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Protocol for Study M18-918

Multiple Sclerosis: Safety and Efficacy Study of Elezanumab (ABT-555) in Relapsing Forms of Multiple Sclerosis

VERSION:	5.0	DATE:	22 March 2021
SPONSOR:	AbbVie*	NUMBER OF SITES:	Approximately 50
ABBVIE INVESTIGATIONAL PRODUCT:	elezanumab		

FULL TITLE: 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

Incorporating Versions 1.0, 2.0, 3.0, 4.0, and 5.0

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TABLE OF CONTENTS

1 SYNOPSIS 5

2 INTRODUCTION 6

2.1 BACKGROUND AND RATIONALE 6

2.2 BENEFITS AND RISKS TO SUBJECTS 6

3 STUDY OBJECTIVES AND ENDPOINTS 7

3.1 OBJECTIVE 7

3.2 PRIMARY ENDPOINT 7

3.3 SECONDARY ENDPOINTS 7

3.4 SAFETY ENDPOINTS 7

3.5 PHARMACOKINETIC ENDPOINTS 8

3.6 BIOMARKER RESEARCH ENDPOINTS FOR TARGET ENGAGEMENT AND NEURO-RESTORATION 8

3.7 EXPLORATORY ENDPOINTS 8

4 INVESTIGATIONAL PLAN 9

4.1 OVERALL STUDY DESIGN AND PLAN 9

4.2 DISCUSSION OF STUDY DESIGN 11

5 STUDY ACTIVITIES 12

5.1 ELIGIBILITY CRITERIA 12

5.2 CONTRACEPTION RECOMMENDATIONS 16

5.3 PROHIBITED MEDICATIONS AND THERAPY 17

5.4 PRIOR AND CONCOMITANT THERAPY 18

5.5 WITHDRAWAL OF SUBJECTS AND DISCONTINUATION OF STUDY 19

5.6 FOLLOW-UP AFTER SUBJECT DISCONTINUATION OF STUDY DRUG OR FROM STUDY 20

5.7 STUDY DRUG 20

5.8 RANDOMIZATION/DRUG ASSIGNMENT 24

5.9 PROTOCOL DEVIATIONS 24

6 SAFETY CONSIDERATIONS 25

6.1 COMPLAINTS AND ADVERSE EVENTS 25

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE 28
7.1 STATISTICAL AND ANALYTICAL PLANS 28
7.2 DEFINITION FOR ANALYSIS SETS 28
7.3 STATISTICAL ANALYSES FOR EFFICACY 28
7.4 STATISTICAL ANALYSES FOR SAFETY 29
7.5 INTERIM ANALYSIS 29
7.6 SUBGROUP ANALYSIS 29
8 ETHICS 29
8.1 INDEPENDENT ETHICS COMMITTEE/INSTITUTIONAL REVIEW BOARD 29
8.2 ETHICAL CONDUCT OF THE STUDY 30
8.3 SUBJECT CONFIDENTIALITY 30
9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION 30
10 DATA QUALITY ASSURANCE 30
11 COMPLETION OF THE STUDY 31
12 REFERENCES 31

LIST OF TABLES

TABLE 1. STUDY DRUG IDENTIFICATION 21
TABLE 2. STUDY DRUG ADMINISTRATION SCHEDULE 22

LIST OF FIGURES

FIGURE 1. STUDY SCHEMATIC 10

LIST OF APPENDICES

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS 32
APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR 35
APPENDIX C. LIST OF PROTOCOL SIGNATORIES 36

APPENDIX D. ACTIVITY SCHEDULE 37

APPENDIX E. PROTOCOL SUMMARY OF CHANGES 41

APPENDIX F. OPERATIONS MANUAL 42

1 SYNOPSIS

Title: 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	
Background and Rationale:	Elezanumab is an investigational product under development for the treatment of multiple sclerosis (MS). It is a monoclonal immunoglobulin (Ig) of the human IgG1 isotype that binds specifically to the soluble and the membrane-bound forms of repulsive guidance molecule A (RGMa). Elezanumab is being evaluated to determine if RGMa neutralization leads to neural restoration and functional improvement in MS patients.
Objectives and Endpoints:	To evaluate the safety and efficacy of elezanumab in subjects with relapsing forms of multiple sclerosis (RMS). Primary endpoint: Mean 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)
Investigator(s):	Multicenter
Study Site(s):	Approximately 50 sites in the United States and Canada
Study Population and Number of Subjects to be Enrolled:	Approximately 165 subjects with RMS (approximately 60 secondary-progressive MS [SPMS] subjects and approximately 105 relapsing remitting MS [RRMS] subjects)
Investigational Plan:	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 RMS.
Key Eligibility Criteria:	Adult male or female, between 18 and 65 years of age, inclusive, with a diagnosis of relapsing remitting multiple sclerosis (RRMS) or secondary-progressive multiple sclerosis (SPMS) with relapses within the past 24 months according to the 2017 revised McDonald criteria and have cranial magnetic resonance imaging (MRI) demonstrating lesion(s) consistent with MS, and evidence of physical disability (EDSS score of 2 to 6.5 or T25FW ≥ 8 sec or 9HPT ≥ 33 sec).
Study Drug and Duration of Treatment:	Eligible subjects will be randomized at the Week 0 - Baseline Visit to receive either elezanumab [redacted] as an intravenous (IV) infusion or placebo in a 1:1:1 ratio. Blinded doses will be administered intravenously every 4 weeks for 48 weeks. Subjects will remain on their current immunomodulatory treatment regimen.
Date of Protocol Synopsis:	22 March 2021

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Elezanumab is an investigational product under development for the treatment of multiple sclerosis (MS). It is a monoclonal immunoglobulin (Ig) of the human immunoglobulin G1 (IgG1) isotype that binds specifically to the soluble and the membrane-bound forms of repulsive guidance molecule A (RGMa).

Neutralization of RGMa is a novel approach that may potentially provide neurorestoration/regeneration and functional recovery in a variety of degenerative central nervous system (CNS) diseases. Repulsive guidance molecule A is a potent inhibitor of neurite outgrowth and is recognized as an important factor in inhibiting neuronal regeneration and functional recovery following CNS trauma or inflammation. Elezanumab binds to human repulsive guidance molecule A (hRGMa), but not to related family members RGMb and RGMc.

Elezanumab is being evaluated to determine whether this novel approach of neutralization of RGMa could lead to neural restoration and improvement in MS-related physical function. This mechanism of action is distinct from those used by the immunomodulatory, anti-inflammatory drugs that are currently approved for the treatment of MS and, if successful, could serve to fulfill an unmet medical need in MS.

Clinical Hypothesis

Elezanumab will improve physical functioning in subjects with relapsing forms of MS (RMS) who have disability.

2.2 Benefits and Risks to Subjects

The safety and efficacy data from the elezanumab clinical program support development of elezanumab in Phase 2 in subjects with RMS.

For further details, please see findings from completed studies, including safety data in the elezanumab Investigator's Brochure.[1]

An internal safety review group will conduct reviews of safety data throughout the conduct of the study.

Considering the coronavirus disease - 2019 (COVID-19) pandemic, the benefit and risk to subjects participating in this study have been re-evaluated. Management of these adverse events (AEs) will be made on a case-by-case basis with consideration of benefit/risk. However, based on the limited information to date, the population and disease being studied, and the anticipation that COVID-19-related risks are not expected to differ substantially between study subjects and the broader population of subjects receiving treatment for MS, no change to the benefit/risk balance for subjects in this study is expected at this time.

3 STUDY OBJECTIVES AND ENDPOINTS

3.1 Objective

To evaluate the safety and efficacy of elezanumab in subjects with RMS.

3.2 Primary Endpoint

Primary endpoint:

Mean 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 ORS is scored with a range from –4 to +4 at each assessment. 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.

The clinically significant change thresholds for T25FW and 9HPT are defined by a 20% change from baseline (≥ 20% decrease from baseline for improvement and ≥ 20% increase from baseline for worsening). For EDSS, improvement is defined as a 1-point decrease (baseline EDSS range of 1 to 5.5), or 0.5-point decrease if the baseline EDSS is 6.0 or greater (baseline EDSS range of 6.0 to 6.5). Corresponding increases in the designated ranges is defined as EDSS worsening.

3.3 Secondary Endpoints

1. Disability improvement response rate on the Expanded Disability Status Scale Plus (EDSS +) (T25FW, 9-Hole Peg test [9HPT, either hand], EDSS) at Week 52
2. ORS at Weeks 12, 24, and 36

3.4 Safety Endpoints

Safety evaluations include AE monitoring, serious adverse event (SAE) monitoring, adverse events of special interest (AESI) monitoring, physical examinations, neurologic examinations, vital sign measurements, clinically significant magnetic resonance imaging (MRI) abnormalities, 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.

3.5 Pharmacokinetic Endpoints

Samples will be collected for serum elezanumab concentrations, elezanumab anti-drug antibody (ADA) titers, and elezanumab neutralizing ADAs. Samples will be obtained at the visits indicated in Figure 1 and Appendix D. Descriptive summary statistics will be provided for all serum elezanumab concentrations. Additional parameters may be estimated if useful in the interpretation of the data.

3.6 Biomarker Research Endpoints for Target Engagement and Neuro-restoration

Blood samples including serum and plasma will be collected at specified time points (Appendix D) throughout the study to evaluate known and/or novel disease-related and target engagement biomarkers and their response to treatment. Types of biomarkers may include nucleic acids, proteins, lipids, and/or metabolites. Biomarker endpoints may include, but are not restricted to RGMa, neurofilament light (NFL), glial fibrillary acidic protein (GFAP) and neuro-restoration markers [e.g., microRNA-338 (miR-338), myelin basic protein (MBP), proteolipid protein 1 (PLP1), growth associated protein-43 (GAP-43), brain-derived neurotrophic factor (BDNF), interleukin-10 (IL-10)] that may be measured as extravesicular protein and/or nucleic acid cargoes in the plasma. Other biomarkers that may be examined in the blood include matrix metalloproteinase 9 (MMP-9) and chemokine (C-X-C motif) ligand 13 (CXCL13), which have been shown to be elevated in MS patients. DNA and RNA samples (transcriptional profiling) will be collected and may be analyzed from all subjects, unless precluded by local regulations or restrictions. This research may be exploratory in nature and the results may not be included with the clinical study report.

3.7 Exploratory Endpoints

1. Disability improvement response rate on the T25FW, 9HPT, either hand, and EDSS at Weeks 12, 24, 36, and 52, and the EDSS + at Weeks 12, 24, and 36.
2. Change from Baseline on the T25FW and 9HPT, either hand, at Weeks 12, 24, 36, and 52
3. Disability progression response rate on the EDSS+ (T25FW, 9HPT, either hand, EDSS) and for each EDSS + component
4. 12- and 24-week confirmed disability improvement response rate on the EDSS + (T25FW, 9HPT, either hand, EDSS) and for each EDSS + component
5. Change from Baseline on the MS Impact Scale (MSIS-29) version 2 at Weeks 12, 24, 36, and 52
6. Change from Baseline on the Modified Fatigue Impact Scale (MFIS) at Weeks 12, 24, 36, and 52
7. Change from Baseline on cognition battery at Weeks 12, 24, 36, and 52:
    - Symbol Digit Modalities Test (SDMT) – Oral Version
    - Brief Assessment of Cognition Verbal Memory - Immediate Recall – BAC App Version

- Brief Assessment of Cognition Tower of London – BAC App Version

8. Change from Baseline on the Low Contrast Visual Acuity (LCVA) assessments at Weeks 12, 24, 36, and 52
9. Change from Baseline in plasma biomarkers at Weeks 12, 24, 36, and 52
10. Change from Baseline on the MS Individualized Outcome Assessment (Multiple Sclerosis Individualized Outcome Assessment [MSIOA]) scale at Weeks 24 and 52
11. Change from Baseline in one week average daily step count and other activity measures (via home actigraphy with wearable biosensor) initiated at Weeks 24, 36, and 52

MRI Endpoints

The following imaging tests will be conducted. Details will be provided in the Statistical Analysis Plan (SAP).

- Lesion counts and volumes
- Brain and spinal cord atrophy measures
- Magnetization transfer ratio (MTR)
- Diffusion tensor imaging (DTI)

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

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 14 visits from Baseline (Week 0) every 4 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 6 follow-up telephone calls that will occur at Weeks 56 through 76. All visits during the Treatment Period and Follow-up Period will be allowed a window of ± 7 days. Safety parameters such as clinical laboratory test results, ECG, and vital signs will be monitored (see Operations Manual [Appendix F]). Throughout the study and for a period of 39 weeks (5 half-lives) after the time of last study drug administration, females of childbearing potential will undergo monthly pregnancy testing; and for all subjects, AEs will be collected, whether solicited or spontaneously reported by the subject.

Eligible subjects will be randomized at the Week 0 - Baseline Visit to receive either elezanumab [redacted] as an IV infusion or placebo in a 1:1:1 ratio (Section 5.8 and Section 7.3). Blinded doses will be administered intravenously every 4 weeks for 48 weeks. Subjects should remain on their current MS treatment regimen throughout the study.

During the Week 0 visit, subjects will be trained on the use of a wearable device. Subjects will be required to use the wearable device for 7 consecutive days at four time points (i.e., starting at the Week 0 visit and after visits at Weeks 24, 36, and 52), in countries where such devices are allowed.

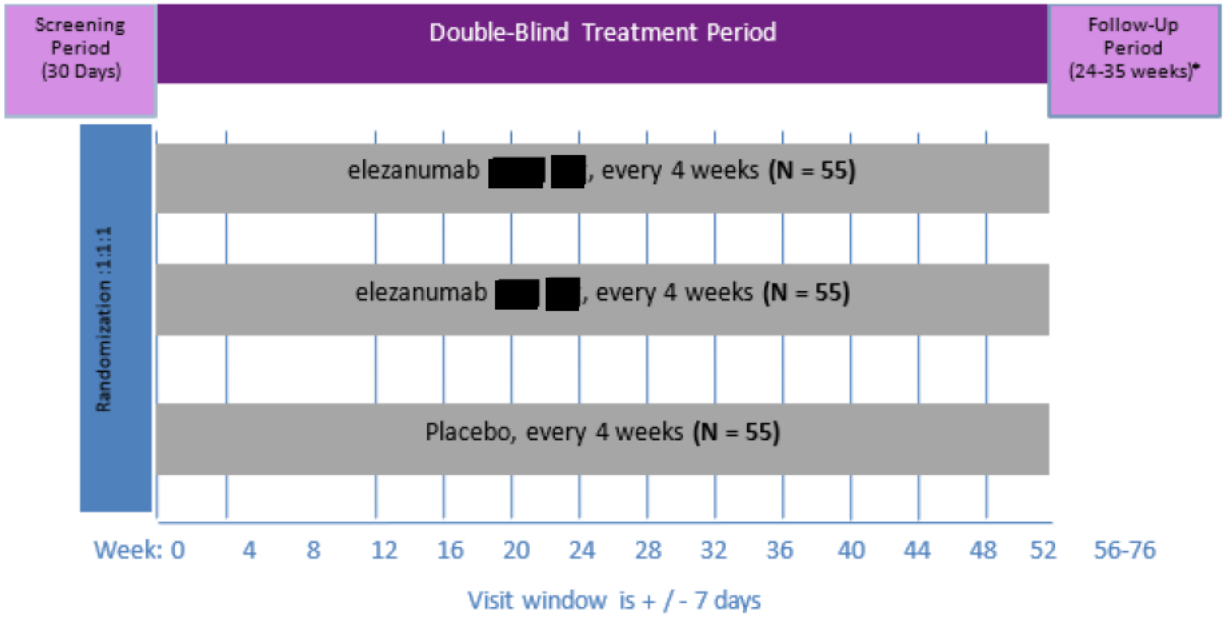
Subjects who discontinue should complete the procedures outlined for the Early Discontinuation (ED) visit as soon as possible, preferably within 2 weeks (Section 5.5 and Section 5.6).

The efficacy and safety analyses during the Treatment Period will be performed after the last subject completes the Week 52 visit. Except for certain pre-specified individuals, the sponsor and sites will remain blinded to group-level treatment efficacy and safety results until the last subject completes the Week 52 visit. Final safety analyses will be performed after the last subject completes the Follow-Up Period. Study sites and subjects will remain blinded for the duration of the study.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F).

See Section 5.1 for information regarding eligibility criteria.

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 AEs 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. The Activity Schedule (Appendix D) includes subject visits through Week 76 only, but as mentioned above, female subjects of childbearing potential should report urine pregnancy results monthly up to 39 weeks after last dose.

4.2 Discussion of Study Design

Choice of Control Group

The control group will be administered placebo infusion every 4 weeks. Subjects will be maintained on their MS standard of care therapy without any adjustment in their treatment so that management of their underlying MS is not compromised. In addition, no neurorestorative treatment is available to improve physical function.

Appropriateness of Measurements

Standard statistical, clinical, and laboratory procedures will be utilized in this study. The EDSS scale, T25FW, and 9HPT are standard tools for assessing disability in patients with MS and are suitable for detecting change.

Suitability of Subject Population

Patients with RMS must have disability in order to enable detection of physical improvement. Relapses occurring during study treatment will confound the ability to detect improvement. Therefore, a study population with reduced risk of relapse is necessary. Consequently, subjects receiving most approved immunomodulators for > 6 months will be included as will subjects not receiving immunomodulators but who are relapse-free (RF) for > 6 months.

Selection of Doses in the Study

The dose levels of [redacted] monthly for this study were selected on the basis of safety and biomarker data from two Phase 1 clinical studies.

