COVER PAGE

Official Title:	A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients with Brain Contusion
NCT Number:	NCT03954041
Document Date:	Protocol Version 3.0: 14 Nov 2022

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PROTOCOL NUMBER: 252BN201

PHASE OF DEVELOPMENT: 2

PROTOCOL TITLE: A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients with Brain Contusion

EUDRA CT NUMBER: **2018-003858-24**

DATE: 14 November 2022
Version 3
FINAL

Supersedes previous Version 2 dated 18 February 2020

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SPONSOR SIGNATURE PAGE

Protocol 252BN201 was approved by:

_____ _____

[redacted] MD Date

[redacted]

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1. SYNOPSIS

Protocol Title:	A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients with Brain Contusion.
Protocol Number:	252BN201
Version Number:	3
Name of Study Treatment:	BIIB093
Study Phase:	2
Study Indication:	Brain Contusion
Study Rationale:	Brain contusion is a devastating public health problem with no approved pharmacologic treatment to stop or slow the progression of the lesion following the initial trauma. Delayed progression of bleeding into the brain is known as the hemorrhagic progression of contusion (HPC). This expansion leads not only to an increase in hematoma volume, but also to the evolution of perihematomal edema surrounding the lesion itself. Sulfonylurea receptor 1-transient receptor potential melastatin 4 (SUR1-TRPM4) is a cation channel, upregulated in human pericontusional endothelium and astrocytes that allows for harmful osmotic cell swelling under adenosine triphosphate-depleted conditions. Increased osmotic flux via the channel leads to the lysis of endothelial cells and the loss of capillary structural integrity. This results in the extravasation of blood, and the resultant expansion of the initial contusion. Moreover, loss of capillary structure permits the development of perihematomal vasogenic edema. Lastly, SUR1TRPM4 also mediates cytotoxic edema, a further sequela worsening contusion progression. BIIB093 explicitly targets the SUR1-TRPM4 channel and mitigates HPC in animal models of brain and spinal cord contusion. BIIB093 has also repeatedly demonstrated anti-perihematomal edema effects in nonclinical models. The aim of this study is to provide evidence that BIIB093 reduces the progression of intracerebral hematoma and contusions in individuals who experience brain contusion, by antagonizing SUR1-TRPM4.

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Study Objectives and Endpoints:

The primary objective of the study is to determine if BIIB093 reduces brain contusion expansion by Hour 96 when compared to placebo. Measurements of contusion expansion are based on a comparison of the baseline images and the scans collected prior to and including the 96-hour scan, or the scan obtained prior to decompressive craniectomy (DC), intraparenchymal hematoma (IPH) evacuation, or comfort measures only (CMO), if earlier.

The primary endpoint as measured by brain imaging, is the change in total contusion volume (hematoma plus perihematomal edema) from baseline to 96 hours, or prior to DC, IPH evacuation, or CMO if these procedures occur before 96 hours.

Secondary objectives and endpoints for the study are as follows:

- To evaluate the effects of BIIB093 on acute neurologic status, functional outcomes, and treatment requirements.
  - Glasgow Outcome Scale – Extended (GOS-E) at Day 180
  - Modified Rankin Scale (mRS) at Day 90
  - Proportion of participants requiring delayed intubation

  Note: delayed intubation is defined as participants requiring intubation (for neurologic deterioration only) at any time between 24 hours and 96 hours post injury.

- To further differentiate the mechanism of action of BIIB093 compared to placebo on contusion expansion by examining differential effects on hematoma and edema expansion.
  - Change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 24 hours or prior to DC, IPH evacuation, or CMO if these procedures occur before 24 hours per the central review.
  - Change in absolute hematoma volume from baseline to 24 hours
  - Change in absolute edema volume from baseline to 96 hours

- To determine if BIIB093 improves survival at Day 90 when compared to placebo.

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- Time to all-cause death, including neurological death, through Day 90

[redacted]

