COVER PAGE

Official Title:	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema Following Large Hemispheric Infarction
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PROTOCOL NUMBER: 252LH301

PHASE OF DEVELOPMENT: 3

Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema following Large Hemispheric Infarction

CHARM Study: Glibenclamide for large hemispheric infarction

analyzing mRS and mortality

IND NUMBER: **128581**

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Protocol 252LH301 was approved by:

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Date

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Biogen

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1. SYNOPSIS

Protocol Title:	Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema following Large Hemispheric Infarction
Protocol Number:	252LH301
Version Number:	3.0
Name of Study Treatment:	BIIB093
Study Phase:	3
Study Indication:	Large Hemispheric Infarction (LHI)
Study Rationale:	LHI is defined as an ischemic stroke affecting the total or sub-total territory of the middle cerebral artery (MCA), with or without involvement of the adjacent supratentorial territories (i.e., anterior cerebral artery [ACA] or posterior cerebral artery [PCA]). LHI is frequently complicated by edema that ultimately may lead to transtentorial herniation. In Study 203 (GAMES-RP), malignant edema complicated approximately 50% of LHI. The prognosis for patients with malignant edema is frequently poor, with case fatality as high as 40% to 80%. BIIB093 (also known as glibenclamide and/or glyburide) is a sulfonylurea that has its effect via antagonism of the sulfonylurea receptor 1 (SUR1). BIIB093 specifically targets the SUR1-TRPM4 channel, a mechanism involved in development of edema through inhibition of newly upregulated SUR1-TRPM4 channels, reducing the formation of edema and its sequalae in multiple models of LHI. Intravenous (IV) BIIB093 has been shown to be safe and well tolerated in patients with LHI at risk for cerebral edema. The current study (Study 252LH301) is a 2-part Phase 3 study to assess efficacy and safety of intravenous (IV) BIIB093 to improve functional outcomes in subjects with LHI. Part 1 is a 90-day efficacy and safety evaluable period following a 72-hour infusion of BIIB093 or matching placebo, and Part 2 is a follow-up period with study visits at Month 6 and Month 12.

Part 1 Study Objectives and Endpoints:

The primary objective is to determine if BIIB093 improves functional outcome at Day 90 as measured by the modified Rankin Scale (mRS) when compared with placebo in subjects with LHI. The endpoint that relates to this objective is Day 90 mRS as a 5-category ordinal scale (the 5-category mRS will combine mRS categories 0 and 1 and mRS categories 5 and 6).

Part 1 secondary objectives and endpoints are as follows:

- To determine if BIIB093 improves overall survival at Day 90 when compared with placebo. The endpoint associated with this objective is time to all-cause death over the 90-day period.
- To determine if BIIB093 improves functional outcome at Day 90 on the mRS dichotomized 0-4 vs. 5-6, when compared with placebo. The endpoint related to this objective is the proportion of subjects who achieved mRS 0-4 at Day 90.
- To determine if BIIB093 reduces midline shift at 72 hours (or at time of decompressive craniectomy [DC] or comfort measures only [CMO], if earlier) when compared with placebo. The endpoint related to this objective is the midline shift at 72 hours (or at time prior to DC or CMO, if earlier).
- To evaluate the safety and tolerability of BIIB093 in subjects with LHI. The endpoint related to this objective is the incidence of adverse events, serious adverse events (SAEs), and clinically significant abnormal vital signs, 12-lead electrocardiogram findings, and laboratory results (including those associated with blood glucose levels).

[redacted]

Part 2 Study Objectives and Endpoints:	The Part 2 study objectives are to evaluate long-term disability and patient outcomes following LHI and to assess safety during the follow-up period. **Part 2 endpoints include the following:** • mRS score at Month 6 and Month 12 as a 5-category ordinal scale (the 5-category mRS combines mRS categories 0 and 1 and mRS categories 5 and 6) • EQ-5D-5L, BI score, and SIS-16 at Month 6 and Month 12 • HealthCare Resource Utilization Questionnaire and Zarit Burden Interview at Month 12 • Incidence of SAEs
Study Design:	This is a Phase 3 randomized, multicenter, placebo-controlled, double-blind study of subjects aged 18 to 85 with a LHI and time from symptom onset to start of Study Drug infusion of ≤ 10 hours. Following a 3-stage 72-hour continuous infusion of BIIB093 or matching placebo, subjects will receive efficacy and safety evaluations for 90 days. The primary efficacy assessment will be the mRS at Day 90. The study will be conducted as a single study in two parts. Part 1 of the study consists of the baseline visit, Study Drug infusion and efficacy and safety period through Study Day 90 (primary endpoint). Part 2 will be a LHI follow-up period from Day 91 to Month 12.
Study Location:	Approximately 200 to 250 sites in 20 to 25 countries globally (excluding the People's Republic of China) are planned.
Number of Planned Subjects:	Approximately 768 subjects will be randomized, ages 18-85 years, of whom approximately 80 may be >70 years of age.
Study Population:	This study will be conducted in subjects aged 18 to 85 years, inclusive, who have a clinical diagnosis of acute ischemic stroke in the MCA

	territory. (Supratentorial PCA and/or ACA territory involvement in addition to primary MCA territory stroke is acceptable.) Detailed criteria are described in Section 8.
Treatment Groups:	Study subjects will be randomized in a 1:1 allocation to receive either BIIB093 IV 8.6 mg total dose or matching placebo administered as a 3-stage continuous infusion over 72 hours. There are 2 age groups (18 to 70 vs. >70-85). Within each age group, subjects will be stratified based on region, recombinant tissue plasminogen activator (yes, no), thrombectomy (yes, no), use of Alberta Stroke Program Early computed tomography (CT) Score (ASPECTS) for screening (yes, no), and baseline NIHSS (≤20 vs. >20). Since there is limited experience with thrombectomy in LHI patients, the number of subjects with thrombectomy performed prior to randomization is targeted at approximately 20% in the ≤ 70 year age group but may vary from this to reflect the evolving standard of care and stroke treatment guidelines. The number of subjects with thrombectomy performed prior to randomization is targeted at approximately 8% in the >70 year age group.
Duration of Treatment and Follow-up:	The primary study outcome is at Day 90 (completion of Part 1). All subjects will be followed for 1 year (completion of Part 2).

2.LIST OF ABBREVIATIONS

ABCC8	ATP Binding Cassette Subfamily C Member 8 protein
ACA	anterior cerebral artery
AE	adverse event
AHA	American Heart Association
ALT	alanine aminotransferase
ASPECTS	Alberta Stroke Program Early CT Score
AST	aspartate aminotransferase
ATP	adenosine triphosphate
BG	blood glucose
BI	Barthel Index
CHW	Cui-Hung-Wang
CMO	comfort measures only
CRO	contract research organization
CTP	computed tomography perfusion
CYP	cytochrome P450
CYP2C9	cytochrome P450 2C9
D10NS	10% dextrose in normal saline
D50W	dextrose 50% in water
D5NS	5% dextrose in normal saline
DC	decompressive craniectomy
DHA	Directions for Handling and Administration
DWI	diffusion-weighted imaging
ECG	electrocardiogram
eCRF	electronic case report form
EQ-5D-5L	EuroQol 5-level assessment of health outcomes
G6PD	glucose-6-phosphate dehydrogenase
GCP	Good Clinical Practice
ICF	informed consent form
ICH	International Council for Harmonisation
ICL	imaging core laboratory
IDMC	independent data monitoring committee
IRT	interactive response technology
IV	intravenous
LAR	legally authorized representative
LHI	large hemispheric infarction
MCA	middle cerebral artery
MI	myocardial infarction
mITT	modified intent-to-treat
[redacted]	[redacted]
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NCCT	non-contrast computed tomography

NIDDM	non-insulin-dependent diabetes mellitus
NIHSS	National Institutes of Health Stroke Scale
OATP1B1	organic-anion-transporting polypeptide 1B1
PCA	posterior cerebral artery
[redacted]	[redacted]
POC	point-of-care
PVC	polyvinyl chloride
QTc	corrected QT interval
rtPA	recombinant tissue plasminogen activator or thrombolysis
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SIS-16	Stroke Impact Scale 16 Questions
SOC	standard of care
SUR1	sulfonylurea receptor 1
SUR1-TRPM4	a nonselective cation channel formed by the sulfonylurea receptor-1 (SUR1) regulatory unit in association with the transient receptor potential cation channel subfamily M member 4 (TRPM4) pore
SUSAR	Suspected Unexpected Serious Adverse Reaction
ULN	upper limit of normal

3.SPONSOR INFORMATION

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For urgent medical issues in which the Medical Monitor should be contacted, please refer to the Study Reference Guide's Official 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

BIIB093 is an investigational product under development for the treatment and prevention of severe cerebral edema in patients with large hemispheric infarction and for the treatment of brain contusion (refer to the Investigator's Brochure).

4.1. Large Hemispheric Infarction Background

Large hemispheric infarction (LHI) is defined as an ischemic stroke affecting the total or sub-total territory of the middle cerebral artery (MCA), involving the basal ganglia at least partially, with or without involvement of the adjacent supratentorial territories (i.e., anterior cerebral artery [ACA] or posterior cerebral artery [PCA]). LHI is frequently complicated by edema that ultimately leads to transtentorial herniation [Torbey 2015].

Life-threatening edema complicates LHI prognosis in approximately 50% of patients with LHI. Such swelling can compromise arterial inflow to surrounding tissues causing further ischemic damage and enlargement of the infarct, and frequently results in brain herniation and death. Clinical characteristics comprise secondary deterioration of neurological symptoms, particularly a disturbance of consciousness and further clinical signs of brain stem herniation. The prognosis for these patients is frequently poor, with case fatality as high as 40% to 80% [Hacke 1996], [Berrouschot 1998].

Decompressive craniectomy (DC) has improved the outlook for LHI and did reduce mortality to 22% in a pooled analysis of DC studies [Vahedi 2007]. However, numerous factors limit the usefulness of DC, including limited eligibility for surgery among patients who are gravely ill and have life-threatening co-morbidities [Arac 2009], and DC is not indicated for patients with LHI prior to development of clinically significant edema.

4.2. Rationale for Glibenclamide in Reducing Edema Formation

Glibenclamide (5-chloro-N-(4-[N-(cyclohexylcarbamoyl) sulfamoyl]phenethyl)-2-methoxybenzamide; also known as glyburide) is an antidiabetic medication in a class of medications known as sulfonylureas. Oral glibenclamide has been used successfully in the treatment of non-insulin-dependent diabetes mellitus (NIDDM) for >20 years. In treating NIDDM, glibenclamide works by inhibiting adenosine triphosphate (ATP)-sensitive potassium channels in pancreatic beta cells by antagonism of sulfonylurea receptor 1 (SUR1). This inhibition causes cell membrane depolarization, which causes voltage-dependent calcium channels to open, which in turn causes an increase in intracellular calcium in the beta cell, stimulating insulin release.

The SUR1-TRPM4 channel is a nonselective cation channel that is expressed in the central nervous system only under conditions of ischemia, hypoxia, and trauma [Chen 2003; Chen and Simard 2001; Simard 2006]. Channel opening, which is triggered by depletion of ATP, results in cytotoxic edema, oncotic cell death, and vasogenic edema [Simard 2007]. If the cell involved in the above pathophysiological sequence is a microvascular endothelial cell, these mechanisms result in formation of space-occupying edema [Simard 2006; Simard 2007]. Brain edema

formation through this mechanism is a serious complication and can lead to mechanical compression of adjacent brain structures, herniation, and death. Additionally, it can impair regional cerebral blood flow, resulting in further ischemia.

