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PROTOCOL NUMBER: 101EP201 / NCT03283371

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects With Drug-Resistant Focal Epilepsy

EUDRA CT NUMBER: 2017-001995-45

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SPONSOR SIGNATURE PAGE

Protocol 101EP201 was approved by:

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June 8, 2018
Date

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1. SYNOPSIS

Protocol Title	A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects With Drug-Resistant Focal Epilepsy
Protocol Number	101EP201
Version Number	2
Name of Study Treatment	BG00002 (natalizumab; Tysabri®)
Study Phase	2
Study Indication	Focal epilepsy
Study Rationale	Evidence from both experimental models of epilepsy and human patients with epilepsy suggest a role for inflammation, including increased expression of cytokines and inflammatory mediators and blood-brain barrier breakdown. Blocking α4-positive leukocytes with natalizumab in subjects with drug-resistant focal epilepsy may improve seizure control by reducing leukocyte vascular interactions and suppressing inflammatory activity at the disease site.
Study Objectives and Endpoints	The primary efficacy objective of the study is to determine if adjunctive therapy of natalizumab 300 mg intravenous (IV) infusion every 4 weeks reduces the frequency of seizures in adult subjects with drug-resistant focal epilepsy. The primary efficacy endpoint is the change from Baseline in log-transformed seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment. Seizures included in efficacy analyses are focal aware seizures (previously termed "simple partial seizures") with motor signs, focal impaired awareness seizures (previously termed "complex partial seizures"), and focal to bilateral tonic-clonic seizures (previously termed "partial onset with secondary generalization"). Focal aware seizures without motor signs will not be included. Seizure clusters (where individual seizures cannot be distinguished) will be counted as 1 seizure per cluster on each day that they are present. The secondary efficacy objective is to assess the effects of natalizumab

versus placebo in drug-resistant focal epilepsy on additional measures of seizure frequency. The secondary efficacy endpoints are as follows:

- Proportion of responders defined as subjects with a ≥50% reduction from Baseline in seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment.
- Proportion of subjects free from seizures during Weeks 8 to 24 of treatment.
- Percentage of seizure-free days gained, standardized over 28 days, during Weeks 8 to 24 of treatment compared with Baseline.
- Proportion of subjects with inadequate treatment response during Weeks 8 to 24, defined as either of the following:
  - Modification of antiepileptic drugs (AEDs) after Week 12 of the placebo-controlled phase due to lack of improvement or ongoing seizures.
  - Discontinuation of study treatment after the 8-week run-in period due to lack of efficacy.

[redacted]

The pharmacokinetic (PK) objective is to evaluate the PK of natalizumab in subjects with focal epilepsy. The PK endpoints are as follows:

- Maximum serum concentration (C_{max}) at steady state.
- Area under the serum concentration-time curve for a dosing interval (AUC_{tau}) at steady state.

The safety objective is to assess the safety and tolerability of natalizumab in subjects with drug-resistant focal epilepsy. Safety and tolerability assessments include adverse event (AE)/serious AE data, clinical laboratory data, and suicide ideation and behavior evaluation (electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]/Columbia-Suicide Severity Rating Scale [C-SSRS]).

Study Design: This is a Phase 2, multicenter, randomized, double-blind, placebo-controlled study.

Study Location: Approximately 44 sites in the United States are planned.

Number of Planned Subjects: Approximately 70 subjects will be enrolled, randomized, and dosed.

Study Population: This study will be conducted in subjects aged 18 to 75 years, inclusive, with focal epilepsy diagnosed on clinical grounds and as applicable supported by electroencephalogram findings [Scheffer 2017] and brain imaging. Subjects must have drug-resistant epilepsy defined as failure of adequate trials of 2 (or more) tolerated and appropriately chosen and used AEDs (whether as monotherapies or in combination) [Kwan 2010]. Subjects must have 6 or more seizures during the 6-week prospective baseline period.

Detailed criteria are described in Section 8.

Treatment Groups: The placebo-controlled phase of the study will comprise 2 treatment groups (natalizumab and placebo) to which subjects will be assigned in

a 1:1 ratio. The randomization will be stratified, as much as possible, based on the presence or absence of structural etiology for focal epilepsy, and based on the presence or absence of a high seizure frequency (≥24 seizures) during the 6-week prospective baseline period.

All subjects will receive 1 dose of study treatment at Week 0 according to their randomization into 1 of the following 2 treatment groups with dosing every 4 weeks for 24 weeks:

- Natalizumab 300 mg IV infusion in approximately 35 subjects
- Placebo IV infusion in approximately 35 subjects

In the open-label phase of the study, all subjects will be assigned natalizumab 300 mg IV infusion every 4 weeks for 24 weeks.

Duration of Treatment and Follow-up:

Study duration for each subject will be approximately 74 weeks for subjects completing the placebo-controlled, open-label, and follow-up phases:

- 6-week prospective baseline period
- 8-week double-blind, placebo-controlled active run-in period
- 16-week double-blind, placebo-controlled efficacy period
- 24-week open-label active treatment period (open-label phase)
- 12-week post-treatment follow-up period (equates to 16 weeks after the last dose of study treatment)
- Follow-Up Safety Phone Call (24 weeks after the last dose of study treatment)

2. LIST OF ABBREVIATIONS

AE	adverse event
AED	antiepileptic drug
ALT	alanine aminotransferase
ANC	absolute neutrophil count
AST	aspartate aminotransferase
AUC_{tau}	area under the serum concentration-time curve for a dosing interval
BBB	blood-brain barrier
CD	Crohn's disease
CI	confidence interval
C_{max}	maximum serum concentration
CNS	central nervous system
CRF	case report form
CRO	contract research organization
C-SSRS	Columbia-Suicide Severity Rating Scale
DHA	Directions for Handling and Administration
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
eCOA	electronic Clinical Outcome Assessment
ECoG	electrocorticogram
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
ET	Early Termination
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
[redacted]	[redacted]
ICF	informed consent form
ICH	International Council for Harmonisation
IERC	independent epilepsy review committee
IRT	interactive response technology
ISM	Independent Safety Monitor
ITT	intent-to-treat
IV	intravenous
JCV	John Cunningham virus
MMRM	mixed model for repeated measures
MRI	magnetic resonance imaging
MS	multiple sclerosis
[redacted]	[redacted]
PK	pharmacokinetic(s)
PML	progressive multifocal leukoencephalopathy
PRN	as needed
[redacted]	[redacted]
RNA	ribonucleic acid

SAE	serious adverse event
SAP	statistical analysis plan
[redacted]	[redacted]
SUSAR	suspected unexpected serious adverse reaction
US	United States
VCAM-1	vascular cell adhesion molecule-1
WBC	white blood cell

3. SPONSOR INFORMATION

Biogen is responsible for the study.

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For urgent medical issues in which the study Medical Director should be contacted, please refer to the Study Contact List for complete contact information.

Biogen may transfer any or all of its study-related responsibilities to a contract research organization (CRO) and other third parties; however, Biogen retains overall accountability for these activities.

4. INTRODUCTION

Natalizumab is a recombinant humanized monoclonal antibody approved in the United States (US), the European Union, and multiple countries in the rest of the world for the treatment of relapsing forms of multiple sclerosis (MS). In the US, it is also approved for the treatment of moderate-to-severe Crohn's disease (CD) in patients with evidence of inflammation who have had inadequate responses to, or are unable to tolerate, conventional CD therapies.

Natalizumab is produced in a murine myeloma cell line (NS0) and binds to the α4 subunit of human integrin, which is expressed at high levels on all circulating human leukocytes except polymorphonuclear leukocytes. Natalizumab binding blocks the interaction of α4β1 integrin (also known as very late antigen-4) on leukocytes with its counter receptor, vascular cell adhesion molecule-1 (VCAM-1) and fibronectin, located on endothelial cells. Likewise, natalizumab blocks the interaction of α4β7 integrin expressed on leukocytes with mucosal addressin cell adhesion molecule-1. Disruption of these cell adhesion molecule interactions prevents trafficking of mononuclear leukocytes across the endothelium and into parenchymal tissue.

In addition, α4 integrins bind additional ligands in tissues, including osteopontin and fibronectin. A further mechanism of natalizumab may be to suppress ongoing inflammatory reactions in diseased tissues by inhibition of binding of α4-positive leukocytes with these ligands. Thus, natalizumab may act to suppress existing inflammatory activity present at the disease site, along with inhibiting further recruitment of immune cells into inflamed tissue by interaction with VCAM-1 (Natalizumab Investigator's Brochure 2016). This is believed to be the basis of its efficacy in MS and CD.

Biogen continues to evaluate natalizumab for the treatment of MS in clinical studies worldwide. This is the first clinical study of natalizumab in subjects with epilepsy.

4.1. Overview of Epilepsy

Epileptic seizures are paroxysmal episodes resulting from abnormally discharging neurons that may be detected through electroencephalographic or clinical means, with the particular site of the brain affected influencing clinical expression. Epileptic seizures fundamentally arise from an imbalance in the basic excitability of neurons that may be related to the neuronal membrane or excitatory and inhibitory processes [Browne and Holmes 2004]. Epilepsy is conceptually defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures and by the neurobiologic, cognitive, psychological, and social consequences of this condition [Fisher 2005]. A recent review of the prevalence and incidence of epilepsy reported a lifetime prevalence of 7.6 per 1000 persons and annual cumulative incidence of 67.77 per 100,000 persons [Fiest 2017].

4.2. Current Therapies for Epilepsy

The mainstay of therapy for patients with epilepsy remains antiepileptic drugs (AEDs), and it is estimated that approximately 70% of patients achieve good seizure control with AED therapy. Patients who fail adequate trials of 2 (or more) tolerated and appropriately chosen and used AEDs are defined as having drug-resistant epilepsy [Kwan 2010]. For these patients, other therapies are considered including epilepsy surgery, neurostimulation devices, specialized diets, behavioral therapies, and other experimental treatments.

AEDs typically work through modulation of voltage-dependent or ligand-gated ion channels or through effects on inhibitory or excitatory neurotransmitter systems. Currently, there are over 20 AEDs available commercially. Despite the launch of many newer AEDs in recent years, both new and old drugs remain generally equally effective in managing epilepsy, and it is still rare for prior drug-resistant epilepsy patients to become seizure free with the newer therapies [Engel 2007].

4.3. Profile of Previous Experience With Natalizumab

See the Investigator's Brochure for detailed information on relevant nonclinical and clinical studies.

4.3.1. Nonclinical Experience

The pharmacology, pharmacokinetics (PK), and toxicology of natalizumab have been characterized in nonclinical in vitro and in vivo experimental systems. Nonclinical studies are outlined in the accompanying Investigator's Brochure for natalizumab.

4.3.2. Clinical Experience

Natalizumab has been used extensively in the setting of relapsing remitting MS and CD, both in clinical studies as well as in the postmarketing setting. As of 07 August 2017, approximately 4027 subjects had received natalizumab for MS in clinical studies, and approximately 171,630 subjects had received natalizumab for MS in the postmarketing setting. Approximately 1639 and 1688 subjects had received natalizumab for CD in clinical studies and in the postmarketing setting, respectively. In the Phase 3 studies, natalizumab was administered every 4 weeks at a 300 mg fixed dose for a minimum of 6 months, and the approved dose is 300 mg every 4 weeks. Therefore, the safety of natalizumab when given as a 300 mg intravenous (IV) infusion every 4 weeks has been well characterized in these specific subject populations. In addition, 231, 210, and 6 subjects have received natalizumab in clinical studies for rheumatoid arthritis, acute ischemic stroke, and multiple myeloma, respectively.

