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Protocol for Study M19-148

Stroke: The Safety and Efficacy of Elezanumab in Acute Ischemic Stroke

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FULL TITLE: A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study to Assess the Safety and Efficacy of Elezanumab in Acute Ischemic Stroke

Incorporating Versions 1.0, 2.0, and 3.0

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1 SYNOPSIS

Title: A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study to Assess the Safety and Efficacy of Elezanumab in Acute Ischemic Stroke	
Background and Rationale:	Elezanumab is an investigational product under development for improvement of neurologic function in patients with acute ischemic stroke. Treatment of acute ischemic stroke patients with elezanumab has the potential to accelerate recovery and/or provide more complete recovery by decreasing neuronal damage and enhancing restoration of neuronal activity.
Objectives and Endpoints:	The objectives are to assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of elezanumab in subjects with acute ischemic stroke. The primary endpoint is the National Institutes of Health Stroke Scale (NIHSS) total score during the Treatment Period. The secondary endpoint is a favorable outcome based on the modified Rankin Scale (mRS) at Week 52. A favorable outcome is defined as having an mRS score of 0, 1, or 2 at the specified time point.
Investigator(s):	Multicenter
Study Site(s):	Approximately 45 sites in multiple countries.
Study Population and Number of Subjects to be Enrolled:	Adult male or female, 30 to 90 years of age, inclusive, with a clinical diagnosis of acute ischemic stroke in anterior circulation and able to randomize within 24 hours of "last known normal" (the time before hospital arrival at which time the subject was last known to be without the signs and symptoms of the current stroke or at his or her baseline state of health), supported by acute brain computed tomography (CT) or magnetic resonance imaging (MRI). Approximately 120 subjects will be randomized to receive elezanumab 1800 mg or placebo in a 1:1 ratio.
Investigational Plan:	This is a 52-week, Phase 2a, randomized, double-blind, parallel-group, placebo-controlled, multicenter proof-of concept study to evaluate the safety and efficacy of elezanumab in subjects with acute ischemic stroke. The Screening Period is up to 24 hours since last known normal, with study drug administration as soon as possible but no later than 6 hours after randomization. Treatment with intravenous (IV) tissue plasminogen activator (tPA) and/or endovascular therapy (EVT) will be allowed before randomization and will be recorded as a concomitant therapy. Randomization will be stratified by IV tPA use (yes/no), by EVT use (yes/no), and by time since last known normal (≤ 11 hours or > 11 hours). The proportion of subjects enrolled who have EVT is targeted to be up to approximately 50% of the study population. A target of approximately 25% to 50% of subjects may be randomized within the time window of ≤ 11 hours since last known normal. The

	proportion of subjects who enroll > 80 to 90 years of age is targeted to be up to approximately 30% of the study population. Eligible subjects will be randomized in a 1:1 ratio to receive either elezanumab 1800 mg or placebo as an IV infusion.
Key Eligibility Criteria:	Adult male or female, between 30 and 90 years of age, inclusive, with a clinical diagnosis of acute ischemic stroke in anterior circulation and able to randomize within 24 hours of "last known normal" supported by acute brain CT or MRI consistent with the clinical diagnosis, and available in subject history. NIHSS total score of 7 to 21, inclusive. NIHSS eligibility must be confirmed within 1 hour before randomization. For subjects treated with IV tPA and/or EVT, NIHSS must be confirmed ≥ 1 hour after completion of all treatments. No evidence of acute seizure at the onset of index stroke unless imaging conclusively demonstrates acute ischemic stroke. No known history of repeated episodes of complex migraine unless imaging conclusively demonstrates acute ischemic stroke. In the judgment of the investigator, symptoms are not considered likely to resolve within the subsequent few hours (e.g., transient ischemic attack [TIA]). No contraindication or inability to tolerate brain MRIs (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
Study Drug and Duration of Treatment:	Eligible subjects will be randomized in a 1:1 ratio to receive either elezanumab 1800 mg or placebo as an IV infusion. Study drug must be administered as soon as possible but no later than 6 hours after randomization and every 4 weeks thereafter through Week 48 for a total of 13 doses. The final double-blind Treatment Period study visit will be at Week 52. Subjects will have 2 post-treatment follow-up visits at 12 and 24 weeks after last dose of study drug.
Date of Protocol Synopsis:	25 March 2022

2 INTRODUCTION

2.1 Background and Rationale

Why Is This Study Being Conducted

Elezanumab is a monoclonal antibody of the human immunoglobulin (Ig) G1 isotype that binds specifically to repulsive guidance molecule A (RGMa). RGMa is a potent inhibitor of neurite outgrowth and, through combined activation of neogenin and bone morphogenetic protein (BMP), is recognized as an important factor in inhibiting neuronal regeneration and functional recovery following central nervous system damage. RGMa accumulates in infarcted regions following ischemic stroke and is associated with limited axonal growth. Neutralization of RGMa is a novel approach that may potentially lead to neuroregeneration (improved neuronal repair), neuroprotection (reduced neuronal damage), and neurorestoration as reflected by functional recovery.

Elezanumab and its parental antibodies, AE12-1 and AE12-1Y, have shown neuroprotective and neurorestorative effects in several animal models of chronic and acute neurologic injury, including rodent experimental autoimmune encephalitis models, rat optic nerve crush and optic neuritis, and a rabbit model of permanent middle cerebral artery occlusion (pMCAO). Thus, it is hypothesized that elezanumab may improve functional recovery following stroke by neutralizing RGMa, hence relieving inhibition of neural repair and enhancing neuroplasticity. Elezanumab is currently being evaluated for enhancement of functional recovery in patients with acute traumatic cervical spinal cord injury and was previously assessed for improvement of physical function in patients with relapsing and progressive forms of multiple sclerosis (MS).

