

Alexion Pharmaceuticals, Inc.

STATISTICAL ANALYSIS PLAN ADDENDUM

PROTOCOL NUMBER: ALXN1210-NMO-307

A Phase 3, External Placebo-Controlled, Open-Label, Multicenter Study to Evaluate the Efficacy and Safety of Ravulizumab in Adult Patients with Neuromyelitis Optica Spectrum Disorder (NMOSD)

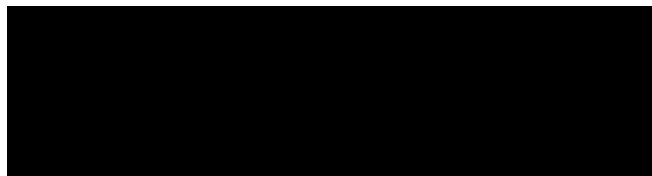
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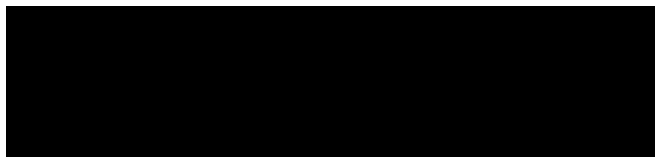
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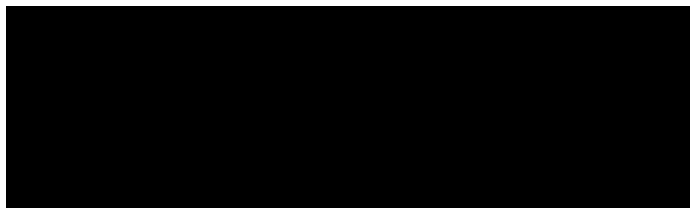
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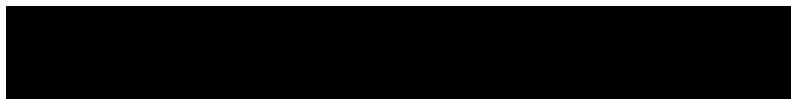
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3. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

The following abbreviations and acronyms are used in this Addendum to the SAP.

Table 1: Abbreviations and Acronyms

Abbreviation or Acronym	Explanation
ADA	antidrug antibody
AE	adverse event
ARR	annualized relapse rate
CI	confidence interval
COVID-19	coronavirus disease 2019
CSR	clinical study report
EDSS	Expanded Disability Status Scale
EOSP	end of the study period
EQ-5D	EuroQol 5 dimension health status
FUP	follow-up
HAI	Hauser Ambulation Index
IST	immunosuppressive therapy
NAb	neutralizing antibody
NMOSD	neuromyelitis optica spectrum disorder
PD	pharmacodynamic(s)
PK	pharmacokinetic(s)
SAE	serious adverse event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software®
SF-36	Short Form Health Outcomes Survey (36 items)
VAS	Visual Analogue Scale

4. SAP ADDENDUM

This SAP is an addendum to the ALXN1210-NMO-307 SAP Version 3.0, dated 09 Jul 2021. It describes the statistical methods for data analyses of long-term efficacy, safety, PK, PD, and immunogenicity parameters for the final CSR for Protocol ALXN1210-NMO-307. This analysis will provide the final analysis results for Study ALXN1210-NMO-307 including the primary treatment period and the long-term extension period combined.

For regulatory purposes, a CSR was produced after the completion of the primary analysis. That CSR, dated 21 Jul 2022, presented analysis results of data collected through the end of the Primary Treatment Period which was triggered after the last patient remaining on study had completed Week 50. [REDACTED]

The final CSR will present long-term efficacy, safety, PK, PD, and immunogenicity summaries on data collected until the end of the study.

Summaries and analyses of endpoints to be included in the final CSR will be limited to those described below. Methods are described in SAP Version 3.0 (09 Jul 2021), with limited modifications described in Section 4.2, if applicable.

1. Study Patients

Summary tables will be provided as specified in **SAP Version 3.0, Section 7.1**, using the Safety Set for the following:

- Disposition of patients and study visits
- Protocol deviations
- Demographics and disease characteristics and history, including medical/surgical history
- Prior and concomitant medications/therapies, including IST use and plasmapheresis/plasma exchange and IST treatments for on-trial relapses
 - Additionally, the number and percentage of patients in the ravulizumab treatment group who had a change in background IST treatment during the study period will be summarized, with details described in Section 4.2 below.