The efficacy of natalizumab in subjects with relapsing forms of MS has been established in 3 controlled studies: a Phase 2 dose-comparison study as well as 2 Phase 3 efficacy and safety studies. In both Phase 3 studies, treatment with natalizumab delayed the time to sustained progression in disability, substantially reduced the frequency of relapses, and markedly attenuated brain magnetic resonance imaging (MRI) measures of inflammation and tissue

destruction in subjects with relapsing forms of MS. Natalizumab as monotherapy significantly reduced the risk of disability progression by 42% relative to placebo.

Natalizumab has also been evaluated in a Phase 2a study that assessed subjects with acute ischemic stroke. Although the primary efficacy analysis demonstrated that natalizumab did not decrease acute infarct volume growth defined by MRI, natalizumab treatment was associated with improved clinical outcomes in prespecified secondary and tertiary clinical endpoints. More recently, a Phase 2b study did not meet primary and secondary efficacy endpoints, and further development of natalizumab in acute ischemic stroke is not being pursued.

A full outline of adverse drug reactions is available in the accompanying Investigator's Brochure for natalizumab. Overall, natalizumab has been well tolerated in subjects with MS, with similar incidences of common adverse events (AEs) and similar proportions of subjects discontinuing the study due to an AE in natalizumab and placebo treatment groups. Serious adverse events (SAEs) occurred slightly less frequently in natalizumab-treated subjects with MS (15.5%) than in subjects with MS who received placebo (18.9%), with MS relapse contributing significantly to the incidence. The most notable complication of treatment with natalizumab is the risk of progressive multifocal leukoencephalopathy (PML). PML is an opportunistic viral infection of the central nervous system (CNS) caused by the John Cunningham virus (JCV). Among the subjects who developed PML, natalizumab exposure ranged from 8 to 134 months, with the majority having received >24 months of treatment. Three established risk factors for the development of PML have been identified: the presence of anti-JCV antibodies, longer treatment duration of natalizumab (especially ≥2 years), and immunosuppressant use prior to receiving natalizumab. A PML risk algorithm is located in the accompanying Investigator's Brochure for natalizumab.

Based on accumulated clinical experience in the treatment of MS and CD, the PML risk estimate with negative antibody status, positive antibody status without index value, or antibody index ≤0.9 is 0.1/1000 during 1 to 12 months of natalizumab exposure. The PML risk with antibody index >1.5 is 0.2/1000 during 1 to 12 months of natalizumab exposure and in subjects previously treated with an immunosuppressant drug, the PML risk is 0.3/1000 during 1 to 12 months of natalizumab exposure. Other risks of natalizumab treatment include hypersensitivity reactions, infections, and hepatic injury. Serious hypersensitivity reactions (e.g., anaphylaxis) have occurred at an incidence of <1%. Approximately 6% of subjects in clinical studies developed persistent antibodies to natalizumab that were associated with a decrease in the effectiveness of natalizumab.

4.4. Study Rationale

There is a high unmet need to develop therapies that improve seizure control or eliminate seizures in drug-resistant epilepsy. Targeting the potential role of the immune system and inflammation in the pathogenesis of epilepsy represents an underexplored area in AED development and clinical studies. Evidence from both experimental models of epilepsy and human patients with epilepsy suggest a role for inflammation.

Preclinical data have demonstrated an inflammatory response after induced seizures, including expression of cytokines and inflammatory mediators [Vezzani and Granata 2005] and modulation of neuronal firing by blood-brain barrier (BBB) breakdown [Marchi 2012]. Furthermore, in a pilocarpine-induced epilepsy mouse model, acute seizure activity increased vascular expression of leukocyte adhesion molecules including VCAM-1 and enhanced leukocyte adhesion to CNS vessels in vivo. Treatment of the pilocarpine-injected mice with α4 integrin-specific monoclonal antibody or antibodies to VCAM-1 after status epilepticus showed marked reduction of spontaneous convulsions during the chronic period. When antibodies to α4 integrin were given 2 hours before pilocarpine injection, it completely prevented convulsions [Fabene 2008].

In human patients, studies show histopathological evidence of increased BBB permeability in surgical specimens from refractory epilepsy patients [Ravizza 2008; van Vliet 2007]. Elevated brain leukocyte numbers have been seen in human cortical CNS tissue from subjects with epilepsy compared to control subjects without epilepsy [Fabene 2008]. Furthermore, significantly higher concentrations of VCAM-1 in serum and cerebrospinal fluid have been detected in patients with drug-refractory epilepsy than in those with new diagnosis and drug-responsive epilepsy [Luo 2014]. Finally, a case report described a substantial benefit in the reduction of seizures after initiating therapy with natalizumab for MS [Sotgiu 2010]. Therefore, blocking α4-positive leukocytes with natalizumab in patients with drug-resistant focal epilepsy may improve seizure control by reducing leukocyte-vascular interactions and suppressing inflammatory activity at the disease site.

4.4.1. Dose Rationale

This Phase 2 study will evaluate the effect of adjunctive therapy of natalizumab 300 mg IV infusion every 4 weeks on seizure control in adult subjects with drug-resistant focal epilepsy. This is the approved dose and schedule of administration for the treatment of MS globally and CD in the US, and the safety profile at this dose has been well established in these indications. Natalizumab has been administered intravenously in single doses as well as in monthly repeated doses at 3.0 mg/kg and 6.0 mg/kg in clinical studies in healthy volunteers and in MS and CD subjects. Efficacy and safety results from Phase 2 studies indicated no statistically significant differences between monthly doses at 3.0 mg/kg and 6.0 mg/kg. In addition, the α4 integrin saturation on peripheral blood mononuclear cells was determined in several studies after single and multiple doses. The fixed 300 mg dose used in Phase 3 studies showed that a 70% saturation was maintained over a 4-week dosing interval in subjects with negative results for anti-natalizumab antibodies.

5. SCHEDULE OF ACTIVITIES

The schedule of activities for Study 101EP201 begins on the next page.

Table 1: Schedule of Activities for Study 101EP201

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	Screening	Placebo-Controlled Phase						Open-Label Phase							Post-Treatment Follow-Up	
Study Days	Day -42 +1 day[5]	Day 1 +5 days[5]	Day 28 ±5 days	Day 56 ±5 days	Day 84 ±5 days	Day 112 ±5 days	Day 140 ±5 days	Day 168 ±5 days	Day 196 ±5 days	Day 224 ±5 days	Day 252 ±5 days	Day 280 ±5 days	Day 308 ±5 days	Day 336 ±5 days	Day 420 ±5 days	Day 476 ±5 days
Informed Consent	X															
Review Inclusion and Exclusion Criteria	X	X														
Demographics and Medical History Including Seizure and Antiepileptic Medication History[6]	X															
Physical and Neurological Examination[7]	X							X						X	X	
Vital Signs[8]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
MRI brain scan[9]	X															
Pregnancy Test[10]	X	X														
Randomization		X														

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	**Screening**	**Placebo-Controlled Phase**						**Open-Label Phase**							**Post-Treatment Follow-Up**	
Study Days	**Day -42 +1 day[5]**	**Day 1 +5 days[5]**	**Day 28 ±5 days**	**Day 56 ±5 days**	**Day 84 ±5 days**	**Day 112 ±5 days**	**Day 140 ±5 days**	**Day 168 ±5 days**	**Day 196 ±5 days**	**Day 224 ±5 days**	**Day 252 ±5 days**	**Day 280 ±5 days**	**Day 308 ±5 days**	**Day 336 ±5 days**	**Day 420 ±5 days**	**Day 476 ±5 days**
Study Treatment Administration[11]		X	X	X	X	X	X	X	X	X	X	X	X			
Distribute Seizure Diary[12]	X															
Review Seizure Diary[12]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Hematology and Blood Chemistry[13, 14]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X			X			X		
Blood Sample for Hepatitis B and C Serologies	X															
Blood Sample for Anti-Natalizumab Antibodies[13]		X			X			X						X		
Blood Sample for Anti-JCV Antibody Index	X							X						X		

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	Screening	Placebo-Controlled Phase							Open-Label Phase						Post-Treatment Follow-Up	
Study Days	Day -42 +1 day[5]	Day 1 +5 days[5]	Day 28 ±5 days	Day 56 ±5 days	Day 84 ±5 days	Day 112 ±5 days	Day 140 ±5 days	Day 168 ±5 days	Day 196 ±5 days	Day 224 ±5 days	Day 252 ±5 days	Day 280 ±5 days	Day 308 ±5 days	Day 336 ±5 days	Day 420 ±5 days	Day 476 ±5 days
[redacted]																
Blood Samples for PK[13]		X[16]	X	X	X	X	X[16]	X		X	X	X	X	X[16]	X		
[redacted]																
eC-SSRS/C-SSRS[18]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X	
AEs and SAEs[19]		Record as detailed in Section 15.3														
Concomitant Therapies/Procedures		Record as detailed in Section 11.5														

Study Visits/Weeks	Screening Visit Week -6	Visit 1 Baseline Week 0	Visit 2 Week 4	Visit 3 Week 8	Visit 4 Week 12	Visit 5 Week 16	Visit 6 Week 20	Visit 7 Week 24[1]	Visit 8 Week 28	Visit 9 Week 32	Visit 10 Week 36	Visit 11 Week 40	Visit 12 Week 44	Visit 13 Week 48 or ET Visit[2]	End of Study Visit Week 60 or Follow-up Visit for ET Subjects (16 weeks after last dose of study treatment[3])	Follow-up Safety Phone Call Week 68 (24 weeks after the last dose of study treatment)[4]
Phase of Study	Screening	Placebo-Controlled Phase							Open-Label Phase						Post-Treatment Follow-Up	
Study Days	Day -42 +1 day[5]	Day 1 +5 days[5]	Day 28 ±5 days	Day 56 ±5 days	Day 84 ±5 days	Day 112 ±5 days	Day 140 ±5 days	Day 168 ±5 days	Day 196 ±5 days	Day 224 ±5 days	Day 252 ±5 days	Day 280 ±5 days	Day 308 ±5 days	Day 336 ±5 days	Day 420 ±5 days	Day 476 ±5 days
Assessment of new neurological symptoms[20]																X

Abbreviations: AE = adverse event; CNS = central nervous system; CRF = case report form; C-SSRS = Columbia Suicide Severity Rating Scale; DNA = deoxyribonucleic acid; eC-SSRS = electronic Columbia Suicide Severity Rating Scale; ET = Early Termination; IERC = independent epilepsy review committee; JCV = John Cunningham virus; [redacted]; MRI = magnetic resonance imaging; PK = pharmacokinetics; PML = progressive multifocal leukoencephalopathy; [redacted]; RNA = ribonucleic acid; SAE = serious adverse event; [redacted]; WBC = white blood cell.

[1] All study assessments at Week 24 must be performed prior to study treatment administration as part of the placebo-controlled phase. Study treatment administration at Week 24 will be the start of the open-label phase.

[2] Subjects who terminate the study early should have an Early Termination Visit 4 weeks after their last dose of study treatment.