Stroke is one of the top causes of death and major functional disability worldwide. Treatment options for acute ischemic stroke are limited and primarily focus on timely clot removal to restore circulation. A small proportion of patients are eligible for tissue plasminogen activator (tPA) and/or endovascular therapy (EVT). However, treatment response is incomplete for many patients, and even patients who respond to treatment may have residual neurologic impairment.[1] A novel treatment like elezanumab, with a potentially neurorestorative mechanism of action, may improve neurologic function, and represents a significant advance in available treatment options for patients suffering from acute ischemic stroke.

Elezanumab is an investigational product under development for improvement of neurologic function in patients with acute ischemic stroke. Treatment of acute ischemic stroke patients with elezanumab has the potential to accelerate recovery and/or provide more complete recovery by decreasing neuronal damage and enhancing restoration of neuronal activity.

2.2 Benefits and Risks to Subjects

Safety and efficacy data from the nonclinical and clinical elezanumab programs support development of elezanumab in subjects with acute ischemic stroke.

The toxicity of elezanumab was evaluated in Good Laboratory Practice (GLP) and non-GLP studies in rats and cynomolgus monkeys following intravenous (IV) administration of up to 26 weeks with a 15-week

recovery phase. No adverse findings were detected at any of the dosages administered in repeat-dose toxicity studies (up to 200 mg/kg) in rats and monkeys. Nonclinical data indicate consistent elezanumab treatment-related improvements in motor scores versus control in numerous animal models of neural injury. Neurorestoration of motor function was supported by evidence of repair on imaging, including remyelination and axonal regrowth.

The safety of elezanumab has been assessed in two Phase 1 clinical studies to date, in which 35 healthy subjects and 15 MS patients have been exposed to elezanumab. Study M14-141 was an escalating single-dose study in healthy subjects. Study M14-173 was an escalating multiple-dose study (4 doses administered every 4 weeks) in subjects with relapsing forms of MS. For both studies, the regimens tested were generally well tolerated by the subjects. There were no treatment-related serious adverse events (SAEs). No clinically significant vital signs or laboratory measurements were observed during the course of the studies.

For further details, please see findings from completed studies, including safety data in the current elezanumab Investigator's Brochure (IB).[2]

An external independent Data Monitoring Committee (DMC) will conduct unblinded reviews of safety and select efficacy data through the conduct of the study. A separate DMC Charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and expectations for blinded communications.

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 event (AEs) will be made on a case-by-case basis with consideration of benefit/risk. However, based on 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 acute ischemic stroke, no change to the benefit/risk balance for subjects in this study is expected.

3 OBJECTIVES AND ENDPOINTS

To assess the efficacy, safety, tolerability, and pharmacokinetics (PK) of elezanumab in subjects with acute ischemic stroke.

3.1 Primary Endpoint

The primary endpoint is the National Institutes of Health Stroke Scale (NIHSS) total score during the Treatment Period. The primary analysis will be a comparison of a model-based area under the curve (AUC) of the NIHSS total score between elezanumab and placebo.

3.2 Secondary Endpoint

The secondary endpoint is a favorable outcome based on the modified Rankin Scale (mRS) at Week 52. A favorable outcome is defined as having an mRS score of 0, 1, or 2 at the specified time point.

3.4 Safety Endpoints

Safety evaluations include AE monitoring, adverse events of special interest (AESI) monitoring, physical examinations, neurological 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 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 Pharmacodynamic Biomarker Endpoints

Blood Biomarkers

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.

Blood samples will be collected to assess the effects of elezanumab on biomarkers of stroke, inflammation, and neurodegeneration, which may include, but are not limited to, levels of RGMa, matrix metalloproteinase-9 (MMP-9), interleukin-6 (IL-6), interleukin-10 (IL-10), and neurofilament light chain (NfL).

This research is exploratory in nature and the results may not be included with the clinical study report. The samples may be retained for no longer than 20 years after study completion or per local requirements.

Brain MRI

Brain MRI scans will be obtained for all subjects at Baseline (collected up to 4 days after randomization) and follow-ups (Week 4 and Week 52). Images will be analyzed to assess infarct (ischemic core and penumbra) and presence of microstructural damage related to myelin loss and axonal destruction.

3.7 Exploratory Research

Optional pharmacogenetic samples may be collected to conduct exploratory investigations into additional known and novel biomarkers. The types of biomarkers to be analyzed may include, but are not limited to nucleic acids, proteins, lipids, or metabolites.

Biomarker assessments may be used to assess and generate prognostic, predictive, pharmacodynamic, or surrogate biomarker signatures. These assessments may be explored in the context of acute ischemic stroke or related conditions and/or elezanumab or drugs of similar classes. The results from these analyses are exploratory in nature and will not be included with the clinical study report.

The samples may also be used to develop new therapies, research methods, or technologies. In addition, samples from this study may be stored for future use. Samples may be used to validate putative biomarker signatures obtained from a prospective study, leading to the development of diagnostic tests. The samples may be retained for no longer than 20 years after study completion or per local requirements.

4 INVESTIGATIONAL PLAN

4.1 Overall Study Design and Plan

This is a 52-week, Phase 2a, randomized, double-blind, parallel-group, placebo-controlled, multicenter proof-of concept study to evaluate the safety and efficacy of elezanumab in subjects with acute ischemic stroke.

