population
O4	Test E4 in ITT population
O5	Test E5 in ITT population

Source: Table 7-5 in the statistical analysis plan

The Bonferroni-based chain procedure was proposed to control the overall Type I error (i.e. alpha) of the study. Denote the primary and secondary endpoints 1-4 as E1, E2, E3, E4, and E5, respectively. **Table 3** shows ten hypotheses planned for this study.

Figure 2. Graphical representation of the muplicity adjustment strategy



Source: Figure 7-7 in the statistical analysis plan

Table 4. The alpha propagation rule

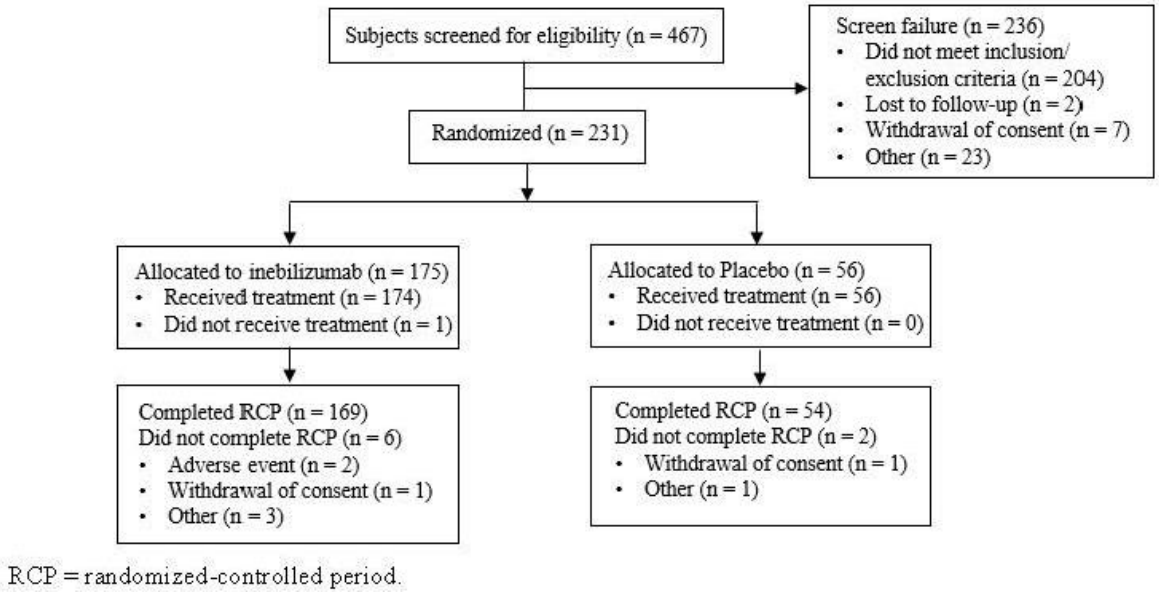
Hypothesis	S1	S2	S3	S4	S5	O1	O2	O3	O4	O5
S1	0	0	0	0	0	1	0	0	0	0
S2	0	0	0	0	0	0	1	0	0	0
S3	0	0	0	0	0	0	0	1	0	0
S4	0	0	0	0	0	0	0	0	1	0
S5	0	0	0	0	0	0	0	0	0	1
O1	0	1/4	1/4	1/4	1/4	0	0	0	0	0
O2	0	0	1/3	1/3	1/3	0	0	0	0	0
O3	0	1/3	0	1/3	1/3	0	0	0	0	0
O4	0	1/3	1/3	0	1/3	0	0	0	0	0
O5	0	1/3	1/3	1/3	0	0	0	0	0	0

Source: Table 7-7 in the statistical analysis plan

Figure 2 shows the graphical representation of the procedure. **Table 4** Shows the alpha propagation rule, which determines the process of re-distributing the available alpha among the non-rejected null hypotheses after each rejection. The initial alpha allocation is 0.05 to S_1. If S_1.is rejected, then O_1 is tested at $\alpha = 0.05$. If O_1 is rejected, S_2, S_3, S_4, and S_5 are each tested at $\alpha = 0.0125$ (i.e. 1/4 of 0.05). If any S_i $(i = 2, 3, 4, 5)$ is rejected, the testing of O_i can still continue, but with adjusted alpha level based on the pre-specified alpha propagation rule.

