1.0 Title Page

Statistical Analysis Plan

Study M18-918

A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Assess the Safety and Efficacy of Elezanumab when Added to Standard of Care in Relapsing Forms of Multiple Sclerosis

Date: 06 Jan 2021

Version 2.0

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3.0 Introduction

This statistical analysis plan (SAP) describes the statistical analyses to be completed by the AbbVie Clinical Statistics Department for the elezanumab Phase 2a Study M18-918.

Pharmacokinetics/pharmacodynamics, pharmacogenetic, and selected biomarkers will be analyzed separately and are not included in this SAP.

Unless noted otherwise, all analyses will be performed using SAS version 9.4 or later (SAS Institute Inc., Cary, NC 27513) under the UNIX operating system.

The SAP will not be updated in case of future administrative or minor amendments to the protocol, unless the changes have an impact on the analysis of study data.

4.0 Study Background

4.1 Objective

The objective of this study is to evaluate the safety and efficacy of elezanumab in subjects with relapsing forms of multiple sclerosis (RMS).

4.2 Study Design

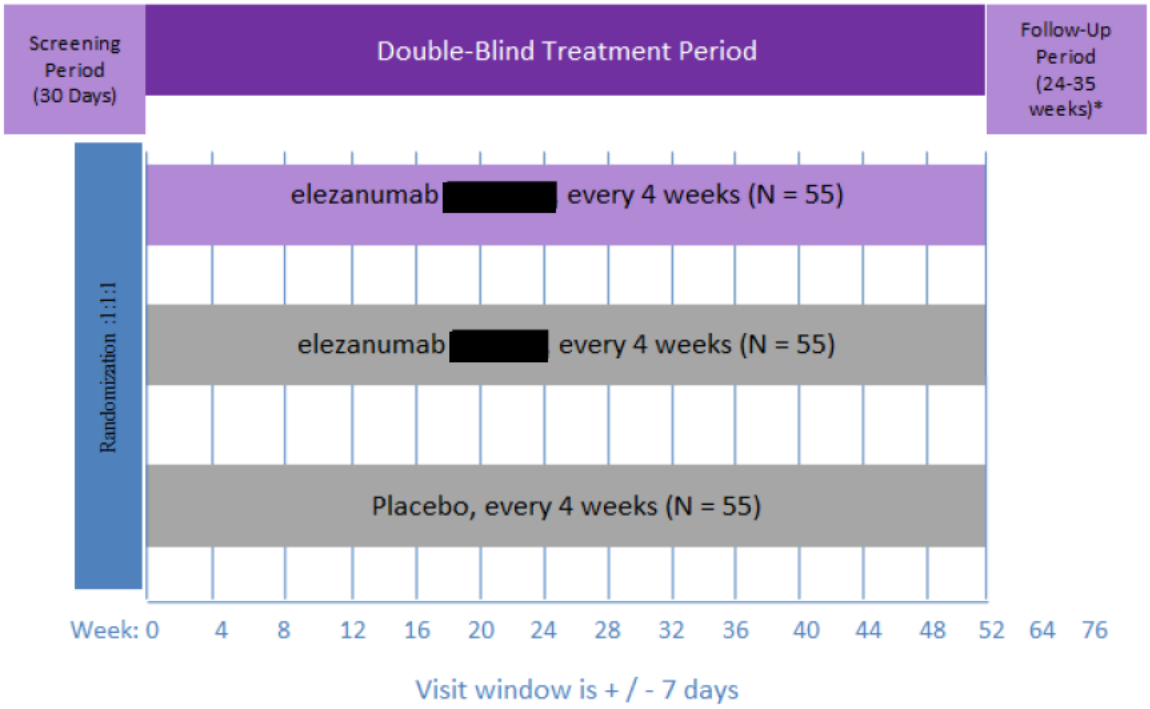
4.2.1 Study Design and Design Diagram

This is a 52-week, Phase 2a, proof-of concept, randomized, double-blinded, parallel-group, placebo-controlled multicenter study to evaluate the safety and efficacy of 2 doses of elezanumab in adult subjects with relapsing forms of MS who have established disability.

This study will include an approximate 30-day Screening period. The Treatment Period will include fourteen (14) visits from Baseline (Week 0) every four weeks through Week 52. Doses will be administered via intravenous (IV) infusion at Week 0 (Baseline) and every 4 weeks thereafter through Week 48 for a total of 13 doses. The follow-up period includes two visits that will occur at Weeks 64 and 76.

The total study duration is up to 80 weeks. The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual.

Figure 1. Study Schematic



* During the Follow–up Period and after the Week 76 visit, female subjects of childbearing potential are to complete monthly home urine pregnancy tests for 39 weeks (5 half-lives) after last dose; and for all subjects adverse events will be collected, whether solicited or spontaneously reported by the subject throughout the study and for a period of 39 weeks after the last dose of study drug.

4.2.2 Variables used for Stratification at Randomization

Randomization will be stratified by diagnosis of MS form [relapsing remitting MS (RRMS) vs. relapsing secondary-progressive MS (rSPMS)], and presence of background MS immunotherapy (Yes vs. No).

The stratification variables used in the analyses will be based on the MS type from the MS Disease History eCRF and MS immunotherapy on the first dose date from the Concomitant Medications eCRF.

4.3 Endpoint

4.3.1 Primary Efficacy Endpoint

The primary efficacy endpoint is the Overall Response Score (ORS) at Week 52.

ORS is a composite score derived from 4 components:

- Expanded Disability Status Scale (EDSS)
- Timed 25-Foot Walk (T25FW)
- 9-Hole Peg Test in the dominant hand (9HPT-D)
- 9HPT in the non-dominant hand (9HPT-ND)

The EDSS + is a composite derived from the EDSS, T25FW, 9HPT-D and 9HPT-ND where responder status is defined as a clinical meaningful improvement on one or more of these endpoints. Hereafter, the EDSS, T25FW, 9HPT-D and 9HPT-ND will also be referred to as "components of the EDSS +" or "components of the ORS."

The ORS is scored with a range from –4 to +4 at each assessment for all post-baseline visits. Scores for each component are assessed relative to their baseline value: –1 if there is clinically significant worsening, 0 if the change does not meet the clinically significant threshold criteria, or +1 if there is clinically significant improvement. The scores for all components are summed at each assessment. If any of the 4 components of the ORS are missing within a visit window, then the ORS will be considered missing for that visit.

The clinically significant change thresholds for EDSS, T25FW and 9HPT are provided in the following table.