The schematic of the study is shown in Figure 1. Further details regarding study procedures are located in the Operations Manual (Appendix F). Also see Section 5 for information regarding eligibility criteria.

The Screening Period is up to 24 hours since "last known normal" (the time before hospital arrival at which the subject was last known to be without the signs and symptoms of the current stroke or at his or her baseline state of health). Treatment with IV tPA and/or EVT will be allowed before randomization and will be recorded as a concomitant therapy.

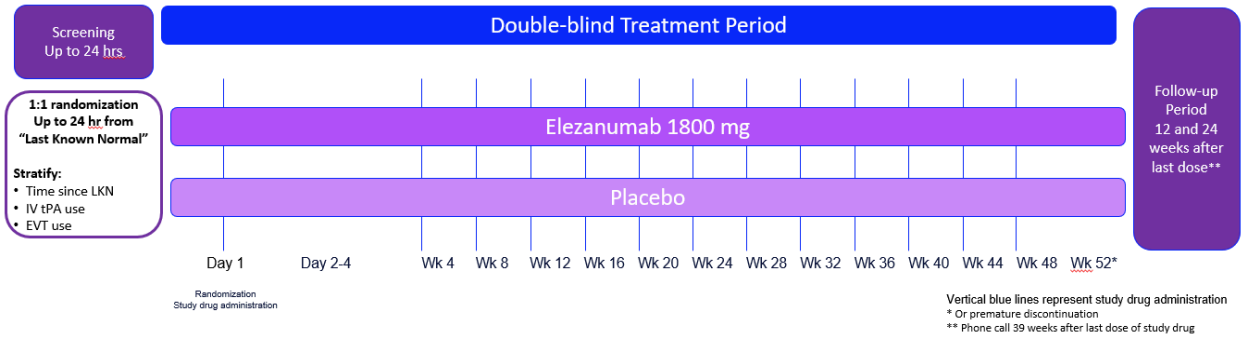
Randomization will be stratified by IV tPA use (yes/no), by EVT use (yes/no), and by time since last known normal (≤ 11 hours or > 11 hours). The proportion of subjects enrolled who have EVT is targeted to be up to approximately 50% of the study population. A target of approximately 25% to 50% of subjects may be randomized within the time window of ≤ 11 hours since last known normal. Lastly, the proportion of subjects who enroll > 80 to 90 years of age is targeted to be up to approximately 30% of the study population. Eligible subjects will be randomized in a 1:1 ratio to receive either elezanumab 1800 mg or placebo as an IV infusion.

Administration of blinded study drug must be initiated as soon as possible but no later than 6 hours after randomization and done every 4 weeks thereafter through Week 48 for a total of 13 doses. The final double-blind Treatment Period study visit will be at Week 52. Subjects will have 2 post-treatment follow-up visits at 12 and 24 weeks after last dose of study drug, and a final follow-up phone call 39 weeks (5 half-lives) after last dose of study drug. All follow-up visits beginning at Week 4 during the Treatment Period and Follow-up Period will be allowed a window of ± 7 days, and study procedures may be conducted over a period of 2 days. Unblinded safety data will be reviewed by an external DMC per the DMC Charter.

Final efficacy analyses will be performed after the last subject completes the Week 52 visit. Final safety analyses will be performed following completion of the post-treatment period and database lock.

Study sites and subjects will remain blinded through the duration of the study.

Figure 1. Study Schematic



EVT = endovascular therapy; hr(s) = hour(s); IV = intravenous; LKN = last known normal; tPA = tissue plasminogen activator; Wk = week

4.2 Discussion of Study Design

Choice of Control Group

Approximately 120 subjects will be randomized to elezanumab 1800 mg or placebo in a 1:1 ratio. Use of placebo as a control is appropriate since participation in the study does not preclude subjects from receiving standard-of-care treatment for acute ischemic stroke including thrombolytic therapy and EVT.

Appropriateness of Measurements

Standard clinical and laboratory procedures will be utilized in this study. All patient-reported outcome (PRO) and clinician-measured scales are standard for assessing stroke severity and recovery in subjects with acute ischemic stroke. All clinical and laboratory procedures in this study are standard and generally accepted.

Suitability of Subject Population

This study will enroll subjects with acute ischemic stroke with an NIHSS total score of 7 to 21, inclusive, who are expected to have residual functional impairment following recovery after standard-of-care

treatment, and thus have the capacity to show a treatment effect in this initial proof-of-concept study. Subjects with milder stroke (as determined by NIHSS score or imaging) may experience notable spontaneous recovery, while subjects with more profound stroke have substantially increased risk of death and permanent disability and may be more likely to discontinue prematurely.

Inclusion of subjects who were treated with IV tPA and/or EVT will allow for assessment of the safety and efficacy of elezanumab in a patient population more aligned with current standard of care for acute ischemic stroke. To maintain the ability to detect a potential treatment effect, subjects treated with IV tPA and/or EVT will be required to have an NIHSS total score of 7 to 21, inclusive, at least 1 hour after completion of the treatment(s). From a safety perspective, there are no expected pharmacokinetic or pharmacodynamic interaction between elezanumab and IV tPA or EVT. Additionally, subjects are required to have no evidence of intracranial hemorrhage to minimize risk to subjects in the study.