3.2.3 Subject Disposition, Demographic and Baseline Characteristics

Figure 3. Subject disposition



Source: Figure 3 in the clinical study report

Figure 3 presents the subject disposition of Study 1155. A total of 467 subjects were screened in 99 study sites in 25 countries; a total of 231 subjects were randomized in 82 study sites in 24 countries. Among the randomized subjects, 175 subjects (75.8%) were randomized to the inebilizumab group and 56 (24.2%) to the placebo group. A total of 230 subjects out of the 231 randomized subjects were included in the ITT population for efficacy analyses. One subject randomized to the inebilizumab group was not treated, therefore excluded from the ITT population.

Table 5. Subject demographics, ITT population

	AQP4-IgG sero+ N = 213			AQP4-IgG sero- N = 17			Total N = 230		
	Placebo N = 52	Inebilizumab N = 161	Overall N = 213	Placebo N = 4	Inebilizumab N = 13	Overall N = 17	Placebo N = 56	Inebilizumab N = 174	Overall N = 230
Age (years)									
n	52	161	213	4	13	17	56	174	230
Mean	42.4	43.2	43.0	44.8	40.8	41.7	42.6	43.0	42.9
SD	14.3	11.6	12.3	7.7	11.4	10.6	13.9	11.6	12.2
Median	43.0	43.0	43.0	42.0	44.0	43.0	42.5	43.0	43.0
(Min, Max)	(18, 74)	(18, 73)	(18, 74)	(39, 56)	(22, 55)	(22, 56)	(18, 74)	(18, 73)	(18, 74)
Age Category									
n	52	161	213	4	13	17	56	174	230
< 65	48 (92.3%)	155 (96.3%)	203 (95.3%)	4 (100%)	13 (100%)	17 (100%)	52 (92.9%)	168 (96.6%)	220 (95.7%)
≥ 65	4 (7.7%)	6 (3.7%)	10 (4.7%)	0	0	0	4 (7.1%)	6 (3.4%)	10 (4.3%)
Sex									
n	52	161	213	4	13	17	56	174	230
Male	3 (5.8%)	10 (6.2%)	13 (6.1%)	3 (75.0%)	5 (38.5%)	8 (47.1%)	6 (10.7%)	15 (8.6%)	21 (9.1%)
Female	49 (94.2%)	151 (93.8%)	200 (93.9%)	1 (25.0%)	8 (61.5%)	9 (52.9%)	50 (89.3%)	159 (91.4%)	209 (90.9%)
Race [a]									
n	52	161	213	4	13	17	56	174	230
American Indian or Alaskan Native [b]	5 (9.6%)	11 (6.8%)	16 (7.5%)	0	3 (23.1%)	3 (17.6%)	5 (8.9%)	14 (8.0%)	19 (8.3%)
Asian	8 (15.4%)	37 (23.0%)	45 (21.1%)	0	2 (15.4%)	2 (11.8%)	8 (14.3%)	39 (22.4%)	47 (20.4%)
Black or African American	5 (9.6%)	14 (8.7%)	19 (8.9%)	0	1 (7.7%)	1 (5.9%)	5 (8.9%)	15 (8.6%)	20 (8.7%)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0	0	0	0
White	24 (46.2%)	86 (53.4%)	110 (51.6%)	4 (100%)	6 (46.2%)	10 (58.8%)	28 (50.0%)	92 (52.9%)	120 (52.2%)
Other	10 (19.2%)	12 (7.5%)	22 (10.3%)	0	1 (7.7%)	1 (5.9%)	10 (17.9%)	13 (7.5%)	23 (10.0%)
Multiple categories checked	0	1 (0.6%)	1 (0.5%)	0	0	0	0	1 (0.6%)	1 (0.4%)
Region US vs Non-US									
n	52	161	213	4	13	17	56	174	230
US	11 (21.2%)	27 (16.8%)	38 (17.8%)	1 (25.0%)	2 (15.4%)	3 (17.6%)	12 (21.4%)	29 (16.7%)	41 (17.8%)
Non-US	41 (78.8%)	134 (83.2%)	175 (82.2%)	3 (75.0%)	11 (84.6%)	14 (82.4%)	44 (78.6%)	145 (83.3%)	189 (82.2%)

AQP4-IgG = autoantibodies against aquaporin-4; ITT = intent-to-treat; Max = maximum; Min = minimum; SD = standard deviation; sero- = seronegative; sero+ = seropositive US = United States.

a Each race category counts subjects who selected only that category; "Multiple Categories Checked" counts subjects who selected > 1 race category.

b The American Indian or Alaskan Native category included subjects from South/Central America.