The safety and tolerability of elezanumab has been demonstrated in ~50 healthy volunteers and ~20 patients with relapsing MS in Phase 1 studies. In Study M14-141, single doses of up to [redacted] were administered to healthy volunteers. All dose levels were safe and well tolerated. With the possible exception of headache, no pattern was evident with regard to the nature or frequency of treatment-emergent AEs following IV infusion or subcutaneous (SC) injection of elezanumab compared with subjects who received placebo. Adverse events were, in general, mild, sporadic, and self-limiting. No dose-related effect was observed with respect to AEs. No other safety findings were observed, including clinical labs, physical and neurological examination, MRI, and ECGs.

In Study M14-173, single doses of up to [redacted] ([redacted] infusions on 2 consecutive days) and monthly doses of up to [redacted] were administered to MS patients for up to 4 months. Similar to the single-dose study in healthy volunteers, no pattern was evident with regard to the nature or frequency of treatment-emergent AEs in subjects who received elezanumab compared with subjects who received placebo. A possible transient, non–dose-related, non-clinically significant elevation in blood pressure immediately following IV infusion was observed in a few subjects who received elezanumab. There were no notable changes on physical or neurological exam, and no ECG, MRI, clinical laboratory, or other vital sign perturbations. Adverse events, when reported, were mild, sporadic, and self-limiting with the exception of two MS relapses that occurred in 1 subject receiving placebo and another receiving [redacted] elezanumab.

Two prespecified cerebrospinal fluid (CSF) biomarkers demonstrated a concentration-response relationship in the Phase 1 studies. Interleukin-10 has been associated with the promotion of remyelination, neuroregeneration, and neuroprotection as well as being able to mitigate inflammatory demyelination. In Study M14-173, a statistically significant increase in CSF IL-10 was observed. The increase was observed only in the high dose of [redacted] monthly. Likewise, in the same study, a statistically significant decrease in CSF neurofilament light (NF-l), a marker of neurodegeneration, was observed at the [redacted] dose when compared with the [redacted] dose group. These data suggest a clinically relevant, dose-related pharmacodynamic effect. Reductions in CSF soluble RGMa were observed in both Studies M14-141 and M14-173. The maximum reduction was approximately 50% from baseline, and the maximum reduction was seen at single doses equal to and exceeding [redacted] in healthy volunteers and repeat doses equal to or exceeding [redacted] monthly in MS patients. It is noteworthy that the maximum CSF reduction in soluble RGMa was achieved in the [redacted] dose group, which was characterized by a range of CSF ABT-555 concentrations from [redacted]. The relationship of sRGMa reduction and clinical efficacy is not understood.

The elezanumab doses selected for the current study are [redacted] every 28 days (Q28D) and are expected to be safe and well tolerated based on previous exposures of these doses in healthy volunteers and MS patients. In addition, to ensure patient safety, intense patient safety monitoring procedures have been implemented. An unblinded internal Data Monitoring Committee (DMC), independent from the study team, will review and evaluate safety information including, but not limited to AEs, vital signs, and clinical laboratory assessments.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

A subject will be eligible for study participation if he/she meets all of the following inclusion and none of the exclusion criteria.

Inclusion Criteria

Consent

- 1. Subjects or their legally authorized representative must voluntarily **sign and date an informed consent**, approved by an independent ethics committee (IEC)/institutional review board (IRB), before the initiation of any screening or study-specific procedures.

Demographic and Laboratory Assessments

- 2. Subject must be an adult **male or female**, between 18 and 65 years of age, inclusive.
- 3. Body mass index (BMI) is 18.0 to 45.0, inclusive at Screening. Body mass index is calculated as weight in kg divided by the square of height measured in meters.
- 4. **Laboratory values** meeting the following criteria within the screening period before the first dose of study drug:
  - Serum alanine transaminase (ALT) < 2 × ULN;

- Total white blood cell (WBC) count > 2,500/µL;
- Absolute neutrophil count (ANC) > 1,300/µL;
- Platelet count > 100,000/µL;
- Absolute lymphocyte count > 700/µL;
- Absolute lymphocyte count > 500/µL for subjects taking fingolimod (Gilenya) or siponimod (Mayzent) or dimethyl fumarate (Tecfidera) or teriflunomide (Aubagio).
- Hemoglobin > 9 g/dL.

5. No positive screen for drugs of abuse, e.g., amphetamines, cocaine, opiates, barbiturates, benzodiazepines as detected at Screening or Day –1. A positive cannabinoid test is allowed if the responsible agent is taken for the management of MS symptoms (either concurrent or within the past 30 days). Positive drug screen resulting from other prescribed medications is only allowed at the discretion of the AbbVie study-designated physician.

6. Willing and able to comply with procedures required in this protocol.

Disease Activity

7. Subject meets the diagnosis of relapsing remitting MS (RRMS) or secondary-progressive MS (SPMS) according to the 2017 revised McDonald criteria and has a brain MRI demonstrating lesion(s) consistent with MS.

8. RRMS subjects must not have experienced or be recovering from a clinical MS relapse within 6 months of Screening.

9. SPMS subjects must have experienced a clinical relapse (reported by subject as diagnosed by a medical professional) between 6 and 24 months before Screening.

10. Baseline EDSS between 2 and 6.5, inclusive,

OR

Baseline T25FW ≥ 8 seconds (if EDSS < 2)

OR

Baseline 9HPT ≥ 33 seconds in either hand (if EDSS < 2)

11. Currently receiving one of the following MS medications for at least 6 months: glatiramer acetate (Copaxone®, others), teriflunomide (Aubagio®), fingolimod (Gilenya®), dimethyl fumarate (Tecfidera®), rituximab (Rituxan®), siponimod (Mayzent®) or ocrelizumab (Ocrevus®) with no dose changes for at least 6 months before Screening and no anticipated change in MS medication or dose during the study. Dalfampridine-ER (Ampyra®) or fampridine-SR (Fampyra®) is allowed if the subject has been on a stable dose for at least 3 months and plans to remain on this dose and regimen throughout the study.

OR

Has not been treated with an MS immunotherapy for the past 6 months (12 months if the subject previously received cyclophosphamide, alemtuzumab, rituximab, or ocrelizumab) before Screening. Has not been treated with dalfampridine-ER (Ampyra®) or fampridine-SR (Fampyra®) for at least 3 months before Screening.

Subject History

- 12. Judged by the principal investigator to be in good general health based upon the results of a medical history, physical examination, laboratory profile, and a 12-lead ECG performed during the Screening period.

Contraception

- 13. For all females of child-bearing potential: a **negative serum pregnancy test** at the Screening Visit and a negative urine pregnancy test before all doses of study drug.
- 14. **Female** subjects of childbearing potential practice at least 1 protocol-specified method of birth control that is effective from Study Week 0 through at least 39 weeks (5 half-lives) after the last dose of study drug. Female subjects of non-childbearing potential do not need to use birth control.
- 15. Female who is not **pregnant, breastfeeding, or considering becoming pregnant** during the study and for at least 39 weeks (5 half-lives) after the last dose of study drug.

Exclusion criteria

Disease Activity

- 1. Prior treatment with any of the following:
  - Total lymphoid irradiation
  - Cladribine or mitoxantrone
  - T cell or T cell receptor vaccination
  - Stem cell therapy
- 2. Treatment with IV, oral, or intrathecal corticosteroids (or corticosteroid precursors such as adrenocorticotropic hormone) within the 6 months before Screening if used for the treatment of MS flare or disability progression (pre- or post-treatment with corticosteroids within 6 months to prevent immunomodulatory infusion reactions is allowed). Treatment with corticosteroids for non-MS conditions within the 6 months before Screening may be allowed at the discretion of the AbbVie study-designated physician.

Subject History

- 3. History of known chronic or relevant acute infections including tuberculosis (TB). Subjects with a positive QuantiFERON® TB/purified protein derivative (purified protein derivative (tuberculin)) test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the subject has no evidence of active TB.
- 4. History of, or positive screening test result for, human immunodeficiency virus (HIV).
- 5. History of, or positive screening test result for, hepatitis B virus (HBsAg), or a positive screening test for hepatitis C with virus titer > 0 following curative treatment.
- 6. Onset of active varicella or herpes zoster virus infection or any severe viral infection requiring medical attention within 6 weeks before Screening.
- 7. Exposure to individuals with active varicella zoster virus infections within 21 days before Screening.
- 8. History of active systemic infection during the last 2 weeks before Week 0 - Baseline Visit (exception: viral rhinitis), as assessed by the investigator.
- 9. Documented active or suspected malignancy or history of any malignancy within the last 5 years except for successfully treated nonmelanoma skin cancer (NMSC) or localized carcinoma in situ of the cervix.
- 10. History of organ transplantation or plans for organ transplantation during the trial.
- 11. MRI is contraindicated, (i.e., aneurysm clip, metal fragments, internal electrical devices such as a cochlear implant, spinal cord stimulator, or pacemaker), contraindicated for or allergic to gadolinium (including renal impairment, previous diagnosis of nephrogenic systemic fibrosis and allergy), subject has claustrophobia that cannot be medically managed, or is not able to lie still for at least 1 hour for the imaging procedures.
- 12. Major surgery performed within 12 weeks before Screening or planned during the conduct of the study (e.g., hip replacement, aneurysm repair, stomach ligation), as assessed by the investigator.
- 13. History of clinically significant medical conditions or any other reason, including any physical, psychological, or psychiatric condition that in the investigator's opinion would compromise the safety or interfere with the subject's participation in this study or would make the subject an unsuitable candidate to receive study drug or would put the subject at risk by participating in the study, history of or abnormal screening lab or imaging results that, in the opinion of the investigator, are indicative of any significant cardiac, endocrinologic, hematologic, hepatic, immunologic, infectious, metabolic, urologic, pulmonary, gastrointestinal, dermatologic, psychiatric, renal, neurologic (other than MS), and/or other major disease that would preclude administration of elezanumab or MS immunomodulatory therapy, including any finding on brain MRI scan indicating clinically significant brain abnormalities other than MS.
- 14. History of drug abuse, misuse, or engagement in non-medical use of either prescribed or over-the-counter medication within 2 years before study drug administration or plans to do so during the study.
- 15. History of alcohol abuse within the last 2 years.

- 16. History of an **allergic reaction** or significant sensitivity to constituents of the study drug (and its excipients) and/or other products in the same class.
- 17. History of epilepsy or unexplained blackouts OR history of a seizure within 6 months of screening. Subjects with febrile seizures before the age of 6 years are allowed.
- 18. History of treatment-refractory DSM-V defined major depressive disorder within 1 month of Screening.
- 19. History of suicidal ideation within 1 year before Screening, as evidenced by answering "yes" to questions 4 or 5 on the suicidal ideation portion of the C-SSRS completed at Screening, or any history of suicide attempts.
- 20. Clinically relevant or **significant ECG abnormalities**, including ECG with QT interval corrected for heart rate (QTc) using Fridericia's formula (QTcF) > 450 msec (males) or > 470 msec (females).

Contraception

- 21. Female who is **pregnant, breastfeeding, or considering becoming pregnant** during the study or within 39 weeks (5 half-lives) after the last dose of study drug.

Concomitant Medications

- 22. Subject has received **any investigational product** within 30 days or 5 half-lives of the drug (whichever is longer) before the first dose of study drug or is currently enrolled in another clinical study. Simultaneous enrollment in a non-interventional study is permitted so long as these studies do not assess the EDSS, T25FW, or 9HPT and are not overly burdensome and likely, in the investigator's opinion, to trigger subject discontinuation.
- 23. Subject has any history of receipt of elezanumab before participation in this study.
- 24. Subject has received **any live vaccine, including**, but not limited to: measles/mumps/rubella vaccine, varicella zoster virus within 4 weeks before randomization, or expected need of live vaccination during study participation including at least 4 weeks after the last dose of study drug.

5.2 Contraception Recommendations

Contraception Requirements for Females

Subjects must follow the following contraceptive guidelines as specified:

- Females, Non-Childbearing Potential

  Females do not need to use birth control during or following study drug treatment if considered of non-childbearing potential due to meeting any of the following criteria:

  - Postmenopausal, age > 55 years with no menses for 12 or more months without an alternative medical cause.

- Postmenopausal, age ≤ 55 years with no menses for 12 or more months without an alternative medical cause AND a follicle-stimulating hormone (FSH) level > 40 IU/L.
- Permanently surgically sterile (bilateral oophorectomy, bilateral salpingectomy, or hysterectomy)

- Females of Childbearing Potential

  Females of childbearing potential must avoid pregnancy while taking study drug and for at least 39 weeks (5 half-lives) after the last dose of study drug. Females must commit to one of the following methods of birth control:

  - Combined (estrogen and progestogen containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation initiated at least 1 month before Screening.
  - Progestogen-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation initiated at least 1 month before Screening.
  - Bilateral tubal occlusion/ligation, i.e., Essure (can be via hysteroscopy, provided a hysterosalpingogram confirms success of the procedure).
  - Intrauterine device (IUD).
  - Intrauterine hormone-releasing system (IUS).
  - Vasectomized sexual partner (provided the vasectomized partner has received medical confirmation of the surgical success of the vasectomy and is the sole sexual partner of the trial subject).
  - Practice true abstinence, defined as: Refraining from heterosexual intercourse when this is in line with the preferred and usual lifestyle of the subject (periodic abstinence [e.g., calendar, ovulation, symptothermal, post-ovulation methods] and withdrawal are not acceptable).

5.3 Prohibited Medications and Therapy

In addition to the medications listed in the eligibility criteria, prior exposure to any of the following is NOT allowed:

1. No prior treatment with the any of the following:
   - Total lymphoid irradiation
   - Cladribine or mitoxantrone
   - T cell or T cell receptor vaccination
   - Stem cell therapy
2. No treatment with any of the following medications or procedures within the 6 months before Screening:
   - Natalizumab

- Cyclosporine
- Azathioprine
- Methotrexate
- Mycophenolate mofetil
- Intravenous immunoglobulin (IVIg)
- Any interferon product

3. No treatment with cyclophosphamide or alemtuzumab within 1 year before Screening.
4. No treatment with IV, oral, or intrathecal corticosteroids (or corticosteroid precursors such as adrenocorticotropic hormone) for the purpose of treating an MS-flare within the 6 months before Screening. Pre- or post-treatment with corticosteroids to prevent immunomodulatory infusion reactions for allowed concomitant medications is allowed. Treatment with corticosteroids for non-MS conditions within the 6 months before Screening may be allowed at the discretion of the AbbVie study-designated physician.

5.4 Prior and Concomitant Therapy

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject received since 30 days before Screening or receives during the study must be recorded through the post-treatment visit (Week 76).

Non-immunomodulatory therapies used for the treatment of MS symptoms may be allowed at the discretion of the AbbVie study-designated physician.

Subjects who experience a suspected MS relapse may be treated with IV methylprednisolone [redacted] for 1 to 5 consecutive days, or another corticosteroid regimen that is consistent with good neurological practice.

For subjects who experience a sustained reduction in lymphocyte level to below 500/µL for at least 6 months, or a level less than 200/µL on a single confirmed test, the investigator, or their treating neurologist if applicable, should consider the need to discontinue or switch their current immunomodulatory therapy.

Any questions regarding concomitant or prior therapy should be raised to the sponsor/AbbVie medical contact. Information regarding potential drug interactions with elezanumab can be located in the elezanumab Investigator's Brochure.

Subjects must be able to safely discontinue any prohibited medications before initial study drug administration (immunomodulator discontinuation criteria listed above). Subjects must be consented for the study before discontinuing any prohibited medications for the purpose of meeting study eligibility.

All allowable concomitant medications must be at a stable dose for at least 30 days before the subject's screening visit (6 months for immunomodulators), and it is anticipated that no change in dose will be required during the study treatment period. All medications should remain at stable doses for the

duration of the study unless a change in regimen is medically necessary. All concomitant medications, including any change in dose must be recorded with the reason for use, dates of administration, dosages and frequency in the electronic case report form (eCRF).

5.5 Withdrawal of Subjects and Discontinuation of Study

A subject may voluntarily withdraw or be withdrawn from the study at any time for reasons including, but not limited to, the following:

- Clinically significant abnormal laboratory results or AEs, which rule out continuation of the study drug, as determined by the investigator or the AbbVie Therapeutic Area Medical Director.
- The investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Eligibility criteria violation was noted after the subject started study drug and continuation of the study drug would place the subject at risk.
- Introduction of prohibited medications or dosages along with continuation of the study drug would place the subject at risk.
- The subject has a positive drug screen, including for cannabis, opioids, and benzodiazepines, unless they have been instructed to use the substance by a medical professional.
- The subject becomes pregnant while on study drug.
- Subject is significantly noncompliant with study procedures, which would put the subject at risk for continued participation in the trial. Subjects who missed visits due to COVID-19 investigator site closures or opted to refrain from on-site visits during the COVID-19 pandemic will not be requested to prematurely discontinue by the sponsor.

For subjects to be considered lost to follow-up, reasonable attempts must be made to obtain information on the subject's final status. At a minimum, 2 telephone calls must be made and 1 certified letter must be sent and documented in the subject's source documentation.

AbbVie may terminate this study prematurely, either in its entirety or at any site. The investigator may also stop the study at his/her site if he/she has safety concerns. If AbbVie terminates the study for safety reasons, AbbVie will promptly notify the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, it has been necessary to employ mitigation strategies to enable the investigator to ensure subject safety and continuity of care. Acceptable mitigation strategies are identified and included in the Operations Manual in Appendix F.

The investigator should contact the sponsor medical contact before discontinuing a subject from the study for a reason other than "planned per protocol," to ensure all acceptable mitigation steps have been explored.

Refer to the Operations Manual in Appendix F for details on how to handle study activities/procedures.