Timing and Duration of Treatment

Published literature shows that levels of RGMa peak within 1 day of ischemic stroke and remain elevated through multiple months post-stroke.[3] Preclinical data indicate that elezanumab was more effective when administered acutely after occlusion in the rabbit pMCAO model. Therefore, subjects will be randomized within 24 hours since last known normal and must be treated as soon as possible, but no later than 6 hours after randomization. Subjects will be treated for 48 weeks to assess the temporal profile of elezanumab. The influence of time of the initial elezanumab treatment will be explored by stratifying randomization by time since last known normal.

Selection of Doses in the Study

The dose level of 1800 mg every 4 weeks for this study was selected based on safety and biomarker data from 2 Phase 1 clinical studies (Study M14-141 and Study M14-173), as well as data from 2 preclinical experiments that suggested efficacy in the corresponding human-equivalent dose range.

Efficacious concentrations of elezanumab in the rabbit model were roughly 2x higher than those found to be safe and well tolerated in a multiple-dose Phase 1 study in MS patients at doses from 150 mg to 1800 mg every 4 weeks for 4 months, and there were no adverse drug-related side effects observed in the rabbit model.

In Study M14-141, single doses of up to 1600 mg were administered to healthy volunteers. In Study M14-173, single doses of up to 3600 mg (1800 mg infusions on 2 consecutive days) and monthly doses of up to 1800 mg were administered to MS patients for up to 4 months. In both Phase 1 studies, the most common AE was headache, which is considered to be at least possibly related to elezanumab. This dose was also studied in the MS Phase 2 studies (Study M14-397 and Study M18-918) with no emerging safety signal.

Two prespecified cerebrospinal fluid (CSF) biomarkers demonstrated a concentration-response relationship in the Phase 1 studies. In Study M14-173, the maximum CSF reduction in soluble RGMa was achieved in the 1800 mg dose group. 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 with elezanumab treatment in the high dose group (1800 mg monthly). These data suggest a clinically relevant, dose-related pharmacodynamic effect. The 1800 mg dose is predicted to result in human exposure within the range of that observed in preclinical stroke models where efficacy was observed.

Therefore, for the current proof-of-concept study, an elezanumab dose of 1800 mg every 4 weeks is justified to maximize the potential for detection of a clinical signal.

5 STUDY ACTIVITIES

5.1 Eligibility Criteria

Subjects must meet all of the following criteria in order to be included in the study.

Consent

- 1. Subjects or their legally authorized representative must voluntarily provide informed consent before the initiation of any study-specific procedure in a form approved by an independent ethics committee (IEC)/institutional review board (IRB). In the absence of subject's ability to provide informed consent, informed consent must be given by a person who has the legal right to act on behalf of the subject in accordance with local laws.

Demographic Assessments

- 2. Adult male or female, 30 to 90 years of age, inclusive.
- 3. Able to be randomized within 24 hours of last known normal.
- 4. Subjects and caregivers (if applicable) are willing and able to comply with procedures required in this protocol.
- 5. In the opinion of the investigator, subject is likely to be available for follow up for the duration of the study (e.g., stable residential address).

Stroke Diagnosis

- 6. Clinical diagnosis of acute ischemic stroke supported by acute brain computed tomography (CT) or MRI consistent with the clinical diagnosis.
  - Evidence of infarct within anterior circulation based on either clinical assessment and/or acute imaging.
  - Subjects who undergo MRI as part of standard of care must have evidence of an infarct diameter ≥ 2 cm, as measured by diffusion-weighted imaging (DWI).
  - No evidence of severe stroke on imaging based on available acute imaging studies performed under the standard of care, defined by either:
    - Alberta Stroke Program Early CT Score (ASPECTS) of 0 to 4 based on CT, or
    - Acute infarct volume on MRI DWI ≥ 70 mL (for subjects who undergo as part of standard of care MRI).
  - No evidence of isolated lacunar infarct (i.e., lacunar syndrome), or isolated brainstem, or cerebellar stroke based on clinical assessment and available acute imaging studies performed under the standard of care.

- No evidence of acute intracranial hemorrhage (e.g., intracerebral hemorrhage, subarachnoid hemorrhage) on acute brain CT or MRI performed under the standard of care. Petechial hemorrhages of ≤ 1 cm are allowed.

- 7. NIHSS total score of 7 to 21, inclusive. NIHSS eligibility must be confirmed within 1 hour before randomization. For subjects treated with IV tPA ± EVT, NIHSS must be confirmed ≥ 1 hour after completion of all treatments and once any confounding effects of sedation or anesthesia have resolved.
- 8. No evidence of acute seizure at the onset of index stroke based on assessments conducted per standard of care. Subjects with evidence of seizure at onset of index stroke, but with imaging conclusively demonstrating an acute ischemic stroke are still allowed.
- 9. No evidence of acute myocardial infarction based on assessments per standard of care (e.g., elevated troponin levels, abnormal ECG).
- 10. In the judgment of the investigator, symptoms are not considered likely to resolve within the subsequent few hours (e.g., transient ischemic attack [TIA]).