Like the ATP-sensitive potassium channels in pancreatic beta cells, the SUR1-TRPM4 channel is regulated by SUR1 and is blocked by sulfonylureas such as glibenclamide. Glibenclamide thus specifically targets a mechanism involved in development of edema, reducing the formation of edema and secondary damage resulting from edema in multiple models of LHI with treatment delays of up to 10 hours following LHI (Table 1).

Table 1: Beneficial Effects of Glibenclamide in Rat Models of Large Hemispheric Infarction

Publication (Tx Delay)	Effects of Glibenclamide (All effects listed were statistically significant: $0.001 \leq P < 0.05$)	SLP[1]
[Simard 2006] (none)	reduced mortality from 65% to 24% at 7 d reduced excess brain water by 42% at 8 h	Yes[A]
[Simard 2010] (6 h)	reduced mortality from 67% to 5% at 24 h reduced hemispheric swelling from 21% to 8% at 24 h better preservation of watershed cortex and white matter, better neuroscores, Garcia scores, and the trajectory of weight gain compared with DC during 2 weeks post-insult	Yes[B]
[Simard 2012a] + rtPA (4.5 & 10 h)	reduced mortality from 53% to 17% or 12% at 48 h (Vehicle vs. Tx at 4.5 h or 10 h, respectively) reduced swelling from 14.7% to 8.1% or 8.8% at 24 h (same groups) improved Garcia scores from 3.8 to 7.6 or 8.4 at 48 h (same groups)	Yes[B]
[Simard 2012b] + rtPA (6 h)	reduced hemispheric swelling from 26% to 12% at 24 h improved neuroscores from 7 to 3 at 2 weeks	Yes[A]

d = days; DC = decompressive craniectomy; h = hours; rtPA = recombinant tissue plasminogen activator; SLP = STAIR laboratory practice; Tx = treatment.
[1]SLP, including monitoring laser doppler flowmetry and blood gases, temperature control, random treatment allocation, and blinded outcome assessment, were performed but not documented (Yes[A]) or performed and documented (Yes[B]).

4.3. Current Therapies for Edema Associated with LHI

Standard of care treatment for ischemic stroke is reperfusion using recombinant tissue plasminogen activator (rtPA). A link between reperfusion and the development of life-threatening edema has been proposed [Hallenbeck and Dutka 1990; Koudstaal 1988; Nielsen 2012], and the use of rtPA may aggravate the development of edema [Rudolf 1998].

In addition to reperfusion therapy, thrombectomy, using a mechanical device for clot disruption for the treatment of stroke has increased in prevalence. Although thrombectomy or other reperfusion therapies may be used in patients at risk for large infarction, these therapies are not always successful; therefore, some treated patients may remain at risk for life-threatening complications of edema.

Mannitol and hypertonic saline are osmotic agents that are approved for reducing intracranial pressure and are used to reduce brain swelling in LHI after the swelling leads to neurological deterioration, although American Heart Association (AHA) guidelines [Jauch 2013; Wijdicks 2014] state that the effects in patients with ischemic brain swelling is unknown.

Furthermore, randomized controlled trials comparing mannitol with placebo or open control were reviewed and found there was not enough evidence to support the routine use of mannitol in all acute stroke patients [Bereczki 2007]. Glucocorticoids are similarly approved for the treatment of cerebral edema ([e.g., Decadron [dexamethasone]). Randomized trials comparing corticosteroids with placebo or control in people with acute ischemic stroke were reviewed, determining there was not enough evidence to recommend corticosteroid treatment [Qizilbash 2002]. AHA and Neurocritical Care Society/German Society for Neurocritical and Emergency Medicine guidelines recommend corticosteroids not be administered in acute stroke [Jauch 2013; Torbey 2015; Wijdicks 2014].

DC has improved the bleak outlook for malignant MCA infarction and reduced mortality to 22% in a pooled analysis of DC studies [Vahedi 2007]. However, numerous factors limit the usefulness of DC, including limited eligibility for surgery among patients who are gravely ill and have important co-morbidities [Arac 2009], and DC is not indicated for patients with LHI prior to development of clinically significant edema.

There are currently no therapeutic approaches targeted at reducing the development of edema early after the index LHI. The ability to prevent the development of life-threatening edema would be a life-saving intervention that would meaningfully reduce mortality and morbidity. Thus, there is an unmet medical need for innovative medical strategies to treat LHI by reducing subsequent edema.

4.4. Profile of Previous Experience with Intravenous BIIB093

Glibenclamide administered as an intravenous (IV) formulation is being studied in LHI. IV glibenclamide is known as BIIB093 and was formerly known as CIRARA or RP-1127 when under development by Remedy Pharmaceuticals.

See the BIIB093 Investigator's Brochure for detailed information on relevant nonclinical and clinical studies.

4.4.1. Nonclinical Experience

The safety profile of 2 oral glibenclamide/glyburide products such as Micronase® and Glynase®, are considered supportive of BIIB093 as it relates to genotoxicity, carcinogenicity, and reproductive toxicity information. Biogen's nonclinical safety testing strategy for BIIB093 includes a completed local irritation and systemic toxicity study in rats (Study No. 0440RR31.001, Remedy No. RPI-TOX1), an in vitro hemolytic potential assay (Study No. 0725XR31.001), and 2 planned studies: a 14-day continuous infusion rat study and an extravascular irritation rabbit study. Further nonclinical information for glibenclamide is based on bibliographical data from peer-reviewed articles on genotoxicity, carcinogenicity, and

reproductive toxicity as well as the pharmacology of the substance published since the early 1970s.

4.4.2. Clinical Experience

A summary of results from the 2 LHI studies using the same dose of IV glibenclamide as proposed for the current study is provided below.

In Study 201 (GAMES-PILOT), 10 subjects with severe ischemic stroke and a baseline magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) lesion between 82 to 210 cc, age of 18 to 80 years, and time from symptom onset to drug infusion of <10 hours were enrolled at 2 clinical sites in the United States. The primary objective of the study was to assess the safety and feasibility of enrolling, evaluating, and treating subjects with LHI with BIIB093, whether or not they were treated IV with rtPA. Subjects who received intra-arterial reperfusion therapy, prophylactic DC, or were on sulfonylurea treatment at presentation were excluded. Nine out of 10 enrolled subjects received rtPA within 4.5 hours from onset of stroke. Baseline National Institute of Health Stroke Scale (NIHSS) scores ranged from 11 to 31, with a median of 18. The mean time from onset of stroke to treatment with BIIB093 was 8.7 hours, with a range of 6.8 to 9.9 hours. The incidence of malignant cerebral edema was 20%. Other than those who developed malignant edema, subjects did not require osmotherapy, intubation, or DC. Results from this study indicated that it was feasible to enroll, evaluate and treat subjects with severe stroke according to the protocol. The regimen was well tolerated, and there were no reported cases of hypoglycemia.

Study 203 (GAMES-RP) was a randomized, double-blind, placebo-controlled, multicenter study of BIIB093 in subjects with LHI. The study enrolled subjects aged 18 to 80 years who had a clinical diagnosis of large anterior circulation ischemic stroke <10 hours from time last known to be neurologically normal, confirmed by a baseline DWI lesion volume of 82 to 300 cm^3. Subjects who received intra-arterial reperfusion therapy, prophylactic DC, or were on sulfonylurea treatment at presentation were excluded. The primary objective was to assess clinical efficacy of BIIB093 compared with placebo in subjects with a severe anterior circulation ischemic stroke likely to develop malignant edema. In Study 203, malignant edema complicated approximately 50% of LHI. This primary efficacy endpoint was the proportion of subjects who achieved a modified Rankin Scale (mRS) score of 0 to 4 at Day 90 without undergoing DC. At Day 90, 17 subjects (41%) who received BIIB093 and 14 (39%) in the placebo group achieved the primary endpoint (adjusted odds ratio 0.87, 95% confidence interval 0.32 to 2.32; p=0.77); thus, the study did not achieve the primary endpoint. However, BIIB093 administration was associated with a potential reduction in mortality, which was accompanied by evidence of reduced brain edema and improved functional outcomes (as measured with mRS). Safety analysis suggested that BIIB093 was well tolerated in critically ill LHI participants [Sheth 2016].

4.4.3. Benefit/Risk

BIIB093 was shown to potentially reduce mortality associated with LHI, reducing brain edema, and improving functional outcomes. Currently, there is no therapy available to reduce brain swelling secondary to LHI and there is an unmet medical need for this life-threating condition.

BIIB093 given intravenously in 3-stage dosing regimen over 72 hours was generally well tolerated in the population of subjects with LHI. The only adverse drug reaction identified was hypoglycemia which can be mitigated by frequent blood glucose measurement and dose adjustment. The safety profile of BIIB093 observed in completed studies in LHI and TBI is detailed in the Investigator's Brochure. Based on the observed benefit in Phase 2 studies of BIIB093 for treatment of LHI and the safety profile, Biogen considers that the benefit/risk profile of BIIB093 remains positive and supports the continued development of BIIB093 for the treatment of patients with LHI.

4.5. Study Rationale

At present, no pharmacotherapy is available to reduce brain swelling secondary to LHI, and no drug therapy has been rigorously investigated for patients at a high risk of developing life-threatening edema. Given the promising results of the GAMES-PILOT and GAMES-RP studies, the current study will evaluate the efficacy and safety of BIIB093 in subjects with LHI.

4.6. Dosing Rationale

The total daily dose for the Phase 3 study (8.6 mg over 72 hours) was determined based on the maximum tolerated dose observed in healthy volunteers that did not produce persistent hypoglycemia in the Phase 1 study. The IV infusion regimen was refined based on Phase 1 data and PK modeling to a 3-stage dosing regimen over a period of 72 hrs. This dosing regimen was shown to be safe and well-tolerated in Phase 2, and systemic exposure is significantly lower than that from the approved therapeutic oral dose (maximum dose of 20 mg/day in in US and EU, and 10 mg/day in Japan for non-micronized glibenclamide [Euglucon®]) taken chronically by patients with diabetes. Therefore, this dosing regimen is selected for Phase 3 as it rapidly achieves and maintains the desired steady-state concentration of BIIB093 while staying below the concentration threshold associated with hypoglycemia. The 3-stage dosing regimen consists of an initial bolus loading dose (given over 2 mins), followed by constant IV infusion administered sequentially at two different flow rates (a rapid IV infusion for 6 hours followed by a maintenance IV infusion for the remaining 66 hours). The treatment period of 72 hours has been selected because in humans with LHI, herniation peaks at 2-3 days; thus, this infusion duration allows for intervention prior to peak edema and treats through the period where patients are at risk for severe edema.