Interruption/Discontinuation of Study Drug Due to COVID-19 Infection

During the Treatment Period, a subject with confirmed (viral test positive) or suspected COVID-19 infection can only be dosed with study drug if the following COVID-19 viral clearance criteria are met:

- Symptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since recovery, defined as resolution of fever without use of antipyretics and improvement in respiratory symptoms (e.g., cough, shortness of breath)
- Asymptomatic subjects: At least 2 negative viral tests in a row, ≥ 24 hours apart after at least 10 days have passed since prior positive result (note: subjects who develop symptoms will follow guidance above for symptomatic subjects)

Delays in study drug dosing due to the above COVID-19 testing guidance for subjects must be discussed with the AbbVie medical contact, along with the possibility of premature discontinuation from the Treatment Period. Follow subsequent protocol Section 5.6 for subjects who discontinued study drug. Frequency or timing of COVID-19 testing and intervals between testing for the above viral clearance criteria may be adjusted to account for epidemiologic trends, updated information regarding infectivity, and local/institutional guidelines.

5.6 Follow-Up After Subject Discontinuation of Study Drug or from Study

If a subject prematurely discontinues study participation (withdrawal of informed consent), the procedures outlined for the Early-Discontinuation (ED) Visit should be completed as soon as possible, preferably within 2 weeks. In addition, if subject is willing, a 30-day follow-up phone call after the last dose of study drug may be completed to ensure any treatment-emergent AEs/SAEs have been resolved.

In the event a subject withdraws consent from the clinical study, biomarker research will continue unless the subject explicitly requests analysis to be stopped. When AbbVie is informed that the subject has withdrawn and no longer wishes biomarker research to continue, samples will not be analyzed and no new biomarker analysis data will be collected for the withdrawn subject or added to the existing data or database(s).

5.7 Study Drug

Elezanumab (ABT-555) is manufactured by AbbVie as shown in Table 1, below. For subjects randomized to the treatment arms, the solution contained in the study vial(s) of ABT-555 will be diluted in the 0.9% Sodium Chloride Injection/Solution for Infusion.

Table 1. Study Drug Identification

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
ABT-555	Infusion	Solution for infusion in a vial	[redacted]	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
Placebo	Infusion	0.9% Sodium Chloride Injection/Solution for Infusion, 250 mL	N/A	Various* (See below)

N/A = Not applicable

* Can be sourced from approved marketed products from various commercial manufacturers depending on availability.

0.9% Sodium Chloride Injection/Solution for Infusion will be administered to those subjects not receiving active elezanumab (ABT-555) and as a vehicle for administration of elezanumab (ABT-555). 0.9% Sodium Chloride Injection/Solution for Infusion will be supplied with commercially available material in either bags or bottles, locally sourced by sites. However, if mandated by local regulation, or in the case of exceptional circumstances when sites are unable to procure on their own, AbbVie may supply 0.9% Sodium Chloride Injection/Solution for Infusion if necessary.

Treatment Administration

The study drug will be administered intravenously at the visits listed in the Operations Manual Section 2.0 (Appendix F). AbbVie will provide study drug as liquid in a vial that requires sterile preparation. The time from start of preparation to start of infusion must not exceed 21 hours. The study drug can be administered without regard to food consumption and infusion time is 90 to 120 minutes. However, infusion time may be increased in subjects who have experienced possible infusion reactions during prior infusions in this study (Operations Manual [Appendix F] Appendix D Criteria for Monitoring Elezanumab Infusion Reactions). Pre-medication with antihistamines or corticosteroids before investigational product infusion is not allowed without the consent of the AbbVie study-designated physician.

The first dose of study drug will be administered after all other Week 0 – Baseline procedures are completed. For this reason, it is recommended that the study drug is not prepared until eligibility is reconfirmed at the Week 0-Baseline visit. Timing of the preparation of subsequent doses is at the discretion of the site.

Study drug will be administered by IV infusion at each visit, as shown in Table 2, below.

Table 2. Study Drug Administration Schedule

Study Drug Treatment Group	Administration
Placebo (0.9% Sodium Chloride Injection/Solution for Infusion)	IV infusions at Week 0-Baseline visit, then every 4 weeks through Week 48
Elezanumab (ABT-555) [redacted]	
Elezanumab (ABT-555) [redacted]	

IV = Intravenous

The start and stop time of each study drug infusion will be recorded to the nearest minute.

Packaging and Labeling

Elezanumab (ABT-555) will be provided in a vial as a solution for infusion [redacted] packaged in a carton, with 1 vial per carton. One carton is equivalent to 1 kit. Each kit (vial and carton) will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug should be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number.

The commercially sourced 0.9% Sodium Chloride Injection/Solution for Infusion (250 ml) will not be labeled as an Investigational Medicinal Product (IMP) before the handling by the unblinded pharmacist or qualified designee. However, after addition of elezanumab (ABT-555) to the 0.9% Sodium Chloride Injection/Solution for Infusion to be administered in the active arm, the unblinded pharmacist or qualified designee will add a blinded dispensing label. Likewise, the unblinded pharmacist or qualified designee will add a blinded dispensing label to the 0.9% Sodium Chloride Injection/Solution for Infusion, to be administered in the placebo arm. Labels must remain affixed to the material.

If an IMP label on the 0.9% Sodium Chloride Injection/Solution for Infusion is mandated by local agencies, labels may be applied on the overwrap and will be removed by the unblinded pharmacist before administration.

Storage and Disposition of Study Drug

Study drug, elezanumab (ABT-555) must be refrigerated (2° to 8°C), protected from light, and cannot be frozen. The investigational product is for investigational use only and is to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under the conditions specified on the label until dispensed for subject use or destroyed on site as appropriate.

A storage temperature log is to be maintained to document proper storage conditions. Sites must record the refrigerator temperature daily on a temperature log. Malfunctions or any temperature excursion must be reported to the sponsor immediately using the AbbVie Temperature Excursion Management System (ATEMS). Study medication should be quarantined and not dispensed until ATEMS deems the medication as acceptable.

0.9% Sodium Chloride Injection/Solution for Infusion should be stored per the locally approved commercial label, Summary of Product Characteristics (SmPC), or clinical study label.

The investigational products are for investigational use only and are to be used only within the context of this study. The study drug supplied for this study must be maintained under adequate security and stored under conditions specified on the label until dispensed for subject use or returned to AbbVie.

Subject Identifier Assignment

An interactive response technology (IRT) system will assign a unique identification number to each subject at the Screening Visit. For subjects who do not meet the study selection criteria, site personnel must register the subject as a screen failure in the IRT system.

Subjects who are enrolled will retain the subject number assigned to them at Screening Visit throughout the study.

Interactive response technology Vendor contact information and user guidelines will be provided to each site.

Timing of Dose for Each Subject

Eligible subjects will receive either elezanumab [redacted] or placebo as an IV infusion at a constant rate by gravity or pump over an interval of 90 to 120 minutes. The start and stop time of each study drug infusion will be recorded to the nearest minute. Interruptions of infusion administration will be recorded to the nearest minute as well. Blinded doses will be administered intravenously every 4 weeks for 48 weeks (13 total infusions).

Study Drug Accountability

The investigator or his representative will verify that study drug supplies are received intact and in the correct amounts. This will be documented by signing and dating a proof of receipt or similar document. A current (running) and accurate inventory of study drug will be maintained in the IRT system.

Throughout the study and at the study site closeout visit, overall accountability will be performed and verified by the AbbVie unblinded clinical research associate (CRA) (Pharmacy CRA).

The unblinded pharmacist or qualified designee will be responsible for maintaining study drug preparation records and drug accountability records for study drug as well as the saline IV solution dispensed by the site, including product description, manufacturer, and lot numbers. Further details are provided in the Pharmacy Manual.

Study Blinding

Subjects in the placebo group will be administered 0.9% Sodium Chloride Injection/Solution for Infusion that is identical in appearance and volume to the elezanumab solution. An unblinded pharmacist or qualified designee will receive assignments and prepare the blinded doses across the treatment groups. The investigator, study site personnel (except the unblinded pharmacist or qualified designee) and the subject will remain blinded to the treatment assignment throughout the course of the study.

Because of the blinding of this study, deliveries of elezanumab and 0.9% Sodium Chloride Injection/Solution, if applicable, will be shipped directly to the pharmacy. The unblinded pharmacist or qualified designee will prepare the dosing of elezanumab (in a blinded manner) following the available preparation instructions in the Pharmacy Manual and based on the subject's assigned treatment group.

For blinding purposes, identical commercial 0.9% Sodium Chloride Injection/Solution for Infusion bag or bottle will be used in the placebo and elezanumab arms at each site.

For investigational product monitoring, there will be an unblinded AbbVie CRA (also referred to as a Pharmacy CRA) for verification of unblinded preparation documentation. The unblinded Pharmacy CRA will be a separate individual than the blinded CRA to ensure blinding is maintained.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team, the unblinded CRA and the AbbVie safety review group), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the study.

The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

AbbVie must be notified before breaking the blind, unless identification of the study drug is required for a medical emergency, i.e., situation in which the knowledge or the specific blinded treatment will affect the immediate management of the subject's conditions (e.g., antidote is available). AbbVie must then be notified within 24 hours of the blind being broken. The date and reason that the blind was broken must be recorded in the source documentation and on the eCRF, as applicable.

5.8 Randomization/Drug Assignment

Subjects will be randomized in a 1:1:1 ratio to one of two doses of elezanumab or placebo according to the randomization schedule generated by the Abbvie statistics department. An IRT system will be used to assign subject numbers and drug kits in accordance with the subject's assigned treatment group. The use of the IRT system is described in the Operations Manual Section 3.15 (Appendix F).

Randomization (Section 7.3) will be stratified between treatment and placebo arms based on the following factors:

- Diagnosis of primary-progressive MS (PPMS) vs. SPMS
- Presence or absence of background MS immunotherapy

5.9 Protocol Deviations

AbbVie does not allow intentional/prospective deviations from the protocol except when necessary to eliminate an immediate hazard to study subjects. The investigator is responsible for complying with all protocol requirements, written instructions, and applicable laws regarding protocol deviations. If a protocol deviation occurs (or is identified, including those that may be due to the COVID-19 pandemic), the investigator is responsible for notifying IEC/IRB, regulatory authorities (as applicable), and AbbVie.

6 SAFETY CONSIDERATIONS

6.1 Complaints and Adverse Events

Complaints

A complaint is any written, electronic, or oral communication that alleges deficiencies related to the physical characteristics, identity, quality, purity, potency, durability, reliability, safety, effectiveness, or performance of a product/device. Complaints associated with any component of this investigational product must be reported to AbbVie.

Product Complaint

A product complaint is any complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling discrepancies/inadequacies in the labeling/instructions (e.g., printing illegible), missing components/product, device not working properly, or packaging issues.

Product complaints concerning the investigational product and/or device must be reported to AbbVie within 24 hours of the study site's knowledge of the event. Product complaints occurring during the study will be followed up to a satisfactory conclusion.

Medical Complaints/Adverse Events and Serious Adverse Event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

The investigators will monitor each subject for clinical and laboratory evidence of AEs on a routine basis throughout the study. All AEs will be followed to a satisfactory conclusion.

An elective surgery/procedure scheduled to occur during a study will not be considered an AE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (e.g., surgery performed earlier than planned), then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an AE.

If an AE, whether associated with the study drug or not, meets any of the following criteria, it is to be reported to AbbVie clinical pharmacovigilance or contract research organization (CRO) (as appropriate) as an SAE within 24 hours of the site's being made aware of the SAE (refer to Section 4.2 of the Operations Manual (Appendix F) for reporting details and contact information):

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization or Prolongation of Hospitalization	An event that results in an admission to the hospital for any length of time or prolongs the subject's hospital stay. This does not include an emergency room visit or visit to an outpatient facility.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or spontaneous abortion or stillbirth is considered an important medical event. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

All AEs reported from the time of study drug administration up to 39 weeks (5 half-lives) from the last dose of study drug (Week 48 visit) will be collected, whether solicited or spontaneously reported by the subject. In addition, SAEs and protocol-related nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the IMP in accordance with global and local requirements. Additional information about SUSAR reporting is presented in the Operations Manual (Appendix F) Section 5.2 SUSAR Reporting.

Adverse Event Severity and Relationship to Study Drug

The investigator will rate the severity of each AE as mild, moderate, or severe. The investigator will use the following definitions to rate the severity of each AE:

Mild: The AE is transient and easily tolerated by the subject.

Moderate: The AE causes the subject discomfort and interrupts the subject's usual activities.

Severe: The AE causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

The investigator will use the following definitions to assess the relationship of the AE to the use of study drug:

Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is sufficient evidence (information) to suggest a causal relationship.

No Reasonable Possibility – After consideration of factors including timing of the event, biologic plausibility, clinical judgment, and potential alternative causes, there is insufficient evidence (information) to suggest a causal relationship.

Adverse events will be monitored throughout the study to identify any of special interest that may indicate a trend or risk to subjects.

Adverse Events of Special Interest

For AESIs, serious and nonserious, 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.

The following AESI will be monitored during the study:

- Infusion reactions

Further information about AESIs is provided in the Operations Manual (Appendix F) Section 4.1.

Pregnancy

While not an AE, pregnancy in a study subject must be reported to AbbVie within 24 hours after the site becomes aware of the pregnancy. Subjects who become pregnant during the study must be discontinued (Section 5.5). If a pregnancy occurs in a study subject, information regarding the pregnancy and the outcome will be collected.

The pregnancy outcome of an elective or spontaneous abortion, stillbirth or congenital anomaly is considered a SAE and must be reported to AbbVie within 24 hours after the site becomes aware of the event.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

Complete and specific details of the statistical analysis will be described and fully documented in the statistical analysis plan (SAP). The SAP will be finalized before the interim database lock. The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Sets

The Modified ITT (mITT) Set includes all randomized subjects who received at least 1 dose of study drug. Subjects will be grouped according to treatment as randomized.

Multiple sclerosis expert(s) will confirm which subjects experienced a clinical relapse(s) through adjudication of study data, including the MS-relapse questionnaire. The RF Set includes all subjects in the mITT data 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.

The Minimal Missed Infusion Analysis (MMIA) Set includes all randomized subjects who received at least 6 infusions total and missed no consecutive infusions before the subject's final dose. Subjects will be grouped according to treatment as randomized.

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

7.3 Statistical Analyses for Efficacy

The ORS scores will be summarized descriptively (including n, mean, standard deviation, minimum, median, and maximum) along with the 95% confidence interval at each visit. The frequency and percentage of ORS for –4 to +4 will also be provided by treatment group at each visit. The ORS for each treatment group at scheduled visits and overall will also be estimated using a mixed-effect model for repeated measures (MMRM) including treatment group, visit, treatment-by-visit interaction, and stratification factors as fixed effects, with the baseline values for the ORS components as covariates.

For other continuous efficacy endpoints, the mean, standard deviation, median, minimum and maximum will be reported for each treatment group. The treatment comparison will be conducted using MMRM model including treatment group, visit, treatment-by-visit interaction, and stratification factors as fixed effects and the baseline value associated with the endpoint as a covariate.

For binary efficacy endpoints, the frequency and percentage will be provided by treatment group. The treatment comparison will be conducted using a logistic regression model adjusted for the stratification factors and baseline score associated with the endpoint.

All efficacy endpoints will be analyzed on mITT population. The RF and MMIA Sets will be used for the primary and other efficacy analyses as specified in the SAP.

Sample Size Estimation

Approximately 165 subjects will be equally randomized 1:1:1 (55 subjects in each treatment group, with a target of 20 SPMS subjects and approximately 35 RRMS subjects per treatment group). There are limited prior data to estimate the magnitude of effect and variance for a neurorestorative therapy. The sample size was therefore selected based on operational feasibility, variance seen in prior MS trials, and the likelihood of predicting success in subsequent phases of development.

7.4 Statistical Analyses for Safety

Analysis of the following safety evaluations will be performed during the study: Adverse events and SAEs, vital signs, laboratory tests, ECG, physical and neurologic examinations, and C-SSRS assessments.

Complete and specific details of the statistical analysis of safety evaluations will be described and fully documented in the SAP.

7.5 Interim Analysis

There are no interim efficacy or futility analyses.

7.6 Subgroup Analysis

The primary efficacy analyses will also be performed in the following subgroups to assess the consistency of the treatment effect:

- Sex (male, female)
- Age (≤ 40 years, > 40 years)
- EDSS baseline (≤ median, > median)
- Diagnosis of MS form (RRMS, SPMS)
- Presence of background MS immunotherapy (yes, no)

8 ETHICS

8.1 Independent Ethics Committee/Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the Independent Ethics Committee/Institutional Review Board (IEC/IRB) for review and approval. Approval of both the protocol and the informed consent form(s) must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IEC/IRB before the changes are implemented to the study. In addition, all changes to the consent form(s) will be IEC/IRB approved.

8.2 Ethical Conduct of the Study

The study will be conducted in accordance with the protocol, Operations Manual, International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines, applicable regulations, and guidelines governing clinical study conduct and the ethical principles that have their origin in the Declaration of Helsinki. Responsibilities of the investigator are specified in Appendix B.

In the event of a state of emergency due to the COVID-19 pandemic leading to difficulties in performing protocol-specified procedures, AbbVie will engage with study site personnel in efforts to ensure the safety of subjects, maintain protocol compliance, and minimize risks to the integrity of the study while trying to best manage subject continuity of care. This may include alternative methods for assessments (e.g., phone contacts, virtual site visits, or hybrid visits to minimize subject face-to-face time), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping of supplies via a direct-to-patient vendor to ensure continuity of treatment where allowed. Refer to the Operations Manual in Appendix F for additional details. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators should notify AbbVie if any urgent safety measures are taken to protect the subjects against any immediate hazard.

8.3 Subject Confidentiality

To protect subjects' confidentiality, all subjects and their associated samples will be assigned numerical study identifiers or "codes." No identifiable information will be provided to AbbVie.