Subject History

- 11. Subjects or their legally authorized representative confirms that before index stroke, there was no substantial impairment in subject's ability to perform activities of daily living (e.g., dressing, eating, walking, bathing, toileting) without assistance, as defined by a modified Rankin Score (mRS) of 0 to 2 before the index stroke.
- 12. Subjects with a history of previous stroke more than 3 months before enrollment are allowed if they are no longer experiencing ongoing functional recovery and mRS remains 0 to 2 prior to index stroke.
- 13. No known history before randomization of clinically significant medical conditions (other than current acute ischemic stroke) 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. Subjects with comorbid conditions that are, in the opinion of the investigator, clinically stable and not expected to meaningfully progress in the following 12 months may be considered eligible.
- 14. No known medical history of repeated episodes of complex migraine (e.g., weakness, vision, difficulty speaking). Subjects with history of complex migraine, but with imaging conclusively demonstrating an acute ischemic stroke are still allowed.
- 15. No contraindication or inability to tolerate brain MRIs (e.g., a pacemaker or any other implanted device or condition that would preclude proximity to a strong magnetic field).
- 16. No hypotension requiring the use of IV vasopressor support or systolic blood pressure < 90 mmHg at the time of randomization.
- 17. No known history within 6 weeks before randomization of active varicella or herpes zoster virus infection or any severe viral infection requiring medical attention.
- 18. No known currently active drug or alcohol abuse.

- 19. No known receipt of any investigational product within 30 days or 5 half-lives of the drug (whichever is longer) before the first dose of study drug. No current enrollment in another interventional clinical study, including pharmacologic and behavioral interventional studies.
- 20. No known history of prior exposure to elezanumab.
- 21. No known history prior to randomization of an allergic reaction or significant sensitivity to constituents of the study drug and its excipients and/or other products in the same class.

Contraception

- 22. Female who is not pregnant, breastfeeding, or considering becoming pregnant during the study or for within 39 weeks (5 half-lives) after the last dose of study drug.
- 23. For all females of childbearing potential, a negative serum pregnancy test at the Screening Visit and negative serum or urine pregnancy test before all doses of study drug.
- 24. Pregnancy tests are to be performed at home every 4 weeks after the Week 52 visit on women of childbearing potential. A follow-up telephone call to females of childbearing potential will be conducted every 4 weeks to obtain the results of the at-home pregnancy test (not including Weeks 12 or 24) up to 39 weeks (5 half-lives) after the last dose of study drug. Results of pregnancy tests must be documented on the subject's medical record/source.
- 25. Female subjects of childbearing potential must practice at least 1 protocol-specified method of birth control from randomization through 39 weeks (5 half-lives) after the last dose of study drug. Female subjects of non-childbearing potential (see below for definition) do not need to use birth control.

5.2 Contraception Recommendations

Contraception Requirements for Females

Female subjects must follow the following contraceptive guidelines as specified:

Females, Non-Childbearing Potential

Females do not need to complete serum or urine pregnancy tests, or 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:

- 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).
- Combined (estrogen and progestin-containing) hormonal birth control (oral, intravaginal, transdermal, injectable) associated with inhibition of ovulation confirmed to have been initiated at least 1 month before Screening (if already using hormonal birth control).
- Progestin-only hormonal birth control (oral, injectable, implantable) associated with inhibition of ovulation confirmed to have been initiated at least 1 month before Screening (if already using hormonal birth control).
- 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).

5.3 Prohibited Medications and Therapy

During the study, investigational drugs and procedures are prohibited.

5.4 Prior and Concomitant Therapy

Use of IV tPA and/or EVT as part of acute care for the index stroke before or after randomization is permitted and must be recorded in the electronic case report form (eCRF). Eligibility according to NIHSS score must be confirmed at least 1 hour after completion of IV tPA and/or EVT (after completion of all treatments) and once any confounding effects of sedation or anesthesia have resolved before a subject can be randomized. All other standard-of-care treatments for the management of acute ischemic stroke and associated complications/comorbidities are permitted at the investigator's discretion.

Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the subject received within 30 days before enrollment or is administered during the study must be recorded through the post-treatment visits (39 weeks after last dose of study drug). Given the acute nature of the Screening Period, medical history and information on prior therapy may be collected and/or confirmed at subsequent visits. All concomitant medications, including any change in dose must be recorded with the reason for use, dates of administration, dosages and frequency in the eCRF.

Rehabilitation is an integral part of post-stroke therapy. For subjects who receive rehabilitation therapy, the type (e.g., physical, occupational, speech), setting, and duration of rehabilitation will be recorded throughout the study as concomitant therapy using a structured patient- or caregiver-reported questionnaire.

Sites are encouraged to raise any questions regarding concomitant or prior therapy to the AbbVie emergency contact, if needed. Information regarding potential drug interactions with elezanumab is located in the elezanumab IB.[2]

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 and continuation of the study drug would place the subject at risk.
- The subject has a positive drug screen, and the investigator believes continuation of the study drug would place the subject at risk, 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.

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 Modification

During the COVID-19 pandemic, it may be 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.

Every effort will be made to mitigate premature discontinuation of subjects; if a subject is prematurely discontinued, the reason for discontinuation will be documented in the subject's chart.

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

5.6 Follow-Up for Subject Withdrawal from Study

Study Drug Discontinuation

For subjects who discontinue the study drug, all efforts should be made to continue conducting all treatment and post-treatment procedures (with the exception of study drug administration) in accordance with the study visit schedule and the subject's continued willingness to participate in order to minimize missing data for efficacy and safety assessments. If a subject discontinued study drug and is unwilling to return to the site, certain assessments may be conducted remotely. At a minimum, subjects should complete the procedures outlined for the Week 52/Premature Discontinuation visit (PD visit), and follow-up visits at 12 and 24 weeks after last dose of study drug. Subjects should be advised on the continued scientific importance of their data even if they discontinue treatment with study drug early.