Source: selected from Table 18 in the clinical study report

Table 5 summarizes the demographics of subjects in the ITT population. The ITT subjects in the inebilizumab group and placebo group appeared similar in terms of age, sex, and race. Overall, the average age of the ITT subjects was approximately 43 years (standard deviation (SD) = 12.2). The majority of the ITT subjects were female. Over 50% of the ITT subjects were white.

3.2.4 Results and Conclusions

Table 6. Analysis of time to AC-determined NMOSD attack, ITT population

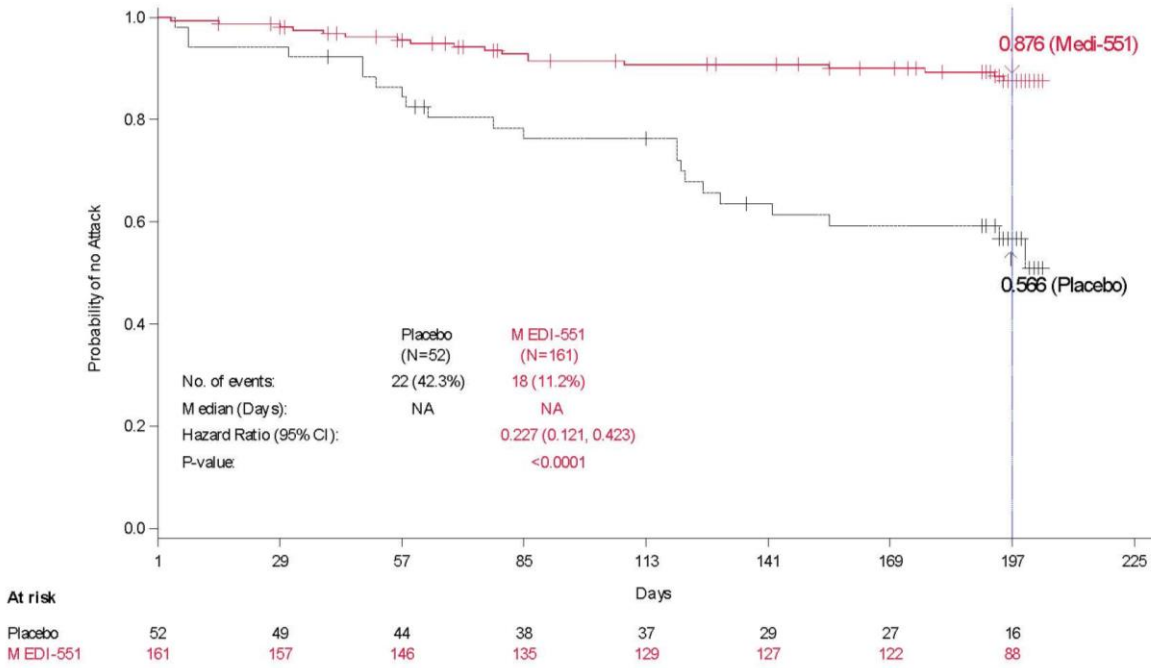
	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Number of subjects with an attack	22 (42.3%)	18 (11.2%)	0	3 (23.1%)	22 (39.3%)	21 (12.1%)
Number of censored subjects	30 (57.7%)	143 (88.8%)	4 (100%)	10 (76.9%)	34 (60.7%)	153 (87.9%)
Hazard ratio[a]		0.227		NA		0.272
95% CI [a]		(0.1214 , 0.4232)		(NA , NA)		(0.1496 , 0.4961)
p-value [a]		<0.0001		0.9977		<0.0001

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; NA = not applicable;
ITT = Intent-to-treat; sero- = seronegative; sero+ = seropositive.
a Based on Cox regression method, with placebo as the reference group.

Source: Table 20 in the clinical study report

Table 6 presents the analysis results of the primary endpoint. For the AQP4-IgG seropositive cohort, inebilizumab was statistically significantly better than placebo with a hazard ratio of 0.227 (p-value < 0.0001, 95% confidence interval = (0.1214, 0.4232)), indicating that the inebilizumab group had a lower risk of having NMO/NMOSD attacks. Although analysis results for all ITT subjects were similar to those for the AQP4-IgG seropositive cohort, it appeared that these results were driven entirely by the data from the AQP4-IgG seropositive cohort.