ORS Components	Score of ORS Components at Post-Baseline Visits		
	–1 (Clinically Significant Worsening)	**0 (No Clinically Significant Change)**	**1 (Clinically Significant Improvement)**
EDSS change from baseline	≥ 1 if baseline EDSS ≤ 5.5; ≥ 0.5 if baseline EDSS ≥ 6.0	–0.5, 0 or 0.5 if baseline EDSS ≤ 5.5; 0 if baseline EDSS ≥ 6.0	≤ –1 if baseline EDSS ≤ 5.5; ≤ –0.5 if baseline EDSS ≥ 6.0
T25FW change from baseline	≥ 20%	> –20% and < 20%	≤ –20%
9HPT-D change from baseline	≥ 20%	> –20% and < 20%	≤ –20%
9HPT-ND change from baseline	≥ 20%	> –20% and < 20%	≤ –20%

4.3.2 Secondary Efficacy Endpoints

The secondary efficacy endpoints include:

- Disability improvement responder status (Yes or No) on the EDSS+ at Week 52
- ORS at Weeks 12, 24, and 36

4.3.3 Exploratory Efficacy Endpoints

The exploratory efficacy endpoints include:

- Disability improvement response rate on the EDSS, T25FW, 9HPT-D, and 9HPT-ND at Weeks 12, 24, 36, and 52, and the EDSS + at Weeks 12, 24, and 36.
- Change from Baseline on the T25FW, 9HPT-D, 9HPT-ND at Weeks 12, 24, 36, and 52
- Disability progression response rate on the Expanded Disability Status Scale Plus (EDSS +) (T25FW, 9-Hole Peg test [9HPT, either hand], EDSS) and for each EDSS + component

- 12- and 24-week confirmed disability improvement response rate on the EDSS + and for each EDSS + component
- Change from Baseline on the Multiple Sclerosis Impact Scale (MSIS-29) total score at Weeks 12, 24, 36, and 52
- Change from Baseline on the Modified Fatigue Impact Scale (MFIS) total score at Weeks 12, 24, 36, and 52
- Change from Baseline on cognition battery at Weeks 12, 24, 36, and 52:
  - Total score of the Symbol Digit Modalities Test (SDMT) – Oral Version
  - Total score and T-score of the Brief Assessment of Cognition Verbal Memory - Immediate Recall – BAC App Version
  - Total score and T-score of the Brief Assessment of Cognition Tower of London – BAC App Version
- Change from Baseline on the Low Contrast Visual Acuity (LCVA) assessments at Weeks 12, 24, 36, and 52
- Change from Baseline in select plasma biomarkers for monitoring target binding, neuroprotection and/or neurorestoration at Weeks 12, 24, 36, and 52
- Change from Baseline on the MS Individualized Outcome Assessment (MSIOA) scale overall symptom score and most bothersome symptom score at Weeks 24, and 52
- Change from Week 0 in average daily step count and other activity measures (as described in Section 9.4.3) via home actigraphy with wearable biosensor initiated at Weeks 24, 36, and 52
- Summary of variables from brain MRI at Baseline, Weeks 24 and 52
  - Presence of active T1 Gadolinium (GAD)-enhancing lesions)
  - Presence of active new and enlarging T2 hyperintense lesions
  - Cumulative number of total T1 GAD-enhancing, lesions
  - Cumulative number of total T2 hyperintense lesions
  - Cumulative number of post-baseline T1 GAD-enhancing lesions
  - Cumulative number of post-baseline new and enlarging T2 lesions
  - Number of T1 GAD-enhancing lesions at each visit
  - Change from Baseline in total volumes of T1 GAD-enhancing, lesions

- Change from Baseline in total volume of T2 hyperintense lesions
- Change from Baseline in whole brain, gray matter (GM), thalamus, white matter (WM) and normal appearing white matter (NAWM) volumes
- Change from Baseline in regional magnetization transfer ratio (MTR) parameters for whole brain, and NAWM, and MTR for T2 lesions
- Change from baseline in lesion MTR for T1 (GAD)-enhancing lesions and delta MTR
- Change from Baseline in diffusion tensor imaging (DTI) parameters (fractional anistropy and Apparent Diffusion Coefficient (ADC)) for whole brain, NAWM and T2 hyperintense lesions

- Summary of variables from cervical spinal MRI at Weeks 24 and 52
  - Change from Baseline in cervical spinal cord area, volume and number of lesions
  - Change from Baseline in regional MTR for cervical spinal cord lesions
  - Change from baseline in DTI parameters (fractional anisotropy and ADC) for cervical spinal cord

4.3.4 Safety Endpoints

Safety variables include adverse events (AEs), serious adverse events (SAEs), adverse events of special interest (AESI), vital sign measurements (including pre and post-infusion blood pressure), MS relapses, electrocardiogram (ECG) variables, Columbia-Suicide Severity Rating Scale (C-SSRS) assessments, and clinical laboratory testing (hematology, chemistry, and urinalysis) as measures of safety and tolerability for the entire study duration.

4.4 Sample Size Justification

Approximately 165 subjects will be equally randomized 1:1:1 to each treatment group (approximately 55 subjects in each treatment, with at least 20 rSPMS subjects and approximately 35 RRMS subjects). There is limited prior data to estimate the magnitude of effect and variance. This sample size will have approximately 80% power to detect an

effect size (ES) of 0.43 with significance level of 0.1 and overall dropout rate of approximately 10%, using a 1-sided t-test.

4.5 Interim Analysis

An interim futility analysis was planned to assess study and/or dose futility when approximately 40% of planned subjects completed the Week 24 assessment. However, due to the pattern of enrollment and missed infusions and efficacy data collection as a result of the COVID-19 pandemic, the interim futility analysis was eliminated.

4.6 Multiplicity Testing Procedures for Type-I Error Control

No multiplicity adjustment will be performed for this Phase 2a proof of concept study.

4.7 Missing Data Imputation

For continuous efficacy variables, data will be summarized using a mixed-effect model for repeated measures (MMRM) model unless otherwise specified. Missing data will not be imputed before applying an MMRM model. The MMRM model relies on a missing at random (MAR) assumption.

For sensitivity analyses of the primary and secondary efficacy variables, missing values will be imputed using multiple imputation (MI) and categorized as responder/non-responder after imputation. The MI model also relies on a MAR assumption.

Justification for the MAR Assumption:

The COVID-19 pandemic is interfering with the conduct of many ongoing trials, with potential impact on treatment duration and the collection, analysis and the interpretation of clinical trial data. Some protocol-specified visits in this clinical trial may be impacted due to COVID-19 infection or logistical restrictions during the pandemic. For example, some scheduled visits may be missed due to self-quarantine or local government restrictions on travel; some visits may also be delayed or canceled due to healthcare resource constraints during the pandemic. These missed visits will be recorded in the

database. The probability of having missed visits and missing data due to COVID-19 infection or logistical restrictions related to the COVID-19 pandemic can be reasonably assumed to be unrelated to the unobserved values conditional on the observed data. Therefore, for the purpose of statistical analysis, it is reasonable to assume that these missing data are missing at random (MAR) and the statistical models that require MAR assumption are appropriate. In some cases, sensitivity analyses may be performed to assess the impact of missing data and the robustness of the conclusion.

Where noted, summaries as observed will not impute values for missing evaluations, and thus a subject who does not have an evaluation on a scheduled visit will be excluded from the as observed for that visit.

Safety variables will be summarized as observed.

5.0 Analysis Sets and Important Subgroups

5.1 Analysis Sets

The Modified Intent-to-Treat (mITT) Analysis Set includes all randomized subjects who receive at least 1 dose of study drug. Subjects will be grouped according to treatment as randomized. The mITT analysis set will be used for all demographic and efficacy analyses, unless otherwise noted.

