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Protocol for Study M14-397

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

VERSION:	5.0	DATE:	19 March 2021
SPONSOR:	AbbVie*	NUMBER OF SITES:	Approximately 30
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 Progressive Forms of Multiple Sclerosis

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

PRINCIPAL INVESTIGATOR(S): Investigator information on file at AbbVie.

SPONSOR/EMERGENCY MEDICAL CONTACT:*

[redacted]
AbbVie
[redacted]
1 North Waukegan Road
North Chicago, IL 60064-6203

Office:
Mobile:
Mobile 2:
Email:
[redacted]
EMERGENCY 24 hour Number: +1 973-784-6402

*The specific contact details of the AbbVie legal/regulatory entity (person) within the relevant country are provided within the clinical trial agreement with the Investigator/Institution and in the Clinical Trial Application with the Competent Authority. Additional study contact information is located in the Operations Manual (Appendix F).

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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 Progressive 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 progressive forms of multiple sclerosis (PMS). 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)
Investigators:	Multicenter
Study Sites:	Approximately 30 sites in the United States and Canada
Study Population and Number of Subjects to be Enrolled:	Approximately 90 subjects with PMS (approximately 60 primary-progressive MS [PPMS] subjects and approximately 30 secondary-progressive MS [SPMS] 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 PMS.
Key Eligibility Criteria:	Adult male or female, between 18 and 65 years of age, inclusive, with a diagnosis of PPMS or non-relapsing SPMS according to the 2017 revised McDonald criteria, and evidence of physical disability (EDSS score of 2 to 6.5 or T25FW ≥ 8 sec or 9HPT ≥ 33 sec) and no relapses for at least 24 months.
Study Drug and Duration of Treatment:	Eligible subjects will be randomized at the Week 0 - Baseline Visit to receive either elezanumab [redacted] or [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:	19 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 progressive forms of MS (Progressive forms of multiple sclerosis [PMS]) 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 PMS.

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 PMS.

3.2 Primary Endpoint

Primary endpoint:

Mean Overall Response Score (ORS) at Week 52.

Overall Response Score 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 progressive 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] or [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.

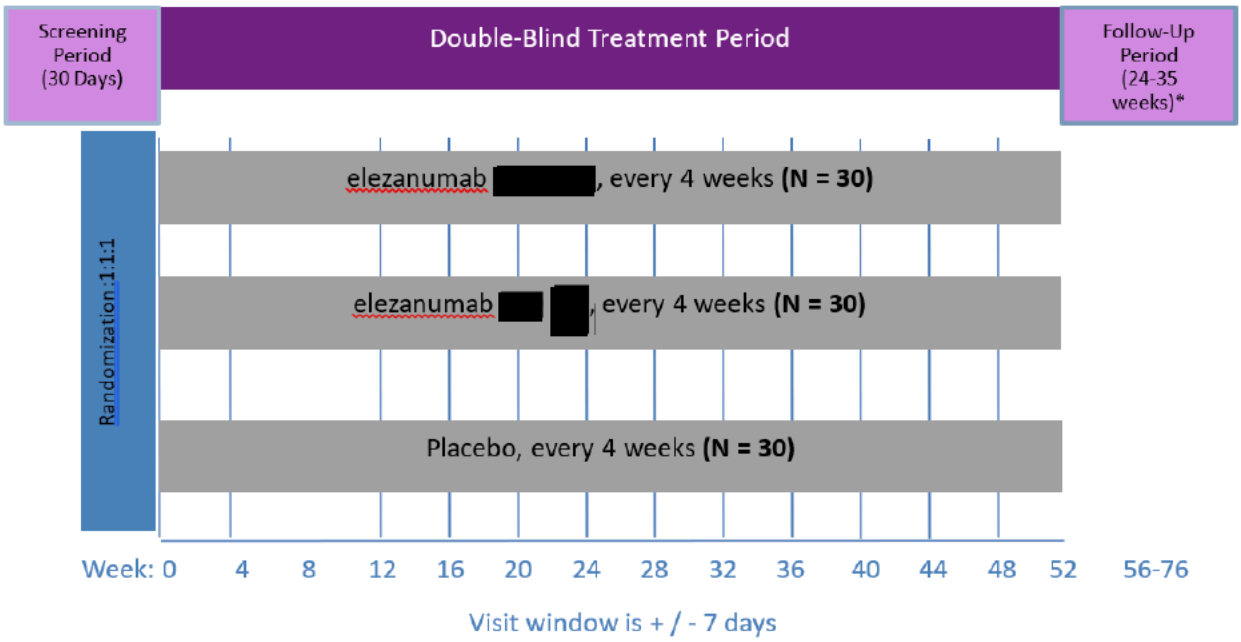
Subjects who discontinue should complete the procedures outlined for the Early Discontinuation (ED) visit as soon as possible, preferably within 2 weeks (Section 5.5 and Section 5.6).

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. Period 1 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 PMS 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 for 6 months. Subjects with PMS must have been relapse-free (RF) for at least 24 months.

Selection of Doses in the Study

The dose levels of [redacted] and [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] mg 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 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 two 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 2 MS relapses that occurred in 1 subject receiving placebo and another receiving [redacted] elezanumab.

Two prespecified 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] 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), siponimod (Mayzent), 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 primary-progressive MS (PPMS) or secondary-progressive MS (SPMS) according to the 2017 revised McDonald criteria and has a brain MRI demonstrating lesion(s) consistent with MS.

8. Not experiencing or recovering from a MS clinical relapse (reported by subject as diagnosed by a medical professional) within 24 months of Screening.

9. 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)

10. 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

- 11. 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

- 12. 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.
- 13. **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.
- 14. 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 [redacted] for at least 6 months, or a level less than [redacted] 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 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/independent review board (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 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 90 subjects will be equally randomized 1:1:1 to each treatment group (30 subjects in each treatment group, with a target of 20 PPMS subjects and approximately 10 SPMS subjects per treatment group). There is 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 (primary-progressive [PPMS], 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
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
ITT	Intent-to-treat
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)
PLP1	proteolipid protein 1
PMS	Progressive forms of multiple sclerosis
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
RNA	Ribonucleic acid
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 M14-397: A Randomized, Double-Blind, Placebo-Controlled, Multiple Dose Study to Assess the Safety and Efficacy of Elezanumab when Added to Standard of Care in Progressive Forms of Multiple Sclerosis

Protocol Date: 19 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		✓																					

	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**
Local urine pregnancy test	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
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	03 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.