9 SOURCE DOCUMENTS AND CASE REPORT FORM COMPLETION

The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be attributable, legible, contemporaneous, original, accurate, and complete to ensure accurate interpretation of data. Clinical site monitoring is conducted to ensure that the rights and well-being of human subjects are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol, ICH Good Clinical Practice (GCP), and applicable local regulatory requirement(s). Remote monitoring of data may be employed if allowed by the local regulatory authority, IRB/IEC, and the study site.

10 DATA QUALITY ASSURANCE

AbbVie will ensure that the clinical trial is conducted with a quality management system that will define quality tolerance limits in order to ensure human subject protection and reliability of study results. Data will be generated, documented, and reported in compliance with the protocol, ICH GCP, and applicable regulatory requirements.

11 COMPLETION OF THE STUDY

The end-of-study is defined as the date of the last subject's last visit.

12 REFERENCES

1. AbbVie. Elezanumab Investigator's Brochure.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	Adverse events of special interest
ALT	Alanine transaminase
ANC	Absolute neutrophil count
ATEMS	AbbVie Temperature Excursion Management System
BDNF	Brain-derived neurotrophic factor
BMI	Body mass index
CNS	Central nervous system
COVID-19	Coronavirus Disease - 2019
CRA	Clinical research associate
CRO	Contract research organization
CSF	Cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CXCL13	C-X-C motif ligand 13
DMC	Data Monitoring Committee
DNA	deoxyribonucleic acid
DTI	Diffusion tensor imaging
ECG	Electrocardiogram
eCRF	Electronic case report form
ED	Early discontinuation
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
EDSS+	Expanded Disability Status Scale Plus
FSH	Follicle-stimulating hormone
GAP-43	Growth associated protein-43
GCP	Good clinical practice
GFAP	Glial fibrillary acidic protein
HBsAg	Hepatitis B surface antigen
HIV	Human immunodeficiency virus
hRGMa	Human repulsive guidance molecule A

ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent ethics committee
IEC/IRB	Independent Ethics Committee/Institutional Review Board
Ig	Immunoglobulin
IgG1	Immunoglobulin G1
IL-10	Interleukin-10
IMP	Investigational medicinal product
IRB	Institutional review board
IRT	Interactive response technology
IU	International Unit
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVIg	Intravenous immunoglobulin
LCVA	Low Contrast Visual Acuity
MBP	Myelin basic protein
MFIS	Modified Fatigue Impact Scale
MFIS-5	Modified Fatigue Impact Scale
miR-338	MicroRNA-338
mITT	Modified intent-to-treat
MMIA	Minimal Missed Infusion Analysis
MMP-9	Matrix metalloproteinase 9
MMRM	Mixed-effect model for repeated measures
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIOA	Multiple Sclerosis Individualized Outcome Assessment
MTR	Magnetization transfer ratio
N/A	Not applicable
NF-l	Neurofilament light
NFL	Neurofilament light
NMSC	Non-melanoma skin cancer
ORS	Overall Response Score
PK	Pharmacokinetic(s)

PPD	Purified protein derivative (tuberculin)
PPMS	Primary-progressive MS
QTc	QT interval corrected for heart rate
QTcF	QT interval corrected for heart rate using Fridericia's formula
RF	Relapse-free
RGMa	Repulsive guidance molecule A
RMS	Relapsing multiple sclerosis
RNA	Ribonucleic acid
RRMS	Relapsing remitting multiple sclerosis
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Subcutaneous
SDMT	Symbol Digit Modalities Test
SmPC	Summary of Product Characteristics
SPMS	Secondary-progressive MS
SUSAR	Suspected unexpected serious adverse reactions
T25FW	Timed 25-Foot Walk
TB	Tuberculosis
ULN	Upper limit of normal
vs.	Versus
WBC	White blood cell

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol 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

Protocol Date: 22 March 2021

Clinical research studies sponsored by AbbVie are subject to the ICH GCP and local regulations and guidelines governing the study at the site location. In signing the Investigator Agreement, the investigator is agreeing to the following:

1. Conducting the study in accordance with ICH GCP, the applicable regulatory requirements, current protocol and Operations Manual, and making changes to a protocol only after notifying AbbVie and the appropriate IRB/IEC, except when necessary to protect the subject from immediate harm.
2. Personally conducting or supervising the described investigation(s).
3. Informing all subjects, or persons used as controls, that the drugs are being used for investigational purposes and complying with the requirements relating to informed consent and ethics committees (e.g., IEC or IRB) review and approval of the protocol and its amendments.
4. Reporting complaints that occur in the course of the investigation(s) to AbbVie.
5. Reading the information in the Investigator's Brochure/safety material provided, including the instructions for use and the potential risks and side effects of the investigational product(s).
6. Informing all associates, colleagues, and employees assisting in the conduct of the study about their obligations in meeting the above commitments.
7. Maintaining adequate and accurate records of the conduct of the study, making those records available for inspection by representatives of AbbVie and/or the appropriate regulatory agency, and retaining all study-related documents until notification from AbbVie.
8. Maintaining records demonstrating that an ethics committee reviewed and approved the initial clinical protocol and all of its amendments.
9. Reporting promptly, all changes in the research activity and all unanticipated problems involving risks to human subjects or others, to the appropriate individuals (e.g., coordinating investigator, institution director) and/or directly to the ethics committees and AbbVie.
10. Providing direct access to source data documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s).

Signature of Principal Investigator	Date

Name of Principal Investigator (printed or typed)

APPENDIX C. LIST OF PROTOCOL SIGNATORIES

Name	Title	Functional Area
[redacted]		Clinical Program Development
		Medical Writing
		Neuroscience
		Data and Statistical Sciences
		Data and Statistical Sciences
		Clinical Pharmacology
		Bioanalytics

APPENDIX D. ACTIVITY SCHEDULE

The following table shows the required activities across the study. The individual activities are described in detail in Section 3 of the Operations Manual (Appendix F). Allowed modifications due to COVID-19 are detailed within the Operations Manual.

	SCREENING	TREATMENT														Early Discontinuation	FOLLOW-UP VIRTUAL TELEPHONE VISITS					
Activity	30 days	Week 0 - Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52		Week 56	Week 60	Week 64	Week 68	Week 72	Week 76/ Follow-up D/C
INTERVIEWS & QUESTIONNAIRES																						
Subject Information and Informed Consent	✓																					
Eligibility criteria	✓	✓																				
Medical history	✓	✓																				
Adverse event assessment	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Follow-up telephone call to obtain home pregnancy testing results from females of childbearing potential																	✓	✓	✓	✓	✓	✓
Prior/concomitant therapy	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
PATIENT-REPORTED OUTCOMES (PRO)																						
Multiple Sclerosis Impact Scale (MSIS-29), version 2		✓			✓			✓			✓				✓	✓						
Modified Fatigue Impact Scale (MFIS-5)		✓			✓			✓			✓				✓	✓						
SCALES - CLINICIAN-MEASURED																						
Columbia Suicide Rating Scale (C-SSRS)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			✓			✓
Multiple Sclerosis Individualized Outcome Assessment (MSIOA)		✓						✓							✓	✓						

		SCREENING	TREATMENT														Early Discontinuation	FOLLOW-UP VIRTUAL TELEPHONE VISITS					
Activity		30 days	Week 0 - Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52		Week 56	Week 60	Week 64	Week 68	Week 72	Week 76/ Follow-up D/C
Expanded Disability Status Scale Plus (EDSS +)	Expanded Disability Status Scale (EDSS)	✓	✓			✓			✓			✓				✓	✓						
	Timed 25 Foot Walk (T25FW)	✓	✓			✓			✓			✓				✓	✓						
	9-Hole Peg Test (9HPT)	✓	✓			✓			✓			✓				✓	✓						
Cognition Scales			✓			✓			✓			✓				✓	✓						
Low Contrast Visual Acuity (LCVA)			✓			✓			✓			✓				✓	✓						
LABS & EXAMINATIONS																							
Central Laboratory Tests		✓	✓	✓	✓	✓			✓			✓				✓	✓						
Urine Drug and Alcohol Test		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
12-lead ECG		✓				✓			✓			✓				✓	✓						
Weight		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
Height		✓																					
Body Mass Index (BMI)		✓																					
Vital signs		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓						
Physical examination		✓	✓													✓	✓						
Neurological exam		✓	✓						✓							✓	✓						
Serum pregnancy test at central lab for females of childbearing potential		✓																					
Local urine pregnancy test		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

	SCREENING	TREATMENT														Early Discontinuation	FOLLOW-UP VIRTUAL TELEPHONE VISITS					
Activity	30 days	Week 0 - Baseline	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24	Week 28	Week 32	Week 36	Week 40	Week 44	Week 48	Week 52		Week 56	Week 60	Week 64	Week 68	Week 72	Week 76/ Follow-up D/C
Pharmacokinetic (PK) and ADA sample collections		✓			✓			✓			✓				✓	✓						
Biomarker Samples whole blood (DNA/RNA/Serum/Plasma)		✓			✓			✓			✓				✓	✓						
IMAGING																						
Brain and cervical spinal cord MRI	✓							✓							✓	✓						
℞ TREATMENT																						
Randomization/Drug assignment		✓																				
Pharmacy Prepares Study Drug or Placebo for Infusion		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓								
Administer Infusion & Observation		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓								
ACTIGRAPHY																						
Wearable device training		✓																				
Reminder telephone call to subject after Week 0 - Baseline to bring in actigraphy equipment to visit. Equipment will be worn during visits and for 7 days afterwards.		✓						✓			✓				✓				✓			
Actigraphy data collected		✓						✓			✓				✓							

APPENDIX E. PROTOCOL SUMMARY OF CHANGES

Previous Protocol Versions

Protocol	Date
Version 1.0	30 August 2018
Version 2.0	01 February 2019
Version 3.0	07 August 2019
Version 4.0	25 November 2020

Protocol Summary of Changes

The purpose of this version is the removal of on-site assessments performed at Weeks 64 and 76 so that all visits in the Follow-up period can be conducted virtually. Other administrative revisions were made throughout the protocol, including the synopsis, and to the Operations Manual, to ensure consistency with the changes below:

1. Protocol Section 4.1, Overall Study Design and Plan, Figure 1. Study Schematic and Protocol Appendix D. Activity Schedule: Remove Weeks 64 and 76 as an on-site visit.
2. Update to Appendix F, Operations Manual: Section 2.1, Individual Treatment Period Visit Activities and Section 2.2, Individual Post-Treatment Period Visit Activities (Week 64 and Week 76) to remove vital signs, EDSS, T25FW, 9HPT, urine drug and alcohol test, PK and ADA sample collections; Section 3.6 Scales and Questionnaires table to remove EDSS T25FW, 9HPT from Follow-up at Weeks 64 and 76.

Rationale:

By January 2021, all study subjects had completed 52 weeks of therapy. A recent, planned efficacy analysis revealed that elezanumab therapy provided no beneficial effects. A lack of efficacy was observed on all endpoints.

The study initially had scheduled in person site visits at Week 64 and Week 76. The purpose of these visits was to perform assessment of the primary endpoint to better understand the durability of improvement observed at Week 52. Because there were no beneficial drug effects at Week 52, there is no scientific purpose to having the subjects return for in person visits. The ongoing COVID-19 pandemic also provides a strong justification for NOT having subjects perform unneeded in person site visits.

The collection of safety-related information by phone every 4 weeks through Week 76, including AEs, C-SSRS assessments, and pregnancy testing results will continue.

APPENDIX F. OPERATIONS MANUAL

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Operations Manual for Clinical Study Protocol M18-918

Multiple Sclerosis: Safety and Efficacy Study of Elezanumab (ABT-555) in Relapsing Forms of Multiple Sclerosis

SPONSOR:	AbbVie	ABBVIE INVESTIGATIONAL PRODUCT:	elezanumab

FULL TITLE: 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

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TABLE OF CONTENTS

1 CONTACTS 2

2 PROTOCOL ACTIVITIES BY VISIT 6

2.1 Individual Treatment Period Visit Activities 6

2.2 Individual Post-Treatment Period Visit Activities 23

3 STUDY PROCEDURES 26

3.1 Subject Information and Informed Consent 26

3.2 Medical History 27

3.3 Drug and Alcohol Screen 27

3.4 Adverse Event Assessment 28

3.5 Prior and Concomitant Medications 28

3.6 Scales and Questionnaires 28

3.7 Pharmacokinetic Sampling 35

3.8 Biomarker Sampling 35

3.9 12-Lead Electrocardiogram 35

3.10 Height, Weight and BMI 36

3.11 Vital Signs 36

3.12 Physical Examination 37

3.13 Neurological Examination 37

3.14 Actigraphy 38

3.15 Assignment of Subject Numbers and Use of Interactive Response Technology (IRT) 38

3.16 Clinical Laboratory Tests 39

3.17 Magnetic Resonance Imaging (MRI) 41

3.18 Dispense Study Drug 42

3.19 Subject Withdrawal from Study 43

3.20 Unscheduled Visits 44

4 SAFETY MANUAL 44

4.1 Methods and Timing of Safety Assessment 44

4.2 Reporting Adverse Events and Intercurrent Illnesses 46

5 COUNTRY-SPECIFIC REQUIREMENTS 48
5.1 SAMPLE RETENTION REQUIREMENTS 48
5.2 SUSAR REPORTING 48
5.3 TREATMENT AFTER END OF STUDY 48

LIST OF APPENDICES

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS 49
APPENDIX B. CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT (PCS) VALUES FOR ELEZANUMAB STUDIES 51
APPENDIX C. MS RELAPSE QUESTIONNAIRE 58
APPENDIX D. CRITERIA FOR MONITORING ELEZANUMAB INFUSION REACTIONS 59

2 PROTOCOL ACTIVITIES BY VISIT

Study visits may be impacted due to the COVID-19 pandemic. This may include changes such as phone or virtual visits, visits at alternative locations, or changes in the visit frequency and timing of study procedures, among others. Additional details are provided in the subsequent section. Every effort should be made to ensure the safety of subjects and site staff, while maintaining the integrity of the study. If visits cannot be conducted onsite due to travel restrictions or other pandemic-related reasons, follow the updates below on how to proceed.

2.1 Individual Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit.

Study procedures may be split over 2 consecutive days, with the study drug administration to occur on the second day. At the Week 0 Baseline Visit, the site will conduct actigraphy training with the subject, and application of sensors should be done on the same day as the timed 25-foot walk. These activities (along with all the pre-dose activities) should occur before dosing.

Activities are grouped by category (Interview, Exam, etc.). Further information about each activity is provided in Section 3.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

During the COVID-19 pandemic, if it is not possible for all study procedures to be performed as specified due to travel restrictions or other reasons, the following modifications are allowed:

- Some study visits and/or activities may be performed by phone/virtually. These are indicated by a hashtag (#) in the appropriate visit table(s) below.
    - During a virtual visit, activities that do not need to be performed are indicated by a minus sign (-).
- Some study visits and/or activities may be performed by a local laboratory. These are indicated by a plus sign (+) in the appropriate visit table(s) below. All procedures performed at local facilities must be performed by appropriately qualified personnel.
- Study Visits and/or activities should be performed as scheduled whenever possible. If it is not possible to do so due to the pandemic, the following modifications are allowed:
    - Study procedures may be split over 7 consecutive days. The Expanded Disability Status Scale (EDSS), 9-Hole Peg Test (9HPT), or Timed 25 Foot Walk (T25FW) should all occur on the same visit day.
    - MRI assessments may be collected up to 12 weeks after the projected visit for the missed timepoints at Week 24 and 52 with the sponsor's consent due to reasons related to the COVID-19 pandemic. However, all MRI assessments projected to be obtained on or before mid-November 2020 must be completed by the end of November 2020. To accommodate scheduling of the vast volume of projected Week 52 MRIs in December 2020, at the discretion of the sponsor, sites may schedule Week 52 MRIs up to -28 days of their projected Week 52 visit.

- If the Week 52 visit is missed, subject should be brought in as soon as possible and perform primary endpoint assessment (e.g., EDSS, 9HPT, or T25FW) for the Week 52 visit.
- If a Week 12, 24, or 36 visit is missed, subject should be brought in as soon as possible for an elezanumab infusion and perform primary endpoint assessments for the most recent missed visit.
- If a Week 16, 20, 28, 32, 40, 44, or 48 visit is missed, subject should be brought in as soon as possible for their missed infusion. Utilize the allowable visit windows to shift the subject into their predicted visit schedule. There must be a minimum of 14 days between infusions.

SCREENING:

INTERVIEW	• Informed consent • Eligibility criteria • Medical history	• Adverse event (AE) assessment • Prior/concomitant therapy
SCALES – CLINICIAN-MEASURED	• Columbia-Suicide Severity Rating Scale (C-SSRS)	• Expanded Disability Status Scale Plus (EDSS) • Timed 25 Foot Walk (T25FW) • 9-Hole Peg Test (9HPT)
EXAMINATIONS	• 12-lead electrocardiogram (ECG) • Weight • Height	• Body mass index (BMI) • Vital signs • Physical examination • Neurological examination
CENTRAL LABORATORY	• Central laboratory tests	• Serum pregnancy test[a] • Urine drug and alcohol test
IMAGING	• Brain and cervical spinal cord magnetic resonance imaging (MRI)[b]	

NOTES:

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

b. Baseline MRI must be performed before first dose. Non-scheduled MRIs after Baseline will be performed at the discretion of the subject's treating physician or in the case of early subject discontinuation, if it has been more than 4 weeks since the subject's most recent MRI. For MRI procedures, the visit window is ± 7 days.