MS expert(s) will confirm which subjects experienced a clinical relapse(s) through adjudication of study data, including the MS-relapse questionnaire. The Relapse-Free (RF) Analysis Set includes all subjects in the mITT analysis set without any MS-related relapse during the Treatment Period (from Week 0 to Week 52). Subjects will be grouped according to treatment as randomized.

Due to the COVID-19 pandemic, a subset of the study population missed one or more study drug infusions. For the purposes of conducting a sensitivity analysis of the primary and secondary endpoints, the Minimal Missed Infusion Analysis (MMIA) Set includes all randomized subjects who received at least 6 infusions total and missed no consecutive

infusions prior to the subject's final dose. Subjects will be grouped according to treatment as randomized.

The Safety Analysis Set consists of all subjects who received at least 1 dose of study drug. Subjects will be grouped according to treatment received regardless of randomization.

If a subject was randomized to treatment X, but received treatment Y during the entire study, this subject will be included in the Y treatment group for analysis purposes. If a subject receives both treatments but one > 50% of the time, the subject will be included in that treatment group. If a subject receives both treatments an equal percentage of the time, the subject will be analyzed in the treatment group to which they were randomized.

5.2 Subgroups

The primary efficacy and secondary variables will also be analyzed by the following subgroups to assess the consistency of the treatment effect:

- Sex (male, female)
- Age (≤ 40, > 40)
- EDSS baseline (≤ Median, > Median)
- Diagnosis of MS form (relapsing remitting MS [RRMS] vs. relapsing secondary-progressive MS [rSPMS]) if at least 20% of subjects are in each stratum
- Presence of background MS immunotherapy (Yes vs. No) if at least 20% of subjects are in each stratum

6.0 Subject Disposition

A summary of subject accountability will be provided where the number of subjects in each of the following categories will be summarized for each treatment group and overall, for the whole study and by investigator based on all randomized subjects:

- Subjects enrolled (randomized) in the study;

- Subjects who took at least one dose of study drug;
- Subjects who completed protocol-specified treatment;
- Subjects who prematurely discontinued study drug
- Subjects who discontinued the study
- Subjects in each of the following analysis sets: Safety Analysis Set, mITT analysis set, RF analysis set, MMIA set

The reasons for study drug discontinuation and study discontinuation will be summarized with the number and percentage of subjects for all reasons and the primary reason for the mITT analysis set by treatment group.

A summary of subject disposition will include the number randomized, number that never received study drug, number that received study drug other than randomized, and the number in each of the analysis sets noted in Section 5.1 for all subjects randomized by treatment group.

7.0 Extent of Exposure and Compliance

For the mITT analysis set, extent of exposure will be summarized for each treatment group. Extent of exposure will be summarized as duration of treatment and number of infusions. Duration of treatment is defined for each subject as last dose date minus first dose date + 28. A gap in treatment due to missed infusions will not be considered in the calculation of study duration. Duration of treatment will be summarized using the number of subjects treated, mean, standard deviation, median, minimum and maximum. In addition, the number and percentage of subjects in each unique treatment duration interval (28, 29 to 56, 57 to 84, 85 to 112, 113 to 140, 141 to 168, 169 to 196, 197 to 224, 225 to 252, 253 to 280, 281 to 308, 309 to 336, 337 to 364, > 364) will be summarized.

The number and percentage of subjects for each number of infusions from 1 to 13 will be summarized.

The number and percentage of completed and missed infusions by visit will be summarized at each visit from Day 1 to Week 48. The reason for missed infusions will be summarized at each visit.

The number of missed infusions by subject prior to the subject's last dose or premature discontinuation from study drug will be summarized by treatment group.

Because the treatment is administered by the site, compliance will not be summarized.

8.0 Demographics, Baseline Characteristics, Medical History, and Prior/Concomitant Medications

Demographics, baseline or disease characteristics, medical history, and prior and concomitant medications will be summarized for the mITT analysis set overall and by treatment group. Categorical variables will be summarized with the number and percentage of subjects; percentages will be calculated based on the number of non-missing observations. Continuous variables will be summarized with descriptive statistics (number of non missing observations, mean and standard deviation, median, minimum and maximum).

8.1 Demographics and Baseline Characteristics

Continuous demographic variables include age, weight, weight by sex, height, and body mass index (BMI). Categorical demographic variables include sex, ethnicity, race, age (<40, 40 – < 65, ≥ 65 years), BMI (< 25 or ≥ 25 kg/m2), country (United States or Canada), tobacco user (current, former, never, unknown), and alcohol user (current, former, never, unknown). The variables used for stratification of randomization as described in Section 4.2.2 will be summarized with the number and percentage of subjects.

8.2 Medical History

Medical history data will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). The actual version of the MedDRA coding dictionary will be noted in the

statistical tables and clinical study report. The number and percentage of subjects in each medical history category (by MedDRA system organ class and preferred term) will be summarized overall and by treatment group for the safety analysis set. The system organ class (SOC) will be presented in alphabetical order, and the preferred terms will be presented in alphabetical order within each SOC. Subjects reporting more than one condition/diagnosis will be counted only once in each row (SOC or preferred term).

8.3 MS Disease History

The number and percentage of subjects with each type of MS and number of relapses in the past 5 years (0, 1, 2, 3, ≥ 4) will be summarized categorically. The time in months since onset of first symptoms, and time in months since most recent relapse will be summarized continuously with descriptive statistics overall and by treatment group.

8.4 Prior and Concomitant Medications

Prior and concomitant medications will be summarized by generic name. A prior medication is defined as any medication taken prior to the date of the first dose of study drug. A concomitant medication is defined as any medication that started prior to the date of the first dose of study drug and continued to be taken after the first dose of study drug or any medication that started on or after the date of the first dose of study drug, but not after the date of the last dose of study drug plus 24 weeks (168 days). The number and percentage of subjects taking medications will be summarized by generic drug name based on the World Health Organization (WHO) Drug Dictionary for both prior and concomitant medications by treatment group and overall.

The number and percentage of subjects taking MS immunmodulators at Baseline, defined as those taking any MS immumodulator on the first dose date, will be summarized by generic drug name by treatment group and overall.

8.5 Protocol Deviations and Visit Modifications

The number and percentage of subjects who reported at least one protocol deviation will be summarized by treatment group and overall.

The number and percentage of subjects with in-person partial visits, virtual visits, and missed visits will be summarized by treatment group and overall for each visit. The primary reason for an impact to a visit will be summarized by treatment group and overall for each visit. The denominator will be the number of subjects in that treatment group for the by-treatment summary, or in the entire mITT analysis set for the overall summary.

9.0 Efficacy Analyses

9.1 General Considerations

All efficacy endpoints will be analyzed on mITT analysis set. The primary and secondary efficacy endpoint analyses will be repeated for the RF analysis set and the MMIA set as described in Section 5.1. Additional exploratory analyses will be repeated based on a subset of the population with a pre-defined deficit at baseline where noted.