5. SCHEDULE OF ACTIVITIES

Table 2: Schedule of Activities – Part 1 (Screening through Day 90)

	Screening / Enroll-ment	Hrs >0-12	Hr 24 (±12h)	Hr 48 (±12h)	Hr 72 (±12h)	Day 7 (±24h)/ Hospital Discharge	Day 30 (±7 d) Telephone/ Telemedicine Visit	Day 90 (±14 d)[1] In-person Visit Preferred	Craniectomy /Comfort Care (if Applicable)	Early Term. Visit[2]
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-
Informed consent	X	-	-	-	-	-	-	-	-	-
Demographics, medical history, physical examination (including height and weight), rtPA/thrombectomy status[3]	X	-	-	-	-	-	-	-	-	-
Time of symptom onset or, if unknown, last known normal	X	-	-	-	-	-	-	-	-	-
Imaging (MRI/CTP/NCCT) for lesion size or ASPECTS estimation[4]	X	-	-	-	-	-	-	-	-	-
Pregnancy test	X	-	-	-	-	-	-	-	-	-
NIHSS[5]	X	[redacted]								
Clinical laboratory samples (hematology, blood chemistry)[6,7]	X	-	X	X	X	X	-	-	-	X[8]
Vital signs[9]	X	-	X	X	X	X	-	-	-	X[8]
12-lead ECG[7,10]	X	Hrs 4-6	X	X	X	X	-	-	-	X[8]
Enrollment/ Randomization[11]	X	-	-	-	-	-	-	-	-	-
Craniectomy/comfort care/cranioplasty assessment form(s)	-	-	-	-	-	-	-	-	X	-

	Screening / Enroll-ment	Hrs >0-12	Hr 24 (±12h)	Hr 48 (±12h)	Hr 72 (±12h)	Day 7 (±24h)/ Hospital Discharge	Day 30 (±7 d) Telephone/ Telemedicine Visit	Day 90 (±14 d)[1] In-person Visit Preferred	Craniectomy /Comfort Care (if Applicable)	Early Term. Visit[2]
[redacted]										
Study treatment administration	-	←……72-hr infusion……→				-	-	-	-	-
Blood glucose measurement[12]	X	X	X	X	X	X	-	-	-	-
Imaging (NCCT or MRI) for midline shift[13]	-	-	-	-	X Hrs72-96	-	-	-	X	X[14]
mRS	-	-	-	-	-	-	X	X	-	X
Subject disposition[15]	-	-	-	-	-	X	X	X	-	X
TOAST classification[16]	-	-	-	-	-	X	-	-	-	
Concomitant medications/procedures	← ……Monitor and record throughout Part 1 of the study……→									
[redacted]										
AEs and SAEs[17]	← ……Monitor and record throughout Part 1 of the study……→									

AE = adverse event; ASPECTS = Alberta Stroke Program Early CT Score;; [redacted]; CMO = comfort measures only; CTP = computed tomography perfusion; DC = decompressive craniectomy; DWI = diffusion-weighted imaging; ECG = electrocardiogram; [redacted]; IV = intravenous; LAR = legally authorized representative; [redacted]; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NCCT = non-contrast computed tomography; NIHSS = National Institutes of Health Stroke Scale; [redacted]; rtPA=recombinant tissue plasminogen activator; SAE = serious adverse event; [redacted]; SOC = standard of care; Term = termination; TOAST = Trial of Org 10172 in Acute Stroke Treatment; [redacted].

[1] The Day 90 visit should be conducted in person whenever possible followed by telemedicine or phone in order of preference. All other visits after hospital discharge can be conducted by telephone/telemedicine or in person at the study subject's/representative's request.

[2] Early termination is defined as withdrawal from the study (see Section 10.3). Subjects who discontinue study treatment for any reason or who move to comfort care/palliative care should not be withdrawn from the study (see Section 10.1). Rather, they should either continue protocol-required tests and assessments or continue in the study with a limited study assessment schedule (see Section 10.1).

[3] Pre-morbid mRS will be collected based on all available information including medical records, patient, family, and/or LAR report.

[4] MRI(DWI)/CTP/NCCT as SOC at screening (prior to enrollment). If not available as SOC, a study-specific MRI(DWI), CTP, or NCCT, in order of preference, will be obtained. If thrombectomy is performed prior to randomization, imaging inclusion must use MRI(DWI) after thrombectomy.

[5] For subjects who undergo thrombectomy, the pre-procedure NIHSS should be used to determine eligibility. For subjects who are designated for DC or CMO/palliative care, NIHSS should be obtained within 12 hours prior to that designation or as close as possible to this decision.

[6] Assessments performed at local laboratory.

[redacted]

[8] Performed only if subject has not yet been discharged.

[9] Supine blood pressure, heart rate, oxygen saturation, respiratory rate, and temperature prior to dosing.

[10] Subject must be supine.

[11] Subjects will be randomized/enrolled after all screening assessments have been completed and after the Investigator has verified that the subject is eligible to participate.

[12] Hourly (±30 min) for Hours 1 to 24, every 2 hours (±30 min) for Hours 24 to 48, and every 4 hours (±60 min) for Hours 48 to 72. If treatment for low blood glucose (<70 mg/dL or ~3.9 mmol/L) is initiated, then blood glucose monitoring is required every 15 min (±10 min) until blood glucose is ≥80 mg/dL (~4.4 mmol/L) for 3 consecutive readings without exogenous bolus glucose supplementation. Blood glucose monitoring may be more often at the discretion of the Investigator.

[13] Imaging by NCCT or MRI for midline shift (method should be consistent with baseline imaging method whenever possible) should be performed between 72 to 96 hours and as close to 72 hours as possible, or within 12 hours prior to DC, or the initiation of CMO/palliative care in subjects designated for DC or CMO/palliative care, respectively.

[14] This only applies if termination visit is prior to 72-96 hours.

[15] Subject disposition: location (e.g., hospice, nursing home, rehabilitation facility, home), level of rehabilitation, and if death occurred, the primary cause of death, and date and time of death will be recorded. Brain death and death associated with withdrawal of care must be documented.

[16] TOAST classification may be performed up to Day 7.

[17] All AEs and SAEs from the beginning of the Study Drug administration and all SAEs from the time of consent. AEs of special interest (i.e., hypoglycemia defined as confirmed glucose <55 mg/dL [~3.1 mmol/L]) will be upgraded as an SAE.

Table 3: Schedule of Activities – Part 2 (Day 91 through Month 12)

	Month 6 (± 30 days) Telephone/Telemedicine Visit[1]	Month 12 (± 30 days) Telephone/Telemedicine Visit[1]
mRS	X	X
Subject disposition[2]	X	X
EQ-5D-5L, BI, SIS-16	X	X
HCRUQ, Zarit	-	X
SAEs	X	X

BI = Barthel Index; EQ-5D-5L = EuroQol 5-level assessment of health outcome; HCRUQ = HealthCare Resource Utilization Questionnaire; mRS = modified Rankin Scale; SIS-16 = Stroke Impact Scale 16 Questions, Zarit = Zarit Burden Interview.

[1] In-person clinic visits may be conducted at the study subject's/representative's request.

[2] Subject disposition: location (e.g., hospice, nursing home, rehabilitation facility, home), level of rehabilitation, and if death occurred, the primary cause of death and date and time of death will be recorded. Brain death and death associated with withdrawal of care must be documented.

6. STUDY OBJECTIVES AND ENDPOINTS

6.1. PART 1 Objectives and Endpoints

Primary Objective	**Primary Endpoint**
To determine if BIIB093 improves functional outcome at Day 90 as measured by modified Rankin Scale (mRS) when compared with placebo in subjects with LHI.	Day 90 mRS score as a 5-category ordinal scale (the 5-category mRS combines mRS categories 0 and 1 and mRS categories 5 and 6).
Secondary Objectives	**Secondary Endpoints**
To determine if BIIB093 improves overall survival at Day 90 when compared with placebo in the modified intent-to-treat (mITT) population.	Time to all-cause death over the 90-day period.
To determine if BIIB093 improves functional outcome at Day 90 on the mRS dichotomized 0-4 vs. 5-6, when compared with placebo in the mITT population.	Proportion of subjects who achieved mRS 0-4 at Day 90.
To determine if BIIB093 reduces midline shift at 72 hours (or at time of DC or comfort measures only [CMO], if earlier) when compared with placebo in the mITT population.	Midline shift at 72 hours (or at time prior to DC or CMO, if earlier).
To evaluate the safety and tolerability of BIIB093 in subjects with LHI.	Incidence of adverse events (AEs), serious adverse events (SAEs), and clinically significant abnormal vital signs, 12-lead electrocardiogram (ECG) findings, and laboratory results (including those associated with blood glucose (BG) levels).
[redacted]	

[redacted]

6.2. PART 2 Objectives and Endpoints

Objectives	Endpoints
To evaluate long-term disability following LHI.	mRS score at Month 6 and Month 12 as a 5-category ordinal scale (the 5-category mRS combines mRS categories 0 and 1 and mRS categories 5 and 6)
To evaluate long-term outcome measures of clinical function, quality of life, and healthcare utilization	• EQ-5D-5L at Months 6 and 12 • BI score at Months 6 and 12 • SIS-16 at Months 6 and 12 • Zarit Burden Interview at Month12 • HealthCare Resource Utilization Questionnaire at Month 12
To assess the safety of BIIB093 in subjects with LHI during the follow-up period.	Incidence of SAEs.

[redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 3, randomized, multicenter, placebo-controlled, double-blind, parallel-group study in subjects aged 18 to 85 years with a LHI and time from symptom onset to start of study treatment infusion of ≤10 hours. Standard of care (SOC) imaging (MRI and/or computed tomography perfusion [CTP] and/or non-contrast computed tomography [NCCT]) is performed at screening to assess lesion size. The lesion must meet the size criteria set forth in Section 8.1 for the subject to be eligible for this study.

The study is a 2-part study: Part 1 is a safety and efficacy study that includes the time from screening/enrollment through the completion of the Day 90 assessments. Part 2 is a long-term functional outcome study and includes Day 91 through the completion of the Month 12 assessments.

The study allows SOC therapy including IV rtPA, thrombectomy, mannitol, hypertonic saline, DC, and other treatments for LHI per local guidelines as determined by the Investigator. Study treatment is administered as a 3-stage continuous infusion over 72 hours in a 1:1 randomization allocation (BIIB093: placebo).

In order to avoid any delays in administration of standard of care stroke therapies, IV thrombolysis and/or thrombectomy must be completed prior to randomization when they are planned for subjects who are being screened for the study. Given the limited experience with the use of thrombectomy in subjects with LHI, a post-thrombectomy MRI is required to determine study eligibility when thrombectomy occurs prior to randomization. In the event that IV thrombolysis or thrombectomy is required in subjects who have already been randomized into the trial, they are allowed per the study protocol.

Since there is limited experience with thrombectomy in LHI patients, the number of subjects with thrombectomy performed prior to randomization is targeted at approximately 20% in the ≤70 year age group but may vary from this to reflect the evolving standard of care and stroke treatment guidelines. The number of subjects with thrombectomy performed prior to randomization is targeted at approximately 8% in the >70 year age group.

After the study treatment infusion is complete, imaging by NCCT or MRI for midline shift (method should be consistent with baseline imaging method whenever possible) should be performed between 72 to 96 hours and as close to 72 hours as possible. For those subjects designated for DC or CMO, the NCCT or MRI for midline shift should occur within 12 hours prior to DC or the initiation of CMO, respectively. In the event a SOC scan is taken that meets the foregoing requirements, the SOC scan will be collected and a study-specific scan need not be obtained. In the case of DC or CMO, if no SOC image within 12 hours prior to DC or CMO is available and taking a study-specific image would, in the opinion of the Investigator, be contrary to the best interest of the subject, a study-specific image will not be obtained.

The efficacy endpoints (mRS and survival) will be recorded at Days 30 and 90 and midline shift at 72 hours. Database lock will take place at Day 90. Safety laboratory values will be assessed through Day 7 or hospital discharge (whichever is earlier). AEs will be collected through Day 90 and SAEs through Month 12. Patient outcome measures (EQ-5D-5L, BI, SIS-16, HealthCare Resource Utilization Questionnaire, and Zaret Burden Interview) will be assessed at selected timepoints.