Withdrawal from the Study

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for discontinuation from the study will be recorded on the appropriate eCRF page. If a subject prematurely discontinues study participation, the procedures outlined for the Week 52/PD visit should be completed as soon as possible, preferably within 2 weeks. In addition, a follow-up phone call 30 days after the last dose of study drug should be attempted to ensure all treatment-emergent AEs/SAEs have been resolved.

5.7 Study Drug

AbbVie will provide study drug for elezanumab and placebo. Elezanumab and placebo are manufactured by AbbVie as shown in Table 1, below. The solution contained in the study vial(s) will be diluted in 250 mL of 0.9% Sodium Chloride Injection/Solution for Infusion. Study drug will be administered intravenously every 4 weeks through Week 48 for a total of 13 doses.

AbbVie-provided study drug must not be substituted or alternately sourced. If a subject is unable or unwilling to come to the study site to receive infusion of study drug due to a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat), a trained home health service may provide off-site infusion of study drug if allowed by local regulations. Refer to the Operations Manual in Appendix F for details on potential home health services.

Table 1. Study Drug Identification

Investigational Product	Mode of Administration	Formulation	Strength	Manufacturer
Elezanumab	Infusion	Solution for infusion in a vial	600 mg/6 mL	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany
Placebo	Infusion	Solution for infusion in a vial	N/A	AbbVie Deutschland GmbH & Co. KG, Ludwigshafen, Germany

N/A = not applicable

0.9% Sodium Chloride Injection/Solution for Infusion will be supplied with commercially available material locally sourced by sites.

Elezanumab and placebo will be packaged in vials with quantities sufficient to accommodate study design. Each kit will be labeled per local requirements and this label must remain affixed to the kit. Upon receipt, study drug must be stored as specified on the label and kept in a secure location. Each kit will contain a unique kit number. This kit number is assigned to a subject via interactive response technology (IRT) and encodes the appropriate study drug to be dispensed at the subject's corresponding study visit. Site staff will complete all blank spaces on the label before administering to subjects. Study drug will only be used for the conduct of this study.

AbbVie will provide study drug as liquid in a vial that requires sterile preparation. The start of the first infusion of study drug must occur as soon as possible but no later than 6 hours after randomization. The study drug can be administered without regard to food consumption and infusion time is 90 to 120 minutes. The start and stop time of each study drug infusion will be recorded to the nearest minute. Please refer to the pharmacy manual for detailed instructions.

5.8 Randomization/Drug Assignment

All subjects will be assigned a unique identification number by the IRT during Screening. The IRT will assign a randomization number that will encode the subject's treatment group assignment according to the randomization schedule generated by the statistics department at AbbVie.

Approximately 120 subjects will be randomized to elezanumab 1800 mg or placebo in a 1:1 ratio. Randomization will be stratified by IV tPA use (yes/no), by EVT use (yes/no), and by time since "last known normal" (≤ 11 hours or > 11 hours). The proportion of subjects enrolled who have EVT is targeted to be up to approximately 50% of the study population. A target of approximately 25% to 50% of subjects may be randomized within the time window of ≤ 11 hours since last known normal. Lastly, the proportion of subjects who enroll > 80 to 90 years of age is targeted to be up to approximately 30% of the study population.

All AbbVie personnel with direct oversight of the conduct and management of the trial (with the exception of AbbVie Drug Supply Management Team), the investigator, study site personnel, and the subject will remain blinded to each subject's treatment throughout the Treatment Period. The investigator, all on-site and remote study site personnel, including those performing efficacy and safety assessments, and the subject will remain blinded to each subject's treatment throughout the study.

Placebo and elezanumab vials for infusion will be provided by AbbVie, and sites will provide saline. Placebo and elezanumab solutions for infusion may range from colorless to slightly yellow. The IRT will provide access to unblinded subject treatment information in the case of a medical emergency.

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 damage or 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 Events

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.

Such an event can result from use of the drug as stipulated in the protocol or labeling, as well as from "special situations," such as accidental or intentional overdose, medication error, occupational or accidental exposure, off-label use, drug abuse, drug misuse, or drug withdrawal, all of which must be reported, whether associated with an AE or not. Any worsening of a pre-existing condition or illness is considered an AE. Worsening in severity of a reported AE must be reported as a new AE. Laboratory abnormalities and changes in vital signs are considered to be AEs only if they result in discontinuation from the study or from study drug, necessitate therapeutic medical intervention, and/or if the investigator considers them to be AEs.

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 clinical research organization (as appropriate) as a SAE within 24 hours of the site being made aware of the SAE (refer to Section 4.3 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 admission 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.

All AEs reported from the time of study drug administration until 39 weeks (5 half-lives) after discontinuation of study drug administration will be collected, whether solicited or spontaneously reported by the subject. In addition, study procedure-related serious and nonserious AEs will be collected from the time the subject signs the study-specific informed consent.

The following definitions will be used for Serious Adverse Reactions (SAR) and Suspected Unexpected Serious Adverse Reactions (SUSAR):

SAR	Defined as all noxious and unintended responses to an Investigational Medicinal Product (IMP) related to any dose administered that result in an SAE as defined above
SUSAR	Refers to individual SAE case reports from clinical trials where a causal relationship between the SAE and the IMP was suspected by either the sponsor or the investigator, is unexpected (not listed in the applicable Reference Safety Information), and meets one of the above serious criteria.

AbbVie will be responsible for SUSAR reporting for the IMP in accordance with global and local requirements.