For all exploratory efficacy analyses other than those related to MRI variables, where a continuous summary by visit is noted, the descriptive statistics based on the observed visit values will be provided by treatment group. The statistics include number of observations, mean, standard deviation, minimum, median, and maximum. The number and percentage will be summarized for categorical variables.

For all efficacy endpoints where change from baseline will be analyzed with an MMRM, the mean at baseline and that visit will be presented, as well as the LS means standard error, and the between group difference, standard error, and 95% confidence interval.

Baseline for efficacy will be defined as the last non-missing observation that is on or before the first dose date.

9.2 Primary Efficacy Analysis

The primary efficacy variable is the ORS at Week 52 and secondary efficacy variables are the ORS at Weeks 12, 24, and 36. The ORS will be summarized continuously as observed (including n, mean, standard deviation, minimum, median and maximum) at each visit.

The frequency and percentage of subjects with each ORS score in the range of –4 to +4 will also be provided by treatment group at each visit. The data will be summarized as observed, i.e., no imputations will be implemented.

The comparisons between the each elezanumab group and placebo for the primary efficacy endpoint ORS at each scheduled visit during the treatment period will be performed using anMMRM. The ORS for each treatment group at scheduled visits and overall will be estimated from the model. The within group LS mean 95% confidence interval, pooled standard deviation, effect size, and 95% confidence interval for the effect size will also be presented by treatment group. The model will include the fixed effects of treatment, visit, the stratification factors of diagnosis of MS (RRMS or rSPMS) and background MS immunotherapy (Yes or No), and the treatment-by-visit interaction, with baseline scores (EDSS, T25FW, 9HPT-D, 9HPT-ND) as covariates. The REPEATED statement will be used for visit with blocks in the covariance matrix identified by subject nested within treatment group. The unstructured covariance structure will be used to estimate the within subject variance-covariance. If the model fails to converge, the first order autoregressive (AR[1]) covariance structure will be substituted. If the model still fails to converge, the compound symmetry (CS) covariance structure will be substituted. Denominator degrees of freedom will be computed using the Kenward-Roger method.

This will be repeated for the RF and MMIA sets.

The posterior probability that each elezanumab group's effect size is greater than 0.1, 0.3, and 0.5 will be presented for the mITT analysis set.

The ORS and corresponding 95% confidence interval based on the MMRM for the mITT analysis set will be plotted at each time point during the treatment period by treatment group.

The post-treatment ORS scores will be summarized continuously as observed.

9.3 Secondary Efficacy Analyses

Disability improvement on the EDSS + indicates clinically significant improvement on at least 1 of the components of the EDSS + (EDSS, T25FW, 9HPT [either hand]) as defined by the clinically significant change thresholds in Section 4.3.1).

Improvement responder status on the EDSS + and each of its components will be analyzed by time point based on the criteria in Section 4.3.1. No confirmation will be required, i.e., improvement at the analysis time point only is required to be considered a responder.

The analysis will be presented at each time point with the number and percentage of responders, and the 95% confidence interval for the proportion of subjects based on Wald confidence limits, and the odds ratio and corresponding 95% confidence interval based on the logistic regression model including baseline as a covariate and treatment as a main effect. The model for the EDSS + will include the baseline EDSS, baseline T25FW, baseline 9HPT-D, baseline 9HPT-ND as covariates and treatment as a main effect. This will be presented based on the mITT, RF and MMIA analysis sets using non-responder imputation. The logistic regression analysis will be repeated for the mITT analysis set based on the same multiple imputation as detailed in Section 9.3.1.

A summary of the improvement responder status on the EDSS + and each of its components will be presented for the mITT analysis set as observed.

9.3.1 Sensitivity Analysis of the Primary and Secondary Endpoints

The primary and secondary endpoint analyses will be repeated for the RF and MMIA analysis sets as noted those respective sections.

Additionally, the analysis of ORS at Weeks 12, 24, 36, and 52, and the number and percentage of subjects with 12- and 24-week confirmed improvement for the EDSS+ and each of its components will be repeated based on multiple imputation (MI). First, a full dataset will be imputed using full data imputation MCMC. Data will be imputed for the

EDSS, T25FW, 9HPT-D and 9HPT-ND in a continuous fashion for each endpoint separately. Then, the definition of clinically significant improvement/no change/clinically significant worsening as seen in Section 4.3.1 will be applied to determine the components of the ORS or 12- or 24- week confirmed improvement status. The imputation model will include treatment group, type of MS, baseline use of immunomodulator therapies, baseline variable for the respective endpoint being imputed, and the non-missing post-baseline values for the variable that will be imputed (value at Week 12, 24, 36, 52, 64 and 76). The number of imputed datasets will be 30, and the random seed will be 123455. The ORS at each visit noted above will be summarized for each treatment group and compared to placebo using ANCOVA, with baseline values for each component of the EDSS + included in the model. The responder status with 12- and 24-week confirmed improvement will be analyzed with a logistic regression as noted in Section 9.4.1.

9.4 Other Efficacy Analyses

Change from baseline treatment comparison at each visit will be conducted using an MMRM model including treatment group, visit, treatment-by-visit interaction, and stratification factors as fixed effects, the baseline values associated with the endpoint as covariates. The REPEATED statement will be used for visit with blocks in the covariance matrix identified by subject nested within treatment group. The unstructured covariance structure will be used to estimate the within subject variance-covariance. If the model fails to converge, the first order autoregressive (AR[1]) covariance structure will be substituted. If the model still fails to converge, the compound symmetry (CS) covariance structure will be substituted. Denominator degrees of freedom will be computed using the Kenward-Roger method.

For binary efficacy endpoints, the frequency and percentage will be provided by treatment group unless otherwise noted.

9.4.1 Confirmed Improvement on the EDSS + and its components

Confirmed 12-week disability improvement on the EDSS + or components of the EDSS + indicates a subject has clinically significant improvement at a visit as well as the next visit for one or more EDSS+ components, or if the next visit is missing, the subsequent visit. Confirmation may include assessments collected in the post-treatment follow-up period. The improvement confirmation must be in the same component of the EDSS +. If a subject has improvement in more than one component of the EDSS +, the subject must have confirmation in at least one of the same components to be considered as having confirmed disability improvement. For example, if a subject has clinically significant improvement in the T25FW at Week 12, the subject must have clinically significant improvement in the same component of the EDSS + at Week 24 (or if Week 24 is missing, Week 36) to be considered to have confirmed improvement.

Confirmed 24-week improvement on the EDSS + or components of the EDSS + indicates a subject has clinically significant improvement at 3 consecutive visits, or if one of the two subsequent visits are missing, subject demonstrates clinically significant improvement at two of the subsequent three visits. Improvement status after confirmed improvement is not considered, i.e., if a subject has disability improvement in one component of the EDSS + at Week 12 and Week 24, then this subject is considered to have 12-week confirmed disability improvement regardless of a Week 36 status of clinically significant worsening, no clinically significant change, or clinically significant improvement.