[3] Subjects who terminate the study early should have a Follow-up Visit 16 weeks after their last dose of study treatment.

[4] Subjects who terminate the study early should have a Follow-Up Safety Phone Call 24 weeks after their last dose of study treatment.

[5] Day -42 is the day of signing the informed consent. Day 1 is the day of eligibility determination and randomization and must be at least 42 days after initiating seizure diary collection. Additional days of diary entry may be completed if required for visit scheduling; however, eligibility criteria apply to diary data completed in the 42 days immediately prior to Day 1. The study day windows allow for completion of other study activities, if necessary.

[6] Medical history should include an assessment of prior substance abuse.

[7] Includes height and weight measurements. Height should only be measured at the Screening Visit (Week -6). Height and weight measurements that are performed as standard of care do not need to be repeated for the study, provided that Biogen has access to the information and data are recorded in subject's CRF.

[8] Vital signs collected at each of the specified timepoints include temperature, systolic and diastolic blood pressure, pulse rate, and respiratory rate. Vital signs collected as part of the subject's standard of care on the same day as a study visit do not need to be repeated for the study, provided that Biogen has access to the information and data are recorded in the subject's CRF. Vital signs at Week 0 through Week 44 must be performed prior to study treatment administration.

[9] MRI scan of the brain is required within 48 months prior to screening to assist in the electroclinical assessment of a structural etiology for focal epilepsy. MRI done as part of the subject's standard of care and that falls within 48 months prior to screening does not need to be repeated for the study, provided that Biogen has access to the information and data are recorded in the subject's CRF. If MRI is not performed within this time frame and the subject meets other inclusion and exclusion criteria, MRI scan of the brain should be performed during the screening period and results should be reviewed by the IERC prior to Visit 1 in order to adjudicate the presence or absence of a structural etiology for

focal epilepsy. 3T MRI scanning is preferred wherever possible. Subjects without an MRI of the brain within 48 months prior to screening and with an absolute contraindication to MRI will be considered on a case-by-case basis.

[10] Required only for women of childbearing potential (for definition, see Section 15.5). A serum pregnancy test should be performed at the Screening Visit (Week -6), and a urine pregnancy test should be performed at Week 0 prior to randomization. The urine pregnancy testing will be performed locally prior to randomization. Follow-up pregnancy testing throughout the study will be done at the discretion of the Investigator or as required by local law.

[11] Subjects must be observed for 1 hour after completion of infusion.

[12] Subjects (or their caregivers) must record their seizure type and frequency daily from Screening Visit (Week -6) through End of Study Visit (Week 60), or for subjects who terminate the study early through the Follow-up Visit 16 weeks after their last dose of study treatment. Subjects must bring their seizure diary with them to each study visit.

[13] Blood samples should be collected prior to study treatment administration at Week 0 through Week 44. The time of collection, along with the start and stop times for the study treatment infusion, must be recorded in the subject's source data and on the subject's CRF.

[14] WBC (other than absolute neutrophil count) data will be reviewed by an Independent Safety Monitor (see Section 19.2.4).

[redacted]

[16] Both predose and postdose blood samples are to be collected for PK at Week 0, Week 20, and Week 44. The postdose sample must be collected within 1 hour after completion of study treatment infusion. The time of collection, along with the start and stop times for the study treatment infusion, must be recorded in the subject's source data and on the subject's CRF.

[redacted]

[18] The "baseline/screening" eC-SSRS/C-SSRS must be completed at the Screening Visit (Week -6); at all other visits, the "since last visit" eC-SSRS/C-SSRS must be used.

[19] SAE reporting for PML or new neurological symptoms indicative of PML (e.g., new or sudden change in thinking, vision, balance, or strength persisting over several days) must continue from the End of Study Visit (Week 60) through the Follow-Up Safety Phone Call. Otherwise, after the End of Study Visit or Follow-up Visit for ET subjects, SAEs should be reported only if the Investigator considers the SAE to be related to study treatment.

[20] Subjects should be contacted by phone 24 weeks after the last dose of study treatment to discuss if there has been any new development of any new neurological symptoms. PML or new neurological symptoms indicative of PML (e.g., new or sudden change in thinking, vision, balance, or strength persisting over several days) must be immediately reported as an SAE.

6. STUDY OBJECTIVES AND ENDPOINTS

Primary Efficacy Objective	Primary Efficacy Endpoint
To determine if adjunctive therapy of natalizumab 300 mg IV infusion every 4 weeks reduces the frequency of seizures in adult subjects with drug-resistant focal epilepsy.	Change from Baseline in log-transformed seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment. Seizures included in efficacy analyses are focal aware seizures (previously termed "simple partial seizures") with motor signs, focal impaired awareness seizures (previously termed "complex partial seizures"), and focal to bilateral tonic-clonic seizures (previously termed "partial onset with secondary generalization"). Focal aware seizures without motor signs will not be included. Seizure clusters (where individual seizures cannot be distinguished) will be counted as 1 seizure per cluster on each day that they are present.
Secondary Efficacy Objective	**Secondary Efficacy Endpoints**
To assess the effects of natalizumab versus placebo in drug-resistant focal epilepsy on additional measures of seizure frequency.	• Proportion of responders defined as subjects with a ≥50% reduction from Baseline in seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment. • Proportion of subjects free from seizures during Weeks 8 to 24 of treatment. • Percentage of seizure-free days gained, standardized over 28 days, during Weeks 8 to 24 of treatment compared with Baseline. • Proportion of subjects with inadequate treatment response during Weeks 8 to 24, defined as either of the following:

	– Modification of AEDs after Week 12 of the placebo-controlled phase due to lack of improvement or ongoing seizures. – Discontinuation of study treatment after the 8-week active run-in period due to lack of efficacy.
Exploratory Efficacy Objective	**Exploratory Efficacy Endpoints**
[redacted]	[redacted]

	[redacted]
PK Objective	**PK Endpoints**
To evaluate the PK of natalizumab in subjects with focal epilepsy.	• Maximum serum concentration (C_{max}) at steady state. • Area under the serum concentration-time curve for a dosing interval (AUC_{tau}) at steady state.
Safety Objective	
To assess the safety and tolerability of natalizumab in subjects with drug-resistant focal epilepsy. Safety and tolerability assessments include AE/SAE data, clinical laboratory data, and suicide ideation and behavior evaluation (electronic Columbia-Suicide Severity Rating Scale [eC-SSRS]/Columbia-Suicide Severity Rating Scale [C-SSRS]).	

[redacted]

7. STUDY DESIGN

This is a 6-month randomized, double-blind, placebo-controlled study to assess the efficacy, safety, and tolerability of natalizumab as adjunctive therapy in the treatment of adult subjects with drug-resistant focal epilepsy.

All subjects will complete a 6-week prospective baseline period without study treatment to establish a baseline seizure frequency. After completing screening assessments and fulfilling the criteria for study entry, eligible subjects will be randomly assigned to 1 of 2 treatment groups in a 1:1 ratio, and each subject will receive 1 dose of study treatment at Week 0 with dosing every 4 weeks for 24 weeks, according to 1 of the following 2 regimens: 300 mg IV natalizumab infused over 1 hour or placebo IV. The randomization will be stratified, as much as possible, based on the presence or absence of structural etiology for focal epilepsy and based on the presence or absence of a high seizure frequency (≥24 seizures) during the 6-week prospective baseline period. Structural etiology for focal epilepsy is defined as abnormalities visible on structural neuroimaging where the electroclinical assessment together with the imaging findings lead to a reasonable inference that the imaging abnormality is the likely cause of the subject's seizures [Scheffer 2017], and this assessment will be adjudicated by an independent epilepsy review committee (IERC) [Section 19.2.2].

There will be no dose titration of natalizumab. The initial 8 weeks of the placebo-controlled phase will constitute an active run-in period in order for natalizumab to achieve approximately 75% of steady state in subjects without anti-natalizumab antibodies, based on prior studies in MS.

At the end of the placebo-controlled phase, subjects will continue into a 24-week open-label safety and efficacy phase in which all subjects will receive natalizumab 300 mg IV infusion every 4 weeks for 24 weeks.

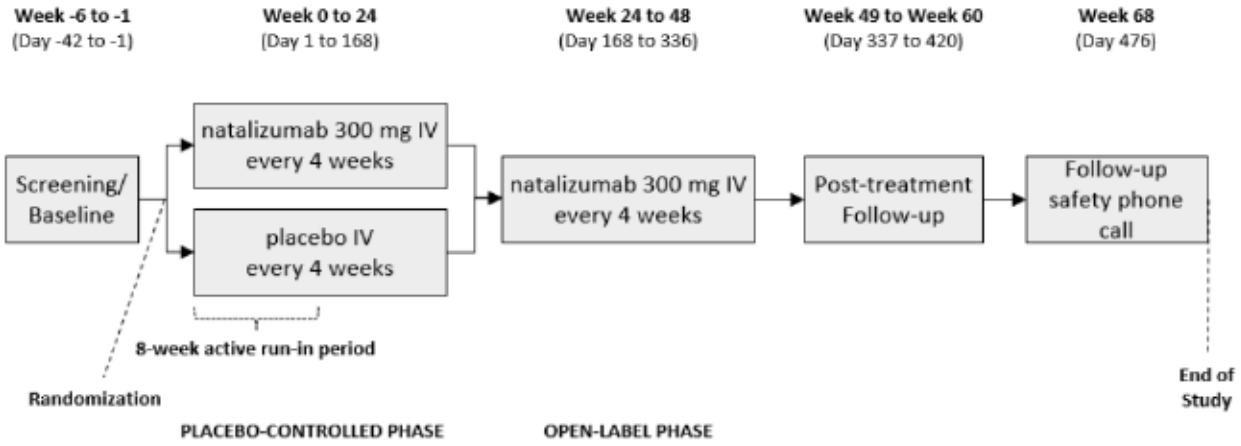
A post-treatment follow-up visit and a Follow-Up Safety Phone Call will occur 16 weeks and 24 weeks, respectively, after the last dose of study treatment.

A database lock and analysis will occur at the end of the placebo-controlled phase.

Approximately 70 subjects are expected to be enrolled, randomized, and dosed (~35 subjects in each treatment group) at approximately 44 sites in the US. The study will aim to include approximately 28 subjects with a structural etiology for focal epilepsy and approximately 28 subjects with a high seizure frequency, and these are not mutually exclusive.

See Figure 1 for a schematic of the study design.

Figure 1: Study Design Schematic



Abbreviation: IV = intravenous.

7.1. Study Duration for Subjects

The total duration of study participation for each subject will be up to approximately 74 weeks for subjects completing the placebo-controlled, open-label, and follow-up phases. This consists of a 6-week prospective baseline period, a 24-week double-blind placebo-controlled phase consisting of an 8-week active run-in period and a 16-week efficacy period, a 24-week open-label phase, a 12-week post-treatment follow-up period, and a Follow-Up Safety Phone Call (24 weeks after the last dose of study treatment).

The end of study date for a subject may be the last study visit, last protocol-specified assessment, or if the subject has ongoing AEs that are being followed-up, the date may be the date of AE resolution.

7.2. Study Stopping Rules

Biogen may terminate this study at any time after informing the Investigators. Biogen, or designee, will notify Investigators when the study is to be placed on hold, completed, or terminated. An independent data safety monitoring committee (DSMC) will be formed and will review efficacy and safety data regularly. Details of the DSMC responsibilities will be provided in the DSMC charter.