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

Adverse Event Severity and Relationship to Study Drug

The investigators 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 adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event 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

The following AESIs will be monitored during the study (see Operations Manual [Appendix F] for more information):

- Infusion reactions

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.

Safety Monitoring

An external DMC composed of persons independent of AbbVie and with relevant expertise in stroke and clinical trial safety monitoring will review unblinded data from the ongoing study. The primary responsibility of the DMC will be to protect the safety of the subjects participating in this study.

A separate DMC Charter will be prepared outside of the protocol and will describe the roles and responsibilities of the DMC members, frequency of data reviews, relevant data to be assessed, and expectations for blinded communications.

7 STATISTICAL METHODS & DETERMINATION OF SAMPLE SIZE

7.1 Statistical and Analytical Plans

The statistical methods provided in this protocol will be focused on primary and key secondary analyses. Complete and specific details of the statistical analyses will be described and fully documented in the Statistical Analysis Plan (SAP). The statistical analyses will be performed using SAS (SAS Institute Inc., Cary, North Carolina, USA).

7.2 Definition for Analysis Populations

The Full Analysis Set (FAS) includes all randomized subjects who received any study drug. The subject will be grouped according to treatment as randomized. The FAS will be used for all efficacy and baseline analyses.

The Safety Analysis Set consists of all subjects who received any study drug. Subjects will be grouped according to treatment received regardless of randomization. The safety analysis set will be used for all safety analyses.

7.3 Statistical Analyses for Efficacy

General Considerations

Analysis of the primary, secondary, and all other efficacy endpoints will be conducted on the FAS based on treatment as randomized, unless otherwise specified in the SAP.

The primary and secondary endpoints will be assessed using Bayesian methodology. No formal hypothesis tests will be performed. Additional efficacy endpoints will be summarized using descriptive statistics including the number of observations, mean, standard deviation, minimum, median, and maximum for continuous variables, and number and percent for categorical variables.

For continuous exploratory efficacy endpoints, the between-group treatment summary at each visit will be conducted using a mixed effects model with repeated measures (MMRM) including treatment group, visit, treatment-by-visit interaction, and stratification factors as fixed effects, the baseline values associated with the endpoint as covariates unless otherwise noted in the SAP. Missing data will not be imputed before performing the MMRM.

For binary efficacy endpoints, the frequency and percentage will be provided by treatment group. Missing values will be imputed as non-responders unless otherwise specified in the SAP.

Primary Efficacy Analysis

The primary analysis on NIHSS total score during the Treatment Period will be based on the AUC derived from an MMRM. The monthly-adjusted AUC of NIHSS total score for each treatment group will be obtained using the trapezoidal method and will be adjusted for month by dividing by 12. The MMRM model will include covariates of time since last known normal (≤ 12 hours, > 12 hours based on actual time of study drug initiation), IV tPA use, EVT use, main effects of treatment group and visit, and treatment-by-visit interaction. Each visit by a subject will serve as a repeated measure.

The posterior probability of the treatment group difference (with treatment showing greater improvement than placebo) in monthly-adjusted AUCs being greater than 0.6 using a noninformative prior will be calculated.

Secondary Efficacy Analysis

The secondary efficacy analysis is the proportion of subjects with a favorable outcome based on an mRS at Week 52 of 0, 1, or 2. The posterior probability of the treatment group difference (with treatment showing greater improvement than placebo) in responder rates being greater than 6.25% will be calculated using a non-informative prior.

Additional Efficacy Analyses

Details on other efficacy analyses will be provided in the SAP.

Subgroup Analysis for Efficacy

Subgroup analysis of the primary endpoint will be conducted for the following subgroups:

- Age (< 70, ≥ 70 years at time of randomization)
- Sex (male, female)
- NIHSS total score at baseline (≤ 15, > 15)
- Time since last known normal based on actual study drug initiation time (≤ 12 hours, > 12 hours)
- Reperfusion as measured by the modified Thrombolysis in Cerebral Infarction (mTICI)[1] score (< 2B, ≥ 2B)
- IV tPA use (yes, no)
- EVT use (yes, no)

7.4 Statistical Analyses for Safety

General Considerations

Safety analyses will be carried out using the Safety Analysis Set. Safety will be assessed by AEs, lab values, vital sign measurements, ECG, clinically significant MRI abnormalities and C-SSRS. For continuous safety outcomes, the change from Baseline will be analyzed in a descriptive manner by treatment group and by visit. For categorical safety outcomes, the number and percentage of each

category will be summarized by treatment group and by visit. Shift of laboratory values from Baseline to defined time points will be tabulated. Hypothesis testing will not be performed for safety parameters.

Analysis of Adverse Events

All AEs will be coded using the current version of the Medical Dictionary for Regulatory Activities (MedDRA). The number and percentage of subjects with treatment-emergent AEs, treatment-emergent SAEs, AEs with a reasonable possibility of being related to study drug, AEs leading to study drug discontinuation will be summarized by treatment group and will be tabulated using primary MedDRA system organ class (SOC) and preferred term (PT). Treatment emergent AEs will be defined as all events that begin or worsen on or after first dose of study drug.

Analysis of Laboratory Data

Changes from Baseline in continuous laboratory parameters will be summarized by n, mean, standard deviation, minimum value, median, and maximum value for each treatment group and all subjects overall for each continuous hematology, chemistry, and urinalysis variable.