Figure 4. Kaplan-Meier curves for time to AC-determined NMOSD attack, ITT population, AQP4-IgG seropositive subjects

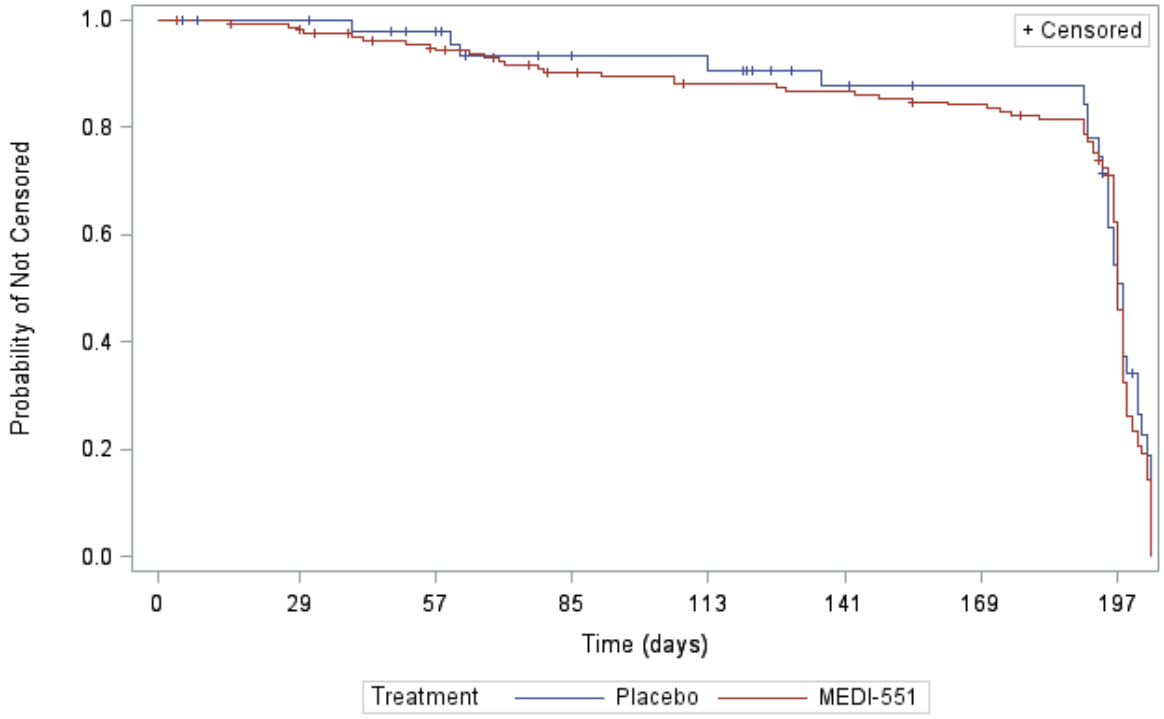


AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; MEDI-551 = inebilizumab; NA = not applicable.

Source: Figure 7 in the clinical study report

Figure 4 demonstrates the Kaplan-Meier curves for time to AC-determined NMOSD attack for all AQP4-IgG seropositive subjects in the ITT population. Because many observed time were censored, the median survival time for either treatment group is not available. However, better treatment effect of the MEDI-551 compared to that of the placebo group can be observed from the Kaplan Meier curves for AQP4-IgG seropositive subjects.

Figure 5. Kaplan-Meier curves for censoring time, ITT population, AQP4-IgG seropositive subjects



Source: statistical reviewer's analysis

Table 7. Descriptive statistics of censoring time (days), ITT population, AQP4-IgG seropositive subjects

	Placebo N = 52	Inebilizumab N = 161
Number of subjects censored	30	143
Mean of censoring time (SD)	178.7 (46.6)	178.1 (47.5)
Median (Min, Max)	196.5 (40.0, 204.0)	197.0 (15.0, 204.0)

Source: statistical reviewer's analysis

Figure 5 demonstrates the Kaplan-Meier curves for censoring time for all AQP4-IgG seropositive subjects in the ITT population. An exploratory log-rank test for censoring time had a nominal p-value of 0.58. **Table 7** shows the descriptive statistics of censoring time for both treatment groups. The Kaplan-Meier curves, p-value from the exploratory log-rank test, and descriptive statistics of censoring time did not reveal substantial difference between the treatment groups in terms of censoring time distribution. Futhermore, the primary analysis model was fitted to data assuming all censored cases are events. This exploratory analysis had a nominal p-value of 0.034, which supports the primary analysis result.