2. Efficacy Analyses

Selected analyses and summaries will be provided using the Full Analysis Set. The analyses for the endpoints will not be repeated using the Per Protocol Set.

a. Primary Efficacy Endpoint

- Time to first adjudicated on-trial relapse

The primary analysis methods specified in **SAP Version 3.0, Section 7.2.1** are used for time to first adjudicated on-trial relapse, although a modification to the definition of the censoring date is described in Section 4.2 below.

Sensitivity analyses described in **SAP Version 3.0, Section 7.2.1** will also be performed.

Additionally, the following will be provided:

- Subgroup analysis including region (Americas, Asia-pacific, and Europe), age group (< 45 years, ≥ 45 years), race, sex, IST subgroups, rituximab use (yes/no) in the year prior to Screening, time since NMOSD onset (< 5 years, ≥ 5 years), baseline EDSS score (< 4.0 , ≥ 4.0), and historical ARR within the 24 months prior to Screening (≤ 1.5 , > 1.5) will be provided as described in **SAP Version 3.0, Section 7.2.1**
- Summary of censoring reasons and adjudication results for on-trial relapses and cases of interest
- Summary and analysis of adjudicated on-trial relapses requiring hospitalization or acute treatments for relapses
- Summary of severity and type of relapses in the subgroup of patients who had adjudicated on-trial relapses
- Time to first on-trial relapse
 - This endpoint will be analyzed using the same statistical analysis methods as the time to first adjudicated on-trial relapse, which is specified in **SAP Version 3.0, Section 7.2.1** and Section 4.2 below.

Additionally, summary statistics will be provided for the following:

- On-trial relapses requiring hospitalization or acute treatments for relapses
- Severity and type of relapses in the subgroup of patients who had on-trial relapses

b. Secondary Efficacy Endpoints

- Adjudicated on-trial ARR

This endpoint will be analyzed using the same primary statistical analysis methods specified in **SAP Version 3.0, Section 7.2.2**. Statistical testing will be performed using the method described in Section 4.2.

Subgroup analysis including region (Americas, Asia-pacific, and Europe), age group (< 45 years, ≥ 45 years), sex, race, IST subgroups, rituximab use (yes/no) in the year prior to Screening, time since NMOSD onset (< 5 years, ≥ 5 years), baseline EDSS score (< 4.0 , ≥ 4.0), historical ARR within the 24 months prior to Screening (≤ 1.5 , > 1.5) will be provided.

- The remaining secondary efficacy endpoints to be summarized include the following:
 - Clinically important changes from Baseline in ambulatory function as measured by the HAI
 - Change from Baseline in EQ-5D index score
 - Change from Baseline in EQ-5D VAS score
 - Clinically important worsening from Baseline in EDSS score

The primary summaries of these endpoints are described in Section 4.2 of this document.

c. Exploratory Efficacy Endpoints

Exploratory efficacy endpoints to be summarized include the following:

- Change in visual acuity, color vision, confrontational visual fields
- Change from Baseline in SF-36 domain scales and summary scores
- Change from Baseline in the EQ-5D dimensions of health

For visual acuity, a summary table over time for each eye will be provided for the ravulizumab arm. For color vision, the analysis specified in **SAP Version 3.0, Section 7.2.3** will be repeated in the final analysis. For confrontational visual fields, the change from Baseline to the EOSP will be summarized as well as over time by combining both eyes in the final analysis among patients in the ravulizumab treatment group.

For SF-36 domain scales and summary scores, and EQ-5D dimensions of health, a summary table over time will be provided for the ravulizumab arm.

d. Other Efficacy Endpoints

Changes from Baseline and changes from the last assessment prior to an adjudicated on-trial relapse to each postrelapse time point for EDSS, HAI, visual acuity, color vision, and confrontational visual field for each adjudicated on-trial relapse will be provided as described in **SAP Version 3.0, Section 7.2.4.1**.

PK and PD endpoints including ravulizumab concentrations and free component 5 in serum will be provided as described in **SAP Version 3.0, Section 7.2.5**. The summary of hospitalizations will be provided as described in **SAP Version 3.0, Section 7.2.7**.

ADA will be summarized as described in Section 4.2 of this document.

3. Safety Endpoints

Safety endpoints include AEs, vital signs (outlier tables only), laboratory parameters (shift tables only), electrocardiogram, and Columbia-Suicide Severity Rating Scale. For vital signs, a summary of outliers as described in **SAP Version 3.0, Section 7.3.3.2** will be provided.