Study Design:	This is a Phase 2, randomized, multicenter, double-blind, multidose, placebo-controlled study.
Study Location:	Approximately 60 sites in 7 countries globally are planned.
Number of Planned Participants:	Approximately 160 participants will be randomized.
Study Population:	This study will be conducted in participants aged 18 to 85 years old, inclusive, with a diagnosis of brain contusion, with lesions within the supratentorial brain parenchyma totaling > 3 mL in volume per Investigator assessment of baseline noncontrast computed tomography scan at Screening or site local radiologic assessment. Participants must have a score of 5 to 15 on the Glasgow Coma Scale (GCS) and have been functionally independent, in the opinion of the Investigator, prior to index head injury. Detailed criteria are described in Section 8.
Treatment Groups:	All participants must be dosed within 10 hours of time of trauma/last known normal (LKN) and within 6 hours of hospital arrival. Dosing should be initiated within 1 hour of randomization and continue for 96 hours (4 days). Participants will receive study treatment (3 mg/day or 5 mg/day) or matching placebo administered as a 3-stage continuous infusion: a bolus IV dose (given over 2 minutes), followed by 2 different infusion rates (a rapid IV infusion for 6 hours followed by a slow IV infusion for the remaining 90 hours) for 96 hours total. Participants will be randomly assigned to 3 mg/day study treatment, 5 mg/day study treatment, 3 mg/day matching placebo, or 5 mg/day matching placebo in a 1:1:1:1 ratio, stratified based on baseline contusion volume per Investigator assessment of noncontrast computed tomography scan or site local radiologic assessment (3 to 10 mL or > 10 mL), baseline GCS (5 to 8, 9 to 12, or 13 to 15), age (≤ 70 years old or > 70 years old), and region (North America [United States] or Rest of World).

Duration of Treatment and Follow-up:	The study treatment or matching placebo will be administered for 96 hours (4 days) in total. All participants will be followed up for functional outcome measures at Day 90 and Day 180.

2. LIST OF ABBREVIATIONS

AE	adverse event
ALT	aminotransferase
ANCOVA	analysis of covariance
AST	aspartate aminotransferase
BG	blood glucose
CI	confidence interval
CMO	comfort measures only
COVID-19	Coronavirus disease 2019
CRO	contract research organization
C_{ss}	concentration at steady state
CYP	cytochrome P450
DC	decompressive craniectomy
DHA	Directions for Handling and Administration
DWI	diffusion-weighted imaging
ECG	electrocardiogram
eCRF	electronic case report form
ET	early termination
[redacted]	
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GOS-E	Glasgow Outcome Scale – Extended
HPC	hemorrhagic progression of contusion
ICF	informed consent form
ICH	International Council for Harmonisation
ICL	imaging core laboratory
ICU	intensive care unit
IDMC	independent data monitoring committee
INR	international normalized ratio
IPH	intraparenchymal hematoma
IRT	interactive response technology
IV	intravenous
LAR	legally authorized representative
LHI	large hemispheric infarction
LKN	last known normal
MMP-9	matrix metalloprotease-9
MRI	magnetic resonance imaging
mRS	modified Rankin Scale
NCCT	noncontrast computed tomography
NOAC	novel oral anticoagulants
NSx	neurosurgical intervention
OATP	organic anion transporting polypeptide

PD	pharmacodynamics
[redacted]	[redacted]
POC	point-of-care
PTT	partial thromboplastin time
PVC	polymerizing vinyl chloride
QTc	QT interval corrected for heart rate
rtPA	recombinant tissue plasminogen activator
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SOC	standard of care
SUR1-TRPM4	sulfonylurea receptor 1-transient receptor potential melastatin 4 channel
SUSAR	suspected unexpected serious adverse reaction
TBI	traumatic brain injury
ULN	upper limit of normal

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4. INTRODUCTION

4.1. Brain Contusion Background

Hemorrhagic lesions following trauma to the brain, which are referred to as contusions, may cause significant long-term morbidity and mortality. Bleeding into the brain parenchyma is problematic, due not only to the mass effect of a hematoma on intracranial pressure and associated brain herniation with compression of vital neurologic centers, but also to the neurotoxicity of hemoglobin [Kurland 2012].

In addition to the initial bleed following trauma, contusions often progress in size during the acute hospitalization period, significantly worsening prognosis. The delayed progression of bleeding into the brain is known as the hemorrhagic progression of contusion (HPC), or "blossoming" [Kurland 2012]. This expansion leads not only to an increase in hematoma volume, but also to the evolution of perihematomal edema surrounding the lesion itself. Both sequelae cause significant secondary brain injury. The prognosis for patients with traumatic brain injury (TBI) is often poor, with case fatality of up to 56%, and is worse for patients with HPC [O'Neil-Pirozzi 2018; Song 2016].

Progression of contusions are largely a function of the initial contusion volume, although other factors also contribute. Use of traditional and novel anticoagulants, antiplatelet agents, coagulopathy, age, and uncontrolled hypertension are all thought to contribute to some degree and are routinely controlled as part of clinical practice. Other processes that contribute to the progression of a contusion are analogous to the dysfunction of the cerebral microvasculature. Microvascular impairment, caused primarily by endothelial cell swelling and fragmentation, worsens hematoma expansion via the ongoing extravasation of blood into the brain parenchyma. In addition to ongoing bleeding, endothelial cell breakdown also permits the formation of perihematomal edema by extravasation of endovascular fluids into the brain's interstitium. [Kurland 2012; Park 2008].