The study has been designed to randomize approximately 688 subjects aged 18 to 70 years, inclusive. In addition, approximately 80 subjects aged >70 years and up to 85 years (inclusive) will also be randomized for safety [redacted] evaluations.

A flowchart of study activities is available in the Study Reference Guide.

7.2. Study Duration for Subjects

The total duration of study participation for each subject will be approximately 12 months; this consists of a concurrent screening and enrollment period, a treatment period of 72 hours, and a follow-up period of 52 weeks. Study Part 1 will be considered screening through Day 90, and Study Part 2 will be Day 91 through Month 12.

The primary study outcome is at Day 90 (the end of Part 1); however, all subjects will be consented for both study parts together and followed for 1 year. The end of the study is considered the final study assessment at Month 12 or in the event of early termination, death or study withdrawal.

7.3. Responsibilities of Study Site Personnel

The attending clinician has ultimate responsibility and discretion for treating subjects. The clinician will use his/her best judgment in treating subjects based upon the specific clinical situation and in accordance with Good Clinical Practice (GCP).

7.4. Study Stopping Rules

Biogen may terminate this study at any time after informing Investigators. Investigators will be notified by Biogen or designee if the study is placed on hold, completed or closed. An independent, external data monitoring committee (IDMC) will be formed and will review safety data regularly. The study may be terminated by the Sponsor at the recommendation of the IDMC, based exclusively on safety data. The Sponsor may perform an interim futility analysis based on the primary endpoint when approximately 30% of planned mITT subjects complete Day 90. Should the Sponsor elect to conduct unblinded interim futility analyses, the study may be terminated by the Sponsor at the recommendation of the IDMC. Details of the IDMC responsibilities will be provided in the IDMC charter.

7.5. End of Study

The end of study is last subject, last visit, i.e., when the last subject completes the 1-year visit or withdraws from the study.

8. SELECTION OF SUBJECTS

8.1. Inclusion Criteria

To be eligible to participate in this study, candidates must meet the following eligibility criteria at Screening, or at the timepoint specified in the individual eligibility criterion listed:

1. Ability 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 *or* consent provided by an independent physician where local regulation allows, and/or provision of informed consent by the subject's legally authorized representative (LAR) in accordance with all local and national regulations *or* according to the local ethics committee's guidelines *or* by another process compliant with applicable national laws and regulations and ethics committee requirements.

2. A clinical diagnosis of acute ischemic stroke in the MCA territory (PCA and/or ACA territory involvement in addition to primary MCA territory stroke is acceptable).

3. Aged 18 to 85 years old, inclusive, at the time of informed consent.

4. Screening NIHSS ≥10.

5. Prior to the current stroke, no significant disability in the opinion of the Investigator (able to independently perform all duties and activities of daily living without assistance from a caregiver, spouse, or another person).

6. A large hemispheric infarction defined, in order of preference, as either:
   a) a magnetic resonance imaging (MRI) diffusion-weighted imaging (DWI) lesion volume of 80 to 300 cm^3, or
   b) a computed tomography perfusion (CTP) core lesion volume of 80 to 300 cm^3, or
   c) an Alberta Stroke Program Early computed tomography (CT) Score (ASPECTS) on non-contrast computed tomography (NCCT) of 1 to 5 with involvement of at least 2 defined cortical regions, if lesion volume from MRI DWI or CTP is not available.

   In the event that more than one scan is available for a particular subject resulting in disagreement, the investigator should make the determination about eligibility considering all patient information including but not limited to: 1) scan timing and 2) scan modality that in the opinion of the investigator best represents the infarct size. The scan used for eligibility will be documented.

   Note: Automated image analysis software will be used whenever possible as a standard method to aid in estimating infarct core volume and/or ASPECTS. The final ASPECTS determination for the purposes of inclusion will be made by the investigator or local reader. In the event that a suitable baseline scan is not available as part of the SOC, a study-specific MRI DWI, CTP, or NCCT, in order of preference, will be obtained. A

repeat scan for study inclusion purposes may be performed if deemed appropriate and would be achievable prior to infusion.

7. For subjects who receive thrombectomy prior to randomization, inclusion into the study must be based on an infarct volume of 80 to 300 cm^3 measured by post-thrombectomy MRI-DWI.

8. At the time of randomization and in the Investigator's judgment, it must be feasible for study drug treatment infusion to be initiated no later than 10 hours after time of symptom onset, if known, or the time last known normal (if time to symptom onset is unknown). Investigators should refer to Section 11.1.

    - Subjects who wake with stroke may be included if neurological and other exclusion criteria are satisfied. These "wake up" strokes are defined as having no symptoms at sleep onset and a known sleep onset time, but stroke symptoms on waking. The time of stroke onset is to be taken as the midpoint between sleep onset and time of waking. The maximum time window for initiation of study drug treatment infusion is then 10 hours from the midpoint as described. If sleep onset time is unknown, then last known normal time must be used and the midpoint does not apply.

8.2. Exclusion Criteria

Candidates will be excluded from study entry if any of the following exclusion criteria exist at Screening, or at the timepoint specified in the individual criterion listed:

1. In the judgment of the Investigator, the subject is likely to have supportive care withdrawn in the first day.

2. Commitment to decompressive craniectomy (DC) prior to enrollment.

3. Evidence (clinical or imaging) of concurrent infarction in the contralateral hemisphere deemed by the Investigator to be sufficiently serious so as to affect functional outcome. This would include, for example, a contralateral ACA infarct that leads to bilateral leg paralysis.

4. Clinical signs of herniation, e.g., 1 or 2 dilated, fixed pupils; unconsciousness related to edema (i.e., ≥2 on item 1a on the NIHSS); and/or loss of other brain stem reflexes, attributable to edema or herniation according to the Investigator's judgment.

5. Brain hemorrhage (other than small petechial/punctate hemorrhages) on NCCT/MRI.

6. NCCT/MRI evidence of anteroseptal/pineal shift >2 mm prior to enrollment.

7. Use of intra-arterial thrombolytic agents, alone or in combination with thrombectomy.

8. Patients who are currently being considered for thrombectomy and/or IV thrombolysis may not be randomized into the study until these procedures have been completed OR the

decision not to perform them has been made. These treatments should not be delayed for study screening procedures. When thrombectomy is performed prior to randomization, study eligibility must be assessed using inclusion criterion #7.

9. Subjects with, in the opinion of the Investigator, life expectancy <3 months not related to current LHI, or those unlikely to be compliant with follow up.

10. Subjects in whom a peripheral IV line cannot be placed.

11. Subjects with mental disability (prior to qualifying LHI) or wards of the state.

12. Subjects whose stroke symptoms are rapidly improving and are not expected in the opinion of the Investigator to have NIHSS≥10 at the time of randomization.

Medical History

13. Known allergy to BIIB093 or to another sulfonylurea drug or any of the components of the formulated BIIB093 or matching placebo.

14. Subjects who are known to have taken oral glibenclamide within the past 10 hours.

15. Known history of clinically significant severe form of renal or hepatic disorder, in the Investigator's opinion (e.g., dialysis or cirrhosis, respectively).

16. Known history of chronic obstructive pulmonary disease that, in the judgment of the Investigator, is severe (e.g., requiring home oxygen).

17. Known history of clinically significant hypoglycemia, in the Investigator's opinion based on known medical history or local screening laboratory assessments (i.e., screening blood glucose <70 mg/dL [~3.9 mmol/L]).

18. Subjects who have or have ever had diabetic ketoacidosis or diabetic coma/precoma.

19. Acute ST elevation myocardial infarction (MI), and/or acute decompensated heart failure, and/or QTc >520 msec, and/or admission for an acute coronary syndrome, MI, cardiac arrest, or non-voluntary coronary intervention (percutaneous coronary intervention or coronary artery surgery) within the past 3 months.

20. New York Heart Association heart failure III/IV (class III: marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g. walking short distances (20-100 m); class IV: severe limitations. Experiences symptoms even while at rest. Mostly bedbound patients).

21. Known cardiac ventricular tachycardia.

22. Subjects with known glucose-6-phosphate dehydrogenase (G6PD) enzyme deficiency.

23. Serious local infection (e.g., cellulitis, abscess) or systemic infection (e.g., septicemia) that required hospitalization or was clinically significant in the opinion of the Investigator within 3 days prior to Screening.

Other

24. Females who are pregnant or women of childbearing potential with a positive pregnancy test at time of admission.

25. Nursing women who are unable to stop breastfeeding during study treatment infusion and for 7 days following the end of study treatment infusion.

26. Known current participation or known history of participation in any other investigational study that involved treatment with an investigational drug within 14 days prior to enrollment**.**

27. Inability to comply with study requirements.

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

9. SCREENING AND RANDOMIZATION

The study will allow SOC therapy including IV thrombolysis, thrombectomy (see inclusion criteria #7), mannitol, hypertonic saline, DC, and other treatments for LHI per local guidelines as determined by the Investigator.

9.1. Screening

Subjects, their legally authorized representative (LAR), or physician per local requirements must provide informed consent before any screening tests are performed (see Section 17.3). Determination of whether consent by a LAR is required (and if so, determination of the LAR) as well as specific details of the consenting process will be determined by country law, state law, and local ethics committee requirements. The study team is encouraged to use fax, telephone, and/or telemedicine consent if allowed by country law, state law, and local ethics committee rules. Participating study sites are required to document all screened candidates initially considered for inclusion in the study.

All subjects arriving at the recruiting site prior to 10 hours of symptom onset or last known normal, having the potential for a large lesion, with a NIHSS ≥10, and meeting all inclusion/exclusion criteria should be considered for potential inclusion in this study.

A screen failure log will be maintained at each site. Subjects are eligible for rescreening (i.e., an additional study-specific imaging scan) provided they meet the protocol-specified time window and all non-lesion size-related inclusion/exclusion criteria. Screen failures are defined as subjects who have been diagnosed with LHI, 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 SAE.

Because pertinent subject information will already be collected as part of SOC, and to reduce additional study-specific procedures, baseline information may be taken from the subject's medical records prior to obtaining informed consent. However, informed consent will be obtained prior to performing any study-specific procedures.

9.2. Randomization

Enrollment and randomization will be concurrent. Subjects will be randomized/enrolled after all screening assessments have been completed and after the Investigator has verified that the subjects are eligible per criteria in Section 8. 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 study treatment or placebo in a 1:1 ratio. As part of randomization, for each age group (18 to 70 years vs. >70 to 85 years), a minimization method will be used to achieve treatment group balance over the following baseline covariates: region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20). For details on enrollment of subjects with thrombectomy, see Section 7.1.

Refer to the Study Reference Guide for details on randomization/enrollment.

9.3. Blinding Procedures

The investigators, study site staff, subjects, and caregivers will be blinded to the subject treatment assignments for the duration of the trial (Parts 1 and 2). To ensure that efficacy and outcome assessors are blinded to study treatment, evaluators performing all efficacy and outcome evaluations will be blinded to knowledge of AEs and SAEs during the acute hospitalization phase of the study (should not have participated in the treatment during the acute hospitalization phase of the study nor review the subject's hospital records from the acute hospitalization study period including BG levels, BG management, or carbohydrate intake).

The study Sponsor and CRO study management team will be fully blinded for Part 1 of the study. After Part 1 is completed and the clinical study database is locked, designated personnel at the Sponsor will be unblinded to the Part 1 data for the purposes of evaluating the Day 90 data. The Sponsor and CRO study management team responsible for all site interactions and data entry will remain blinded to individual treatment assignments during Part 2 of the study.