7.3. End of Study

The end of study is last subject, last phone call for final collection of data. The end of the placebo-controlled phase will be after the assessments are taken at Week 24, before study treatment administration for the open-label phase.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at the time of screening or at the timepoint specified in the individual eligibility criterion listed, and must be reconfirmed at the time of randomization:

1. Ability of the subject or his/her legally authorized representative (e.g., parent or legal guardian) to understand the purpose and risks of the study and provide signed and dated informed consent and authorization to use confidential health information in accordance with national and local subject privacy regulations.

2. Aged 18 to 75 years, inclusive, at the time of informed consent or subject meets the minimum age of consent in accordance with national regulations (whichever is higher).

3. Must have focal epilepsy diagnosed on clinical grounds and as applicable supported by electroencephalogram findings [Scheffer 2017] and brain imaging. Subjects with multifocal epilepsy may be included if all other entry criteria are met.

4. Must have a drug-resistant epilepsy defined as failure of adequate trials of 2 (or more) tolerated and appropriately chosen and used AEDs (whether as monotherapies or in combination) [Kwan 2010].

5. Must have had a MRI scan of the brain within 48 months of the Screening Visit (Week -6) to assist in the electroclinical assessment of a structural etiology for focal epilepsy. For subjects not meeting this criterion, an MRI may be obtained within the prospective baseline period. Subjects without an MRI of the brain within 48 months prior to screening and with an absolute contraindication to MRI will be considered on a case-by-case basis (see Table 1).

6. Must have confirmation of diagnosis of drug-resistant focal epilepsy by a member of the IERC [Section 19.2.2]. The independent reviewer will also adjudicate the presence or absence of a structural etiology for focal epilepsy. Appropriate diagnostic information must be sent to the reviewer as soon as possible after the Screening Visit (Week -6) but preferably should not be less than 2 weeks prior to randomization.

   The study will aim to include approximately 28 subjects with a structural etiology for focal epilepsy and approximately 28 subjects with a high seizure frequency (≥24 seizures during the 6-week prospective baseline period), and these are not mutually exclusive.

7. Experiences 6 or more seizures during the 6-week prospective baseline period and is not seizure free for more than 21 consecutive days during the prospective baseline period. Seizures included in counts are focal aware seizures (previously termed "simple partial

seizures") with motor signs, focal impaired awareness seizures (previously termed "complex partial seizures"), and focal to bilateral tonic-clonic seizures (previously termed "partial onset with secondary generalization"). Focal aware seizures without motor signs will not be included.

8. Stable regimen of 1 to 5 AEDs. Stable is defined as no modification of AED dosing within 4 weeks prior to the Screening Visit (Week -6). Dosing regimen must also be stable throughout the 6-week prospective baseline period. Benzodiazepines used on a regular basis for any indication at stable dosing will be considered as an AED. As needed (PRN) benzodiazepine use for occasional seizure exacerbation is allowed and must be documented. PRN benzodiazepine use for any other indication (e.g., sleep or anxiety) must also be documented as such. PRN benzodiazepine use for any indication averaging more than twice weekly (more than 12 doses) during the 6-week prospective baseline period will be considered as an AED. Neurostimulation, including vagus nerve stimulation and the RNS System, is allowed and must be documented; however, implantation must have occurred at least 6 months prior to the Screening Visit (Week -6). Dosing parameters for neurostimulation must be stable for 4 weeks prior to enrollment and throughout the 6-week prospective baseline period. Prior epilepsy surgery is allowed; however, surgery must have occurred at least 6 months prior to the Screening Visit (Week -6). A ketogenic diet is allowed and must be documented; however, initiation must have occurred and the patient must be at a stable ratio at least 4 weeks prior to the Screening Visit (Week -6) and throughout the 6-week prospective baseline period.

9. All women of childbearing potential and all men must practice highly effective contraception during the study and for at least 3 months after their last dose of study treatment. For further details of contraceptive requirements for this study, please refer to Section 15.5.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at the time of screening, or at the timepoint specified in the individual criterion listed, and must be reconfirmed at the time of randomization:

1. Focal aware seizures without motor signs are the only seizure type.

2. Diagnosis of generalized, combined generalized and focal, or unknown epilepsy [Scheffer 2017].

3. Known progressive structural CNS lesion.

4. History of seizures occurring in predominantly clustered patterns, as determined by the Investigator, over the 12 months prior to the Screening Visit (Week -6) or during the 6-week prospective baseline period, where individual seizures cannot be counted.

5. History of status epilepticus within the previous 6 months.

6. Known history or presence of non-epileptic seizures.

7. Current major depressive episode, a positive report on the "baseline/screening" eC-SSRS at the Screening Visit (Week -6) or on the "since last visit" eC-SSRS at Week 0, or considered at risk of suicide or self-harm based on the clinical judgement of the Investigator (Section 14.1).

8. Known planned epilepsy surgery or admission to the epilepsy monitoring unit with intended drug change within 12 months of Week 0.

9. Any clinically significant medical condition that may contraindicate the use of natalizumab, impair reliable participation in the study, or necessitate the use of medication not allowed per protocol.

10. Evidence of significant active hepatic disease including elevations of aspartate aminotransferase (AST) or alanine aminotransferase (ALT) above 3 times the upper limit of normal or bilirubin above 2 times the upper limit of normal.

11. Evidence of significant active renal disease including creatinine above 2 times the upper limit of normal.

12. Evidence of significant active hematologic disease including absolute neutrophil count (ANC) <1000 µL, platelet count <80,000, absolute lymphocyte count <800 cells/µL.

13. Known history of positive test result for human immunodeficiency virus.

14. Known history of positive test result for hepatitis C virus antibody or hepatitis B virus (defined as positive for hepatitis B surface antigen AND hepatitis B core antibody).

15. Signs of active herpes simplex type 1 or 2 or varicella within 4 weeks prior to randomization.

16. Symptoms of bacterial, fungal, or viral infection (including upper respiratory tract infection) within 14 days prior to randomization.

17. A clinically significant infectious illness (e.g., cellulitis, abscess, pneumonia, septicemia, tuberculosis) within 3 months prior to randomization, or PML or other opportunistic infections at any time.

18. Signs or symptoms suggestive of any ongoing serious infection, based on medical history, physical examination, or laboratory testing, as considered by the Investigator.

19. Immunocompromised subjects as determined by the Investigator, based on medical history, physical examination, laboratory testing, or immunosuppressive or immunomodulating treatment. Immunosuppressive or immunomodulating treatment,

including chronic oral or IV steroids, must be discontinued at least 4 weeks prior to screening.

20. History of any clinically significant (as determined by the Investigator) cardiac, endocrinologic, hematologic, hepatic, immunologic, metabolic (including uncontrolled diabetes), urologic, pulmonary, neurologic, dermatologic, psychiatric, renal, or other major disease that would preclude participation in a clinical study.

21. History of malignant disease, including solid tumors and hematologic malignancies (with the exception of basal cell and squamous cell carcinomas of the skin that have been completely excised and are considered cured).

22. History of transplantation or any antirejection therapy.

23. History of drug or alcohol abuse (as defined by the Investigator) within 2 years prior to the Screening Visit (Week -6). Stable cannabinoid use is allowed if started at least 4 weeks prior to the Screening Visit (Week -6) and must be documented.

24. Exposure to monoclonal antibodies, cytokines, growth factors, soluble receptors, other recombinant products, or fusion proteins within 6 months prior to the Screening Visit (Week -6).

25. Women who are pregnant or breastfeeding, and women intending to become pregnant during the study.

26. Prior exposure to natalizumab.

27. Current enrollment or a plan to enroll in any interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered within 6 months prior to the Screening Visit (Week -6).

28. Inability to comply with study requirements including completing or updating seizure diary. Subjects missing more than 6 days of seizure diary data during the 6-week prospective baseline period cannot be randomized and will be considered as screen failures. [redacted] At the discretion of the Investigator, the C-SSRS may be completed in place of the eC-SSRS in these patients.

29. Subjects with modification of AEDs during the 6-week prospective baseline period cannot be randomized and will be considered as screen failures.

30. Other unspecified reasons that, in the opinion of the Investigator or Biogen, make the subject unsuitable for enrollment.

9. SCREENING AND RANDOMIZATION

9.1. Screening

Subjects or their legally authorized representative (e.g., parent or legal guardian must provide informed consent before any screening tests are performed) [see Section 17.3]. Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

Screen failures are defined as subjects who sign the informed consent form (ICF) but are not subsequently randomized. If a subject is considered a screen failure, the reasons for exclusion must be documented in the subject's source documents and on the screening log. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure details, eligibility criteria, and any SAEs. Individuals who do not meet the criteria for participation in this study (i.e., a screen failure) may be rescreened once per Investigator discretion.

9.2. Randomization

Subjects will be randomized after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Sections 8.1 and 8.2. Subjects will be assigned a unique identification number that will be used on study-related documents pertaining to the subject. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment or continue in the study.

Randomization will be performed using interactive response technology (IRT). Subjects will be randomized to receive natalizumab:placebo in a 1:1 ratio. The randomization will be stratified, as much as possible, based on the presence or absence of structural etiology for focal epilepsy and based on the presence or absence of a high seizure frequency (≥24 seizures) during the 6-week prospective baseline period. In the open-label phase, all subjects will be assigned natalizumab.

9.3. Blinding Procedures

The Investigator, study site staff, and subjects will remain blinded to the subject treatment assignments throughout the study. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, both at the study site and at Biogen and the CRO. The study sponsor and CRO study management team will be fully blinded for the placebo-controlled phase of the study. After the placebo-controlled phase is completed and the clinical study database is locked, designated study sponsor personnel will be unblinded to the placebo-controlled data for the purpose of evaluating the Week 24 data.

At the end of the study and following finalization of the clinical study report, if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their subjects about the treatment received.

10. DISCONTINUATION OF STUDY TREATMENT AND WITHDRAWAL OF SUBJECTS FROM THE STUDY

10.1. Discontinuation of Study Treatment

A subject *must* permanently discontinue study treatment for any of the following reasons:

- The subject becomes pregnant. Study treatment must be discontinued immediately. Report the pregnancy according to the instructions in Section 15.4.1.
- The subject withdraws consent to continue study treatment.
- The subject desires to discontinue treatment under this protocol.
- The subject is unwilling or unable to comply with the protocol.
- The subject experiences a medical emergency that necessitates permanent discontinuation of treatment.
- The subject requires modification of AEDs due to a clinically significant increase in seizure frequency or intensity or due to emergence of a new seizure type.
- The subject experiences hypersensitivity or suspected allergic reaction to study treatment.
- The subject experiences a change in laboratory values that necessitates permanent discontinuation of treatment including the development of active hepatic, renal, or hematological disease.
- The subject misses 2 or more consecutive doses of study treatment or does not receive study treatment for a period of 10 weeks.
- PML or other AEs/SAEs that the Investigator believes necessitates discontinuation.
- At the discretion of the Investigator for medical reasons, for noncompliance, or for reasons listed in the current prescribing information.

The primary reason for discontinuation of study treatment must be recorded in the subject's case report form (CRF). Once the subject discontinues study treatment, the subject will not be eligible to restart study treatment. All subjects who discontinue study treatment prematurely should remain in the study and undergo an Early Termination (ET) Visit (4 weeks after the last study dose), Follow-up Visit (16 weeks after the last study dose), and Follow-up Safety Phone Call (24 weeks after the last study dose).