RESCREEN

Subjects can be rescreened if they previously screen failed for the following reasons:

- Discontinuation of an immunomodulatory less than 6 months before Screening

- Initiation of a new immunomodulatory or immunomodulatory dose change within 6 months of Screening
- Fall outside the 30-day screening period
- Experienced an MS relapse within 24 months before screening.
- Have a non-clinically significant laboratory abnormality that has now normalized.

If it is anticipated that fewer than 60 days will pass from initial testing to randomization, the following procedures do not need to be repeated during rescreening: screening MRI, clinical scales, weight/height, medical history (unless subject reported change), physical examination (unless new symptoms), neurological examination (unless new symptoms), and central laboratory tests.

WEEK 0 - BASELINE:

INTERVIEW	• Eligibility criteria • Medical history	• AE assessment • Prior/concomitant therapy
Patient Reported Outcomes (PRO)	• Multiple Sclerosis Impact Scale (MSIS-29), version 2	• Modified Fatigue Impact Scale (MFIS-5)
SCALES – CLINICIAN-MEASURED	• C-SSRS • EDSS • T25FW • 9HPT • Multiple Sclerosis Individualized Outcome Assessment (MSIOA) • Low Contrast Visual Acuity (LCVA)	• Cognition scales: Symbol Digit Modalities Test (SDMT)-Oral/Written, Brief Assessment of Cognition, (BAC) APP Verbal Memory Test (Immediate Recall), BAC App Tower of London (BAC App ToL)
EXAMINATIONS	• Weight • Vital signs[a]	• Physical examination • Neurological examination
LABORATORY	• Urine drug and alcohol test	• Local urine pregnancy test[b]
CENTRAL LABORATORY	• Central laboratory tests	• Pharmacokinetic (PK) and antidrug antibody (ADA) sample collections • Biomarker samples whole blood (DNA/RNA/Serum/Plasma)
TREATMENT	• Randomization/Drug assignment • Pharmacy prepares study drug or placebo for infusion	• Administer infusion and Observation
ACTIGRAPHY	• Wearable device training & Data Collected	

Notes:

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 4:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
SCALES – CLINICIAN-MEASURED	• C-SSRS	
EXAMINATIONS	• Weight	• Vital signs[a]
LABORATORY	• Urine drug and alcohol test	• Local urine pregnancy test[b]
CENTRAL LABORATORY	• Hematology only	
TREATMENT	• Pharmacy prepares study drug or placebo for infusion	• Administer infusion and Observation

NOTES:

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 8:

INTERVIEW	• AE assessment	• Prior/concomitant therapy
SCALES – CLINICIAN-MEASURED	• C-SSRS	
EXAMINATIONS	• Weight	• Vital signs[a]
LABORATORY	• Urine drug and alcohol test	• Local urine pregnancy test[b]
CENTRAL LABORATORY	• Hematology only	
TREATMENT	• Pharmacy prepares study drug or placebo for infusion	• Administer infusion and Observation

NOTES:

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 12:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
PRO	• MSIS-29, version 2[#]	• MFIS-5[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#] • Cognition scales: SDMT, BAC App, BAC App ToL[-]	• EDSS[-] • T25FW[-] • 9HPT[-] • LCVA[-]
EXAMINATIONS	• Weight[-] • 12-lead ECG[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
CENTRAL LABORATORY	• Central laboratory tests[+]	• PK and ADA sample collections[-] • Biomarker samples whole blood[-] (DNA/RNA/Serum/Plasma)[-]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up 39 weeks (5 half-lives), after their last study drug dose.

WEEK 16:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 20:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 24:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
PRO	• MSIS-29, version 2[#]	• MFIS-5[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#] • MSIOA[-] • Cognition scales: SDMT, BAC App, BAC App ToL[-]	• EDSS[-] • T25FW[-] • 9HPT[-] • LCVA[-]
EXAMINATIONS	• Weight[-] • Neurological examination[-]	• Vital signs[-,a] • 12-lead ECG[-]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
CENTRAL LABORATORY	• Central laboratory tests[+]	• PK and ADA sample collections[-] • Biomarker samples whole blood (DNA/RNA/Serum/Plasma)[-]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]
ACTIGRAPHY[c]	• Actigraphy data collected[-]	
IMAGING	• Brain and cervical spinal cord MRI[-,d]	

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

c. Reminder phone call from site staff to subject approximately 3 days before visit. Collection of actigraphy data may not be possible if the subject does not have actigraphy supplies during the COVID-19 pandemic.

d. Non-scheduled MRIs after baseline will be performed at the discretion of the subject's treating physician or in the case of early subject discontinuation, if it has been more than 4 weeks since the subject's most recent MRI. Refer to Section 3.17, MRI for visit window allowances.

WEEK 28:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 32:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 36:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
PRO	• MSIS-29, version 2[#]	• MFIS-5[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#] • Cognition scales: SDMT, BAC App, BAC App ToL[-]	• EDSS[-] • T25FW[-] • 9HPT[-] • LCVA[-]
EXAMINATIONS	• Weight[-] • Vital signs[-,a]	• 12-lead ECG[-]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
CENTRAL LABORATORY	• Central laboratory tests[+]	• PK and ADA sample collections[-] • Biomarker samples whole blood (DNA/RNA/Serum/Plasma)[-]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]
ACTIGRAPHY[c]	• Actigraphy data collected[-]	

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

c. Reminder phone call from site staff to subject approximately 3 days before visit. Collection of actigraphy data may not be possible if the subject does not have actigraphy supplies during the COVID-19 pandemic.

WEEK 40:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 44:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 48:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
EXAMINATIONS	• Weight[-]	• Vital signs[-,a]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,b]
TREATMENT	• Pharmacy prepares study drug or placebo for infusion[-]	• Administer infusion and Observation[-]

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Measure blood pressure before and 2 hours (± 3 minutes) post start of infusion.

b. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

WEEK 52:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
PRO	• MSIS-29, version 2[#]	• MFIS-5[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#] • MSIOA[-] • Cognition scales: SDMT, BAC App, BAC App ToL[-]	• EDSS[-] • T25FW[-] • 9HPT[-] • LCVA[-]
EXAMINATIONS	• Weight[-] • Neurological examination[-] • Physical examination[-]	• Vital signs[-] • 12-lead ECG[-]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,a]
CENTRAL LABORATORY	• Central laboratory tests[+]	• PK and ADA sample collections[-] • Biomarker samples whole blood (DNA/RNA/Serum/Plasma)[-]
IMAGING	• Brain and cervical spinal cord MRI[-,b]	
ACTIGRAPHY[c]	• Actigraphy data collected[-]	

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

b. Non-scheduled MRIs after baseline will be performed at the discretion of the subject's treating physician or in the case of early subject discontinuation, if it has been more than 4 weeks since the subject's most recent MRI. Refer to Section 3.17, MRI for visit window allowances.

c. Reminder phone call from site staff to subject approximately 3 days before visit. Collection of actigraphy data may not be possible if the subject does not have actigraphy supplies during the COVID-19 pandemic.

Early Discontinuation:

INTERVIEW	• AE assessment[#]	• Prior/concomitant therapy[#]
PRO	• MSIS-29, version 2[#]	• MFIS-5[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#] • Multiple Sclerosis Individualized Outcome Assessment[-] • Cognition scales: SDMT, BAC App, BAC App ToL[-]	• EDSS[-] • T25FW[-] • 9HPT[-] • LCVA[-]
EXAMINATIONS	• Weight[-] • Neurological examination[-] • Physical examination[-]	• Vital signs[-] • 12-lead ECG[-]
LABORATORY	• Urine drug and alcohol test[+]	• Local urine pregnancy test[+,a]
CENTRAL LABORATORY	• Central laboratory tests[+]	• PK and ADA sample collections[-] • Biomarker samples whole blood (DNA/RNA/Serum/Plasma)[-]
IMAGING	• Brain and cervical spinal cord MRI[-,b]	

NOTES:

Phone/virtual; - Not needed if done by phone/virtual; + May be done by a local laboratory if phone/virtual visit.

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives), after their last study drug dose.

b. Baseline MRI must be performed before first dose. Non-scheduled MRIs after baseline will be performed at the discretion of the subject's treating physician or in the case of early subject discontinuation, if it has been more than 4 weeks since the subject's most recent MRI. For MRI procedures, the visit window is ± 7 days. Refer to Section 3.17, MRI, for COVID-19 pandemic-related modifications.

2.2 Individual Post-Treatment Period Visit Activities

This section presents a list of activities performed during each visit, organized by visit.

Activities are grouped by category (Interview, Exam, etc.). Further information about the activities is presented in Section 3.

FOLLOW-UP WEEK 56:

INTERVIEW	• Telephone call to collect home pregnancy test results from females of childbearing potential[#,a]	• AE assessment[#] • Prior/concomitant therapy[#]

NOTES:

Phone/virtual.

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives) after their last study drug dose.

FOLLOW-UP WEEK 60:

INTERVIEW	• Telephone call to collect home pregnancy test results from females of childbearing potential[#,a]	• AE assessment[#] • Prior/concomitant therapy[#]

NOTES:

Phone/virtual.

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives) after their last study drug dose.

FOLLOW-UP WEEK 64:

INTERVIEW	• Telephone call to collect home pregnancy test results from females of childbearing potential[#,a]	• AE assessment[#] • Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	
ACTIGRAPHY	• Reminder phone call from site staff to subject approximately 3 days before visit to return all actigraphy supplies to site	

NOTES:

Phone/virtual.

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives) after their last study drug dose.

FOLLOW-UP WEEK 68:

INTERVIEW	• Telephone call to collect home pregnancy test results from females of childbearing potential[#,a]	• AE assessment[#] • Prior/concomitant therapy[#]

NOTES:

Phone/virtual.

a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives) after their last study drug dose.

FOLLOW-UP WEEK 72:

INTERVIEW	• Telephone call to collect home pregnancy test results from females of childbearing potential[#,a]	• AE assessment[#] • Prior/concomitant therapy[#]

NOTES:
Phone/virtual.
a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during follow-up for 39 weeks (5 half-lives) after their last study drug dose.

FOLLOW-UP WEEK 76/FOLLOW-UP D/C:

INTERVIEW	• Telephone call to collect home pregnancy test results from females of childbearing potential[#,a]	• AE assessment[#] • Prior/concomitant therapy[#]
SCALES – CLINICIAN-MEASURED	• C-SSRS[#]	

NOTES:
Phone/virtual.
a. Pregnancy tests are for females of childbearing potential. Results must be negative for study participation. Female subjects will perform monthly home urine pregnancy test during and post follow-up for 39 weeks (5 half-lives) after their last study drug dose. The results of the post follow-up monthly at home pregnancy tests must be communicated to the site.

3 STUDY PROCEDURES

3.1 Subject Information and Informed Consent

The investigator or his/her representative will explain the nature of the study to the subject and answer all questions regarding this study. Before any study-related screening procedures being performed on the subject or any medications being discontinued by the subject in order to participate in this study, the institutional review board/independent ethics committee (IRB/IEC) approved informed consent statement will be reviewed, signed, and dated by the subject or their legally authorized representative, the person who administered the informed consent, and any other signatories according to local requirements. A copy of the signed informed consent will be given to the subject and the original will be

placed in the subject's medical record. An entry must also be made in the subject's dated source documents to confirm that informed consent was obtained before any study-related procedures and that the subject received a signed copy.

Information regarding benefits for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the study can be found in the informed consent form.

Due to the COVID-19 pandemic, it is possible that additional protocol modifications not outlined in this protocol may become necessary. If this situation arises, in addition to the study informed consent, additional verbal consent may be obtained and documented in subject's source documents before, if possible, these adaptations or substantial changes in study conduct in accordance with local regulations.

3.2 Medical History

For all subjects, a complete medical history including subject's history of multiple sclerosis (MS), demographics, history of tobacco, alcohol, and drug use will be taken at screening. Additionally, chronic disorders (such as, but not limited to, diabetes, hypertension, and hay fever) that began before Screening and are still present at Screening should be recorded on the medical history form. All psychiatric, neurological, behavioral, and/or cognitive diagnoses that are noted in the subject's medical records should also be recorded on the Medical History electronic case report form (eCRF). Medication (prescription or over-the-counter, including vitamins and herbal supplements) use from 30 days before informed consent form signature through the end of the study will also be recorded. The subject's medical history will be updated at the Week 0 - Baseline visit. This updated medical history will serve as the baseline for clinical assessment.

3.3 Drug and Alcohol Screen

Subjects should have no history of clinically significant (per investigator's judgment) drug or alcohol abuse within the last 2 years.

Urine specimens will be tested for the presence of drugs of abuse. The panel for drugs of abuse will minimally include the drugs listed below. Any positive result must be assessed for clinical significance. Depending on the visit, these analyses will be performed by the certified central laboratory chosen for the study or by a site with a kit provided by the central lab. Refer to Inclusion Criterion #5 of the protocol for additional urine drug screen information.

Urine specimens will be tested at the Screening visit for the presence of drugs of abuse. These analyses will be performed by the certified central laboratory chosen for the study.

- Cannabinoids
- Opiates
- Barbiturates
- Amphetamines
- Cocaine

- Benzodiazepines
- Alcohol
- Phencyclidine
- Propoxyphene
- Methadone

A positive cannabinoid test is allowed if the responsible agent is taken for the management of MS symptoms (either concurrent or within the past 30 days). A positive drug screen resulting from other prescribed medications is allowed at the discretion of the AbbVie study-designated physician.

3.4 Adverse Event Assessment

Please refer to Section 4.1.

3.5 Prior and Concomitant Medications

Investigators and/or trained site staff will review and record all prior and concomitant medications at every visit throughout the study as shown in Section 2. Refer to the protocol Section 5.4, Prior and Concomitant Therapy, for additional information.

Subjects who are currently receiving intravenous (IV) MS immunotherapies (e.g., ocrelizumab) should not receive these agents on the same day as study drug infusion at Week 0. On subsequent study visits, subjects receiving IV immunotherapies should wait to receive the drug for at least two (2) hours after the completion of investigational product infusion. Exceptions to the 2-hour waiting period between infusions after Baseline may be approved on a case-by-case basis but always in consultation with the AbbVie TA MD. Subjects who receive IV immunotherapies the same day as investigational product should have received the immunotherapy at least two (2) times prior and have no history of infusion reaction within the last 12 months in response to the immunotherapy.

Corticosteroids (or corticosteroid precursors such as adrenocorticotropic hormone) are an allowed class of medication if used before or after ocrelizumab or other drug infusion to limit infusion reactions. Pre-medication for study drug infusion is not allowed without the consent of the AbbVie study-designated physician.

3.6 Scales and Questionnaires

Diagnostic Tools and Rating Scales

Before the start of the study, designated raters will be certified/trained by VeraSci in the use of all scales used in this study. The objective of this certification/training is to establish uniformity across sites in the administration, interpretation and scoring of these rating instruments. It is the responsibility of the investigator to ensure that the raters at his/her site are appropriately trained and certified in the use of selected rating scales. Every effort must be made by the investigative sites to ensure that each subject is rated by the same rater for each scale throughout their participation in the study.

AbbVie, in conjunction with the rater training vendor, NCT, will determine the minimum rater qualifications for each of the rating scales. All raters must meet these qualifications before participation in the training process. The qualifications of the raters will be verified through the training vendor. Individual exceptions to these requirements must be approved by the sponsor via the training vendor.

Administration of selected scales will be audio recorded to allow for central review of the data and to ensure consistency and reliability.

Assessments will be performed at the times indicated in Section 2.

Subjects will complete the self-administered patient-reported outcome (PRO) instruments (when allowed per local regulatory guidelines). Subjects should be instructed to follow the instructions provided with the instruments and to provide the best possible response to each item. Site personnel shall not provide interpretation or assistance to subjects other than encouragement to complete the tasks. Subjects who are functionally unable to read any of the instruments may have site personnel read the questionnaire to them. Site personnel will encourage completion of the instrument at all specified visits and will ensure that a response is entered for all items.

The following Patient Reported Outcome (PRO) instruments will be used in this study:

- Multiple Sclerosis Impact Scale (MSIS-29), version 2: The MSIS-29 version 2 consists of 29 questions; 20 address the physical impact of MS and nine assess the psychological impact. Subjects are asked the questions about the impact of MS on their day-to-day life during the previous 2 weeks. For each statement, the subject is asked to circle a number from 1 to 5 that best describes their situation (1 = 1 not at all; 2 = a little; 3 = moderately; 4 = quite a bit; 5 = extremely). It should take 5 - 8 minutes for the subject to complete the scale.
- Modified Fatigue Impact Scale (MFIS-5): The MFIS-5 includes five statements about how fatigue affects the individual who has MS. For each of the five statements, the subject indicates on a scale from 0 (never) to 4 (almost always) how their fatigue has affected them over the past 4 weeks. It should take 2 - 3 minutes for the subject to complete this scale.

The following clinician-measured scales will be used in this study:

- Columbia-Suicide Severity Rating Scale (C-SSRS): The C-SSRS is a systematically administered instrument developed to track suicidality across a treatment study. The instrument is designed to assess suicidal behavior and ideation, track and assess all suicidal events, as well as the lethality of attempts. Additional features assessed include frequency, duration, controllability, reason for ideation, and deterrents. The C-SSRS takes less than 5 minutes to administer.

  Any subject noted to have suicidal ideation with plan within the prior month, either via answering "yes" to questions 4 or 5 to the suicidal ideation portion of the C-SSRS or via clinical interview, or noted to have suicidal behavior based on the positive responses to suicidal behavior portion of the C-SSRS, will be evaluated immediately by the study site physician. The AbbVie study designated physician will also be informed. Appropriate steps will be taken to protect the subject, including but not limited to possible discontinuation from the study and referral for appropriate psychiatric care. Any such subject at Screening or on Week 0 – Baseline will also be excluded from the study.