The 12-week and 24-week confirmed disability improvement response rate will be summarized for the study for the EDSS +, as well as each of the individual components for the mITT, RF, and MMIA analysis sets based on a non-responder imputation. The frequency and percentage will be provided by treatment group. The treatment comparison will be conducted using the logistic regression model adjusted for the stratification factors and baseline scores associated with the endpoint. The proportion of responders, difference in responder rate, and 95% confidence interval for the responder rate based on

Wald confidence limits will be presented based on the univariate summary. The odds ratio, and 95% confidence interval will be derived from the logistic regression model.

The analyses for confirmed disability improvement will be repeated for the RF and MMIA analysis sets as noted those respective sections.

9.4.2 Disability Progression

Disability progression on the EDSS + indicates clinically significant worsening on at least 1 of the components of the EDSS + (EDSS, T25FW, 9HPT [either hand]) as defined by the clinically significant change thresholds in Section 4.3.1.) This will be based on the imputed dataset described in Section 9.3.1.

Progression on the EDSS + and each of its components will be analyzed by time point based on the criteria in Section 4.3.1. No confirmation will be required, i.e., progression at the analysis time point only is required.

The analysis will be presented at each time point with the number and percentage of subjects, and the 95% confidence interval for the proportion of subjects based on Wald confidence limits, and the odds ratio and corresponding 95% confidence interval based on the logistic regression model including baseline as a covariate and treatment as a main effect.

9.4.3 T25FW

The change from baseline in the T25FW during the Treatment Period will be analyzed using an MMRM. In addition to the summaries noted in Section 9.1, the pooled standard deviation, effect size, and 95% confidence interval of the effect size will be noted.

9.4.4 9HPT

The change from baseline in the 9HPT-D and 9HPT-ND during the Treatment Period will be analyzed using an MMRM. In addition to the summaries noted in Section 9.1, the

pooled standard deviation, effect size, and 95% confidence interval of the effect size will be noted.

9.4.5 Exploratory Patient and Clinician Measured Scales

The change from baseline in the total score for the MSIS-29, the total score for the BAC - Tower of London, the total score for the BAC – Verbal Memory, BAC - Tower of London T-score, BAC - Verbal Memory T-score, and the overall symptom score and most bothersome symptom score for the MSIOA will be analyzed at the collected time points using an MMRM.

9.4.6 SDMT

The change from baseline for the SDMT total score will be summarized based on the mITT analysis set using an MMRM.

The above analysis of change from baseline will be repeated for the subset of subjects with an SDMT total score < 50 at baseline using the same MMRM as described in the previous paragraph. The posterior probability of the difference of the group means being greater than 1 based on the SDMT total score will be presented. A non-informative prior will be used.

The number and percentage of subjects with a change from baseline in the SDMT total score ≥ 4 will be analyzed as observed. The analysis will be presented at each time point with the number and percentage of subjects, difference from placebo in responder rate, and the 95% confidence interval for the difference in proportion of subjects based on Wald confidence limits, and the odds ratio and corresponding 95% confidence interval based on the logistic regression model including baseline as a covariate and treatment as a main effect.

9.4.7 MFIS-5

The change from baseline for the MFIS-5 total score will be summarized based on the mITT analysis set using an MMRM.

The above analysis of change from baseline will be repeated for the subset of subjects with an MFIS-5 total score of ≥ 9 at baseline using the same MMRM as described in the previous paragraph. The posterior probability of the difference of the group means being greater than 1 based on the MFIS-5 total score will be presented. A non-informative prior will be used.

9.4.8 Low Contrast Visual Acuity

The change from baseline in low contrast visual acuity variables will be summarized as observed at each time point for the following parameters:

- Number of characters read, bilateral, 100% contrast level
- Number of characters read, bilateral, 2.5% contrast level
- Number of characters read, bilateral, 1.25% contrast level
- Number of characters read, right eye, 100% contrast level
- Number of characters read, right eye, 2.5% contrast level
- Number of characters read, right eye, 1.25% contrast level
- Number of characters read, left eye, 100% contrast level
- Number of characters read, left eye, 2.5% contrast level
- Number of characters read, left eye, 1.25% contrast level

The number of observations, mean, standard deviation, median, min and max will be presented.

The change from baseline in the number of characters read, bilateral at the 1.25% contrast level, will be summarized using an MMRM based on the population of subjects with a baseline deficit, defined as ≤ 11 characters (bilateral at the 1.25% contrast level) at baseline. The posterior probability that the mean difference between groups is > 2 using a non-informative prior will be calculated.

9.4.9 Actigraphy

Actigraphy was collected for 7 days starting at the visits at Week 0 (Baseline), 24, 36, and 52. The actigraphy parameters of movement including average gait cadence, moving duration, walking duration, number of steps and resting duration will be analyzed.

Moving duration, walking duration, number of steps, and resting duration will be normalized for the number of hours per day the subject is wearing the device, i.e., divided by the (device wear time duration [in seconds] ÷ 3600).

The analysis of change from Week 0 for each of the moving duration, walking duration, number of steps, and resting duration will be based on the average hourly value for that visit, i.e., the Week X value will be the sum of the daily average hourly values for that parameter divided by the number of days the subject wore a sensor within a window. The analysis of change from Week 0 for average gait cadence will be based on the average daily value of gait cadence for that visit, i.e., the Week X value will be the sum of the daily mean gait cadence values divided by the number of days the subject wore a sensor within a window. The pooled standard deviation, effect size, and 95% confidence interval of the effect size will also be noted.

9.4.10 Biomarkers

The change from baseline in the serum/plasma biomarkers repulsive guidance molecule a (RGMa), neurofilament light (NFL), micro RNA miR-146a and miR-338, mRNAs for PLP1 (proteolipid protein 1), glial fibrillary acidic protein (GFAP), and BDNF (brain-derived neurotrophic factor), will be summarized using an MMRM The model will include the fixed effects of treatment, visit, the stratification factors of diagnosis of MS (RRMS or rSPMS) and background MS immunotherapy (Yes or No), and the treatment-by-visit interaction, with baseline value for the respective parameter as a covariate. The REPEATED statement will be used for visit with blocks in the covariance matrix identified by subject nested within treatment group. The unstructured covariance structure will be used to estimate the within subject variance-covariance.

9.4.11 MRI Parameters

The MRI parameters of interest and analyses are listed in Section 4.3.3.

The number and percentage of subjects with active lesions will be summarized for T1 GAD-enhancing lesions and T2 hyperintense lesions (separately). The difference in the proportion between elezanumab and placebo groups with the 95% confidence interval for the difference based on Wald confidence limits will be presented.

The cumulative number of total T1 GAD-enhancing lesions, cumulative number of total T2 hyperintense lesions, cumulative number of post-baseline T1 GAD-enhancing lesions, cumulative number of post-baseline new and enlarging T2-lesions, will be summarized with continuously and analyzed using an analysis of covariance (ANCOVA). The model for the analysis of the cumulative number of total lesions will include treatment, the stratification factors of diagnosis of MS (RRMS or rSPMS) and background MS immunotherapy (Yes or No). For the cumulative number of lesions during the treatment period, only subjects with Baseline, Week 24, and Week 52 MRIs will be included. For the cumulative number of lesions post-baseline, only subjects with Week 24 and Week 52 will be included.