10.2. Lost to Follow-Up

Subjects will be considered lost to follow-up if they repeatedly fail to return for scheduled visits and are unable to be contacted by the study site.

The following actions must be taken if a subject fails to return to the study site for a required study visit:

- The study site must attempt to contact the subject and reschedule the missed visit as soon as possible and counsel the subject on the importance of maintaining the assigned visit schedule and ascertain whether the subject wishes to and/or should continue in the study.
- In cases in which the subject is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the subject. These contact attempts should be documented in the subject's medical record.
- Should the subject continue to be unreachable, that subject will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10.3. Withdrawal of Subjects From the Study

Subjects must be withdrawn from the study for any one of the following reasons:

- The subject withdraws consent.
- The subject enrolls into another interventional clinical study in which an investigational treatment or approved therapy for investigational use is administered.
- The subject is unwilling or unable to comply with the protocol.

The primary reason for the subject's withdrawal from the study must be recorded in the subject's CRF.

Subjects who withdraw from the study after randomization may not be replaced.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the Directions for Handling and Administration (DHA).

Doses should be given within the visit windows provided in the schedule of activities (Table 1). In the event of a missed dose, the dose should be given as soon as possible, as long as it is at least 21 days from the next dose as study treatments must occur at least 21 days apart. Missed doses are otherwise not allowed to be given.

If the subject misses 2 or more consecutive study treatments or does not receive study treatment for a period of 10 weeks, the subject must permanently discontinue study treatment (Section 10.1).

11.2. Modification of Dose

The dosage of natalizumab cannot be modified.

11.3. Precautions

The subject must be observed for 1 hour after completion of the infusion.

11.4. Compliance

All doses of study treatment will be administered by the study site staff.

11.5. Concomitant Therapy and Procedures

11.5.1. Concomitant Therapy

A concomitant therapy is any drug or substance, including nonprescription medications or herbal preparations, other than the study treatment administered between the Screening Visit (Week -6) and the End of Study Visit (Week 60) or the Follow-up Visit (16 weeks after the last dose of study treatment). All concomitant therapies must be recorded in the subject's medical record and on the appropriate CRF. Given the mechanism of action of natalizumab, no significant drug-drug interactions are expected with concomitant AEDs. Felbamate is only allowed if the laboratory criteria are met and the patient is on stable dosing for at least 24 months prior to the Screening Visit (Week -6) because of the warnings of aplastic anemia and hepatic failure in the labeling. Other disallowed concomitant therapies are listed in Section 11.5.1.2. Biogen may be consulted for assistance regarding whether a specific medication is allowed or disallowed.

11.5.1.1. Modification of AEDs

Subjects entering the study must be on a stable regimen of AED treatment throughout the 6-week prospective baseline period and throughout Week 12 of the placebo-controlled phase. PRN benzodiazepine use for occasional seizure exacerbation is allowed and must be documented. Subjects who use PRN benzodiazepines for reasons unrelated to seizures should not change their frequency of use from the prospective baseline period.

Any subject requiring modification of AEDs during the 6-week prospective baseline period constitutes a screen failure. In the judgement of the Investigator, if after randomization the subject requires modification of AEDs due to a clinically significant increase in seizure frequency or intensity or for emergence of a new seizure type, the subject must permanently discontinue study treatment; after the 8-week run-in period this constitutes lack of efficacy of study treatment.

In the judgement of the Investigator, if after Week 12 of the placebo-controlled phase the subject requires modification of AEDs due to lack of improvement or ongoing seizures, this must be approved by a member of the IERC (Section 19.2.2) prior to AED therapy change. Modification of AEDs must be approved through the End of Study Visit (Week 60) or Follow-up Visit for ET Subjects (16 weeks after the last dose of study treatment). Modification of AEDs must be recorded in the subject's CRF.

Changes in dosing parameters of neurostimulation and in ketogenic diet ratios are included as modifications of AEDs.

11.5.1.2. Disallowed Concomitant Therapy

Subjects should be instructed to contact their Investigators before taking any new medications, including nonprescription drugs and herbal preparations. Concomitant therapy with any investigational product for epilepsy or for non-epilepsy indications is not allowed, with the exception of cannabinoid preparations started at stable dosing at least 4 weeks prior to the Screening Visit (Week -6); initiation of cannabinoid preparations is not allowed after the Screening Visit (Week -6).

Initiation of new AEDs or change in AED dosing may not be performed after the Screening Visit (Week -6) except as per Section 11.5.1.1.

Other disallowed concomitant therapies include, but are not limited to the following:

- interferon-β or interferon-α
- glatiramer acetate
- cyclophosphamide
- teriflunomide

- methotrexate
- dimethyl fumarate
- azathioprine
- cladribine
- mitoxantrone
- IV immunoglobulin
- mycophenolate mofetil
- fingolimod
- natalizumab (for another indication), daclizumab, rituximab, ocrelizumab, alemtuzumab, or any therapeutic monoclonal antibody
- felbamate, unless on stable dosing for at least 24 months prior to the Screening Visit (Week -6)
- fumaric acid esters
- chronic oral or IV steroids

11.5.2. Concomitant Procedures

A concomitant procedure is any therapeutic intervention (e.g., surgery/biopsy, physical therapy) or diagnostic assessment (e.g., blood gas measurement, bacterial cultures) performed between the Screening Visit (Week -6) and the End of Study Visit (Week 60) or the Follow-up Visit (16 weeks after the last dose of study treatment).

11.6. Continuation of Treatment

No further provisions are made for access to the study treatment. If natalizumab is proven to be beneficial, all regulatory requirements regarding poststudy access will be met.

12. STUDY TREATMENT MANAGEMENT

Study treatment will be manufactured, handled, and stored in accordance with applicable Good Manufacturing Practice.

Study site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA supersedes all other references (e.g., protocol).

Study treatment must be dispensed only by a pharmacist or appropriately qualified staff. Study treatment is to be dispensed only to subjects enrolled in this study. Once study treatment is prepared for a subject, it can be administered only to that subject. Study treatment vials are for one-time use only; do not use any study treatment remaining in the vial for another subject.

12.1. Natalizumab

Natalizumab is supplied as a liquid in 15 mL vials containing 300 mg of natalizumab per vial. Natalizumab contains recombinant humanized anti-α4 integrin antibody and excipient materials (sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, and polysorbate 80).

Natalizumab is manufactured by Biogen.

The contents of the natalizumab label will be in accordance with all applicable regulatory requirements. At a minimum, the label will include a study reference code, study treatment identifier, quantity of dosage units, lot number, and other pertinent information in accordance with local law. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to study site staff. Study treatment should not be used after the expiration, expiry, or use-by date.

12.1.1. Natalizumab Preparation

The individual preparing natalizumab should carefully review the instructions provided in the DHA.

If the packaging is damaged, or if there is anything unusual about the appearance or attributes of the vials or study treatment, do not use the study treatment. The vials in question should be saved at the study site and the problem immediately reported to Biogen.

12.1.2. Natalizumab Storage

Study treatment must be stored in a secure location.

Natalizumab is to be stored at 2°C to 8°C (36°F to 46°F), protected from light in a monitored and locked refrigerator with limited access. Study treatment is not to be frozen. For the most up-to-date storage requirements, follow the instructions provided in the DHA.

12.1.3. Natalizumab Handling and Disposal

The Investigator must return all used and unused vials of natalizumab as instructed by Biogen, unless approved for onsite destruction.

If any natalizumab supplies are to be destroyed at the study site, the institution or appropriate study site staff must obtain prior approval from Biogen, by providing, in writing, the destruction policy or details of the method of destruction. After such destruction, Biogen must be notified, in writing, of the details of the study treatment destroyed (e.g., lot or kit numbers, quantities), the date of destruction, and proof of destruction.

12.1.4. Natalizumab Accountability

Accountability for study treatment is the responsibility of the Investigator. The study site must maintain accurate records demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed or lost.

Unless otherwise notified, all vials, both used and unused, must be saved for study treatment accountability. By the end of the study, reconciliation must be made between the amount of natalizumab supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

Placebo is supplied as a liquid in 15 mL vials containing sodium phosphate monobasic monohydrate, sodium phosphate dibasic heptahydrate, sodium chloride, and polysorbate 80.

Placebo is manufactured by Biogen.

The label will include conditions for storage and other pertinent information required by local law, such as the lot/kit number and caution statement. Placebo should not be used after the expiration date.

13. EFFICACY, [redacted] ASSESSMENTS

See Table 1 for the timing of all assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the study site to have the evaluations repeated.

13.1. Clinical Efficacy Assessments

Efficacy assessments (including seizures) will be made using data from electronic Clinical Outcome Assessment (eCOA), on a device developed and supported by the eCOA vendor. Study site staff will monitor data via a secure Web portal developed and supported by the eCOA vendor. Paper versions of the Clinical Outcome Assessments are available to sites in case of problems or difficulty with connectivity of the e-devices. [redacted]

The following clinical assessments will be performed to evaluate the efficacy of natalizumab:

- Daily record of seizures: subjects (or their caregivers) must record their seizure type and frequency. Subjects must bring their seizure diary with them to each study visit.
- [redacted]
- [redacted]
- [redacted]

Seizures (with the exception of status epilepticus or clinically significant increase in seizure frequency or intensity or emergence of a new seizure type resulting in discontinuation of study treatment, which should be reported as an SAE) will not be collected as AEs as they are considered part of the primary efficacy endpoint; however, they should be recorded in the seizure diary. In addition to the eCOA record of seizures, a paper back-up form will be allowed for documentation in the eCRF in the event that a seizure cannot be captured in the eCOA. The inclusion of these data in the efficacy endpoints will be described in the statistical analysis plan (SAP).

[redacted]

[redacted]

14. SAFETY ASSESSMENTS

Refer to Table 1 for the timing of all safety assessments.

Tests and evaluations affecting primary endpoints and/or analyses may need to be repeated if the original results are lost or damaged. In these cases, subjects will be asked to return to the study site to have the evaluations repeated.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety of the study treatment:

- Medical history: should include an assessment of prior substance abuse.
- Physical examinations and neurological assessments, including height and weight measurements.
- Vital sign measurements: temperature, pulse rate, systolic and diastolic blood pressure, and respiratory rate.
- eC-SSRS/C-SSRS: The United States Food and Drug Administration (FDA) recommends prospective assessment of suicidal ideation and behavior in all clinical studies of AEDs [FDA 2012]. The C-SSRS is a prospective assessment tool to evaluate suicidal ideation and behavior developed by Dr. Kelly Posner and colleagues from Columbia University, the University of Pennsylvania and the University of Pittsburgh [Posner 2011]. It has been identified by the FDA as an acceptable prospective suicidal ideation and behavior assessment instrument [FDA 2012]. This study will employ the electronic, computer-automated, patient-reported version of the scale, the eC-SSRS. However, if the ePRO eC-SSRS cannot be completed, for example, due to system maintenance, unavailability of device at any visit, or if the subject is unable to independently complete the eC-SSRS (e.g., due to cognitive limitation), the site may administer a paper C-SSRS version of the assessment. At the discretion of the Investigator, if the eC-SSRS cannot be completed due to patient limitation, the paper C-SSRS should be administered throughout the study for consistency. The subject will complete the "baseline/screening" version of the scale at the Screening Visit (Week -6) and the "since last visit" version at all subsequent visits. Subjects with a positive report on the eC-SSRS/C-SSRS at the Screening Visit (Week -6) or Week 0 will be excluded from the study. A positive report is defined as a "yes" response on ideation items 4 and/or 5, or a "yes" response to any behavior item (except non-suicidal self-injury). All responses at each assessment should be reviewed for both positive and negative reports; the Investigator should determine the appropriate level of care for the subject for any "yes" response even if it does not constitute a positive report.