Study duration and treatment duration will also be provided.

AE summary tables will be provided for the ravulizumab treatment group only.

4.1. Changes from Analyses Specified in the Protocol

1. Statistical analyses of the HAI, EQ-5D index, EQ-5D VAS, and EDSS evaluating the treatment effect of ravulizumab as compared to placebo will not be performed.
2. Summaries will not be presented using the Per Protocol Set.
3. Sensitivity analyses using propensity score methodologies will not be performed.

4.2. Changes from Analyses Specified in the Previous Version of the SAP

1. The number and percentage of patients in the ravulizumab treatment group who had a change in background IST treatment during the study period will be summarized for the treatment period, as well as for patients who had a change in background IST treatment by Week 106 and patients who had a change in background IST treatment after Week 106.
2. For the analysis of the time to first adjudicated on-trial relapse, the censoring time will be defined as the EOSP date minus the first dose date plus 1. The EOSP date is defined as the earlier of the following 3 dates: (1) 35 days after a dose was expected but not administered due to COVID-19-related reasons, (2) the Last Dose Date + 63 days (or 16 days, if the last dose was a Day 1 dose), and (3) the final disposition date (eg, Safety Follow-up date). Relapses observed after the EOSP date will not be included in the primary analysis of the time to first adjudicated on-trial relapse.
3. For the analysis of the adjudicated on-trial ARR, an exact method will be applied as the primary analysis if 0 adjudicated on-trial relapses are observed by the EOSP date. The EOSP date is the minimum nonmissing value of the following dates: the Last Dose Date + 63 days (or 14 days, if the last dose was a Day 1 dose), and the final disposition date (eg, Safety Follow-up date); the duration of the study period is the days from the Day 1 dose to the EOSP + 1, excluding the time from 36 days after a dose that was missed or delayed due to COVID-19-related reasons until the day before the next dose. Relapses observed after the EOSP date will not be included in the analysis.

The p-value is derived using the Poisson distribution, the follow-up time, and the number of relapses to compare to the null hypothesis of a 0.25 ARR. The exact method of the upper limit of the 95% CI, will use the Chi-square distribution as described by Ulm (Ulm, 1990). The SAS code for the p-value is as follows:

$$\text{CDF}(\text{"POISSON"}, \text{count}, 0.25 * \text{FUP}) \times 2$$

where FUP is the person-years of time in the study period, $0.25 * \text{FUP}$ is the mean number of relapses expected under the null hypothesis, the count is the observed number of relapses, and $\times$ is the probability of having observed the count or less, given the number of relapses expected under the null hypothesis.

4. Summaries will be limited to the ravulizumab treatment group for the following endpoints: HAI, EQ-5D index, EQ-5D VAS, EDSS, visual acuity, SF-36 domain scales and summary scores, and EQ-5D dimensions of health.

The change from Baseline for these endpoints will be evaluated at the end of the study, which is defined as the last visit at which the endpoint was collected.

A summary of the change from Baseline to the end of the study will be presented along with the 95% CI of the mean.

For the HAI score, EQ-5D index, EQ-5D VAS, and EDSS figures showing the change from Baseline [mean (SD)] over time will be presented in addition to tabular summaries of observed values and change from Baseline specified in SAP Version 3.0.

5. For the analysis of change from baseline in HAI score, the clinically important change (clinical improvement, stable HAI, and clinical worsening) from Baseline to the end of the study will be presented, showing the number and proportion of patients with clinically important change categories along with Clopper-Pearson 95% CIs. Clinically important change categories are defined in **SAP Version 3.0, Section 9.5.4**.
6. For the analysis of change from Baseline to end of the study in EDSS score, the clinically important worsening from Baseline to the end of the study will be presented, showing the number and proportion of patients with clinically important worsening (yes/no) along with Clopper-Pearson 95% CIs. Clinically important worsening categories are defined in **SAP Version 3.0, Section 9.5.6**.
7. ADAs data will be summarized as follows:

Immunogenicity variables including ADA status, ADA-response categories, ADA and NAb incidence, and ADA titer will be summarized over the duration of the study. ADA status, ADA-response categories, and NAb status will be summarized as absolute occurrence (n) and percentage (%) of all participants.