The number of T1 GAD-enhancing lesions at each visit (Baseline, Week 24, Week 52) will be summarized categorically with the number and percent of subjects for the following categories: 0, 1, 2, 3, 4, 5, > 5.

The following endpoints will be analyzed using change or percent change from baseline using an ANCOVA model.

- Change from Baseline in total volumes of T1 GAD-enhancing lesions
- Change from Baseline in total volume of T2 hyperintense lesions
- Percent change from Baseline in whole brain, gray matter (GM), thalamus, white matter (WM) and normal appearing white matter (NAWM) volumes
- Change from Baseline in regional magnetization transfer ratio (MTR) parameters for whole brain, and NAWM, and MTR for T2 lesions

- Change from Baseline in diffusion tensor imaging (DTI) parameters (fractional anisotropy and Apparent Diffusion Coefficient (ADC)) for whole brain, NAWM and T2 hyperintense lesions
- Change from Baseline in cervical spinal cord area, volume and number of lesions
- Change from Baseline in regional MTR for cervical spinal cord lesions
- Change from baseline in DTI parameters (fractional anisotropy and ADC) for cervical spinal cord

The model for the change from baseline analysis will include treatment, the stratification factors of diagnosis of MS (RRMS or rSPMS) and background MS immunotherapy (Yes or No), and the baseline value. For each treatment group, the number of subjects, mean, standard deviation, minimum, and maximum, will be presented, as well as the LS means and standard error, and the between group difference, standard error, and 95% confidence interval.

The change from baseline in lesion MTR for T1 GAD-enhancing lesions and delta MTR will be analyzed using an MMRM. The change from baseline will be calculated for each unique lesion within a treatment group. A dummy code will be created based on each subject-lesion to describe each unique lesion. The model will include the fixed effects of treatment, visit, the stratification factors of diagnosis of MS (RRMS or rSPMS) and background MS immunotherapy (Yes or No), and the treatment-by-visit interaction, with baseline MTR value as a covariate. The RANDOM statement will be used for each subject. The REPEATED statement will be used for visit with blocks in the covariance matrix identified by unique lesion nested within subject nested within treatment group. The unstructured covariance structure will be used to estimate the within subject variance-covariance. If the model fails to converge, the first order autoregressive (AR[1]) covariance structure will be substituted. If the model still fails to converge, the compound symmetry (CS) covariance structure will be substituted. Denominator degrees of freedom will be computed using the Kenward-Roger method.

9.5 Efficacy Subgroup Analyses

Subgroup analysis for the primary endpoint (ORS) based on the mITT analysis set will be conducted by the subgroups specified in Section 5.2. This will be based on the MMRM analysis and the analysis will be presented for Week 12, 24, 36, and 52. The model will include the fixed effects of treatment, visit, the stratification factors of diagnosis of MS (RRMS or rSPMS) and background MS immunotherapy (Yes or No), subgroup, treatment-by-visit interaction, treatment by subgroup interaction, and treatment by subgroup by visit interaction with baseline EDSS, T25FW, 9HPT-D and 9HPT-ND values as covariates. The REPEATED statement will be used for visit with blocks in the covariance matrix identified by subject nested within treatment group. The unstructured covariance structure will be used to estimate the within subject variance-covariance. If the model fails to converge, the first order autoregressive (AR[1]) covariance structure will be substituted. If the model still fails to converge, the compound symmetry (CS) covariance structure will be substituted. Denominator degrees of freedom will be computed using the Kenward-Roger method.

9.6 Figures Based on the EDSS + and Its Components

A line plot of the LS mean and 95% confidence intervals of the ORS during the Treatment Period by treatment group based on the mITT analysis set and MMIA set will be produced.

A stacked bar plot displaying the proportion of subjects within each bucket of clinically significant change (see Section 4.3.1) in EDSS, T25FW, 9HPT-D, and 9HPT-ND by treatment will be produced for Week 12, 24, 36, and 52 based on the mITT analysis set and MMIA set as observed.

A bar plot displaying the proportion of subjects with each value of the ORS {-4, -3, -2, -1, 0, 1, 2, 3, 4} by treatment group will be produced for Week 12, 24, 36, and 52 based on the mITT analysis set and MMIA set as observed.

A forest plot of the ORS by subgroups at Week 52 will be produced for the mITT analysis set.

10.0 Safety Analyses

10.1 General Considerations

Safety analyses will be carried out using the Safety Analysis Set. Safety will be assessed by AEs, lab values, vital sign measurements (including change from pre- to post-infusion vital signs), ECG, and Columbia-Suicide Severity Rating Scale (C-SSRS). Frequency tables and lists of subjects with treatment emergent AEs by preferred term as in the Medical Dictionary for Regulatory Activities (MedDRA), by system organ class and preferred term, by severity, and by relationship to the study treatment as assessed by the Investigator will be provided. For continuous safety outcomes, the change from Baseline will be analyzed in a descriptive manner by treatment group and by visit. For each variable in which change from baseline is analyzed, the raw visit values will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. For categorical safety outcomes, the number and percentage of each category will be summarized by treatment group and by visit. Shift of laboratory values from Baseline to defined time points will be tabulated. Shift to final visit will include data collected during the follow-up period. Hypothesis testing will not be performed for safety parameters.

10.2 Analysis of Adverse Events

10.2.1 Treatment-Emergent Adverse Events

Treatment emergent adverse events (TEAE) will be defined as all events that begin or worsen on or after first dose of the study drug.

10.2.2 Adverse Event Overview

The number and percentage of subjects experiencing one or more TEAEs in the following adverse event categories will be summarized for each treatment group, combined elezanumab group and all subjects overall:

- Any TEAE
- Any TEAE that are considered related to study treatment
- Any severe TEAE
- Any serious TEAE
- Any TEAE leading to discontinuation of study treatment
- Any AE of Special Interest
- Any TEAE leading to death
- Death

10.2.3 Adverse Events by System Organ Class and Preferred Term

The number and percentage of subjects experiencing TEAEs will be tabulated using primary Medical Dictionary for Regulatory Activities (MedDRA) system organ classes (SOCs) and preferred terms (PTs) for each treatment group and combined elezanumab group. The SOCs will be presented in alphabetical order, and the PTs will be presented in alphabetical order within each SOC.

A subject who reports more than 1 AE in different SOCs will be counted only once in the overall total. A subject who reports 2 or more different PTs, which are in the same SOC, will be counted only once in the SOC total. Subjects reporting more than 1 AE for a given PT will be counted only once for that term (most severe incident for the severity tables and most related incident for the relationship tables).

10.2.4 Adverse Event Incidence

The number and percentage of subjects experiencing one or more adverse events in the following adverse event categories will be summarized by primary SOC and PT for each treatment group, combined elezanumab total group and all subjects overall.

- Any TEAE
- Any serious TEAE
- Any TEAE that was moderate or severe
- Any TEAE that led to discontinuation of study treatment
- Any TEAE that have reasonable possibility being related to study treatment

A list of subject numbers associated with each PT will also be presented for all TEAEs.