- Concomitant therapy and procedure recording.

- AE and SAE recording: Seizures (with the exception of status epilepticus or a clinically significant increase in seizure frequency or intensity or emergence of a new seizure type resulting in discontinuation of study treatment, which should be reported as an SAE) will not be collected as AEs as they are considered part of the primary efficacy endpoint; however, they should be recorded in the seizure diary.

14.2. Laboratory Safety Assessments

Samples will be analyzed using Good Laboratory Practice-validated assays.

The following laboratory assessments will be performed to evaluate the safety of the study treatment:

- Hematology: complete blood count with differential and platelet count, and ANC. Note: White blood cell (WBC) [other than ANC] data will be reviewed by an Independent Safety Monitor (ISM) [see Section 19.2.4].

- Blood chemistry: total protein, albumin, creatinine, blood urea nitrogen, uric acid, bilirubin (total and direct), alkaline phosphatase, ALT, AST, gamma-glutamyl transferase, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium.

- Serology: hepatitis B and C serologies.

- Urinalysis: dipstick for blood, protein, and glucose (microscopic examination, if abnormal).

- Serum and urine pregnancy tests: required only for women of childbearing potential (for definition, see Section 15.5). The urine pregnancy testing will be performed locally prior to randomization.

14.3. Natalizumab-Specific Safety Assessments

Anti-JCV antibodies are being collected in all studies of natalizumab. Assessment of anti-JCV antibody status including index values will be performed to understand the seropositivity to JCV in this population of drug-resistant focal epilepsy. Testing will be performed at the Screening Visit (Week -6), as well as at Week 24 (the beginning of the open-label phase), and at Week 48. Results of the testing will be provided to the Investigator and may be provided to the subject upon request.

AEs and SAEs will be recorded during the study as described in Section 15.2. In addition, the reporting of PML or neurological symptoms indicative of PML must also continue from the End of Study Visit (Week 60) through the Follow-Up Safety Phone Call (24 weeks after the last dose of study treatment). Neurological symptoms that may be indicative of PML include behavioral

or cognitive changes as well as focal symptoms including aphasia, visual field deficits, hemiparesis, and ataxia. PML can be associated with seizures and therefore considered in subjects with a clinically significant increase in seizure frequency or intensity or with emergence of a new seizure type.

15. SAFETY DEFINITIONS, RECORDING, REPORTING, AND RESPONSIBILITIES

Throughout the course of the study, every effort must be made to remain alert to possible AEs. If an AE occurs, the first concern should be for the safety of the subject. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each subject or his/her legally authorized representative and/or main caregiver must be given the names and telephone numbers of study site staff for reporting AEs and medical emergencies.

15.1. Definitions

15.1.1. Adverse Event

An AE is any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and that 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 related to the medicinal (investigational) product.

Determination of whether an abnormal laboratory value and/or vital sign result meets the definition of an AE will be made by the Investigator. Abnormal results are not considered AEs unless one or more of the following criteria are met:

- The result meets the criteria for an SAE
- The result requires the subject to receive specific corrective therapy
- The result is considered by the Investigator to be clinically significant

15.1.2. Serious Adverse Event

An SAE is any untoward medical occurrence that at any dose:

- Results in death
- In the view of the Investigator, places the subject at immediate risk of death (a life-threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity

- Results in a congenital anomaly/birth defect
- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. (An example of such a medical events includes allergic bronchospasm requiring intensive treatment in an emergency room.)

15.1.3. Prescheduled or Elective Procedures or Routinely Scheduled Treatments

A prescheduled or elective procedure or a routinely scheduled treatment will not be considered an SAE, even if the subject is hospitalized. The study site must document all of the following:

- The prescheduled or elective procedure or routinely scheduled treatment was scheduled (or was on a waiting list to be scheduled) prior to obtaining the subject's consent to participate in the study.
- The condition requiring the prescheduled or elective procedure or routinely scheduled treatment was present before and did not worsen or progress in the opinion of the Investigator between the subject's consent to participate in the study and the time of the procedure or treatment.
- The prescheduled or elective procedure or routinely scheduled treatment is the sole reason for the intervention or hospital admission.
  - If a subject is hospitalized due to local requirements for administration of the study treatment, the hospitalization should not be considered an SAE unless one of the requirements in Section 15.1.2 is met.

15.2. Safety Classifications

15.2.1. Investigator Assessment of Events

All events must be assessed to determine the following:

- If the event meets the criteria for an SAE as defined in Section 15.1.2.
- The relationship of the event to study treatment as defined in Section 15.2.2.
- The severity of the event as defined in Section 15.2.3.

15.2.2. Relationship of Events to Study Treatment

The following definitions should be considered when evaluating the relationship of AEs and SAEs to the study treatment:

Relationship of Event to Study Treatment	
Not related	An AE will be considered "not related" to the use of the investigational product if there is not a reasonable possibility that the event has been caused by the product under investigation. Factors pointing toward this assessment include but are not limited to the lack of reasonable temporal relationship between administration of the investigational product and the AE, the presence of a biologically implausible relationship between the product and the AE, or the presence of a more likely alternative explanation for the AE.
Related	An AE will be considered "related" to the use of the investigational product if there is a reasonable possibility that the event may have been caused by the product under investigation. Factors that point toward this assessment include but are not limited to a positive rechallenge, a reasonable temporal sequence between administration of the investigational product and the AE, a known response pattern of the suspected product, improvement following discontinuation or dose reduction, a biologically plausible relationship between the product and the AE, or a lack of an alternative explanation for the AE.

15.2.3. Severity of Events

The following definitions should be considered when evaluating the severity of AEs and SAEs:

Severity of Event	
Mild	Symptoms barely noticeable to subject or does not make subject uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of subject.
Moderate	Symptoms of a sufficient severity to make subject uncomfortable; performance of daily activity is influenced; subject is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on subject's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or subject hospitalized.

15.2.4. Expectedness of Events

Expectedness of all AEs will be determined by Biogen according to the Investigator's Brochure.

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the subject between the time of first dose of study treatment and the End of Study Visit or Follow-up Visit for ET Subjects is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the CRF.

AEs that are ongoing when the subject completes or discontinues the study will be followed up by the Investigator until the event has resolved, stabilized, or returned to baseline status. AE outcome should be recorded on the CRF, as applicable.

Seizures (with the exception of status epilepticus or a clinically significant increase in seizure frequency or intensity or emergence of a new seizure type resulting in discontinuation of study treatment, which should be reported as an SAE), will not be collected as AEs as they are considered part of the primary efficacy endpoint; however, they should be recorded in the seizure diary.

15.3.2. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the End of Study Visit or Follow-up Visit for ET Subjects is to be recorded on an SAE form, regardless of the severity of the event or its relationship to study treatment. SAEs must be reported to Biogen or designee within 24 hours as described in Section 15.3.3. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed up for all SAEs until the End of Study Visit or Follow-up Visit for ET Subjects (16 weeks after the last dose of study treatment). Thereafter, SAEs should be reported only if the Investigator considers the SAE to be related to study treatment. Any SAE that is ongoing when the subject completes or discontinues the study should be followed up by the Investigator until the event has resolved, stabilized, or returned to baseline status. SAE outcome should be recorded on the CRF, as applicable.

In addition, subjects should be contacted by phone 24 weeks after the last dose of study treatment to discuss the development of any new neurological symptoms indicative of PML (e.g., new or sudden change in thinking, vision, balance, or strength persisting over several days), as PML has been reported up to 6 months after the end of treatment. At the time of the phone call, any other non-PML but ongoing SAEs (or AEs) should be followed-up and updated on the CRF as well.

Seizures that require hospitalization, with the exception of status epilepticus, are not considered SAEs as they are considered part of the primary efficacy endpoint; however, they should be recorded in the seizure diary. A clinically significant increase in seizure frequency or intensity or emergence of a new seizure type resulting in discontinuation of study treatment would also be considered as an SAE. Of note, PML can be associated with seizures and therefore also considered in subjects with a clinically significant increase in seizure frequency or intensity or with emergence of a new seizure type (Section 14.3).

15.3.3. Immediate Reporting of Serious Adverse Events

In order to adhere to all applicable laws and regulations for reporting an SAE, the study site must formally notify Biogen or designee within 24 hours of the study site staff becoming aware of the SAE. It is the Investigator's responsibility to ensure that the SAE reporting information and procedures are used and followed appropriately.

Reporting Information for SAEs
A report ***must be submitted*** to Biogen or designee regardless of the following: • Whether or not the subject has undergone study-related procedures • Whether or not the subject has received study treatment • The severity of the event • The relationship of the event to study treatment To report initial or follow-up information on an SAE, fax or email a completed SAE form; refer to the Contact List for complete contact information.

15.3.3.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate CRF. All causes of death must be reported as SAEs within 24 hours of the study site becoming aware of the event. The Investigator should make every effort to obtain and send death certificates and autopsy reports to Biogen or designee. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.4. Suspected Unexpected Serious Adverse Reactions

Suspected unexpected serious adverse reactions (SUSARs) are SAEs that are unexpected and judged by the Investigator or Biogen to be related to the study treatment administered.

During the randomized placebo-controlled phase, appropriate personnel at Biogen or designee will unblind SUSARs for the purpose of regulatory reporting. Biogen will submit SUSARs (in blinded or unblinded fashion) to regulatory agencies according to local law. Biogen will submit SUSARs to Investigators in a blinded fashion.

During the open-label phase, Biogen or designee will report SUSARs to the appropriate regulatory authorities and Investigators as required, according to local law.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study and for 3 months after their last dose of study treatment. If a female subject becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female subject by faxing or emailing the appropriate form to Biogen or designee within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Contact List for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to Biogen or designee. A pregnancy is not considered an AE and should not be recorded on the AE CRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as an SAE if conception occurred during the study treatment period.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a subject or taken by a subject that exceeds the dose assigned to the subject according to the protocol. Overdoses are not considered AEs and should not be recorded as an AE on the CRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to Biogen or designee within 24 hours of the study site becoming aware of the overdose. An overdose must be reported to Biogen or designee even if the overdose does not result in an AE. If an overdose results in an AE, the AE must be recorded. If an overdose results in an SAE, both the SAE and Overdose forms must be completed and faxed or emailed to Biogen or designee. All study treatment-related dosing information must be recorded on the dosing CRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current standards of care. The Investigator (or designee) should contact the study's Medical Director. Refer to the Study Contact List for complete contact information.

15.4.3.1. Unblinding for Medical Emergency

In a medical emergency when knowledge of the subject's treatment assignment may influence the subject's clinical care, the Investigator may access the subject's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the subject's source documents. The Investigator is strongly advised not to divulge the subject's treatment assignment to any individual not directly involved in managing the medical emergency, or to personnel involved with the analysis and conduct of the study. The Investigator can contact Biogen or designee to discuss such situations.