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

10.1. Discontinuation of Study Treatment

Note: Subjects who discontinue study treatment for any reason should not be withdrawn from the study and should continue protocol-required tests and assessments.

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

- The subject/LAR withdraws consent to continue study treatment. Subject withdrawal may occur any time the subject or LAR wishes to no longer continue with the study. Every attempt must be made to obtain information about the reason(s) for discontinuation, and any possible AEs.
- The subject has a positive pregnancy test during the 72-hour time window of treatment.
- The subject experiences an AE that necessitates permanent discontinuation of study treatment.
- The subject experiences a medical emergency that necessitates unblinding of the subject's treatment assignment.
- The subject is unwilling or unable to comply with the protocol.
- At the discretion of the Investigator for medical reasons.
- Study drug must be discontinued if hypoglycemia cannot be rectified by the treating team, the severity and length of hypoglycemia is determined by the Investigator to be harmful to the subject, and the infusion rate has already been reduced to 0.0795 mg/h (refer to Directions for Handling and Administration [DHA] for corresponding mL/h rate) for >30 minutes.
- Increases in QT/QTc (formula not specified) to >550 msec, if the measurement is obtained and confirmed with a second ECG reading within 15 minutes
- The subject has confirmed alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >5×upper limit of normal (ULN), or confirmed ALT or AST >3×ULN and bilirubin >2×ULN.
- The subject experiences a severe hypersensitivity to study treatment based on the Investigator's assessment.

If the study treatment infusion is reduced or discontinued as a result of BG<55 mg/dL (~3.1 mmol/L), dextrose 50% in water (D50W; or another concentration of dextrose, if D50W is

not available) must be administered by bolus in order to achieve a BG level ≥80 mg/dL (~4.4 mmol/L). Multiple boluses may be administered, the timing and volume of which are at the discretion of the Investigator. BG monitoring is then required every 15 (±10) minutes until BG ≥ 80 mg/dL (~4.4 mmol/L) for 3 consecutive readings **without bolus glucose supplementation**.

The primary reason for discontinuation of study treatment must be recorded in the subject's electronic case report form (eCRF). All subjects who discontinue study treatment, except for those who withdraw consent, will be followed to the end of study (i.e., end of Part 2).

If a site learns, while a subject is receiving study treatment, that the subject had taken sulfonylureas within 24 hours prior or during the hospital stay, this will not be a cause for discontinuation of study treatment or of withdrawal from the study.

If possible, the study Medical Monitor should be contacted before early discontinuation of study treatment. The Medical Monitor must be informed within 24 hours of early study treatment discontinuation.

Institution of Comfort Care/Palliative Care Measures

If a decision is made to move the subject to CMO/palliative care during the study, the Investigator should complete all assessments specified by the CMO (or palliative care)/DC visit (see Table 2) prior to CMO/palliative care (i.e., final imaging, NIHSS). In addition, the comfort care eCRF and NIHSS should be completed. If a brain imaging study has not been performed within the prior 12 hours of the decision, it should be obtained whenever possible. CMO/palliative care subjects do not need to be terminated early from the study unless informed consent is withdrawn or as determined by the Investigator.

CMO/palliative care subjects are encouraged to remain in the study to enable the collection of protocol assessments if feasible; however, the minimum assessments required are collection of AEs/SAEs and mRS.

10.2. Lost to Follow-Up

Potential sources of follow-up information will include subject medical records, the subject, LAR, family members, and personal physician. In addition, information may be collected by contacting the rehabilitation facility/nursing home, accessing a shared healthcare database, or reviewing publicly available death records. Subjects will be considered lost to follow-up if all attempts to collect the follow-up assessments are unsuccessful. The subject should not be classified as "lost to follow-up" until the final assessment has been missed and a certified letter has been sent to both the LAR and subject with no response within 30 days of sending.

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

- The 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 Study

Early termination is defined as withdrawal from the study. Subjects must be withdrawn from the study if the subject or LAR withdraws consent for any reason. Subjects who discontinue study treatment for any reason or who move to comfort care/palliative care should not be withdrawn from the study (see Section 10.1).

The primary reason for the subject's withdrawal from the study must be recorded in the subject's CRF. If a subject is withdrawn due to pregnancy, early termination study procedures will be performed. Subjects must undergo end-of-treatment assessments (Day 90 assessments if Part 1 at the time of termination or Month 12 assessments if Part 2 at the time of termination) unless withdrawal is due to death or withdrawal of consent. Subjects who withdraw from the study may not be replaced.

11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA.

Study drug treatment infusion should be initiated **as soon as possible** but no later than 10 hours after time of symptom onset, if known, or the time last known normal (if time to symptom onset is unknown) [refer to Section 8.1, inclusion criterion 8]. Study treatment administration will initiate with 0.13 mg administered as a bolus over approximately 2 minutes, followed by 0.16 mg/h for 6 hours, followed by 0.11 mg/h for the remaining 66 hours (or 0 mg in all cases for placebo) [refer to DHA for corresponding mL/h rate]. The total volume of infusion will be 8.6 mg over 72 hours. Infusion should be stopped 72 hours from the start of infusion whenever possible. If stopping at precisely 72 hours is not possible, a ±30-minute window is permitted. The infusion will be prepared in 1000 mL IV bags, which must be replaced every 24 hours. See DHA for a summary of the study dosing. The bolus may be administered either by programming the infusion pump appropriately per instructions in the DHA, or by withdrawing the study treatment from the bag and injecting it by syringe through peripheral IV over an approximately 2-minute period, depending on site standards.

BIIB093 cannot be administered with PVC bags and lines due to adsorption issues. Additionally, the drug adsorbs to inline filters. Refer to DHA for additional information. The use of any bags, administration or extension sets, or any configuration of the components other than those specified per DHA is strictly prohibited, unless permission to do so is provided by the Sponsor in writing (e-mail).

The infusion of study treatment should only be through a dedicated peripheral IV line. A calibrated infusion pump with a dedicated infusion line will be used to ensure infusion at the specified rates. The study treatment may not be delivered through a central line or peripherally inserted central catheter line. No other medication may be administered in the same line as the study treatment, nor should the line be used for blood withdrawal.

The date and time of the start and end of the infusion of each bag will be recorded in the eCRF. At the end of the infusion of each bag, tubing, bags, and IV catheters must be visually inspected to confirm that the fluid path is composed of only the allowed components. If any components other than allowed components are found, these must be removed, and the incident documented and described in the eCRF. The length of, and reason for, any stoppage of the infusion that lasts >15 minutes must be recorded.

11.2. Modification of Dose and/or Treatment Schedule

The dosage should not be modified unless due to hypoglycemia (sustained BG <55 mg/dL [~3.1 mmol/L]). If hypoglycemia cannot be rectified by the treating team and the severity and length of hypoglycemia is determined by the Investigator to be harmful to the subject, then the study drug flow rate must be reduced to 0.0795 mg/h. Note that if the dose reduction occurs within the first 6 hours of treatment, the flow rate must be reduced to 0.0795 mg/h and must not

be increased at the end of the 6-hour period (refer to DHA for corresponding mL/h rate). If dose reduction occurs, maintenance fluids must be continued until BG ≥ 80 mg/dL (~4.4 mmol/L) for 3 consecutive measures.

In the event administration of study treatment is halted due, for example, to IV infiltration, study treatment should be restarted per restart instructions provided in the DHA.

The infusion period will not be extended to account for any stoppages or reduction.

Study treatment should not be stopped if the subject undergoes DC; however, frequent BG monitoring should continue. An effort should be made to obtain imaging prior to DC whenever possible.

11.3. Precautions

BIIB093 cannot be administered with PVC bags and lines due to adsorption issues. Additionally, the drug has adsorption to inline filters. Refer to DHA for additional information.

11.4. Concomitant Therapy and Procedures

Specific treatment guidelines are provided in the Study Reference Guide. These guidelines are a template for the care of subjects participating in the study and should be followed whenever clinically feasible.

11.4.1. Concomitant Therapy

A concomitant therapy is any medication administered between enrollment through Day 90 or early discontinuation (whichever is earlier). All concomitant therapy including but not limited to dextrose solutions, osmotherapy, paralytics, sedatives, and vasoactive drugs will be recorded in the eCRF.

11.4.1.1. Allowed Concomitant Therapy

11.4.1.1.1. IV thrombolysis (rtPA)

In general, IV thrombolysis, when indicated, should be administered to treat the index stroke prior to subject randomization as described in exclusion criteria #8. However, if a decision was made to randomize the subject into the study and it was later determined that IV thrombolysis should be administered to the subject as part of standard of care, then this is allowed per the protocol.

11.4.1.1.2. Interventions Related to Blood Glucose

In a joint statement from the American Diabetes Association and the European Association for the Study of Diabetes, the International Hypoglycemia Study Group concluded that a BG level of <54 mg/dL (~3.0 mmol/L) alone, without symptoms, is clinically important and should be included in reports of clinical trials involving glucose-lowering drugs [International

Hypoglycaemia Study Group 2017]. The statement further recommends an "alert" level of 70 mg/dL (~3.9 mmol/L) for BG. The following interventions are designed in accordance with those recommendations.

Insulin

Insulin and other BG-lowering agents are not permitted during study treatment administration when BG <120 mg/dL (~6.7 mmol/L).

Nutrition

Enteral nutrition is encouraged to be initiated within 24 hours of admission if consistent with SOC. Subjects may need post-pyloric administration of nutritional support.

Maintenance Fluids

- If the BG at baseline is <120 mg/dL (~6.7 mmol/L), the initial maintenance fluid should be 5% dextrose in normal saline (D5NS, or fluid containing 5% dextrose) at a rate of 70 to 100 cc/h.

- When BG falls below 100 mg/dL (~5.6 mmol/L), 5% dextrose in normal saline (D5NS, or fluid containing 5% dextrose) should be started at 70 to 100 cc/hr. Titration of the IV fluid rate up or down can be used to maintain BG ≥ 80 mg/dL (~4.4 mmol/L).

- If BG < 80 mg/dL (~4.4 mmol/L), 5% dextrose in normal saline (D5NS, or fluid containing 5% dextrose) must be started or, if D5NS is already being administered, then the subject should be switched to 10% dextrose in normal saline (D10NS, or fluid containing 10% dextrose).

- If there is a rapid or continuous downward trend in BG, 5% dextrose in normal saline (D5NS, or fluid containing 5% dextrose) should be started or, if D5NS is already being administered, then the subject should be switched to 10% dextrose in normal saline (D10NS, or fluid containing 10% dextrose).

- In the event of BG > 140 mg/dL (~7.8 mmol/L), neither 5% nor 10% dextrose in normal saline (D5NS, or fluid containing 5% dextrose; D10NS, or fluid containing 10% dextrose) should be administered.

- Total fluid volume, inclusive of study treatment volume, should be consistent with site practice and the clinical status of the subject.

Low Blood Glucose Treatment

Any confirmed BG of < 70 mg/dL (~3.9 mmol/L) must be treated with 40-50 mL of dextrose 50% in water (D50W). If D50W is not available, another concentration of dextrose fluid may be used at a sufficient volume to achieve an equivalent amount of dextrose.