10.2.5 Adverse Events by Maximum Severity

The number and percentage of subjects experiencing one or more TEAEs will also be summarized by maximum severity category (mild, moderate, severe, or unknown) and primary SOC for each treatment group, combined elezanumab group and all subjects overall. Subjects reporting more than one TEAE for a given PT will be counted only once for that term in the most severe category reported. If a subject has an adverse event with unknown severity, then the subject will be counted in the severity category of "unknown," even if the subject has another occurrence of the same event with a severity present. The only exception is if the subject has another occurrence of the same adverse event with the most extreme severity – "Severe." In this case, the subject will be counted under the "Severe" category.

10.2.6 Adverse Events by Maximum Relationship

The number and percentage of subjects experiencing one or more TEAEs will also be summarized by maximum relationship category (reasonable possibility, no reasonable possibility, or unknown), as assessed by the investigator, and primary SOC and PT for each treatment group, combined elezanumab group and all subjects overall. Subjects

reporting more than one TEAE for a given PT will be counted only once for that term in the most related category reported. If a subject has an adverse event with unknown relationship, then the subject will be counted in the relationship category of "unknown," even if the subject has another occurrence of the same event with a relationship present. The only exception is if the subject has another occurrence of the same adverse event with a relationship assessment of "reasonable possibility." In this case, the subject will be counted under the "reasonable possibility" category.

10.2.7 Adverse Events of Special Interest

For adverse events of special interest (AESIs), serious and non-serious, meeting predefined criteria, specific questionnaires will be used to standardize the collection of follow-up information. The AESI questionnaires will be issued within the electronic data capture (EDC) system once applicable. The investigator will enter the information into the EDC system once applicable. Further information about AESIs is provided in the protocol operations manual.

Adverse events of special interest (AESIs) include:

- Infusion reactions.

The number and percentage of subjects reporting AEs in each AESI category will be summarized by primary SOC and PT for each treatment group, combined elezanumab group and all subjects overall.

10.2.8 Listings of Adverse Events

The following additional summaries of adverse events will be prepared.

- Listing of all deaths for all subjects screened
- Listing of all serious TEAEs
- Listing of all pre-treatment serious AEs for all subjects screened
- Listing of all TEAEs that led to discontinuation of study treatment

- Listing of subjects with treatment-emergent adverse event of special interest

10.2.9 Adverse Events by Preferred Term in Decreasing Frequency

TEAEs occurring in any of the treatment arms will be summarized by MedDRA PT in decreasing frequency in combined elezanumab group.

10.3 Analysis of Laboratory Data

Hematology variables include: hematocrit, hemoglobin, red blood cell (RBC) count, white blood cell (WBC) count, neutrophils, bands, lymphocytes, monocytes, basophils, eosinophils, platelet count, Partial thromboplastin time (PTT) and Activated partial thromboplastin time (aPTT).

Chemistry variables include: blood urea nitrogen (BUN), creatinine, total bilirubin (TBL), albumin, glutamic pyruvic transaminase/Alanine transaminase (SGPT/ALT), glutamic-oxaloacetic transaminase/Aspartate transaminase (SGOT/AST), alkaline phosphatase, sodium, potassium, calcium, inorganic phosphorus, uric acid, cholesterol, total protein, glucose, triglycerides, bicarbonate/CO2, chloride and CPK.

Urinalysis variables include: blood, glucose, ketones, pH, protein and specific gravity.

The baseline value of lab is defined as the last non-missing lab measurement recorded before the first dose of study drug and final value will be defined as the last non-missing lab measurement post-baseline during the entire study.

10.3.1 Analysis of Laboratory Tests

Each laboratory variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Changes from Baseline in laboratory parameters for WBC count, CPK, and lymphocytes will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group. The baseline and

visit means will be calculated for each visit for subjects who have both a baseline and visit value.

10.3.2 Shifts Between Normal and Abnormal for Laboratory Tests

Laboratory observations will be categorized as normal, low, or high relative to the reference (normal) range associated with the laboratory that performed the assay. For each hematology, chemistry and urinalysis with a reference range, shift tables will be prepared for shifts from baseline to lowest, highest and final value during the entire study for each treatment group and all subjects overall. The tables will present:

- The numbers and percentages of subjects with low or normal observations at baseline who have a high observation at any post-baseline visit
- The numbers and percentages of subjects with normal or high observations at baseline who have a low observations at any post-baseline visit
- The numbers and percentages of subjects with low or normal observations at baseline who have a high observation at the final visit
- The numbers and percentages of subjects with normal or high observations at baseline who have a low observations at the final visit

10.3.3 Analysis for Potentially Clinically Significant (PCS) Laboratory Values

Criteria for potentially clinically significant (PCS) values have been predefined for selected laboratory variables as outlined in Appendix 12.2. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided for each treatment group and all subjects overall. A listing will also be prepared that will include, for each variable, all observations for each subject that met the PCS criteria for that variable at any time during the study.

The following criteria will be used to assess for potential hepatotoxicity. The number and percentage of subjects meeting each of the following criteria will be summarized by

treatment group, and a listing of ALT, AST, TBL, and alkaline phosphatase at each time for all subjects that met any of the criteria below at any time will be produced.

- ALT > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- AST > 3 × ULN, > 5 × ULN, > 10 × ULN, > 20 × ULN
- TBL > 1.5 x ULN, > 2 × ULN
- ALT and/or AST > 3 × ULN and TBL > 1.5 × ULN
- ALT and/or AST > 3 × ULN and TBL > 2 × ULN
- ALT > 3 × ULN and TBL > 1.5 × ULN
- ALT > 3 × ULN and TBL > 2 × ULN
- Alkaline phosphatase > 1.5 × ULN

10.4 Analysis of Vital Signs and Weight

Vital sign variables include: body temperature, pulse and pre and post-infusion systolic and diastolic blood pressures (including retesting due to post-infusion elevations seen).

Weight variables include: weight and BMI.

BMI will be calculated using height as measured during screening.

10.4.1 Vital Sign and Weight

Each vital sign variable will be summarized for all time points (starting with Baseline) with the number of non-missing observations, mean and standard deviation, median, minimum and maximum. Change from baseline to each planned visit and to the minimum, maximum and final value during the Treatment Period will be summarized in a descriptive manner for each treatment group and all subjects overall for each vital sign and weight variable. During the Treatment Period, this will be based on the pre-infusion value.

For each change from baseline analysis, the following summary statistics will be presented: sample size, baseline mean, visit (time point) mean, and the mean, standard

deviation, and median of the change from baseline. The baseline and visit (time point) means will be calculated for each visit (time point) for subjects who have both a baseline and visit (time point) value.

The change from pre-infusion to post-infusion in systolic blood pressure, diastolic blood pressure, and pulse at each infusion visit will be summarized in a descriptive manner for each treatment group and all subjects overall through Week 48. The following summary statistics will be presented: sample size, pre-infusion mean, post-infusion mean, and the mean, standard deviation, and median of the change from pre-infusion to post-infusion. The pre-infusion and post-infusion means will be calculated for each infusion visit (time point) for subjects who have both values.