The summaries of ADA incidence over the duration of the study will include the following status categories:

- **ADA negative:** All post-first-dose samples with an ADA-negative response, with baseline sample negative or missing
- **ADA positive:** An ADA-positive response at any time point

Participants who are ADA positive may be further categorized into ADA-response categories as follows:

- **Pre-existing immunoreactivity:** An ADA-positive response with either of the following 2 conditions met:
 - ADA-positive response at Baseline with all post-first-dose ADA results negative,
OR
 - ADA-positive response at Baseline with all post-first-dose ADA responses < 4-fold over the baseline titer level.
- **Treatment-emergent ADA responses:** An ADA-positive response post-first-dose when baseline results are negative or missing.
- **Treatment-boosted ADA responses:** An ADA-positive response post-first-dose that is ≥ 4 -fold over the baseline titer level when the baseline result is positive.

Participants with treatment-emergent or treatment-boosted ADA responses may be further categorized as follows:

- **Persistent responses:** ADA responses with 2 or more consecutive ADA-positive samples separated by at least a 16-week period, with no ADA-negative samples in between, irrespective of missing samples.

- **Indeterminate responses:** ADA-positive sample only at the last collected sample.
- **Transient responses:** ADA response that is neither a persistent nor an indeterminate response.

ADA-positive samples will be further characterized for neutralizing activity in the NAb assay. NAb status categories are as follows:

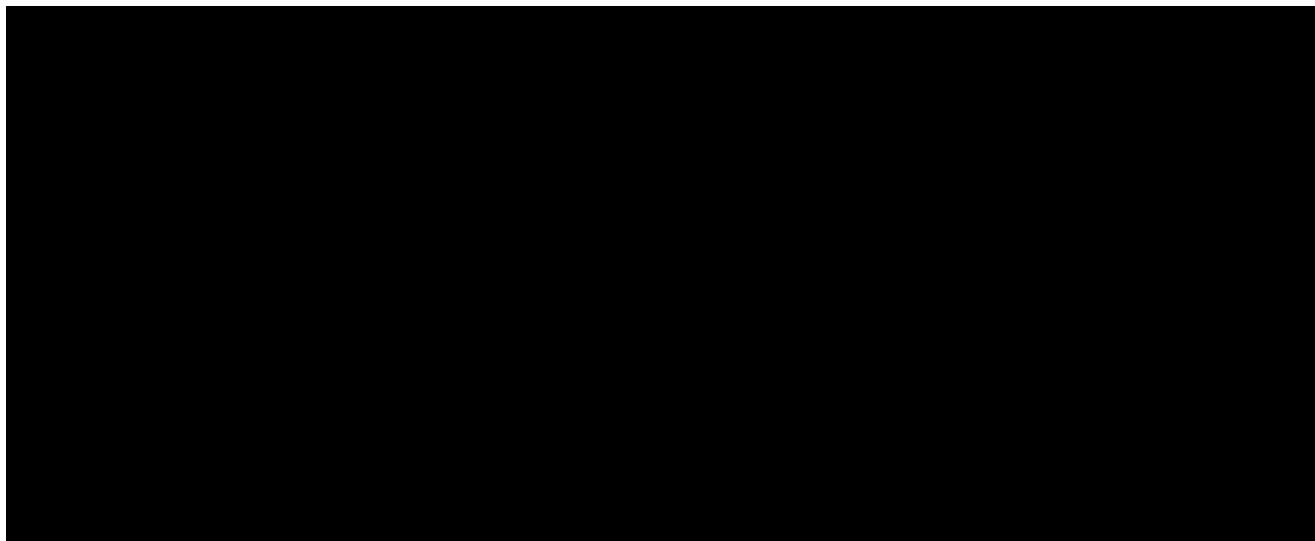
- NAb positive
- NAb negative

Associations between ADA-response categories and systemic exposure to ravulizumab may be explored to assess the potential impact of immunogenicity on drug concentration-time (PK) profiles.

Associations between ADA-response categories and SAEs may be explored, including SAEs like systemic hypersensitivity, anaphylaxis, injection/infusion site reactions lasting more than 24 hours, and other immune-related SAEs.

Associations between ADA-response categories and key efficacy endpoints or variables may be explored to assess the potential impact of immunogenicity on drug efficacy.

8. Adverse Events will be summarized for the ravulizumab treatment group.



5. REFERENCES

Ulm K. A Brief Original Contribution: A simple method to calculate the confidence interval of a standardized mortality ratio (SMR). American Journal of Epidemiology. 1990;Vol.131,No. 2:373-375.

ALXN1210-NMO-307 final study SAP

Final Audit Report

2024-08-29

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