11.4.1.1.3. CYP2C9/CYP3A4 and Bosentan

BIIB093 is metabolized by cytochrome P450 (CYP) 2C9 and CYP3A4. Medications that are strong inhibitors or inducers of the CYP enzymes may elicit significant PK-mediated drug interactions with BIIB093 (see Appendix 1). Oral glibenclamide products do not contraindicate nor require dosage adjustment for concomitant use of inhibitors or inducer of CYP2C9 and CYP3A4. Therefore, for subjects who require these medications during BIIB093 treatment, the use of these agents will be permitted in the study with additional monitoring per the Investigator's judgment (e.g., BG levels) to ensure subject safety.

Subjects receiving treatment with bosentan during Screening can be included in the study, and liver function tests should be collected more frequently if necessary at the discretion of the Investigator.

11.4.1.2. Disallowed Concomitant Therapy

- Insulin and other BG-lowering agents are not permitted during study treatment administration when BG <120 mg/dL (~6.7 mmol/L).
- No other sulfonylurea agents may be administered during the hospital stay.
- No other investigational drugs may be administered during the 90-day follow-up period.
- The use of sphenopalatine ganglion stimulation (SPG-Stim) is not allowed.

11.4.2. 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 time the subject is enrolled in the study and Day 90. The use of unapproved therapies and/or procedures is not permitted.

Concomitant procedures will be recorded through Day 90 or early discontinuation, whichever is earlier.

11.4.2.1. Thrombectomy

In general, thrombectomy, when indicated, should be performed to treat the index stroke prior to subject randomization as described in exclusion criteria #8. However, if a decision was made to randomize the subject into the study and it was later determined that thrombectomy should be administered to the subject as part of standard of care, then this procedure is allowed per the

protocol. In the event that a thrombectomy is performed after subject randomization, standard of care imaging should be performed following the procedure.

11.4.2.2. Decompressive Craniectomy

DC may be performed according to local SOC. Timing of, and reasons for DC, including whether the DC was due to 1) radiographic changes, 2) change in level of alertness, 3) both [1] and [2] radiographic changes and change in level of alertness, or 4) neither (i.e., prophylactic) will be recorded in the eCRF. Record NIHSS either at the time of decision to perform DC or between such time and the DC. If a brain imaging scan was not performed in the prior 12 hours as part of the assessment to perform a hemicraniectomy, a follow-up brain imaging study should be performed when possible but prior to DC. Study treatment should not be stopped if the subject undergoes DC.

Adherence to the Study Reference Guide (supplied separately) with regard to DC is particularly important in order to ensure uniformity of practice across the study. Data collected that pertain to the decision to do a DC will be reviewed by a clinical committee on a study-wide, geographical, and site level to assess uniformity of practice. The Sponsor may make certain results of this review available to all study investigators during the study in an ongoing effort to encourage uniformity. The Sponsor may pause or end recruitment at specific sites where the Study Reference Guide is not followed sufficiently closely or DC rates are substantially higher than at other sites.

11.5. Continuation of Treatment

There is no provision to provide study treatment after the study.

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 aligns with all other references (including the 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 is for one-time use only; do not use any study treatment remaining in the vial for another subject.

Each study treatment kit will contain 1 vial. Any additional components provided will be described in the DHA. Study treatment vials (i.e., BIIB093 or placebo) contain a white to off-white lyophilized powder for IV administration after reconstitution; vials of BIIB093 and placebo look identical.

12.1. BIIB093

The contents of the BIIB093 label will be in accordance with all applicable regulatory requirements. The expiry or use-by date is stored in the IRT system, and printable assignment reports are available to site personnel. Study treatment should not be used after the expiration, expiry, or use-by date.

Each vial of BIIB093 contains glibenclamide 6.0 mg, mannitol 180 mg, and sodium hydroxide to adjust the pH during manufacture. Once reconstituted, study treatment is administered in 0.9% normal saline.

Stability at room temperature of study treatment in normal saline is 30 hours. A new vial is used for dosing on each day of the 3-day infusion.

12.1.1. BIIB093 Preparation

Study treatment will be prepared at the site by a properly qualified blinded individual according to institutional standards. The individual preparing BIIB093 should carefully review the instructions provided in the DHA. As noted previously, BIIB093 cannot be administered with PVC bags and lines due to adsorption issues. Additionally, the drug has adsorption to inline filters. Refer to DHA for additional information.

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 vial in question should be saved at the study site, and the problem immediately reported to Biogen.

Please refer to the DHA for detailed instructions regarding reconstitution of the Study Drug.

12.1.2. BIIB093 Storage

Study treatment must be stored in a secure location.

All vials of BIIB093 are to be stored at 1°C to ≤25°C (34°F to ≤77°F) and protected from light in a locked location with limited access until used, in accordance with labeled storage requirements. Storage temperature must be monitored and recorded per the instructions provided in the DHA.

12.1.3. BIIB093 Handling and Disposal

The Investigator must return all used and unused vials of BIIB093 as instructed by Biogen unless approved for onsite destruction.

If any BIIB093 supplies are to be destroyed at the study site, the institution or appropriate site personnel 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., kit numbers, quantities), the date of destruction, and proof of destruction.

The Investigator must notify the Sponsor of any damaged or unusable study supplies that were supplied to the site.

12.1.4. BIIB093 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 BIIB093 supplied, dispensed, and subsequently destroyed, lost, or returned to Biogen. A written explanation must be provided for any discrepancies.

12.2. Placebo

Placebo vials are to be stored at 1°C to ≤25°C (34°F to ≤77°F) and protected from light in a secured location with limited access until used, in accordance with labeled storage requirements. Each vial of matching placebo contains mannitol 180 mg, as well as sufficient sodium hydroxide to adjust pH during manufacture. The pH of the infusion is approximately 6 to 8.

13. EFFICACY ASSESSMENTS

See Section 5 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

NOTE: The 90-Day efficacy outcomes will be performed by personnel who are blinded to on-treatment BG levels, BG-related AEs, and carbohydrate administration. Such persons will not have access to the subject's medical record from the acute hospitalization study period but will instead be provided with subject/family/LAR contact details (if they are required to schedule the follow up); the source documents for the assessments to be performed; and for 30- and 90-day follow ups, the list of unresolved AEs.

13.1.1. Functional Outcome (mRS)

The subject's functional outcome will be measured by mRS as an ordinal scale.

The mRS will be performed by independent personnel who have mRS training and certification. Biogen will provide an mRS source document that outlines the procedures and key questions to ask to assess mRS (see also blinding Section 9.3). Details will be provided in the Study Reference Guide.

mRS assessments at Day 90 should be conducted in person where possible and otherwise by telemedicine or phone call, in order of preference. The mRS raters should be available to travel to the subject at Day 90 when possible if the subject is unable to attend the clinic visit. mRS assessments at other timepoints can be conducted by telemedicine visit or phone call. The same mRS rater should follow a subject for the duration of the trial whenever possible. The Day 90 mRS assessments may be reviewed centrally and if so, queries will be issued in the event of discrepancies or inconsistencies.

13.1.2. Subject Disposition

Subject status will be categorized as alive or dead, location (e.g., hospice, nursing home, rehabilitation facility, home), and level of rehabilitation.

If a subject death occurs during the study, the primary cause of death and date and time of death will be determined and recorded. Brain death and death associated with withdrawal of care must be documented.

For subjects who are lost to follow-up, publicly available death records will be sought.

13.1.3. Midline Shift

Midline shift will be assessed by NCCT or MRI performed at 72 hours [or prior to DC or CMO, if earlier]. Only images acquired prior to DC can facilitate an accurate measure of midline shift. Images will be acquired per specifications outlined in the Imaging Manual. Reading of the midline shift, the perpendicular distance between the septum pellucidum and the line drawn

between the anterior and posterior attachments of the falx to the inner table of the skull, will be performed by trained and certified central readers blinded to treatment assignment.

13.1.4. Patient Outcome Measures

Complete instructions for outcomes measure assessments will be provided separately. Raters must be trained and qualified to perform any assessment and meet the guidelines outlined in the Study Reference Guide. To eliminate inter-rater bias, the same rater should follow a subject whenever possible for the duration of the study.

13.1.4.1. European Quality of Life Assessment (EQ-5D-5L)

EQ-5D-5L is a standardized instrument developed by the EuroQol Group for measuring generic health status. The health status measured with EQ-5D-5L is used for estimating preference weight for that health status. The measure of quality-adjusted life-years gained is used as an outcome in cost-utility analysis, which is a type of economic evaluation that compares the benefit and cost of health care programs or interventions.

13.1.4.2. Zarit Burden Interview

The Zarit Burden Interview was originally developed to measure subjective burden among caregivers of adults with dementia. Items were generated based on clinical experience with caregivers and prior studies resulting in a 22-item self-report inventory that examines burden associated with functional/behavioral impairments and the home care situation. The items are worded subjectively, focusing on the affective response of the caregiver.

13.1.4.3. Barthel Index

This index measures the extent to which somebody can function independently and has mobility in their activities of daily living (i.e., feeding, bathing, grooming, dressing, bowel control, bladder control, toileting, chair transfer, ambulation, and stair climbing). The index also indicates the need for assistance in care. The BI is a widely used measure of functional disability. The index was developed for use in rehabilitation patients with stroke and other neuromuscular or musculoskeletal disorders but may also be used for oncology patients.

13.1.4.4. Stroke Impact Scale 16

The SIS-16 was developed to assess physical function in patients with stroke at approximately 1 to 3 months poststroke using items from the composite physical domain of the SIS version 3.0; and compare the SIS-16 and a commonly used disability measure, the BI, in terms of their ability to discriminate disability.

13.1.4.5. HealthCare Resource Utilization Questionnaire

Healthcare Resource Utilization Questionnaires are developed to address the need for valid costing estimates of a particular disease state. They are critical components when building economic models for submission to health technology assessment agencies and pharmacy &

therapeutics committees. They are developed to capture the quantity of resources used to extrapolate the overall cost of a disease or impact of an intervention.

[redacted]

14. SAFETY ASSESSMENTS

Refer to Section 5 for the timing of all safety assessments.

14.1. Clinical Safety Assessments

The following clinical assessments will be performed to evaluate the safety profile of BIIB093:

- Medical history
- Physical examinations, including height and weight (may be estimated)
- Vital sign measurements: temperature, heart rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation
- 12-lead ECGs
- Concomitant therapy and procedure recording

  All medications including but not limited to dextrose solutions, osmotherapy, paralytics, sedatives, and vasoactive drugs used through Day 90 be recorded in the eCRF. Concomitant procedures will be recorded through Day 7 or hospital discharge, whichever is earlier.

  Timing of, and reasons for DC, including whether the DC was due to radiographic changes, change in level of alertness, both radiographic changes and change in level of alertness, or neither (i.e., prophylactic) will be recorded in the eCRF.
- AE and SAE recording

14.2. Laboratory Safety Assessments

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

The following laboratory assessments, in accordance with the schedule of activities, will be performed to evaluate the safety profile of BIIB093. All assessments will be performed at a local laboratory where possible.

- Hematology: complete blood count, platelet count, and absolute neutrophil count
- Blood chemistry: albumin, creatinine, blood urea nitrogen, bilirubin (total and direct), alkaline phosphatase, ALT, AST, glucose, calcium bicarbonate (when available), chloride (when available), sodium, and potassium
- Note that in any case of confirmed hemolytic anemia, a G6PD genetic or enzymatic test should be performed in accordance with local practice.