- Multiple Sclerosis Individualized Outcome Assessment (MSIOA): The MSIOA is a novel clinician-reported outcome assessment that has been developed for this study to identify the impact of MS and MS treatment on an individual subject's activities of daily living across multiple domains. MS affects subjects differently and the importance of certain abilities is different for each subject. This outcome will determine the areas of daily living (based on existing activities of daily living [ADLs] within the MSIS) that are most impacted and most important to each subject and these will be ranked on a standardized, ordinal rating scale and tracked during the course of the study.
- Expanded Disability Status Scale Plus (EDSS+) is comprised of the following three scales:
  - EDSS: The Expanded Disability Status Scale (EDSS) is a method of quantifying disability in multiple sclerosis and monitoring changes in the level of disability over time. The EDSS scale ranges from 0 to 10, with 0 referring to normal neurological examination and 10 referring to death. It changes in 0.5 unit increments that represent higher levels of disability. Scoring is based on an examination by a neurologist. It takes about 15 - 30 minutes to conduct the neurological examination and do the scoring.
  - Timed 25-Foot Walk (T25FW): The T25FW quantifies the MS subject's mobility and leg function during a timed walk over a designated and clearly marked twenty-five foot course. The subject is to walk as quickly and safely as possible over the course to the designated twenty-five foot mark. The walk is measured in seconds from the time the initial instructions are provided to the subject reaching the twenty-five foot mark. The subject is then instructed to walk quickly and safely following the course back to the starting point. Again the time for the walk is recorded in seconds. The T25FW will be conducted by a trained examiner. The examiner does not necessarily have to be a nurse or physician. Assistive devices (i.e., cane, crutches, walker) may be used. Scoring is the average of the two trial walks. Additional instructions will be provided for scoring of individuals unable to complete the walk due to severity of impairment. Total time to administer the T25FW is 1 - 5 minutes.
  - 9-Hole Peg Tests (9HPT): The 9HPT is a standardized measure of upper extremity mobility and will test both the dominant hand and non-dominant hand twice consecutively. A 9HPT kit will be provided for the site to use in administration of this test while the subject is seated at a table. The kit includes a shallow container in which 9 small pegs are placed, and a plastic, wooden or cardboard block which has 9 holes. The subject will be instructed to remove the pegs one at a time as quickly as possible from the shallow dish and place the pegs into each of the 9 holes. Once the pegs are in place the subject is to remove the pegs from the holes one at a time as quickly as possible and place the pegs back in the shallow container. The dominant hand will be tested first, twice consecutively and then the non-dominant hand will be tested twice consecutively. For each hand, scoring is the average of the two trials. The total time to administer the 9HPT is approximately 10 minutes or less.
- Low Contrast Visual Acuity (LCVA): The LCVA uses an eye chart specifically designed to test low contrast vision. Subjects identify the letters on the chart and recite them to the tester. Instructions for the clinic setting use and specific lighting requirements will be provided to the site during training by VeraSci. If possible, this test should be administered in the same room and with the same light level at each subject visit. The rater vendor will also purchase and provide all relevant materials in order to support the Low Contrast Visual Acuity Test. All

participating sites must use the LCVA study materials provided by the AbbVie vendor to ensure consistency across the study. The test takes approximately 5 minutes to administer.

- Symbol Digit Modalities Test (SDMT) (oral): Subjects are presented with a page headed by a key that pairs the single digits 1 - 9 with nine symbols. They are then shown a row containing only symbols and asked to orally report the correct number in the space below each symbol. After completing the first 10 items with guidance, the subject is timed to determine how many responses can be made in 90 seconds. In total, it takes approximately 5 minutes to complete the test.
- Brief Assessment of Cognition (BAC) App Verbal Memory Test (Immediate Recall): The subject is to read words and is to recall and repeat the words back to the clinician. It takes approximately 10 minutes to complete the test.
- BAC App Tower of London (BAC App ToL): The subject is presented a diagram of two images, picture A and picture B. Both pictures have three pegs with colored balls arranged on the pegs. The subject is asked to identify how many moves it will take to make the picture A look like picture B. The test takes approximately 10 minutes to complete.

The PRO instruments and clinician-measured scales should be completed at the Week 0 – Baseline visit before any discussion of AEs or any review of laboratory findings. The PRO instruments and clinician measured scales should be completed at subsequent visits before any discussion of AEs, any review of laboratory findings, and before drug administration.

The following scale ***must be*** completed before IP infusion:

- Columbia-Suicide Severity Rating Scale (C-SSRS)

The following scales ***should be*** completed before IP infusion:

- 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 following scales ***may be*** completed during IP infusion:

- MS Impact Scale (MSIS-29)
- Modified Fatigue Impact Scale (MFIS-5)
- Multiple Sclerosis Individualized Outcome Assessment (MSIOA)
- Low Contrast Visual Acuity (LCVA) – *to be performed in a windowless room and using light box*

The following scales ***may be*** completed at any time except during IP infusion:

- All cognition scales

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Due to the COVID-19 pandemic, subject visits may be conducted via phone. PROs eligible for completion by interview at such visits are the C-SSRS, MSIS-29, and MFIS-5. In this situation, sites will read the PRO questions and response options to the subject and record the subject's responses. The date and time of PRO data collection should be recorded along with who collected the information. Once the subject is able to attend onsite visits, the highest priority for completing missed assessments from the previous visit is the EDSS, 9HPT, and T25FW and then, if time permits, any of the exploratory outcome measures.

- C-SSRS: Preferred method is to collect data using direct entry into the iPad provided by VeraSci. Paper assessment can be utilized as a backup plan in event the tablet is not available at the time of the assessment.
- MSIS-29 and MFIS-5: Assessments will be collected using paper assessment forms provided by VeraSci for assessments that are administered over the telephone.

Diagnostic Tools and Scales	Approx. Duration (min.)	Patient Reported Outcome (PRO) Or Clinician Reported Outcome (ClinRO)	Screening	Week 0, Baseline	Weeks 4, 8	Week 12	Weeks 16, 20	Week 24	Weeks 28, 32	Week 36	Weeks 40, 44, 48	Week 52 Completion/ Premature Discontinuation	Follow-up Weeks 64, 76
EDSS+ (Expanded Disability Status Scale (EDSS), Timed 25 Foot Walk (T25FW), 9-Hole Peg Test (9HPT-Dominant Hand & 9HP Non-Dominant Hand)	30 - 45	ClinRO	X	X		X		X		X		X	
MS Impact Scale (MSIS-29), version 2	5 - 8	PRO		X		X		X		X		X	
MS Fatigue Impact Scale-5 (MFIS-5)	2 - 3	PRO		X		X		X		X		X	
MS Individualized Outcome Assessment (MSIOA)	10 - 20	ClinRO		X				X				X	
Low Contrast Visual Acuity (LCVA)	5	ClinRO		X		X		X		X		X	

Diagnostic Tools and Scales	Approx. Duration (min.)	Patient Reported Outcome (PRO) Or Clinician Reported Outcome (ClinRO)	Screening	Week 0, Baseline	Weeks 4, 8	Week 12	Weeks 16, 20	Week 24	Weeks 28, 32	Week 36	Weeks 40, 44, 48	Week 52 Completion/ Premature Discontinuation	Follow-up Weeks 64, 76
Cognitive Scales													
Symbol Digit Modalities Test (oral/written) (SDMT-29)	5	ClinRO		X		X		X		X		X	
Brief Assessment of Cognition App. Verbal Memory Test	5 - 10	ClinRO		X		X		X		X		X	
Brief Assessment of Cognition App. Tower of London Test	5 - 10	ClinRO		X		X		X		X		X	
Safety Scale													
Columbia Suicide Severity Rating Scale (C-SSRS)	< 5	ClinRO	X	X	X	X	X	X	X	X	X	X	X

3.7 Pharmacokinetic Sampling

Collection of Blood Samples for Elezanumab Assay

Blood samples for analysis of elezanumab serum concentrations will be collected before infusion at Week 0 - Baseline and Weeks 12, 24, 36, 52, and Early Discontinuation. PK samples should not be drawn from the same arm (or port) in which elezanumab is administered. Samples will be collected by venipuncture into appropriately labeled, evacuated serum collection tubes.

Collection of Blood Samples for Elezanumab Antidrug Antibody (ADA) Assay and Elezanumab Neutralizing Antibody (nAb) Assay

Blood samples for elezanumab ADA assay and elezanumab nAb assay will be collected before infusion at Week 0 – Baseline and Weeks 12, 24, 36, 52, and Early Discontinuation.

Additional information on the disposition, handling, and measurement methods can be found in the Covance Laboratory Manual.

Serum concentrations of elezanumab and relative titers of elezanumab ADA will be determined using validated methods at or under the supervision of the Bioanalysis Department at AbbVie. Any additional analytes may be analyzed using non-validated methods. Serum samples collected for elezanumab and elezanumab ADA analysis may be used for future assay development or validation activities. Elezanumab nAb samples may be used for the analysis of neutralizing anti-drug antibodies.

3.8 Biomarker Sampling

Whole blood samples will be collected for biomarker research (protocol Section 3.6, Biomarker Sampling). Please refer to Section 2 for the schedule of biomarker research sample collections. All biomarker samples should be labeled and shipped as outlined in the study-specific Covance Laboratory Manual.

3.9 12-Lead Electrocardiogram

A 12-lead ECG will be performed at the designated study visits as specified in Section 2. The ECG should be performed before blood collection.

An appropriately trained physician at the site ("local reader") will evaluate the ECGs. In a timely manner following the performance of the ECG, the local reader will sign and date all ECG tracings and will provide his/her global interpretation as a written comment on the tracing using the following categories:

- Normal ECG
- Abnormal ECG – not clinically significant
- Abnormal ECG – clinically significant

The automatic machine reading (i.e., machine-generated measurements and interpretation that are automatically printed on the ECG tracing) will not be collected.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, perform the 12-lead ECG at the next earliest feasible visit.

3.10 Height, Weight and BMI

Height will be measured at Screening only. Body weight will be measured at scheduled visits as specified in Section 2. The subject will wear lightweight clothing and no shoes during weighing. BMI calculations will be done at the Screening Visit to assess Inclusion criterion #3 of the protocol.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, body weight will be measured at the next earliest feasible visit.

3.11 Vital Signs

Vital sign determinations of systolic and diastolic blood pressure, pulse rate, and body temperature will be obtained at visits as specified in Section 2. Blood pressure and pulse rate should be measured and documented after the subject has been sitting for at least 3 minutes both before infusion and at the end of infusion. Repeat vital sign determinations should be taken from the same extremity as initial determination.

Following infusion, if the blood pressure is elevated above 160 mmHg systolic (and 20 mmHg over pre-infusion value) OR 105 diastolic (and 15 mmHg over pre-infusion value), then the heart rate and blood pressure measurement should be repeated. If the blood pressure remains elevated above these thresholds, the investigator should repeat the measurement after one hour. If the elevation persists, the investigator should further assess and manage the subject according to standard of care. If the subject is symptomatic (e.g., chest pain, headache, neurologic symptoms, visual disturbances, perturbations in other vital signs) or has cardiovascular comorbidities of concern, an ECG, additional cardiac monitoring, and treatment with anti-hypertensive agents at the site or emergency care setting should be considered. If a subject leaves the site with a blood pressure exceeding the above thresholds, a follow-up phone call from the site to the subject approximately 12 hours later is recommended and the subject should return for an unscheduled follow-up visit approximately 48 hours later with blood pressure and heart rate documented by the site. While not anticipated, sustained blood pressure elevations beyond the thresholds described above should be assessed and managed by the investigator or the subject's physician.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, vital signs will be measured at the next earliest feasible visit.

3.12 Physical Examination

A complete physical examination will be performed at the designated study visits as specified in Section 2. Height and body weight will be measured at Screening in order to calculate body mass index (BMI). Body weight will also be measured at Week 0 – Baseline and at each treatment visit or upon subject discontinuation. The subject will wear lightweight clothing and not wear shoes when taking height and weight at Screening and when taking weight at subsequent visits. The physical examination performed on Week 0 – Baseline will serve as the baseline physical examination for the entire study. Any significant physical examination findings after the first dose will be recorded as AEs. All findings, whether related to an AE or part of each subject's medical history, will be captured on the appropriate eCRF page.

At any time, a symptom-directed physical examination can be performed as deemed necessary by the investigator.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, physical examination will be performed at the next earliest feasible visit.

3.13 Neurological Examination

A neurological examination will be performed at the designated study visits as specified in Section 2. A symptom-directed neurological examination will be performed when necessary. Portions of the neurologic exam that are required to complete the EDSS will be performed at visits where the EDSS is calculated. The neurological examination performed at Week 0 - Baseline will serve as the Baseline for clinical assessment. Symptoms identified during screening will not be recorded as adverse events, however, new symptoms or current symptoms that change in severity or frequency after the first infusion of study drug will be recorded as adverse events.

The neurological examination will assess:

- Mental status – assessment of orientation, speech, and memory.
- Cranial nerves – assessment of cranial nerves II - XII.
- Motor system –assessment of tone and strength, including assessment for tremor.
- Sensory system – assessment of light touch, temperature and distal proprioception
- Reflexes – assessment of deep tendon reflexes and plantar responses (Babinski sign)
- Coordination – assessment of upper and lower extremities
- Gait – gait, including tandem

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, neurological examination will be performed at the next earliest feasible visit.

3.14 Actigraphy

A wearable sensor will be used (when allowed per local regulatory guidelines) to enable data capture on actigraphy (activity, rest cycles) and daily step count. If regulatory approval in a participating country has not been received by the manufacturer, actigraphy data monitoring will not be done in that country. The actigraphy assessment will use BioStamp nPoint, which is a wireless remote monitoring platform intended for use by healthcare professionals and researchers for the continuous collection of physiological data in healthcare and home settings. BioStamp nPoint is designed to capture objective, real-world data from study subjects participating in clinical or academic studies and may be used wherever collection of relevant data is needed. BioStamp nPoint centers on body-worn BioStamp Sensors that can be worn for up to 24 hours at a time.

When BioStamp nPoint is used in the home or outside of the clinic ("Remote") setting, study subjects interact with the system through a Mobile Phone Application called the "Link App." The recharging and data transmission hub ("Link Hub") is used to recharge the sensors and synchronize data from the Sensors. The system is also capable of surface electromyography (sEMG) and monitoring limb and body movements during daily living and sleep. Training will be provided to site staff with instructions for subject use. Refer to Section 2 for the required administration times.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event this may not be performed due to study modifications related to the COVID-19 pandemic, actigraphy data will be captured at the next earliest feasible visit.

3.15 Assignment of Subject Numbers and Use of Interactive Response Technology (IRT)

Contact information and user guidelines for IRT use will be provided to each site.

At the Screening visit, all subjects will be assigned a unique subject number through the use of the IRT system.

IRT has adopted the following numbering convention:

- 1st digit - Lead 1
- 2nd, 3rd, and 4th digits – 3 digit site # 100 – 199 (sequence for Canada begins with 200)
- 5th and 6th digits – sequential subject number

For subjects who do not meet the study selection criteria, the site personnel must update the IRT system and identify the subject as a screen failure.

Subjects who are enrolled will retain their subject number assigned at the Screening visit throughout the study.

Upon receipt of study drug, the site unblinded pharmacist will acknowledge receipt in the IRT system.

Eligible subjects will be randomized in a 1:1:1 ratio to elezanumab [redacted] or elezanumab [redacted] or placebo through the IRT. The IRT system will assign the kit number(s) to be used at each visit for dose preparation for a given subject in accordance with the subject's assigned randomized treatment.

3.16 Clinical Laboratory Tests

Blood samples will be collected before study drug administration. The baseline laboratory test results for clinical assessment for a particular test will be defined as the last measurement before the initial dose of study drug. Laboratory re-tests during Screening are allowed if, in the investigator's opinion, the initial result potentially resulted from test variability or was a non-clinically significant perturbation that has since resolved.

<table>
<tr><th colspan="3">Clinical Laboratory Tests</th></tr>
<tr><th>Hematology</th><th>Clinical Chemistry</th><th>Other Tests</th></tr>
<tr><td>Hematocrit
Hemoglobin
Red blood cell (RBC) count
White blood cell (WBC) count
Neutrophils
Bands
Lymphocytes
Monocytes
Basophils
Eosinophils
Platelet count (estimate not acceptable)
Activated partial thromboplastin time (aPTT)</td><td rowspan="3">Blood urea nitrogen (BUN)
Creatinine
Creatine phosphokinase (CPK)
Total bilirubin
Albumin
Alanine transaminase (SGPT/ALT)
Aspartate transaminase (SGOT/AST)
Alkaline phosphatase
Sodium
Potassium
Calcium
Inorganic phosphorus
Uric acid
Cholesterol
Total protein
Glucose
Triglycerides
Bicarbonate/CO_2
Chloride</td><td rowspan="3">Human immunodeficiency virus (HIV)
Hepatitis B surface antigen (HBsAg)
Hepatitis C virus (HCV)
Serum pregnancy test
Serum PK
Serum PD
Serum ADA
DNA/RNA pharmacogenetics</td></tr>
<tr><th>Urinalysis</th></tr>
<tr><td>Specific gravity
Ketones
pH
Leukocytes
Nitrite
Protein
Blood
Glucose
Urine pregnancy test
Microscopic exam</td></tr>
</table>

Covance, a certified central laboratory, will be utilized to process and provide results for the clinical laboratory tests. Laboratory reference ranges will be obtained before the initiation of the study.