Table 8. Analysis of worsening from Baseline in EDSS at the last visit, ITT population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Worsening [a] from baseline in EDSS at last visit [b]	18/52 (34.6%)	25/161 (15.5%)	1/4 (25.0%)	2/13 (15.4%)	19/56 (33.9%)	27/174 (15.5%)
Odds ratio [c]		0.371		0.911		0.370
95% CI of Odds ratio [c]		(0.1807, 0.7633)		(0.0528, 15.7083)		(0.1850, 0.7389)
p-value [c]		0.0070		0.9487		0.0049

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; EDSS = Expanded Disability Status Scale; ITT = intent-to-treat sero+ = seropositive; sero- = seronegative.

a A subject was considered to have a worsening in EDSS score if one of the following criteria was met: (1) Worsening of 2 or more points in EDSS score for subjects with baseline score of 0; (2) Worsening of 1 or more points in EDSS score for subjects with baseline score of 1 to 5; (3) Worsening of 0.5 points or more in EDSS score for subjects with baseline score of 5.5 or more.

b Subjects with missing data are imputed as 'worsening'. Denominator represents the total number of subjects in each group with baseline.

c Odds ratio, its 95% CI, and p-value are estimated by logistic regression model, using non-responder imputation, i.e., missing values will be considered as 'worsening'.

Source: Table 26 in the clinical study report

Table 9. Analysis of cumulative number of active MRI leisions during the RCP, ITT population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Cumulative number of active MRI lesions						
n	31	74	1	5	32	79
Mean	2.3	1.7	4.0	1.4	2.3	1.6
SD	1.3	1.0	NA	0.9	1.3	1.0
Median	2.0	1.0	4.0	1.0	2.0	1.0
(Min, Max)	(1, 5)	(1, 6)	(4, 4)	(1, 3)	(1, 5)	(1, 6)
Rate ratio[a]		0.568		0.538		0.566
95% CI		(0.3851, 0.8363)		(0.0818, 3.5462)		(0.3866, 0.8279)
p-value		0.0042		0.5198		0.0034

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; MRI = magnetic resonance imaging; SD = standard deviation; sero- = seronegative; sero+ = seropositive.

a Rate ratio reduction in cumulative number of active MRI lesions. Rate ratio analysis is based on the entire population, not just those who had an event. Treatment effect and its 95% CI , and p-value are estimated from the negative binomial regression.

Source: Table 27 in the clinical study report

Table 10. Analysis of number of NMOSD-related in-patient hospitalizations, ITT population

	AQP4-IgG sero+ N = 213		AQP4-IgG sero- N = 17		Total N = 230	
	Placebo N = 52	Inebilizumab N = 161	Placebo N = 4	Inebilizumab N = 13	Placebo N = 56	Inebilizumab N = 174
Cumulative number of NMOSD-related in-patient hospitalizations						
n	7	8	1	2	8	10
Mean	1.4	1.0	1.0	1.0	1.4	1.0
SD	0.8	0	NA	0	0.7	0
Median	1.0	1.0	1.0	1.0	1.0	1.0
(Min, Max)	(1, 3)	(1, 1)	(1, 1)	(1, 1)	(1, 3)	(1, 1)
Rate ratio [a]		0.258		0.615		0.286
95% CI		(0.0904, 0.7384)		(0.0558, 6.7866)		(0.1105, 0.7411)
p-value		0.0115		0.6918		0.0100

AQP4-IgG = autoantibodies against aquaporin-4; CI = confidence interval; ITT = intent-to-treat; max = maximum; min = minimum; NMOSD = neuromyelitis optica spectrum disorders; SD = standard deviation; sero- = seronegative; sero+ = seropositive.

a Rate ratio reduction in number of NMOSD-related in-patient hospitalizations. Rate ratio analysis is based on the entire population, not just those who had an event. Treatment effect and its 95% CI , and p-value are estimated from the negative binomial regression.

Source: Table 28 in the clinical study report

Table 8, **Table 9**, and **Table 10** present the analysis results of the worsening from Baseline in EDSS at the last visit, analysis results of the cumulative number of active MRI leisions during the RCCT, and analysis results of the number of NMOSD-related in-patient hospitalizations, respectively. The analysis results for the three pre-specified secondary endpoints were nominally significant for AQP4-IgG seropositive subjects. Analysis results of the low-contrast visual acuity score was not significant (p-value = 0.9736) for the AQP4-IgG seropositive subjects. The details are thus omitted.