14.3. Product-Specific Safety Assessments

The following additional laboratory safety assessment will be performed to determine the safety of BIIB093:

- Blood glucose

  BG concentrations are to be measured by point-of-care (POC) testing of capillary blood (e.g., Accu-Chek). Venous blood is also acceptable for monitoring BG concentrations. Alternatively, blood from an arterial line may be used if one is in place, with POC or laboratory testing performed. If blood from an arterial line is used, the line must be back-flushed with sufficient discard volume of arterial blood (at least 5 ml) to avoid falsely low BG readings from dilution with the arterial line carrier (i.e., heparinized saline).

  If BG measures <70 mg/dL (~3.9 mmol/L), it must be verified by repeat test to confirm. The source of the blood (capillary vs. arterial line vs. venous) and whether the analysis was performed by POC or laboratory must be recorded in the eCRF.

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 patient 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, vital sign result, and/or ECG 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 or substantial disruption of the ability to conduct normal life functions

- 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. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

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 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

In Part 1 of the study, any AE experienced by the subject between the time of first dose of study treatment and through Day 90 is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. At each study visit in Part 1, the Investigator will assess the subject for AEs and will record any new AEs or updates to previously reported AEs on the eCRF.

15.3.2. Adverse Events of Special Interest

Hypoglycemia, defined as confirmed glucose <55 mg/dL (~3.1 mmol/L), is considered an AE of special interest and will be upgraded to an SAE. Occurrences of these events should be submitted on an SAE form per the guidelines in Section 15.3.3.

15.3.3. Serious Adverse Events

Any SAE experienced by the subject between the time of the signing of the ICF and the last follow-up visit in Part 2 of the study 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 within 24 hours as described in Section 15.3.4. Follow-up information regarding an SAE also must be reported within 24 hours.

Subjects will be followed for all SAEs until the final study visit in Part 2. Thereafter, the event should be reported to Biogen 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 will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status.

15.3.4. 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 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 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 Study Reference Guide for complete contact information.

15.3.4.1. Deaths

Death is an outcome of an event. The event that resulted in death should be recorded on the appropriate eCRF. All causes of death must be reported as SAEs within 24 hours of the site becoming aware of the event. The Investigator should make every effort to obtain and send

death certificates and autopsy reports to Biogen. The term death should be reported as an SAE only if the cause of death is not known and cannot be determined.

15.3.5. 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.

Appropriate personnel at Biogen 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.

15.4. Procedures for Handling Special Situations

15.4.1. Pregnancy

Subjects should not become pregnant or impregnate their partners during the study treatment and for 3 months after their last day 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 within 24 hours of the study site staff becoming aware of the pregnancy. Refer to the Study Reference Guide's Official Study Contact List for complete contact information. The Investigator or study site staff must report the outcome of the pregnancy to Biogen. A pregnancy is not considered an AE and should not be recorded on the AE eCRF.

Congenital abnormalities and birth defects in the offspring of male or female subjects should be reported as SAEs if conception occurred during the first 3-months of the study.

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 eCRF; however, all overdoses must be recorded on an Overdose form and faxed or emailed to Biogen within 24 hours of the study site staff becoming aware of the overdose. An overdose must be reported to Biogen 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. All study treatment-related dosing information must be recorded on the dosing eCRF.

15.4.3. Medical Emergency

In a medical emergency requiring immediate attention, study site staff will apply appropriate medical intervention, according to current SOC. The Investigator should contact the study's

Medical Monitor. Refer to the Study Reference Guide's Official 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 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 Part 1 of the study and for 3 months after their last day of completing study treatment infusion. In addition, subjects should not donate sperm or eggs for the duration of the study and for 3 months after their last day of completing study treatment infusion.

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 and a serum follicle-stimulating hormone level >40 mIU/mL
    - 6 weeks after surgical bilateral oophorectomy with or without hysterectomy
- Posthysterectomy

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.

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 hormonal methods of contraception associated with the inhibition of ovulation.
- Placement of an intrauterine device or intrauterine hormone-releasing system.

- Sex with a male who has undergone surgical sterilization (with the appropriate postvasectomy documentation of the absence of sperm in the ejaculate).

- Female surgical sterilization (e.g., bilateral tubal ligation)

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 trial. 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 eCRF 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 and follow up on the outcome of all pregnancies.

- Complete an SAE form for each SAE and fax or email it to Biogen 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 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 eCRF, 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 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 objectives of the study and the endpoints to be analyzed are listed in Section 6. The study database will be locked after the last subject completes the Day 90 visit, and the endpoints for Part 1 of the study will be analyzed. A second database lock will occur after the last subject completes the Month 12 visit to analyze the Part 2 endpoints. A detailed SAP will be prepared prior to the corresponding database lock.

A summary of Part 1 demography, baseline disease characteristics, primary and secondary efficacy endpoints, pharmacokinetics, and safety endpoints is provided in this section, but information on the analysis of [redacted] from Part 1 and data from all of Part 2 will be detailed in the SAP, which will contain the final details on the statistical methods used in this study.

16.1. Demography and Baseline Disease Characteristics

Demographics and baseline data will be summarized by treatment group with summary statistics (mean, standard deviation [SD], median, and range) or with frequency distributions.

16.2. Efficacy

16.2.1. Analysis Population

The efficacy analysis will be conducted in the mITT population, which is defined as those subjects aged 18 to 70 years (inclusive) who are randomized, receive study treatment, and who have at least 1 post-baseline mRS before or at the Day 90 visit.

Analyses for subjects aged >70 to 85 years will be descriptive. Details of the analyses will be specified in the SAP.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented. For continuous endpoints, summary statistics will generally include: number of subjects with data, mean, SD, median, and range. For categorical endpoints, frequency and percentage of subjects in each category will be presented. Statistical testing for efficacy endpoints will be performed between the BIIB093 treatment group and placebo. All tests will be 2-sided with a significance level equal to 0.05 (unless otherwise specified). To control for a type 1 error, a sequential closed testing procedure will be used for the secondary endpoints such that if statistical significance is not achieved from an endpoint for a comparison, all endpoints of a lower rank for that comparison will not be considered statistically significant.

16.2.2.2. Analysis of the Primary Endpoint

The primary endpoint of mRS as a 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90 will be analyzed using ordinal logistic regression, adjusting for covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20). Multiple imputation will be used to account for missing values for the 90-day mRS.

Sensitivity analyses will be performed to evaluate the impact of missing data, and the missing data handling will be specified in the SAP.

16.2.2.3. Analysis of the Secondary Endpoints

The secondary endpoints are ranked in a descending order below, and a sequential closed testing procedure will be employed as defined in Section 16.2.2.1.

- Time to all-cause death through Day 90

  Cox proportional hazards regression models will be used to assess the treatment effects on overall survival at Day 90 after adjusting for covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no) and baseline NIHSS (≤20 vs. >20). Kaplan-Meier curves will be presented for both treatment groups.

- Proportion of subjects who achieved mRS 0-4 at Day 90

  Logistic regression will be used to estimate an odds ratio of improvement on the Day 90 mRS dichotomized at 0-4 vs. 5-6, adjusting for covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no) and baseline NIHSS (≤20 vs. >20).

- Midline shift at 72 hours (or prior to DC or CMO, if earlier)

  Midline shift at 72 hours will be analyzed using analysis of variance adjusting for covariates including region, rtPA (yes, no), thrombectomy (yes, no), use of ASPECTS for screening (yes, no), and baseline NIHSS (≤20 vs. >20).

[redacted]

[redacted]

16.6. Safety

16.6.1. Analysis Population

The safety population is defined as all enrolled subjects who receive any portion of the study treatment.

16.6.2. Methods of Analysis

All AEs, laboratory data, ECG, physical examination results, and vital signs will be evaluated for safety.

16.6.2.1. Adverse Events

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

AEs will be analyzed based on the principle of treatment emergence. A treatment-emergent event is defined as follows:

- had onset any time after the start of study treatment, and/or
- worsened since the event was previously reported (this includes worsening of signs, symptoms, laboratory values, or diagnoses that were present prior to the first dose of study treatment but then worsened any time after the start of study treatment).

The incidence of treatment-emergent AEs will be summarized for each treatment group overall, by severity, and by relationship to study treatment. SAEs will be presented by treatment group and by relationship to study treatment. The summary tables will include incidence estimates for overall system organ classes, as well as for individual events within each system organ class. If

a subject experiences an event more than once with varying severity during the study, he/she will be counted only once with the maximum severity within each system organ class/preferred term. For incidence of relationship to study treatment, a subject will be counted only once and only in the category of the strongest relationship to study treatment within each system organ class/preferred term.

16.6.2.2. Clinical Laboratory Results

Clinical laboratory evaluations include hematology, blood chemistry including blood glucose.

Laboratory abnormalities will be summarized with shift tables. Tables will present changes relative to each parameter's normal ranges. Laboratory values and the corresponding changes from baseline may be summarized over time.

16.6.2.3. ECG

The number and percentage of subjects with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by treatment group.

16.6.2.4. Vital Signs

Vital signs measures include oxygen saturation, heart rate (pulse), respiratory rate, temperature, and systolic and diastolic blood pressure. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities, which will be defined in more detail in the SAP. The number of subjects evaluated and the number and percentage of subjects with clinically relevant post-baseline abnormalities will be presented by treatment group. Summary statistics for actual values and change from baseline will also be presented. The definitions of these abnormalities for temperature, pulse, and blood pressure values are provided in Table 4.

Table 4: Criteria to Determine Clinically Relevant Vital Signs Abnormalities

Vital Sign	Criteria for Abnormalities
Temperature	>38°C and an increase from pre-dosing of at least 1°C
Pulse	>120 beats per minute and an increase from pre-dosing of >20 beats per minute, or <50 beats per minute and a decrease from pre-dosing of >20 beats per minute
Systolic Blood Pressure	>180 mmHg and an increase from pre-dosing of >40 mmHg, or <90 mmHg and a decrease from pre-dosing of >30 mmHg
Diastolic Blood Pressure	>105 mmHg and an increase from pre-dosing of >30 mmHg, or <50 mmHg and a decrease from pre-dosing of >20 mmHg

16.7. Interim Analyses

An interim futility analysis may be performed based on the primary endpoint when approximately 30% of planned mITT subjects complete Day 90. At the same interim analysis, an unblinded sample size re-estimation may be performed. The sample size re-estimation

employs an approach in which the sample size will be increased when the interim results are in the promising zone [Mehta and Pocock 2011]. Criteria for futility and sample size increase and details for the interim analysis will be prespecified in the SAP and included in the DMC charter. The interim analysis will be conducted by an external independent team and be reviewed by the IDMC. The IDMC may recommend stopping for futility based on prespecified criteria. If the interim sample size re-estimation is performed, then the IDMC may recommend a single-step sample size increase to approximately 1044 subjects based on prespecified criteria. To control the type I error after the sample size adaptation, if it occurs, the final hypothesis testing for the primary endpoint will be conducted using the Cui-Hung-Wang (CHW) method [Cui 1999; Mehta and Pocock 2011] at the significance level of α=0.05 two sided. The decision whether or not to conduct the sample size re-estimation at the interim analysis will be documented by an official communication from the study Sponsor to the IDMC that will occur within 30 days after randomization of approximately 30% of the planned enrollment has been achieved. A clear process will be specified and implemented to ensure that the blind will be strictly maintained for investigators, subjects, and Sponsor's study personnel.

The final CHW test statistic is defined as follows:

$$Z^*_{2,chw} = \sqrt{\frac{n_1}{n_2}}Z_1 + \sqrt{\frac{\tilde{n}_2}{n_2}}\tilde{Z}^*_2$$

where n_1 is the sample size at interim, n_2 is the total planned sample size for the study, $\tilde{n}_2 = n_2 - n_1$ is the sample size after interim, Z_1 is the Wald test statistic from the proportional odds model calculated from the interim data, and $\tilde{Z}^*_2$ is the incremental Wald test statistic based on the data observed after the interim analysis.