Instructions regarding the collection, processing, and shipping of these samples will be provided by the central laboratory and sent to the following certified laboratory address:

Covance Central Laboratories Services, Inc.
8211 SciCor Drive
Indianapolis, IN 46214-2985

All laboratory abnormalities that occur during the study must be evaluated by the investigator to determine if they indicate a new disease process, an exacerbation or worsening of an existing condition, or require further action to be taken, and therefore, may need to be reported as AEs. Accordingly, for any values outside of the reference range, the investigator will indicate on the report if the result is clinically significant (CS) or not clinically significant (NCS). If a laboratory abnormality meets criteria for a potentially clinically significant (PCS) laboratory value, as defined in Appendix B, the investigator must either report an associated AE or document in source the reason(s) the finding was not considered an AE.

Any laboratory value that remains abnormal at Completion/Early Discontinuation and was judged to be CS, will be followed according to accepted medical standards until resolution of the abnormality.

Pregnancy Tests (Serum and Urine)

A pregnant or breastfeeding female will not be eligible for participation or continuation in this study.

Pregnancy testing should not be performed for postmenopausal females. Determination of postmenopausal status is made during screening based on the subject's history.

A quantitative serum pregnancy test will be performed at Screening and a urine pregnancy test will be performed at the Week 0 – Baseline visit for all female of childbearing potential subjects.

The serum pregnancy test will be sent to and performed by the central laboratory. If the serum pregnancy test is positive, the subject is considered a screen failure. If the serum pregnancy test is borderline, it should be repeated ≥ 3 days later to determine subject eligibility.

If the repeat serum pregnancy test is:

- Positive, the subject is considered a screen failure;
- Negative, the subject can be enrolled into the trial;
- Borderline > 3 days later, this will be considered documentation of continued lack of a positive result and the subject can be enrolled into the study (unless prohibited per local requirements) in the absence of clinical suspicion of pregnancy and other pathological causes of borderline results.

Additional urine pregnancy tests will be performed at visits indicated in the Activity Schedule. The results of the monthly at home pregnancy tests must be communicated to the site. More frequent pregnancy tests can be performed throughout the study at the investigator's discretion or if required per local/country requirements.

- If the baseline urine pregnancy test is negative, then dosing with study drug may begin.
- If the baseline or post-baseline urine pregnancy test is positive, dosing with study drug must be withheld and a serum pregnancy test is required (as stated above).

Urinalysis

Urinalysis will be completed by the central laboratory at all visits that state "Central Laboratory Tests" per Appendix D, Activity Schedule, in the protocol. Specified abnormal macroscopic urinalyses defined as leukocytes, nitrite, protein, ketones, or blood greater than negative, or glucose greater than normal will be followed up with a microscopic analysis at the central laboratory.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

If travel restrictions or other changes in local regulations in light of the COVID-19 pandemic prevent the subject from having blood drawn for laboratory testing at the study site, if possible, arrange for subjects to have laboratory work done at a local laboratory, hospital, or other facility. Local laboratory results should be obtained along with reference ranges and kept within the subjects' source documentation. Local laboratory results should be reviewed by the investigator as soon as possible.

3.17 Magnetic Resonance Imaging (MRI)

Preparation for the MRI exam before the subject's arrival is critical in order to ensure that all scans can be acquired within the allotted time frame and for accommodation of any unforeseen delays. MRI scanner must have a magnetic field strength of 1.5 Tesla or 3 Tesla. 3 Tesla scanners are preferred so these should be used whenever both field strengths are available. The total scan time, not including subject position, is estimated to take approximately 50 minutes depending on the type of scanner. The imaging facility is responsible for the MRI safety of subjects who are scanned at the imaging facilities, all procedures and guidelines for safety consideration should be followed. A MRI safety questionnaire, if part of the standard of care at the investigative site, should be administered to ensure that the subject does not have any of the MRI contraindications.

For imaging session involving gadolinium contrast agent administration, an intravenous catheter for gadolinium contrast agent infusion will be inserted according to standard clinical practice to all subjects. The subjects will be positioned supine on MRI bed and their head will be positioned within a head coil with appropriate foam padding to minimize movement during the scan and to standardize the orientation of the head. The subjects will then be positioned within the MRI scanner for imaging. Scans that are of poor quality (e.g., due to head motion during the scan, inadequate coverage of the brain, improper positioning of the head, use of incorrect scan or geometry parameters, or noisy image) as determined by the MRI technologist, reviewing radiologist or sponsor, will be repeated at earliest time possible and within 15 days of the protocol-required time point.

Following completion of the MRI scan, subjects will be transported from the imaging center back to the study site, if applicable. Sedation is not recommended but is allowed. Subjects who might need sedation should discuss this with the principal investigator before the imaging procedure. Sites are to record any sedation medication on the Concomitant Medications eCRF. The MRI technician is responsible for performing brain MRI scans at all protocol-required time points.

During the course of the study, MRI scans will be performed at three time points: at Screening (Baseline MRI), Week 24 and Week 52/Early Discontinuation. The screening MRI will be evaluated by the local radiologist and the radiologist's report reviewed by the investigator before Dose 1 at Week 0-Baseline visit to determine subject's eligibility. For the subjects enrolled in the study, the Screening MRI will

serve as the Baseline MRI for assessment of MRI outcome measures. The time window for MRI is ± 7 days. MRI scans from all protocol-required time points will be evaluated by a local radiologist, and the local radiologist's reports will be reviewed by the site investigator for disease activity. Sites should use the same local radiologist to evaluate all the MRI collected through the entire duration of the study to the extent possible.

The MRI scans will include all or a subset of the following parameters:

- 3D T1 weighted
- T2 FLAIR
- MTR
- PD/T2
- T1 post Gadolinium
- DTI
- Spine STIR

For each study site, the MRI scanner, associated equipment and imaging parameters may not be changed during the length of the study without prior sponsor approval.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

MRI assessments may be collected up to 12 weeks after the projected visit for the missed time points at Weeks 24 and 52 with the sponsor's consent due to reasons related to the COVID-19 pandemic. However, all MRI assessments projected to be obtained on or before mid-November 2020 must be completed by the end of November 2020.

To accommodate scheduling of the vast volume of projected Week 52 MRIs in December 2020, at the discretion of the sponsor, sites may schedule Week 52 MRIs up to –28 days of their projected Week 52 visit.

3.18 Dispense Study Drug

The unblinded pharmacist or qualified designee, under direct supervision of the unblinded pharmacist, will prepare study drug for IV administration. The unblinded pharmacist or qualified designee will dispense the blinded study solution to the clinic staff for IV administration to subjects beginning at the Week 0 – Baseline visit after all other Week 0 – Baseline procedures are completed.

Each site will be responsible for maintaining drug accountability records including product description, manufacturer, and lot numbers for all non-investigational products dispensed by the site.

Further information about study drug is in protocol Section 5.7.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

In the event that study drug is not able to be administered due to study modifications related to the COVID-19 pandemic, bring the subject in as soon as possible for their missed infusion. Utilize the

allowable visit windows to shift the subject into their predicted visit schedule. There needs to be a minimum of 14 days between infusions.

3.19 Subject Withdrawal from Study

All attempts must be made to determine the primary reason for discontinuation of study drug or study participation. The information will be recorded on the appropriate eCRF page. Following discontinuation of study drug, the subject will be treated in accordance with the investigator's best clinical judgment.

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

Severe allergic reactions or other adverse events that require the immediate interruption of elezanumab treatment will be taken into consideration by the AbbVie TA MD for permanent discontinuation from further treatment and initiation of appropriate medical therapy and follow-up.

Any treatment-emergent, clinically significant, symptomatic neurological abnormalities and treatment-emergent MRI findings will be reported to the AbbVie TA MD and subjects will be considered for discontinuation from treatment if clinically indicated.

Subjects at risk of suicide as indicated by answering yes to question 4 or 5 on the C-SSRS and/or determined by the investigator to be at risk of suicide, should be promptly referred for appropriate follow-up care. Subjects determined to be at ongoing risk of suicide should be discontinued from study participation.

If a subject has a positive drug screen, including for amphetamines, cannabis, opioids, and benzodiazepines, the subject will be discontinued from study participation unless allowed to be taken in accordance with a physician's prescription.

If for any reason the subject becomes unable to continue treatment with elezanumab (other than missed doses due to COVID-19 pandemic modification), undergo protocol required procedures, or otherwise continue to participate in the study, discontinuation should be discussed with the AbbVie TA MD.

In the event that a subject withdraws or undergoes early discontinuation from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded and the Early Discontinuation assessment will be performed as per Section 2 and protocol Appendix D, Activity Schedule. The Early Discontinuation visit should be performed as soon as possible, preferably within 2 weeks, after discontinuation from the study. Additional blood samples for drug measurement may be collected at the time of discontinuation from subjects who are discontinued due to adverse events; the clock time, time in relation to dose and date the sample was taken will be recorded.

If a subject is discontinued from the study with an ongoing adverse event or an unresolved laboratory result that is significantly outside of the reference range, the investigator will attempt to provide follow-up until a satisfactory clinical resolution of the laboratory result or adverse event is achieved.

In the event that a positive result is obtained on a pregnancy test for a subject or a subject reports becoming pregnant during the study, the administration of study drug to that subject must be discontinued immediately. The investigator must report a pregnancy within 1 working day of the site being aware to one of the AbbVie representatives listed in Section 1.

3.20 Unscheduled Visits

An unscheduled visit should be performed when the subject comes in for a medical visit for evaluation and assessment. During Unscheduled Visits, blood and urine samples may be obtained for the laboratory tests listed in Section 3, or for other tests, at the investigator's discretion.

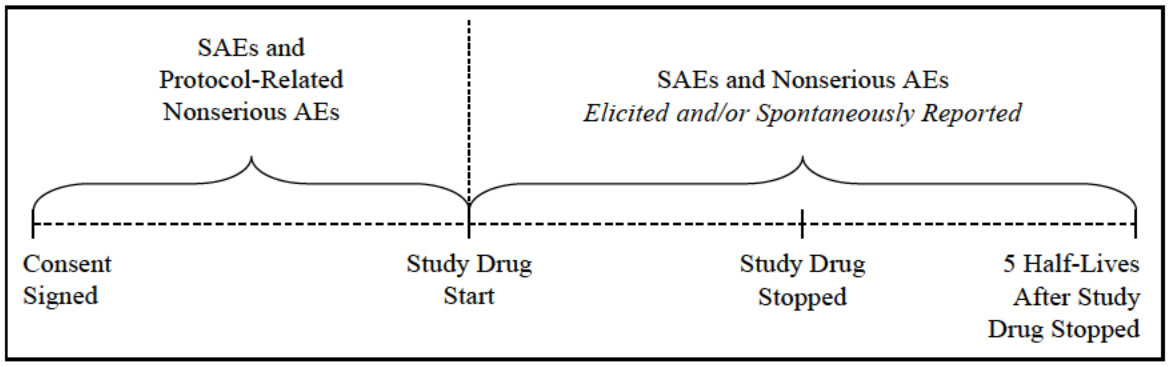
Visits to only retest a lab will not be considered an Unscheduled Visit.

4 SAFETY MANUAL

4.1 Methods and Timing of Safety Assessment

All adverse events reported from the time of study drug administration until 39 weeks (5 half-lives) following discontinuation of study drug administration have elapsed will be collected, whether elicited or spontaneously reported by the subjects. In addition, serious adverse events and protocol-related nonserious adverse events will be collected from the time the subject signed the study-specific informed consent.

Adverse event information will be collected as shown below.



Relapse Assessments

Any appropriate new neurological abnormality which is consistent with new or worsening neurological symptoms reported by the subject, which may or may not be accompanied by new findings in other systems, may qualify as a relapse. This also includes focal neurological dysfunction that may not be accompanied by objective neurological findings (e.g., change in sensory perception with myelitis or change in visual acuity/color perception with optic neuritis). Qualification as a relapse requires meeting the following criteria:

- A new or worsening neurological symptom or set of symptoms
- Occurring in the absence of fever
- Lasting for ≥ 24 hours
- Preceded by at least 30 days of clinical stability or improvement

Documentation and follow-up of each suspected relapse will be conducted throughout the study period with scheduled and unscheduled neurological assessments. Subjects will be instructed to inform the study site within 48 hours of the onset of relapse symptoms. When a subject calls to report a suspected relapse, the study site personnel will discuss the symptoms with the subject and determine whether a neurological assessment is indicated.

If so, an unscheduled visit to the study site should be arranged for the subject as quickly as possible, preferably within no more than seven (7) days of onset of relapse symptoms. During each suspected relapse, the blinded physician investigator will determine the nature of the relapse and conduct a full neurological assessment before reviewing previous neurological assessments. After completing the neurological assessment and the source document, the blinded physician investigator may then discuss the new neurological symptoms with the subject. The study nurse/coordinator may then provide the previous neurological examination document to the blinded physician investigator to help determine if a relapse has occurred and to assess its severity (based on revision of the current and previous neurological examinations and discussion with the subject about activities of daily living).

The blinded physician investigator will determine whether a relapse has occurred or not, and whether it will count as a qualifying relapse as defined above.

Subjects who experience a suspected MS relapse may be treated with intravenous (IV) methylprednisolone [redacted] for 1 to 5 consecutive days, or another corticosteroid or corticosteroid precursor regimen so long as consistent with good neurological practice. Subjects not currently receiving maintenance immunomodulators, must be counseled that immunomodulators have been demonstrated to significantly decrease relapse frequency. Site staff are to ensure eCRFs are completed capturing rescue concomitant medication and documenting relapse on the AE eCRF.

They will subsequently be handled as follows:

- Subjects may elect to receive no IV methylprednisolone or other corticosteroids/corticosteroid precursor as described above and not initiate maintenance immunosuppressive therapy. As stated above, they must be counseled that approved MS immunomodulators have been demonstrated to significantly decrease flare frequency in MS subjects. They will continue to receive elezanumab or placebo.
- Subjects may receive IV methylprednisolone [redacted] for 1 to 5 consecutive days (or other corticosteroids/corticosteroid precursor according to good neurological practice) but elect not to begin maintenance immunosuppressive therapy. They must be counseled that approved MS immunomodulators have been demonstrated to significantly decrease flare frequency in MS subjects. They will continue to receive elezanumab or placebo.
- Subjects may begin receiving an immunomodulator that is recommended by their treating physician and is considered to provide the best balance of benefit versus risk. If the prescribed

medication is one that is allowed in the protocol's Inclusion Criterion #10, the subject can continue in the trial. If another immunomodulator is prescribed, they will not receive further infusions and should be discontinued from the study.

In the event of a clinical MS relapse, a supplemental AE eCRF form should be completed (See Appendix C, Relapse Questionnaire).

Adverse Events of Special Interest (AESI)

Infusion Reactions

The investigator or qualified designee will evaluate the infusion site area from Week 0 – Baseline through the end of the study. Any observation of infusion site reaction after the start of infusion must be recorded as an adverse event (AE).

Further information on monitoring of elezanumab infusion reactions is presented in Appendix D.

Collection of Data Regarding Known Complications of the Disease Under Study

Natural progression of MS (including new or worsening neurological symptoms and signs) is expected in the subjects. Disease progression will be assessed at pre-determined intervals throughout the treatment period by standardized criteria (such as the EDSS+, MSIS-29 version 2, MFIS, MSIOA) and recorded within the electronic Clinical Outcome Assessments (eCOA) for risk/benefit determinations. Therefore, "disease progression" or other similar verbatim terms related to disease status SHOULD NOT be recorded on the AE case report form (CRF) pages. Falls will not be recorded as AEs unless they lead to other injury or represent a change in frequency or character from pre-randomization falls.

Similarly, the slow progression of pre-existing disease-related signs and symptoms clearly associated with the disease during the treatment period will not be reported as AEs unless these signs and symptoms are judged by the investigator to have become unusually severe or accelerated, or if the investigator suspects the deterioration of disease-related signs and symptoms to be potentially related to the investigational drug. If there is any uncertainty about the worsening of an AE being due solely to the disease under the treatment protocol, it should be reported as an AE or SAE as appropriate.

Discontinuation from this treatment protocol because of progression or deterioration of the disease should be recorded on the Study Completion eCRF page as discontinuation due to "disease progression" and NOT as discontinuation due to an AE.

4.2 Reporting Adverse Events and Intercurrent Illnesses

In the event of an SAE, whether associated with study drug or not, the investigator will notify Clinical Pharmacovigilance within 24 hours after the site becomes aware of the SAE by entering the SAE data into the electronic data capture (EDC) system. SAEs that occur before the site having access to the RAVE® system, or if RAVE is not operable, should be documented on the SAE non-CRF forms and emailed (preferred route) or faxed to Clinical Pharmacovigilance within 24 hours after the site becomes aware of the SAE.

Email: PPDINDPharmacovigilance@abbvie.com
FAX to: +1 (847) 938-0660

For safety concerns, contact the Neuroscience Safety Team at:

Neuroscience Safety Team Dept. R48S, Bldg. AP51-3
1 North Waukegan Road
North Chicago, Illinois 60064-6203
Office: +1 (847) 938-4191
Email: SafetyManagement_Neuroscience@abbvie.com

For any subject safety concerns, please contact the physician listed below:

Primary Therapeutic Area Medical Director
EMERGENCY MEDICAL CONTACT:
[redacted] **PhD**
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064-6203

Contact Information:

Office:
Mobile:
Mobile 2:
Email:
[redacted]

In emergency situations involving study subjects when the primary Therapeutic Area Medical Director is not available by phone, please contact the 24-hour AbbVie Medical Escalation Hotline where your call will be re-directed to a designated backup AbbVie Therapeutic Area Medical Director:

HOTLINE: +1 (973) 784-6402

The sponsor will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with Directive 2001/20/EC.

COVID-19 Pandemic-Related Acceptable Protocol Modifications

Supplemental study case report forms should be completed in the event of COVID-19-related missed/virtual visits, study drug interruptions or discontinuations, or adverse events (including capture of specific signs/symptoms of infection and testing results).