15.5. Contraception Requirements

All women of childbearing potential and all men must ensure that highly effective contraception is used during the study and for at least 3 months after their last dose of study treatment. In addition, subjects should not donate sperm or eggs for the duration of the study and for at least 3 months after their last dose of study treatment.

For the purposes of this study, women who do not meet one of the following criteria are considered to be physiologically capable of becoming pregnant and are, therefore, defined as women of childbearing potential:

- Postmenopausal
    - 12 continuous months of natural (spontaneous) amenorrhea without an alternative medical cause
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy
- Female surgical sterilization (e.g., bilateral tubal ligation)

For the purposes of the study, highly effective contraception is defined as contraception that achieves a failure rate of less than 1% when used consistently and correctly and includes the use of 1 of the following:

For females:

- Established use of oral, intravaginal, or transdermal combined (estrogen and progestogen containing) hormonal methods of contraception associated with the inhibition of ovulation.
- Established use of oral, injected, or implanted progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

Note: Female subjects using concomitant enzyme-inducing AEDs should be advised that highly effective contraception would be limited to:

- Established use of injected progestogen-only hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.
- Bilateral tubal occlusion.
- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

For males:

- Vasectomy with negative semen analysis at follow-up.
- Sex with a woman who uses the methods described for females if she is of childbearing potential.

True abstinence, when this is consistent with the preferred and usual lifestyle of the subject, can be considered an acceptable method of contraception based on the evaluation of the Investigator who should also take into consideration the duration of the clinical study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the CRF regardless of the severity or relationship to study treatment.
- Determine the seriousness, relationship, and severity of each event.
- Determine the onset and resolution dates of each event.
- Monitor and record all pregnancies in female subjects and follow up on the outcome of all pregnancies.
- Complete an SAE form for each SAE and fax or email it to Biogen or designee within 24 hours of the study site staff becoming aware of the event.
- Pursue SAE follow-up information actively and persistently. Follow-up information must be reported to Biogen or designee within 24 hours of the study site staff becoming aware of new information.
- Ensure all AE and SAE reports are supported by documentation in the subjects' medical records.
- Pursue AE follow-up information, if possible, until the event has resolved or become stable. Record AE follow-up information, including resolution, on the CRF, as applicable.
- Report SAEs to local ethics committees, as required by local law.

15.6.2. Biogen

Biogen's responsibilities include the following:

- Before a study site can enroll any subjects, the Clinical Monitor is responsible for reviewing with study site staff the definitions of AE and SAE, as well as the instructions for monitoring, recording, and reporting AEs and SAEs.

- Biogen is to notify all appropriate regulatory authorities, central ethics committees, and Investigators of SAEs, as required by local law, within required time frames.

16. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The study objectives and the endpoints of the placebo-controlled phase are described in Section 6. This section describes the analyses of the placebo-controlled phase endpoints; details of the endpoints and the method of analysis for the open-label phase will be described in the SAP.

16.1. Efficacy

16.1.1. Analysis Population

The efficacy endpoints will be analyzed for the intent-to-treat (ITT) population at the end of placebo-controlled phase of the study. The ITT population will include all randomized subjects who receive at least 1 dose of double-blind treatment. Subjects will be analyzed in the groups to which they were randomized.

16.1.2. General Methods of Analysis

Unless otherwise specified, continuous variables will be summarized using summary statistics (mean, standard deviation, median, minimum, and maximum) by treatment group, and categorical variables will be presented using frequency distributions by timepoint and treatment group. Point estimates and 95% confidence intervals (CIs) will be provided where applicable.

For the assessment of seizure frequency, the seizure frequency (number of seizures per 28 days) at each visit will be calculated based on the sum of the seizures reported in the subject seizure diary and the number of days with nonmissing seizure frequency data in the subject seizure diary after the previous visit. If an infusion is missed, the seizure frequency will be calculated based on the target visit date. Baseline seizure frequency (number of seizure per 28 days) will be calculated based on the subject seizure diary data during the prospective baseline period, as follows:

$$\text{Baseline seizure frequency} = \frac{\text{Number of seizures during baseline period}}{\text{Number of days with non-missing seizure frequency}} \times 28$$

For other assessments, Baseline will be defined as the closest nonmissing value prior to the first infusion of study treatment.

16.1.2.1. Analysis of the Primary Endpoint

The primary efficacy endpoint of change from baseline of log-transformed seizure frequency (number of seizures per 28 days) over Weeks 8 to 24 of treatment will be summarized using descriptive statistics by treatment groups and visits. A mixed model for repeated measures (MMRM) will be used to analyze the change from Baseline of log-transformed seizure frequency

(number of seizures per 28 days). Treatment, visit, treatment-by-visit interaction, log-transformed baseline seizure frequency (number of seizures per 28 days), and stratification factors, such as high seizure frequency category and epilepsy types, will be included in the MMRM as fixed effects. The average effect over Weeks 8 to 24 of each treatment group, as well as the treatment difference, will be displayed with a 95% CI and p-value.

Seizure data will be censored after the protocol-specified modification of AEDs. Sensitivity analyses will be performed based on all the seizure diary data, including the data after the protocol-specified modification of AEDs.

Sensitivity analyses will be performed to evaluate the impact of missing data. Multiple imputations will be used to handle the missing data, and the details will be specified in the SAP.

16.1.2.2. Analysis of the Secondary Endpoints

16.1.2.2.1. Proportion of Responders

A responder is defined as subject with a ≥50% reduction from Baseline in seizure frequency (number of seizures per 28 days) during Weeks 8 to 24 of treatment. This analysis includes all randomized subjects in ITT population who has at least 1 postbaseline seizure assessment after Week 8. Subjects who withdraw from treatment or require protocol-specified modifications of AEDs prior to Week 24 (completion of the placebo-controlled phase) will be considered as nonresponders in the responder analysis. The proportion of responders will be analyzed using a logistic regression model, with effects for treatment and stratification variables (where possible) as factors (fixed covariates), and log-transformed baseline seizure frequency (number of seizures per 28 days) as a continuous covariate (measured over the prospective baseline period). The odds ratio from the logistic regression model will be displayed with 95% CI and p-value.

Sensitivity analyses will be performed to evaluate the proportion of responders with a ≥75% reduction from Baseline.

16.1.2.2.2. Proportion of Subjects Free From Seizures

The proportion of subjects free from seizures during Weeks 8 to 24 of treatment will be analyzed using a logistic regression model, with effects for treatment and stratification variables (where possible) as factors (fixed covariates), and log-transformed baseline seizure frequency (number of seizures per 28 days) as a continuous covariate (measured over the prospective baseline period). The odds ratio from the logistic regression model will be displayed with 95% CI and p-value.

All subjects in the ITT population who have at least 1 postbaseline seizure assessment after Week 8 will be included in this analysis. Subjects who withdraw from treatment, require protocol-specified modification of AEDs prior to Week 24 (completion of the placebo-controlled phase), or have any missing diary data during Weeks 8 to 24 of treatment will be considered as not free from seizures in this analysis.

16.1.2.2.3. Percentage of Seizure-Free Days Gained, Standardized Over 28 Days, During Weeks 8 to 24 of Treatment Compared With Baseline

An MMRM will be used to analyze the change from Baseline of log-transformed seizure-free days (number of seizure-free days per 28 days). Treatment, visit, treatment-by-visit interaction, log-transformed baseline seizure-free days (number of seizure-free days per 28 days), and stratification factors, such as high seizure frequency category and epilepsy types, will be included in the MMRM as fixed effects. The average effect over Weeks 8 to 24 of each treatment group, as well as the treatment difference, will be displayed with a 95% CI and p-value.

16.1.2.2.4. Proportion of Subjects With Inadequate Treatment Response During Weeks 8 to 24

The proportion of subjects with protocol-defined inadequate treatment response will be analyzed using a logistic regression model with effects for treatment and stratification variables (where possible) as factors (fixed covariates), and log-transformed baseline seizure frequency (number of seizures per 28 days) as a continuous covariate (measured over the prospective baseline period). The odds ratio from the logistic regression will be displayed with 95% CI and p-value.

16.1.2.3. Analysis of Additional Endpoints

Analyses for exploratory efficacy endpoints will be provided in the SAP.

16.2. Pharmacokinetics

16.2.1. Analysis Population

The PK population is defined as all subjects who receive at least 1 dose of study treatment and have at least 1 measurable concentration of natalizumab in serum.

16.2.2. Methods of Analysis

The serum concentration of natalizumab will be summarized by visit using standard descriptive statistics (e.g., median, mean, standard deviation, range). Additionally, a population PK analysis will be conducted to characterize the PK of natalizumab in subjects with focal epilepsy, to estimate population PK parameters of natalizumab, and to derive the C_{max} and AUC_{tau} at steady state. In addition, an exposure-response analysis will be performed to evaluate the relationship between exposure of natalizumab and clinical endpoints. The results of the analysis will be reported in a separate population PK report.

[redacted]

[redacted]

16.5. Safety

16.5.1. Analysis Population

The safety population will include subjects who are randomized and have received at least 1 infusion of study treatment.

16.5.2. Methods of Analysis

No formal statistical testing will be performed on the safety data.

16.5.2.1. Adverse Events

AEs will be coded using the Medical Dictionary for Regulatory Activities.

The incidence of treatment-emergent AEs will be tabulated by treatment group, severity, and relationship to study treatment. The tabular summaries will include incidence by system organ class and by preferred term. AEs and SAEs resulting in study withdrawal will be summarized by treatment group.

Treatment-emergent AEs are those defined as having onset after the start of study treatment, or a sign, symptom, or diagnosis that worsens since the event was previously reported. For the analysis of incidence by severity, the occurrence of the AE with the greatest severity will be used, and a subject will be counted only once and only in the category of the greatest severity for each event. For the analysis of incidence by relationship to study treatment, the occurrence of the AE with the strongest relationship to study treatment will be used, and a subject will be counted only once and only in the category of the strongest relationship to study treatment for each event.

16.5.2.2. Clinical Laboratory Results

Clinically relevant abnormalities for laboratory parameters will be identified by treatment group using shift tables and evaluated for their clinical relevance.

16.5.2.3. Vital Signs

The analysis of vital signs will focus on the incidence of clinically relevant abnormalities by treatment group.

16.5.2.4. eC-SSRS/C-SSRS

Summary statistics of the eC-SSRS/C-SSRS at each visit will be presented by treatment group using observed data.

16.6. Immunogenicity (Anti-Natalizumab Antibodies)

Anti-natalizumab antibodies in serum will be collected at timepoints outlined in the schedule of activities (Table 1) and analyzed at the end of the study. Results including percentage of subjects who develop antibodies will be summarized by treatment group at each scheduled timepoint.

16.7. Interim Analyses

One interim analysis is planned to assess futility and sample size re-estimation after approximately 50% of the enrolled subjects have completed at least 16 weeks of the 24-week placebo-controlled phase. The interim analysis will be based on the change (in natural logarithmic scale) from Baseline in seizure frequency, standardized over 28 days, from the subjects who have completed treatment or terminated early. Interim analyses will include the following:

- Futility criteria will be based on the predictive probability of demonstrating prespecified treatment differences at study completion given the interim observations. The details of the futility criteria will be fully specified in the SAP.