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

Analysis of Vital Signs

Change from baseline to each planned visit and to the minimum, maximum and final value during the Treatment Period will be summarized in a descriptive manner for each treatment group and all subjects overall for each vital sign and weight. For each variable, a summary of the number and percentage of subjects who have at least one post-baseline observation that meets the potentially clinically significant (PCS) criteria and is more extreme than their baseline value will be provided for each treatment group and all subjects overall.

Other Safety Analysis

Further details and additional safety analyses will be specified in the SAP.

7.5 Interim Analysis

Safety and select efficacy data will be reviewed by an external DMC as described in Section 2.2 and Section 6.1.

7.6 Multiplicity Adjustment and Overall Type I Error Control

This is a Phase 2a, exploratory, hypothesis-generating study; therefore, there will be no control of Type I error for primary, secondary, or exploratory analyses for this study.

7.7 Sample Size Determination

The primary efficacy endpoint is the monthly-adjusted, model-based AUC of the NIHSS total score during the Treatment Period. Approximately [redacted] subjects will be randomized to elezanumab [redacted] mg or placebo in a [redacted] ratio. Assuming a true difference in AUC of [redacted], this sample size is sufficient to show a [redacted] difference in AUC between treatment and placebo with a posterior probability greater than [redacted]%. This sample size was calculated based on simulations and included a [redacted]% mortality rate for the population under [redacted] years of age, [redacted]% mortality rate for the population greater than or equal to [redacted] years of age, and an additional [redacted]% dropout rate.

The number and proportion of missing assessments (due to missed visits or study drug discontinuation) will be monitored on an ongoing basis and, if the proportion of missing assessments is higher than planned, additional subjects may be added.

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 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 at that site. 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 a significant disaster/crisis (e.g., epidemic/pandemic, natural disaster, conflict/combat) occurs leading to difficulties in performing protocol-specified procedures, AbbVie may 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 or virtual site visits), alternative locations for data collection (e.g., use of a local lab instead of a central lab), and shipping investigational product and/or supplies directly to subjects to ensure continuity of treatment where allowed. In all cases, these alternative measures must be allowed by local regulations and permitted by IRB/IEC. Investigators must 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 must 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). During the COVID-19 pandemic, 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. Zaidat OO, Yoo AJ, Khatri P, et al. Recommendations on angiographic revascularization grading standards for acute ischemic stroke: a consensus statement. Stroke. 2013;44(9):2650-63.

2. AbbVie. Elezanumab Investigator's Brochure.

3. Schwab JM, Monnier PP, Schluesener HJ, et al. Central nervous system injury-induced repulsive guidance molecule expression in the adult human brain. Arch Neurol. 2005;62(10):1561-8.

APPENDIX A. STUDY-SPECIFIC ABBREVIATIONS AND TERMS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse events of special interest
ASPECTS	Alberta Stroke Program Early CT Score
ATEMS	AbbVie Temperature Excursion Management System
AUC	area under the curve
BI	Barthel Index
BDI-II	Beck Depression Inventory-II
BMP	bone morphogenetic protein
COVID-19	Coronavirus disease – 2019
CS	clinically significant
CSF	cerebrospinal fluid
C-SSRS	Columbia-Suicide Severity Rating Scale
CT	computed tomography
DMC	data monitoring committee
DTP	direct-to-patient
DWI	diffusion-weighted imaging
EC	ethics committee
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5 Dimensions 5 Levels Health State Instrument
EVT	endovascular therapy
FAS	full analysis set
FSH	follicle-stimulating hormone
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
IB	Investigator's Brochure
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee

Ig	immunoglobulin
IL-10	interleukin-10
IL-6	interleukin-6
IMP	investigational medicinal product
INR	international normalized ratio
IRB	Institutional Review Board
IRT	interactive response technology
IU	international unit
IUD	intrauterine device
IUS	intrauterine hormone-releasing system
IV	intravenous
LDH	lactate dehydrogenase
MedDRA	Medical Dictionary for Regulatory Activities
MMIA	minimal missed infusion analysis
MMP-9	matrix metalloproteinase-9
MMRM	mixed effects model with repeated measures
MoCA	Montreal Cognitive Assessment
MRI	magnetic resonance imaging
mRS	Modified Rankin Scale
MS	multiple sclerosis
MT	magnetization transfer
mTICI	modified thrombolysis in cerebral infarction
nAb	neutralizing antibody
NCS	not clinically significant
NfL	neurofilament light chain
NIHSS	National Institutes of Health Stroke Scale
PCS	potentially clinically significant
PD visit	Premature Discontinuation visit
pMCAO	permanent middle cerebral artery occlusion
PK	pharmacokinetic(s)
PRO	patient-reported outcome
PT	Preferred Term
RGMa	Repulsive guidance molecule A
RSI	Reference Safety Information

SAE	serious adverse event
SAP	statistical analysis plan
SAR	serious adverse reaction
SIS-16	Stroke Impact Scale-16
SOC	System Organ Class
SUSAR	suspected unexpected serious adverse reactions
TIA	transient ischemic attack
TOAST	Trial of ORG 10172 in Acute Stroke Treatment
tPA	tissue plasminogen activator

APPENDIX B. RESPONSIBILITIES OF THE INVESTIGATOR

Protocol M19-148: A Randomized, Double-Blind, Placebo-Controlled Proof-of-Concept Study to Assess the Safety and Efficacy of Elezanumab in Acute Ischemic Stroke

Protocol Date: 25 March 2022

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 IB/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]	[redacted]	Clinical Program Development Medical Writing Neuroscience Data and Statistical Sciences Data and Statistical Sciences Clinical Pharmacology and Pharmacometrics