COVID-19 infections should be captured as adverse events. If the event meets the criteria for a serious adverse event (SAE), then follow the SAE reporting directions per the protocol and above. The following COVID-19-related supplemental eCRFs should be completed (for both serious and nonserious events):

- COVID-19 Supplemental Signs/Symptoms
- COVID-19 Status Form

If a subject has a confirmed or suspected COVID-19 infection and study drug was interrupted, the investigator should contact the sponsor emergency medical contact listed above before reintroducing study drug.

5 COUNTRY-SPECIFIC REQUIREMENTS

5.1 Sample Retention Requirements

AbbVie (or people or companies working with AbbVie) will store the biomarker samples and data in a secure storage space with adequate measures to protect confidentiality. The samples may be retained while research on elezanumab (or drugs of this class) or MS and related conditions continues, but for no longer than 20 years after study completion or according to local requirements.

5.2 SUSAR Reporting

AbbVie will be responsible for Suspected Unexpected Serious Adverse Reactions (SUSAR) reporting for the Investigational Medicinal Product (IMP) in accordance with global and local guidelines and Appendix A of the Investigator Brochure will serve as the Reference Safety Information (RSI). The RSI in effect at the start of a DSUR reporting period serves as the RSI during the reporting period. For follow-up reports, the RSI in place at the time of occurrence of the 'suspected' Serious Adverse Reaction will be used to assess expectedness.

5.3 Treatment After End of Study

For active subjects randomized to elezanumab or placebo, subjects will continue on study treatment throughout the study for a period of up to 52 weeks or until premature discontinuation of study drug. At the subject's last study visit, the investigator will discuss the appropriate subsequent treatment with the subject. AbbVie will not provide drug or any other therapy once the subject's participation is concluded.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
9HPT	9-hole peg test
ADA	Antidrug antibody
ADLs	Activities of daily living
AE	Adverse event
AESI	Adverse event of special interest
aPTT	Activated partial thromboplastin time
ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
BAC	Brief Assessment of Cognition
BMI	Body mass index
BUN	Blood urea nitrogen
ClinRo	Clinician reported outcome
COVID-19	Coronavirus Disease - 2019
CPK	Creatine phosphokinase
CRF	Case report form
CS	Clinically significant
C-SSRS	Columbia-Suicide Severity Rating Scale
D/C	Discontinuation
DNA	Deoxyribonucleic acid
ECG	Electrocardiogram
eCOA	Electronic Clinical Outcome Assessments
eCRF	Electronic case report form
EDC	Electronic data capture
EDSS	Expanded Disability Status Scale
EDSS +	Expanded Disability Status Scale Plus (EDSS +)
HBsAg	Hepatitis B surface antigen
HCV	Hepatitis C virus
HIV	Human immunodeficiency virus
IEC	Independent ethics committee
IMP	Investigational medical product
INR	International normalized ratio

IRB	Institutional review board
IRT	Interactive response technology
IV	Intravenous
LCVA	Low Contrast Visual Acuity
LLN	Lower limit of normal
MedDRA	Medical Dictionary for Regulatory Activities
MFIS-5	Modified Fatigue Impact Scale
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSIOA	Multiple Sclerosis Individualized Outcome Assessment
MSIS-29	Multiple Sclerosis Impact Scale
nAb	Elezanumab neutralizing antibody
NCS	Not clinically significant
PCS	Potentially clinically significant
PK	Pharmacokinetic(s)
PRO	Patient reported outcome
PT	Preferred term
RBC	Red blood cells
RNA	Ribonucleic acid
RSI	Reference safety information
SAE	Serious adverse event
SDMT	Symbol Digit Modalities Test
sEMG	Surface electromyography
SOC	System organ class
SUSAR	Suspected unexpected serious adverse reaction
TA MD	Therapeutic Area Medical Doctor
T25FW	Timed 25 Foot Walk
ULN	Upper limit of normal
WBC	White blood cell

APPENDIX B. CRITERIA FOR POTENTIALLY CLINICALLY SIGNIFICANT (PCS) VALUES FOR ELEZANUMAB STUDIES

CTCAE v4.0 Term*	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology						
Activated partial thromboplastin time prolonged (aPTT)	1	**> ULN**	> ULN – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN; hemorrhage	--
Hemoglobin decreased	2	**< 10.0 g/dL**	< LLN – 10.0 g/dL	< 9 – 8.0 g/dL	< 8.0 g/dL	Life-threatening consequences; urgent intervention indicated
		< 6.2 mmol/L	< LLN – 6.2 mmol/L	< 6.2 – 4.9 mmol/L	< 4.9 mmol/L	
		< 100 g/L	< LLN – 100 g/L	< 100 – 80 g/L	< 80 g/L; transfusion	
Hemoglobin increased	3	**> 4 gm/dL above ULN**	Increase in > 0 – 2 gm/dL above ULN or above baseline if baseline is above ULN	Increase in > 2 – 4 gm/dL above ULN or above baseline if baseline is above ULN	Increase in > 4 gm/dL above ULN or above baseline if baseline is above ULN	--
INR increased	1	**> ULN**	> 1 – 1.5 × ULN	> 1.5 – 2.5 × ULN	> 2.5 × ULN	--
			> 1 – 1.5 times above baseline if on anticoagulation	> 1.5 – 2.5 times above baseline if on anticoagulation	> 2.5 times above baseline if on anticoagulation	
Leukocytosis (WBC increased)	3	**> 100,000/mm^3**	--	--	> 100,000/mm^3	Clinical manifestations of leucostasis; urgent intervention indicated
Lymphocyte count decreased	3	**< 500/mm^3**	< LLN – 800/mm^3	< 800 – 500/mm^3	< 500 – 200/mm^3	< 200/mm^3
		< 0.5 × 10^9/L	< LLN – 0.8 × 10^9/L	< 0.8 – 0.5 × 10^9/L	< 0.5 – 0.2 × 10^9/L	< 0.2 × 10^9/L
Lymphocyte count increased	3	**> 20,000/mm^3**	--	> 4000 – 20,000/mm^3	> 20,000/mm^3	--

CTCAE v4.0 Term*	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Hematology (continued)						
Neutrophil count decreased	3	**< 1000/mm³**	< LLN – 1500/mm³	< 1500 – 1000/mm³	< 1000 – 500/mm³	< 500/mm³
		< 1.0 × 10⁹/L	< LLN – 1.5 × 10⁹/L	< 1.5 – 1.0 × 10⁹/L	< 1.0 – 0.5 × 10⁹/L	< 0.5 × 10⁹/L
Platelet count decreased	2	**< 75,000/mm³**	< LLN – 75,000/mm³	< 75,000 – 50,000/mm³	< 50,000 – 25,000/mm³	< 25,000/mm³
		< 75.0 × 10⁹/L	< LLN – 75.0 × 10⁹/L	< 75.0 – 50.0 × 10⁹/L	< 50.0 – 25.0 × 10⁹/L	< 25.0 × 10⁹/L
White blood cell decreased	3	**< 2000/mm³**	< LLN – 3000/mm³	< 3000 – 2000/mm³	< 2000 – 1000/mm³	< 1000/mm³
		< 2.0 × 10⁹/L	< LLN – 3.0 × 10⁹/L	< 3.0 – 2.0 × 10⁹/L	< 2.0 – 1.0 × 10⁹/L	< 1.0 × 10⁹/L
Chemistry						
Blood bilirubin increased	2	**> 1.5 × ULN**	> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 10.0 × ULN	> 10.0 × ULN
Cholesterol high	4	**> 500 mg/dL**	> ULN – 300 mg/dL	> 300 – 400 mg/dL	> 400 – 500 mg/dL	> 500 mg/dL
		> 12.92 mmol/L	> ULN – 7.75 mmol/L	> 7.75 – 10.34 mmol/L	> 10.34 – 12.92 mmol/L	> 12.92 mmol/L
Creatinine increased	2	**> 1.5 × ULN**	> 1 – 1.5 × baseline	> 1.5 – 3.0 × baseline	> 3.0 baseline	> 6.0 × ULN
			> ULN – 1.5 × ULN	> 1.5 – 3.0 × ULN	> 3.0 – 6.0 × ULN	
GGT increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN

CTCAE v4.0 Term*	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
		Corrected Serum Calcium of:				
Hypercalcemia	3	**> 12.5 mg/dL**	> ULN – 11.5 mg/dL	> 11.5 – 12.5 mg/dL	> 12.5 – 13.5 mg/dL	> 13.5 mg/dL
		> 3.1 mmol/L	> ULN – 2.9 mmol/L	> 2.9 – 3.1 mmol/L	> 3.1 – 3.4 mmol/L	> 3.4 mmol/L
		Ionized Calcium				
		> 1.6 mmol/L	> ULN – 1.5 mmol/L	> 1.5 – 1.6 mmol/L; symptomatic	> 1.6 – 1.8 mmol/L; hospitalization indicated	> 1.8 mmol/L; life-threatening consequences
			Fasting Glucose Value			
Hyperglycemia	3	**> 250 mg/dL**	> ULN – 160 mg/dL	> 160 – 250 mg/dL	> 250 – 500 mg/dL	> 500 mg/dL
		> 13.9 mmol/L	> ULN – 8.9 mmol/L	> 8.9 – 13.9 mmol/L	> 13.9 – 27.8 mmol/L; hospitalization indicated	> 27.8 mmol/L; life-threatening consequences
Hyperkalemia	3	**> 6.0 mmol/L**	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L; hospitalization indicated	> 7.0 mmol/L; life-threatening consequences
Hypermagnesemia	3	**> 3.0 mg/dL**	> ULN – 3.0 mg/dL	--	> 3.0 – 8.0 mg/dL	> 8.0 mg/dL
		> 1.23 mmol/L	> ULN – 1.23 mmol/L		> 1.23 – 3.30 mmol/L	> 3.30 mmol/L; life-threatening consequences
Hypernatremia	3	**> 155 mmol/L**	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L; hospitalization indicated	> 160 mmol/L; life-threatening consequences

CTCAE v4.0 Term*	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
Hypertriglyceridemia	3	**> 500 mg/dL**	150 – 300 mg/dL	> 300 – 500 mg/dL	> 500 – 1000 mg/dL	> 1000 mg/dL
		> 5.7 mmol/L	1.71 – 3.42 mmol/L	> 3.42 – 5.7 mmol/L	> 5.7 – 11.4 mmol/L	> 11.4 mmol/L; life-threatening consequences
Hyperuricemia (Uric Acid Increased)	4	**> 10 mg/dL**	> ULN – 10 mg/dL (0.59 mmol/L) without physiologic consequences	--	> ULN – 10 mg/dL (0.59 mmol/L) with physiologic consequences	> 10 mg/dL
		> 0.59 mmol/L				> 0.59 mmol/L; life-threatening consequences
Hypoalbuminemia	3	**< 2 g/dL**	< LLN – 3 g/dL	< 3 – 2 g/dL	< 2 g/dL	Life-threatening consequences; urgent intervention indicated
		< 20 g/L	< LLN – 30 g/L	< 30 – 20 g/L	< 20 g/L	
		Corrected Serum Calcium				
Hypocalcemia	3	**< 7.0 mg/dL**	< LLN – 8.0 mg/dL	< 8.0 – 7.0 mg/dL	< 7.0 – 6.0 mg/dL	< 6.0 mg/dL
		< 1.75 mmol/L	< LLN – 2.0 mmol/L	< 2.0 – 1.75 mmol/L	< 1.75 – 1.5 mmol/L	< 1.5 mmol/L
		Ionized Calcium				
		< 0.9 mmol/L	< LLN – 1.0 mmol/L	< 1.0 – 0.9 mmol/L; symptomatic	< 0.9 – 0.8 mmol/L; hospitalization indicated	< 0.8 mmol/L; life-threatening consequences
Hypoglycemia	3	**< 40 mg/dL**	< LLN – 55 mg/dL	< 55 – 40 mg/dL	< 40 – 30 mg/dL	< 30 mg/dL
		< 2.2 mmol/L	< LLN – 3.0 mmol/L	< 3.0 – 2.2 mmol/L	< 2.2 – 1.7 mmol/L	< 1.7 mmol/L; life-threatening consequences; seizures

CTCAE v4.0 Term*	PCS Value/ Grade	PCS Value	Grade 1	Grade 2	Grade 3	Grade 4
Chemistry (continued)						
Hypokalemia	3	**< 3.0 mmol/L**	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L; hospitalization indicated	< 2.5 mmol/L; life-threatening consequences
Hypomagnesemia	3	**< 0.9 mg/dL**	< LLN – 1.2 mg/dL	< 1.2 – 0.9 mg/dL	< 0.9 – 0.7 mg/dL	< 0.7 mg/dL
		< 0.4 mmol/L	< LLN – 0.5 mmol/L	< 0.5 – 0.4 mmol/L	< 0.4 – 0.3 mmol/L	< 0.3 mmol/L; life-threatening consequences
Hyponatremia	3	**< 130 mmol/L**	< LLN – 130 mmol/L	--	< 130 – 120 mmol/L	< 120 mmol/L; life-threatening consequences
Hypophosphatemia	3	**< 2.0 mg/dL**	< LLN – 2.5 mg/dL	< 2.5 – 2.0 mg/dL	< 2.0 – 1.0 mg/dL	< 1.0 mg/dL
		< 0.6 mmol/L	< LLN – 0.8 mmol/L	< 0.8 – 0.6 mmol/L	< 0.6 – 0.3 mmol/L	< 0.3 mmol/L; life-threatening consequences
Enzymes						
Alanine aminotransferase (ALT) increased	2	**> 3 × ULN**	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Alkaline phosphatase increased	2	**> 2.5 × ULN**	> ULN – 2.5 × ULN	> 2.5 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
Aspartate aminotransferase (AST) increased	2	**> 3 × ULN**	> ULN – 3.0 × ULN	> 3.0 – 5.0 × ULN	> 5.0 – 20.0 × ULN	> 20.0 × ULN
CPK increased	3	**> 5 × ULN**	> ULN – 2.5 × ULN	> 2.5 × ULN – 5 × ULN	> 5 × ULN – 10 × ULN	> 10 × ULN

Adapted from the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 Published: May 28, 2009 (v4.03: June 14, 2010)

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Criteria for Potentially Clinically Significant (PCS) Vital Sign Values for Elezanumab Studies

Vital Signs Variables	Criterion	Potentially Clinically Significant (PCS) Value
Systolic blood pressure (mm Hg)	Low	≤ 90 mm Hg and decrease ≥ 20 mm Hg from Baseline
	High	≥ 180 mm Hg and increase ≥ 20 mm Hg from Baseline
Diastolic blood pressure (mm Hg)	Low	≤ 50 mm Hg and decrease ≥ 15 mm Hg from Baseline
	High	≥ 105 mm Hg and increase ≥ 15 mm Hg 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

APPENDIX C. MS RELAPSE QUESTIONNAIRE

1. **Adverse Event Serial number:**_____
2. **Provide Individual Symptom(s) (New or increasing MS symptoms from baseline):**

   _____

   _____

   _____

   _____

   _____

3. **Diagnosis made by:** □ Symptoms □ MRI □ Both MRI and Symptoms
4. **Change in Neurological Examination from baseline consistent with MS relapse?** □ Yes □ No
5. **Have the symptoms lasted at least 24 hours?** □ Yes □ No
6. **Have the symptoms occurred in the absence of fever?** □ Yes □ No
7. Has it been more than 30 days since the prior relapse? □ Yes □ No
8. **Is there an alternative etiology for symptoms beside MS Relapse?** □ Yes □ No
9. **Narrative for course of event for symptom(s) recorded above. Include details of neurological findings, treatment, and response as applicable.** Treatment medications should also be entered into the Concomitant Medication eCRF.

   _____

   _____

   _____

   _____

   _____

10. Date Review Completed by MS Relapse Adjudication Committee (RAC) _____
11. RAC panel confirmed MS Relapse? □ Yes □ No

APPENDIX D. CRITERIA FOR MONITORING ELEZANUMAB INFUSION REACTIONS

Infusion Reactions

Potential infusion reactions have been observed in the Phase 1b Study M14-173, though no reactions were consistent with anaphylaxis or required medical intervention. Subjects will be closely monitored for treatment-related adverse events, especially infusion reactions during all study drug infusions.

Treatment of Infusion Reactions

Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms. In the event of a suspected infusion/anaphylactic reaction, in addition to the standard AE and Concomitant Medication eCRFs, a supplemental AESI eCRF should also be completed by site staff.

Reflexive Testing Following Infusion Reactions

If any infusion or suspected allergic-type reaction is observed, a blood draw is required within 2 hours after the first sign of a reaction for the following laboratory tests:

- C3a, C5 complement functional assay, IgE level, and serum tryptase level.

Anaphylactic Infusion Reactions

In the event of an anaphylactic reaction, blood samples will be drawn after the onset of the reaction for: histamine and tryptase. A blood sample for serum anti-drug antibody (ADA) assessment will also be collected within 2 hours of onset of anaphylactic reaction along with 1 hour blood samples for C3a, C5 complement functional assay, IgE level, and serum tryptase level. Separate instructions for the collection, handling, storage and shipping of these lab samples will be provided in the Covance Laboratory Manual.

Moderate Infusion Reactions

In situations where an infusion reaction occurs before the end of infusion and leads to clinically significant vital signs, skin or persistent gastrointestinal symptoms, treatment should be immediately interrupted. Once symptoms have resolved, re-initiating treatment is allowed with an infusion over 180 minutes. If infusion reactions persist despite the use of extended infusion times and medication, sites should contact the Therapeutic Area Medical Director regarding continued subject eligibility.

In the event of a suspected infusion/anaphylactic reaction, in addition to the standard AE eCRF, a supplemental AESI eCRF should also be completed by the site.