- Sample size re-estimation may be performed at the time of the interim analysis based on the principle of the promising zone approach [Mehta and Pocock 2011]. The details of sample size re-estimation and the rule of sample size increase will be specified in the SAP. Sample size may be increased to a maximum of 100 subjects in total.

Neither the futility analysis nor the sample size re-estimation is expected to increase the type I error rate; no multiplicity adjustment will be made to the primary analysis.

In order to maintain the treatment blind, an independent group not involved in study conduct, including the DSMC, will perform the interim analyses. Details for data transfer will be included in the unblinding plan for the study.

16.8. Sample Size Considerations

Twenty-nine subjects per treatment arm will provide 80% power to detect a treatment difference of -0.375 between natalizumab and placebo in the natural log-transformed seizure frequency,

standardized over 28 days, at a 2-sided significance level of 0.050, assuming a common standard deviation of the log-transformed frequency of 0.5. For example, if the placebo group has a 20% reduction from Baseline in seizure frequency and the active group has a 45% reduction from Baseline in seizure frequency, the sample size would provide 80% power to detect this difference. To account for a discontinuation rate up to 15%, a total of approximately 70 subjects will be randomized.

17. ETHICAL REQUIREMENTS

Biogen, the CRO, and the Investigator must comply with all instructions, regulations, and agreements in this protocol and applicable International Council for Harmonisation (ICH) and Good Clinical Practice (GCP) guidelines and conduct the study according to local regulations.

The Investigator may delegate responsibilities for study-related tasks where appropriate to individuals sufficiently qualified by education, training, and experience, in accordance with applicable ICH and GCP guidelines. The Investigator should maintain a list of the appropriately qualified persons to whom significant study-related duties have been delegated. The Investigator is responsible for supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

This study will be performed in alignment with the ethical principles outlined in the Declaration of Helsinki.

17.2. Ethics Committee

The Investigator must obtain ethics committee approval of the protocol, ICF, and other required study documents prior to starting the study.

If the Investigator makes any changes to the ICF, Biogen must approve the changes before the ICF is submitted to the ethics committee. A copy of the approved ICF must be provided to Biogen. After approval, the ICF must not be altered without the agreement of the relevant ethics committee and Biogen.

It is the responsibility of the Investigators to ensure that all aspects of institutional review are conducted in accordance with current applicable regulations.

Biogen must receive a letter documenting ethics committee approval, which specifically identifies the protocol, protocol number, and ICF, prior to the initiation of the study. Protocol amendments will be subject to the same requirements as the original protocol.

A progress report must be submitted to the ethics committee at required intervals and not less than annually.

At the completion or termination of the study, the study site must submit a close-out letter to the ethics committee and Biogen.

17.3. Subject Information and Consent

Prior to performing any study-related activities under this protocol, including screening tests and assessments, written informed consent with the approved ICF must be obtained from the subject or subject's legally authorized representative (e.g., parent or legal guardian), as applicable, in accordance with local practice and regulations.

The background of the proposed study, the procedures, the benefits and risks of the study, and that study participation is voluntary for the subject must be explained to the subject (or the subject's legally authorized representative). The subject must be given sufficient time to consider whether to participate in the study.

Subjects will be informed that their race and ethnicity will be collected and will be used during analysis of study results.

A copy of the signed and dated ICF must be given to the subject or the subject's legally authorized representative. The original signed and dated ICF will be retained with the study records. Local regulations must be complied with in respect to the final disposition of the original (wet signature) and copies of the signed and dated ICFs.

Confirmation of informed consent must also be documented in the subject's medical record.

17.4. Subject Data Protection

Prior to any testing under this protocol, including screening tests and assessments, candidates must also provide all authorizations required by local law (e.g., Protected Health Information authorization in North America).

During the study, subjects' race and ethnicity will be collected. These data may be used in the analysis of the safety and/or PK profile of the study treatment. It is unknown whether the effects of the study treatment are influenced by race or ethnicity.

Study reports will be used for research purposes only. The subject will not be identified by name in CRFs, study-related forms, study reports, or any related publications. Biogen, its partners and designees, ethics committees, and various government health agencies may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential.

17.5. Compensation for Injury

Biogen maintains appropriate insurance coverage for clinical studies and will follow applicable local compensation laws.

17.6. Conflict of Interest

The Investigators should address any potential conflicts of interest (e.g., financial interest in Biogen or the CRO) with the subject before the subject makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

Biogen will register the study and poststudy results regardless of outcome on a publicly accessible website in accordance with the applicable laws and regulations.

18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any subjects prior to completion of a study initiation visit, conducted by Biogen or the CRO. This initiation visit will include a detailed review of the protocol and study procedures.

18.2. Quality Control and Quality Assurance

Quality control procedures will be implemented at each stage of data handling to ensure that all data are reliable and have been processed correctly. Data anomalies will be communicated to the sites for clarification and resolution, as appropriate.

During and/or after completion of the study, quality assurance officers named by Biogen or the regulatory authorities may wish to perform onsite audits or inspections. The Investigator will be expected to cooperate with any audit or inspection and to provide assistance and documentation (including source data) as requested.

18.3. Monitoring of the Study

The Investigator must permit study-related monitoring by providing direct access to source data and to the subjects' medical histories. Source data must be attributable, legible, contemporaneous, original, accurate, and complete. Changes to source data must be traceable, not obscure the original entry, and be explained if necessary (e.g., with an audit trail). The Investigator should maintain a record of the location(s) of essential documents.

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, and critical data and processes.

During these visits, CRFs, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be resolved. Documentation of results will be provided to Biogen or designee in a timely fashion to allow follow-up and verification of compliance with the monitoring plan. Remote evaluation of data (centralized monitoring) may also be conducted and reported as defined in the monitoring plan.

Monitoring visits must be conducted according to the applicable ICH and GCP guidelines to ensure the protection of subject rights and well-being, protocol adherence, quality of data (accurate, complete, and verifiable), study treatment accountability, compliance with regulatory requirements, and continued adequacy of the study site and its facilities.

18.4. Study Funding

Biogen is the Sponsor of the study and is funding the study. All financial details are provided in the separate contracts between the institution, Investigator, and Biogen.

18.5. Publications

Details are included in the clinical trial agreement for this study.

19. FURTHER REQUIREMENTS AND GENERAL INFORMATION

19.1. External Contract Organizations

Biogen will ensure oversight of any study-related duties and functions carried out on its behalf and will specify in writing all duties and functions that are transferred.

19.1.1. Contract Research Organization

A CRO will be responsible for all administrative aspects of the study including but not limited to study initiation, monitoring, management of AEs and SAE reports, and data management. Before subjects are screened at each study site, the CRO will review study responsibilities with the Investigators and other study site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before subjects are screened or enrolled, the IRT vendor will provide each study site with the necessary training, a user manual, and access rights to the system.

19.1.3. Electronic Data Capture

Subject information will be captured and managed by study sites on electronic CRFs by a Web-based electronic data capture tool developed by the CRO and configured by the electronic data capture vendor.

The eCOA will be entered by the subject or caregiver on a device developed and supported by the eCOA vendor. Study site staff will monitor data via a secure Web portal developed and supported by the eCOA vendor.

19.1.4. Central Laboratories for Laboratory Assessments

Central laboratories have been selected by Biogen to analyze all hematology, blood chemistry, urinalysis, serum pregnancy, hepatitis B and C, anti-natalizumab antibody, anti-JCV antibody, PK, [redacted] samples collected for this study.

19.2. Study Committees

19.2.1. Advisory Committee

An advisory committee will be formed to provide scientific and medical direction for the study and to oversee the administrative progress of the study. The advisory committee will meet periodically as needed to monitor subject accrual and to monitor compliance with the protocol at individual study sites. The advisory committee will be blinded to subject treatment assignments.

Members of the advisory committee will include the Medical Director, Clinical Operations Lead, and Project Statistician from Biogen (and/or their designees), and select Investigators. Biogen will designate 1 of the participating Investigators to be the chairperson of the advisory committee.

19.2.2. Independent Epilepsy Review Committee

An IERC will be formed to oversee subject selection and modification of AEDs. The review committee will consist of board-certified physicians with expertise in epilepsy. Specifically, members of the review committee will carry out the following:

- Confirm the diagnosis of drug-resistant focal epilepsy in each subject (Inclusion Criterion 6).
- Adjudicate the presence or absence of a structural etiology for focal epilepsy (Inclusion Criterion 6).
- Approve any change in AEDs after Week 12 of the placebo-controlled phase through the End of Study Visit (Week 60) or Follow-up Visit for ET Subjects (16 weeks after the last dose of study treatment) for lack of improvement or ongoing seizures.

19.2.3. Drug Safety Monitoring Committee

An independent DSMC will be formed to review data regularly to assess safety and risk-benefit and recommend appropriate modification to the study or termination of the study. The DSMC will receive reports of, for example, all SUSARs, AEs, and key laboratory tests and will meet throughout the study at regular timepoints, as described in the DSMC charter. Although seizures will not be reported as AEs, the committee will also have oversight of these data as seizure frequency is the primary endpoint.

19.2.4. Independent Safety Monitor

The ISM is an individual board-certified physician who is neither an employee of Biogen nor a participating Investigator. The ISM will regularly assess WBC data (other than ANC) in order to monitor subject safety. The ISM will inform the Investigator of any clinically significant findings on a specific subject through the Medical Monitor without disclosing any potential treatment assignment information. The ISM may request any additional information on individual subjects to confirm safety of an individual subject. The ISM will also inform the DSMC of any safety concerns arising from the review of WBC data.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect subject safety, the scope of the investigation, or the scientific quality of the study must be approved by the ethics committee before implementation of such modifications to the conduct of the study. If required by local

law, such modifications must also be approved by the appropriate regulatory agency prior to implementation.

However, Biogen may, at any time, amend this protocol to eliminate an apparent immediate hazard to a subject. In this case, the appropriate regulatory authorities will be notified subsequent to the modification.

In the event of a protocol modification, the ICF may require similar modifications (see Section 17).

19.4. Ethics Committee Notification of Study Completion or Termination

Where required, the regulatory authorities and ethics committees must be notified of completion or termination of this study and sent a copy of the study synopsis in accordance with necessary timelines.

19.5. Retention of Study Data

The minimum retention time for study records will meet the strictest standard applicable to that study site, as dictated by any institutional requirements or local, national, or regional laws or regulations. Prior to proceeding with destruction of records, the Investigator must notify Biogen in writing and receive written authorization from Biogen to destroy study records. In addition, the Investigator must notify Biogen of any changes in the archival arrangements including but not limited to archival at an offsite facility or transfer of ownership if the Investigator leaves the study site.

19.6. Study Report Signatory

Biogen will designate one of the participating Investigators as a signatory for the study report. This determination will be made by several factors, including but not limited to, the Investigator's experience and reputation in the studied indication; the Investigator's contribution to the study in terms of design, management, and/or subject enrollment; or by other factors determined to be relevant by Biogen.

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Randomized, Double-Blind, Placebo-Controlled, Phase 2 Study Exploring the Efficacy, Safety, and Tolerability of Natalizumab (BG00002) as Adjunctive Therapy in Adult Subjects With Drug-Resistant Focal Epilepsy" and agree to conduct the study according to the protocol and the applicable ICH guidelines and GCP regulations, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

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Investigator's Signature Date

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Investigator's Name (Print)

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Study Site (Print)