One issue with the pre-specified analyses for these secondary endpoints is that subjects were not followed up for the same amount of time, therefore, missing data might introduce biases into these analyses. For example, the analysis for the worsening from Baseline in EDSS at the last visit used all available values at the last visit. In such a case, if a subject had a AC-detemined NMOSD attack, his/her last EDSS score was evaluated around the time he/she had the attack; if a subject did have an attack and stayed in the study until the end of the study, his/her last EDSS score was evaluated at around Day 197. Approximately 42.2% and 61.5% AQP4-IgG seropositive subjects in the ITT population for the inebilizumab group and placebo group, respectively, did not have observed EDSS data for Week 28. Owing to the high percentages of missing data, using the last available values in the EDSS analysis may not be adequate for addressing the impact of missing data, and the results are difficult to interpret.

Please also refere to Dr. Lawrence Rodichok's clinical review for a discussion of these secondary endpoints.

3.3 Evaluation of Safety

Please refer to Dr. Lawrence Rodichok's clinical review for a detailed evaluation of safety.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race, Age, and Geographic Region

Table 11. Subgroup analyses of time to AC-determined NMOSD attack, ITT population, AQP4-IgG seropositive subjects

	Number of Subjects with Attack (%)		Hazard Ratio (95% CI)*
	Placebo N = 52	Inebilizumab N = 161	
Gender			
Female	20/49 (40.8)	16/151 (10.6)	0.225 (0.116, 0.435)
Male	2/3 (66.7)	2/10 (20.0)	0.160 (0.022, 1.195)
Race			
American indian or alaskan native	2/5 (40.0)	3/11 (27.3)	0.532 (0.088, 3.213)
Asian	5/8 (62.5)	6/37 (16.2)	0.198 (0.060, 0.653)
Black or african american	1/5 (20.0)	1/14 (7.1)	0.331 (0.021, 5.310)
White	10/24 (41.7)	8/86 (9.3)	0.189 (0.074, 0.480)
Other	4/10 (40.0)	0/13 (0.0)	NA
Age Group			
< 65 years	21/48 (43.8)	16/155 (10.3)	0.199 (0.104, 0.382)
≥65 years	1/4 (25.0)	2/6 (33.3)	1.371 (0.124, 15.179)
Region			
non-US	19/41 (46.3)	16/134 (11.9)	0.224 (0.115, 0.435)
US	3/11 (27.3)	2/27 (7.4)	0.226 (0.038, 1.360)

* CI: confidence interval. Hazard ratios and confidence intervals were obtained from fitting Cox proportional hazards models with treatment as an exploratory factor to the subgroup specific AQP4-IgG seropositive subjects.

Source: statistical reviewer's analyses

Table 11 present the analyses of the primary endpoint by gender, race, age group, and geographic region. There is no compelling evidence from the subgroup analyses that a specific gender, race, or geographic region benefits differently from inebilizumab. One unusual observation is that for subjects who were 65 years or older, in terms of numbers of subjects with attack and hazard ratio, inebilizumab did not appear to perform better than placebo. However, the numbers of subjects who were 65 years or older in the two treatment groups were too small to draw conclusions. The study

was not powered for the subgroups, therefore, it is not usually to find that the 95% confidence intervals of the hazard ratios for small subgroups contain 1.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues

Although Study 1155 included both AQP4-IgG seropostive and AQP4-IgG seronegative subjects, AQP4-IgG seronegative subjects had a small sample size and their data were not sufficient to demonstrate the effectiveness of inebilizumab.

In addition, pre-specified design and analysis for the secondary endpoints were considered not adequate. Analysis results for these secondary endpoints are not appropriate to be included in the label.

5.2 Collective Evidence

This section is not applicable because the BLA only included one efficacy study.

5.3 Conclusions and Recommendations

Inebilizumab is approvable from a statistical standpoint. Study CD-IA-MEDI-551-1155 provided sufficient statistical evidence that inebilizumab is effective for the treatment of neuromyelitis optica spectrum disorders in adult patients who are aquaporin-4-antibody (AQP4-IgG) seropostive.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

XIANGMIN ZHANG
03/06/2020 09:54:36 AM

KUN JIN
03/06/2020 01:38:19 PM
I concur with the review.

HSIEN MING J HUNG
03/06/2020 01:44:48 PM