10.4.2 Potentially Clinically Significant (PCS) Vital Signs

Criteria for PCS values have been predefined for selected vital sign and variables as outlined in Appendix 12.3. For each variable including both pre- and post-infusion variables, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the PCS criteria and is more extreme than their baseline value will be provided for each treatment group and all subjects overall. A listing will also be prepared that will include, for each variable, all observations for each subject that met the PCS criteria for that variable at any time during the study.

10.5 Analysis of ECG Parameters

The proportion of subjects with Normal, Abnormal – not clinically significant and Abnormal – clinically significant electrocardiogram (ECG) readings will be summarized at each visit ECG is performed for each treatment group and all subjects overall.

10.6 Analysis of Columbia-Suicide Severity Rating Scale (C-SSRS)

The Columbia-Suicide Severity Rating Scale (C-SSRS) is a systematically administered instrument developed to track suicidal adverse events across a treatment study. At Screening Visit 1 the C-SSRS will be administered to collect lifetime history as well as

experience during the past year. At all other visits, the C-SSRS will collect experience since the last visit. Affirmative responses on the C-SSRS will be summarized for the initial screening and each subsequent visit for each treatment group and all subjects overall.

Each summary will include the number and percentage of subjects with one or more affirmative responses to each of the 5 suicidal ideation questions, each of the 6 suicidal behavior questions, any of the 5 suicidal ideation questions, any of the 6 suicidal behavior questions, any suicidal ideation or behavior question, and the self-injurious behavior without suicidal intent. A listing will also be prepared that includes all subjects with 1 or more affirmative responses.

10.7 MS Relapses

The number and percentage of subjects with confirmed MS relapses will be summarized.

10.8 Pregnancy

Pregnancy information will be presented in listings only.

11.0 Summary of Changes

11.1 Summary of Changes Between the Previous Version and the Current Version

Minor typographical corrections and text clarifications were made throughout.

An interim futility analysis previously planned was eliminated. Sample size calculations have been corrected.

Due to an update to the format corresponding document to further define programming, the statistical programming plan, the following sections were added:

- Subject Disposition
- Extent of Exposure and Compliance

- Demographics, Baseline Characteristics, Medical History and Prior/Concomitant Medications
- Protocol Deviations and Visit Modifications

Due to the COVID-19 pandemic, significant modifications were made to the secondary and exploratory endpoints in the protocol. These changes are reflected in the SAP. Additionally, due to increased missing data, an additional analysis set (MMIA set) was added, and missing data handling rules were updated.

Details of the analyses of exploratory endpoints and MRI were added.

Additional efficacy analyses were added to further characterize the treatment effect, including:

- Improvement by visit on the EDSS + and its components
- Disability progression
- Continuous analyses of the change from baseline in T25FW and 9HPT
- Analyses of the SDMT, MFIS-5, and LCVA based on a subset of the population with a deficit at baseline
- Exploratory analyses related to biomarkers and actigraphy
- Figures specified in Section 9.6

Minor clarifications and updates were made to the safety analyses. The adverse events of special interest were updated in the protocol and is reflected in this SAP. A change from baseline summary is planned for specified laboratory values only. A summary of liver function tests including possible Hy's Law cases is specified. The PCS laboratory table was updated to reflect only the parameters which were collected in this study. A summary of the number MS relapses is planned. Details of the vital signs summaries were added.

11.2 Summary of Changes in Previous Version

This is the second version. All changes from the initial version are summarized in the previous section.

12.0 Appendix

12.1 Adverse Events of Special Interest

See the statistical programming plan for further description of AESIs.

12.2 Criteria for Potentially Clinically Significant Laboratory Values

Variable Measured	Potentially Clinically Significant (PCS) Criteria	
	Very Low	**Very High**
Hematology		
Activated partial thromboplastin time prolonged (aPTT)	NA	> ULN
Hemoglobin	< 10.0 g/dL (6.2 mmol/L, 100 g/L)	> 4 gm/dL above ULN
Lymphocyte count	< 500/mm^3 (0.5 × 10^9/L)	> 20,000/mm^3
Neutrophil count	< 1000/mm^3 (1.0 × 10^9/L)	NA
Platelet count	< 75,000/mm^3 (75.0 × 10^9/L)	NA
White blood cell (WBC)	< 2000/mm^3 (2.0 × 10^9/L)	> 100,000/mm^3
Chemistry		
Blood bilirubin	NA	> 1.5 × ULN
Cholesterol	NA	> 500 mg/dL (12.92 mmol/L)
Creatinine	NA	> 1.5 × ULN
Corrected Serum Calcium	< 7.0 mg/dL (1.75 mmol/L)	> 12.5 mg/dL (3.1 mmol/L)
Fasting Glucose	< 40 mg/dL (2.2 mmol/L)	> 250 mg/dL (13.9 mmol/L)
Potassium	< 3.0 mmol/L	> 6.0 mmol/L
Sodium	< 130 mmol/L	> 155 mmol/L
Triglycerides	NA	> 500 mg/dL (5.7 mmol/L)
Uric acid	NA	> 10 mg/dL (0.59 mmol/L)
Albumin	< 2 g/dL (20 g/L)	NA
phosphate	< 2.0 mg/dL (0.6 mmol/L)	NA
Enzymes		
Alanine aminotransferase (ALT)	NA	> 3.0 × ULN
Alkaline phosphatase	NA	> 2.5 × ULN
Aspartate aminotransferase (AST)	NA	> 3.0 × ULN
Variable Measured	**Potentially Clinically Significant (PCS) Criteria**	
	Very Low	**Very High**
Enzymes (continued)		
CPK	NA	> 5.0 × ULN

12.3 Criteria for Potentially Clinically Significant Vital Sign Values

Vital Signs Variables	Criterion	Potentially Clinically Significant (PCS) Value
Systolic blood pressure (mmHg)	Low	≤ 90 mm Hg and decrease ≥ 20 mmHg from Baseline
	High	≥ 180 mm Hg and increase ≥ 20 mmHg from Baseline
Diastolic blood pressure (mmHg)	Low	≤ 50 mm Hg and decrease ≥ 15 mmHg from Baseline
	High	≥ 105 mm Hg and increase ≥ 15 mmHg from Baseline
Heart rate (bpm)	Low	≤ 50 bpm and decrease ≥ 15 bpm from Baseline
	High	≥ 120 bpm and increase ≥ 15 bpm from Baseline
Temperature	High	≥ 38.3°C and ≥ 1.1°C above baseline value
Post-infusion systolic blood pressure	High	> 160 mmHg systolic and > 20 mm Hg above pre-infusion value
Post-infusion diastolic blood pressure	High	> 105 mm Hg diastolic and > 15 mm Hg above pre-infusion value

13.0 References

1. Protocol for Study M18-918, A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Assess the Safety and Efficacy of Elezanumab when Added to Standard of Care in Relapsing Forms of Multiple Sclerosis.
2. Operations manual for Clinical Study Protocol M18-918.