16.8. Sample Size Considerations

The study will randomize approximately 768 subjects aged 18 to 85 years. Based on the observed Day 90 5-category mRS distributions of the BIIB093 group and the placebo group in the mITT population aged 18 to 70 years from the GAMES-RP Phase 2 trial, a sample size of 327 subjects aged 18 to 70 years per arm (total of 654 subjects) will have approximately 90% power using ordinal logistic regression to detect, with 5% significance, an odds ratio of 1.595 in shifting the distributions of the 5-category mRS in the direction of lower disability. Assuming up to 5% of the sample will not be evaluable for the primary analysis, it is planned to randomize up to approximately 688 subjects to the population aged 18 to 70 years, inclusive. In addition, approximately 80 subjects aged >70 and up to 85 years (inclusive) will also be randomized for safety [redacted] evaluations. Final sample size may be determined by the potential interim sample size re-estimation (Section 16.7).

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 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 investigational 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,

the subject's LAR (e.g., spouse, parent, or legal guardian), or physician, 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 LAR). 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 (*unless not permitted by local law or not approved by the governing ethics committees*) and will be used during analysis of study results.

In addition, subjects who have the capacity should provide their assent to participate in the study. The level of information provided to subjects should match their level of understanding as determined by the Investigator and in accordance with applicable regulations and guidelines.

A copy of the signed and dated ICF or assent must be given to the subject or the subject's LAR. 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 or assent 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 *(unless not permitted by local law or not approved by the governing ethics committee)*. These data will 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 eCRFs, 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) 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 post study 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 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. The Investigator is responsible for endorsing all CRF data prior to any database lock.

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 the review. It also will provide the monitoring strategy, with emphasis on subject safety, data integrity, critical data, and processes.

During monitoring visits, the eCRF, supporting documentation, and essential documentation related to the study will be reviewed and any discrepancies or omissions will be queried until fully resolved. Documentation of results will be provided to Biogen 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 investigational 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

19.1.1. Contract Research Organization

A CRO will be responsible for administrative aspects of the study including but not limited to study initiation, monitoring, and management of 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 or Remote Data Capture

Subject data will be captured and managed by study sites on a Web-based electronic data capture tool (eCRF) configured by the CRO and hosted by the electronic data capture vendor.

[redacted]

19.1.5. Central Facility for Other Assessments

An independent imaging core laboratory (ICL) will collect, review, and analyze medical images acquired during this study. A study-specific imaging charter, developed by the Sponsor and the ICL, details the personnel, processes, and methods involved in managing and evaluating imaging data. The Imaging Manual provides standardized settings for imaging data acquisition and describes the process for evaluating infarct volume/size by MRI, CTP, and NCCT for study inclusion with support from automated image analysis software whenever possible. Automated ASPECTS may be used as an aid to the investigator or local reader; however, the final ASPECTS determination for study inclusion will be made by the investigator or local reader.

All imaging data, including screening scans from subjects consented prior to screen-failure and those scans acquired as part of SOC for enrolled subjects, will be transferred to the ICL. The ICL will perform a quality review of the screening and follow-up imaging data and site-based eligibility determinations.

The ICL will also evaluate the follow-up NCCT and MRI scans for midline shift. The ICL will remain blinded to treatment assignment throughout the 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. Further details will be available in the Advisory Committee charter. The advisory committee will be blinded to treatment assignment.

19.2.2. Independent Data Monitoring Committee

An IDMC will be established to assess the overall safety profile of BIIB093 during the study. An IDMC charter will guide the overall governance plan for the IDMC. IDMC may recommend the Sponsor to terminate the study based on safety data or following the interim futility analysis. If the interim sample size re-estimation is performed, then the IDMC may recommend a sample size increase based on prespecified criteria in the SAP and IDMC charter.

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 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 site.

19.6. Study Report Signatory

Biogen will designate one or more 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.

Biogen will follow all applicable local regulations pertaining to study report signatories.

20. REFERENCES

Arac A, Blanchard V, Lee M, et al. Assessment of outcome following decompressive craniectomy for malignant middle cerebral artery infarction in patients older than 60 years of age. Neurosurg Focus. 2009;26(6):E3.

Bereczki D, Fekete I, Prado GF, et al. Mannitol for acute stroke. Cochrane Database Syst Rev. 2007(3):CD001153. Epub 2007/07/18.

Berrouschot J, Sterker M, Bettin S, et al. Mortality of space-occupying ('malignant') middle cerebral artery infarction under conservative intensive care. Intensive Care Med. 1998;24(6):620-3.

Chen M, Dong Y, Simard JM. Functional coupling between sulfonylurea receptor type 1 and a nonselective cation channel in reactive astrocytes from adult rat brain. J Neurosci. 2003;23(24):8568-77.

Chen M, Simard JM. Cell swelling and a nonselective cation channel regulated by internal Ca2+ and ATP in native reactive astrocytes from adult rat brain. J Neurosci. 2001;21(17):6512-21.

Cui L, Hung HM, Wang SJ. Modification of sample size in group sequential clinical trials. Biometrics. 1999;55(3):853-7.

Hacke W, Schwab S, Horn M, et al. 'Malignant' middle cerebral artery territory infarction: clinical course and prognostic signs. Arch Neurol. 1996;53(4):309-15.

Hallenbeck JM, Dutka AJ. Background review and current concepts of reperfusion injury. Arch Neurol. 1990;47(11):1245-54.

International Hypoglycaemia Study Group. Glucose Concentrations of Less Than 3.0 mmol/L (54 mg/dL) Should Be Reported in Clinical Trials: A Joint Position Statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2017;40(1):155-157. Epub 2016/11/21.

Jauch EC, Saver JL, Adams HP, et al. Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2013;44(3):870-947.

Koudstaal PJ, Stibbe J, Vermeulen M. Fatal ischaemic brain oedema after early thrombolysis with tissue plasminogen activator in acute stroke. BMJ. 1988;297(6663):1571-4.

Mehta CR, Pocock SJ. Adaptive increase in sample size when interim results are promising: a practical guide with examples. Statistics in medicine. 2011;30(28):3267-84. Epub 2010/11/30.

Nielsen TH, Ståhl N, Schalén W, et al. Recirculation usually precedes malignant edema in middle cerebral artery infarcts. Acta neurologica Scandinavica. 2012;126(6):404-10. Epub 2012/04/12.

Qizilbash N, Lewington SL, Lopez-Arrieta JM. Corticosteroids for acute ischaemic stroke. Cochrane Database Syst Rev. 2002(2):CD000064.

Rudolf J, Grond M, Stenzel C, et al. Incidence of space-occupying brain edema following systemic thrombolysis of acute supratentorial ischemia. Cerebrovasc Dis. 1998;8(3):166-71.

Sheth KN, Elm JJ, Molyneaux BJ, et al. Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial. Lancet Neurol. 2016;15(11):1160-9. Epub 2016/08/23.

Simard JM, Chen M, Tarasov KV, et al. Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. Nat Med. 2006;12(4):433-40. Epub 2006/03/19.

Simard JM, Geng Z, Silver FL, et al. Does inhibiting Sur1 complement rt-PA in cerebral ischemia? Annals of the New York Academy of Sciences. 2012a;1268:95-107.

Simard JM, Kent TA, Chen M, et al. Brain oedema in focal ischaemia: molecular pathophysiology and theoretical implications. Lancet Neurol. 2007;6(3):258-68.

Simard JM, Tsymbalyuk N, Tsymbalyuk O, et al. Glibenclamide is superior to decompressive craniectomy in a rat model of malignant stroke. Stroke. 2010;41(3):531-7. Epub 2010/01/21.

Simard JM, Tsymbalyuk O, Keledjian K, et al. Comparative effects of glibenclamide and riluzole in a rat model of severe cervical spinal cord injury. Exp Neurol. 2012b;233(1):566-74. Epub 2011/12/08.

Torbey MT, Bösel J, Rhoney DH, et al. Evidence-based guidelines for the management of large hemispheric infarction : a statement for health care professionals from the Neurocritical Care Society and the German Society for Neuro-intensive Care and Emergency Medicine. Neurocrit Care. 2015;22(1):146-64.

Vahedi K, Hofmeijer J, Juettler E, et al. Early decompressive surgery in malignant infarction of the middle cerebral artery: a pooled analysis of three randomised controlled trials. Lancet Neurol. 2007;6(3):215-22.

Wijdicks EF, Sheth KN, Carter BS, et al. Recommendations for the management of cerebral and cerebellar infarction with swelling: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45(4):1222-38. Epub 2014/01/30.

APPENDIX 1. MEDICATIONS THAT MODULATE CYP2C9 AND CYP3A4

CYP2C9

SUBSTRATES	INHIBITORS	INDUCERS
celecoxib	***Strong***	
Glimepiride	-	
phenytoin	***Moderate***	***Moderate***
tolbutamide	amiodarone	rifampin
warfarin	felbamate	enzalutamide
	fluconazole	aprepitan
	miconazole	carbamazepine
	piperine	ritonavir
	Weak	
	diosmin	
	disulfiram	
	fluvastatin	
	fluvoxamine	
	voriconazole	

Source: FDA 9/26/2016 Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

CYP3A4

SUBSTRATES	INHIBITORS	INDUCERS
midazolam	***Strong***	***Strong***
tacrolimus	ritonavir	phenytoin
sirolimus	indinavir	carbamazepine
naloxegol	nelfinavir	rifampin
nisoldipine	saquinavir	
saquinavir	clarithromycin	
simvastatin	troleandomycin	
tipranavir	voriconazole	
triazolam	ketoconazole	
vardenafil	itraconazole	
budesonide	nefazodone	
dasatinib	grapefruit juice (bergamottin)	
alfentanil	boceprevir	
avanafil	cobicistat	
buspirone	conivaptan	
conivaptan	danoprevir	
darifenacin	elvitegravir	
darunavir	lopinavir	
ebastine	paritaprevir	
everolimus	posaconazole	
ibrutinib	telaprevir	
lomitapide	tipranavir	
lovastatin		
dronedarone	***Moderate***	***Moderate***
eletriptan	verapamil	bosentan
eplerenone	tofisopam	efavirenz
felodipine	aprepitant	etravirine
indinavir	erythromycin	modafinil
lurasidone	fluconazole	
maraviroc	cimetidine	
quetiapine	ciprofloxacin	
sildenafil	clotrimazole	
ticagrelor	crizotinib	
tolvaptan	cyclosporine	
alprazolam	dronedarone	
aprepitant	imatinib	
atorvastatin	fluvoxamine	

colchicine		
eliglustat	***Weak***	***Weak***
pimozide	ticagrelor	armodafinil
rilpivirine	chlorzoxazone	rufinamide
rivaroxaban	cilostazol	
tadalafil	fosaprepitant	
	istradefylline	
	ivacaftor	
	lomitapide	
	ranitidine	
	ranolazine	
	tacrolimus	

Source: FDA 9/26/2016 Drug Development and Drug Interactions: Table of Substrates, Inhibitors and Inducers

21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "Randomized, Double-Blind, Placebo-Controlled, Parallel-Group, Multicenter, Phase 3 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 (Glibenclamide) for Severe Cerebral Edema following Large Hemispheric Infarction" 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.

Investigator's Signature_____Date

Investigator's Name (Print)_____

Study Site (Print)_____