4.2. Current Therapies for Brain Contusion

Brain contusion is a devastating public health problem with no approved pharmacologic treatment to stop or slow the progression of lesions following the initial trauma. The standard of care remains primarily supportive, with the maintenance of hemostasis to limit ongoing bleeding, and with surgical evacuation or other means to reduce intracranial pressure (i.e., insertion of ventricular drains, osmotherapy, or decompressive craniectomy [DC]) [Carney 2016; Haddad and Arabi 2012]. Despite these interventions, brain contusions may continue to progress, particularly during the first 12 hours following a TBI. There is no standard of care to limit HPC, leaving an urgent unmet medical need. Studies of hemostatic agents, including recombinant factor 7 and tranexamic acid, have yielded mixed results and are not routinely used in clinical practice.

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4.3. Profile of Previous Experience With BIIB093

As a treatment for cytotoxic and vasogenic edema, glibenclamide administered as an intravenous (IV) formulation is currently being studied in a global Phase 3 randomized clinical study for large hemispheric infarction (LHI), a development program complementary to the protocol proposed here. IV glibenclamide is known as BIIB093 and was formerly known as CIRARA or RP 1127 when it was under development by Remedy Pharmaceuticals.

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

4.3.1. 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 0440RR31.001, Remedy Study RPI-TOX1), an in vitro hemolytic potential assay (Study 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.

4.3.2. Clinical Experience

BIIB093 has been assessed in the following completed clinical studies: 1 Phase 1 study in healthy volunteers (Study 101), 2 Phase 2 studies in participants with LHI (Study 201 and Study 203), and 1 Phase 2 study in participants with TBI (Study 202). It is also being assessed in the ongoing Phase 3 study in participants with LHI (Study 301).

In Study 201 (GAMES-PILOT), 10 participants 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 study treatment 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 participants with LHI with BIIB093, whether or not they were treated with IV recombinant tissue plasminogen activator (rtPA). Participants who received intra-arterial reperfusion therapy, prophylactic DC, or were on sulfonylurea treatment at presentation were excluded. Nine out of 10 enrolled participants received rtPA within 4.5 hours from onset of stroke. Baseline National Institute of Health Stroke Scale 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, participants did not require osmotherapy, intubation, or DC. Results from this study indicated that it was feasible to enroll, evaluate, and treat participants with severe stroke according to the protocol. The regimen was well tolerated, and there were no reported cases of hypoglycemia.

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Study 203 (GAMES-RP) was a randomized, double-blind, placebo-controlled, multicenter study of BIIB093 in participants with LHI. The study enrolled participants 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. Participants 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 participants 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 participants who achieved a modified Rankin Scale (mRS) score of 0 to 4 at Day 90 without undergoing DC. At Day 90, 17 participants (41%) who received BIIB093 and 14 (39%) in the placebo group achieved the primary endpoint (adjusted odds ratio 0.87, 95% confidence interval [CI] 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].

Study 202 was a randomized, double-blind, placebo-controlled, multi-institutional study of BIIB093 in participants with moderate or severe TBI. The study enrolled participants aged 18 to 75 years with documented closed head TBI, Glasgow Coma Scale (GCS) of 4 to 14, and time of injury to study treatment infusion of ≤ 10 hours. The dosing regimen was identical to that used in the LHI studies. The primary safety objective of the study was to assess the safety and tolerability of BIIB093 compared with placebo in participants with severe, moderate, or complicated mild TBI. No deaths were reported in Study 202 in participants with TBI. Seven serious adverse events (SAEs) were reported in 5 participants (3 participants in the BIIB093 group and 2 participants in the placebo group). These included catheter site infection, pneumonia, septic shock, and hypoglycemia in the BIIB093 group, and vascular pseudoaneurysm, carotid artery thrombosis, and convulsion in the placebo group. Except for the SAE of hypoglycemia reported in 1 participant in the BIIB093 group, all other events were considered unrelated to study treatment. The incidence of adverse events (AEs) was comparable between the 2 treatment groups; a total of 170 events were reported in 27 participants (13 participants in the BIIB093 group and 14 participants in the placebo group).

4.3.3. Benefit/Risk

BIIB093 has been shown to potentially reduce mortality associated with LHI, reducing brain edema, and improving functional outcomes.

BIIB093 given intravenously in a 3-stage dosing regimen over 72 hours was generally well tolerated in the population of participants with LHI and TBI. The only adverse drug reaction identified was hypoglycemia, which can be mitigated by frequent blood glucose (BG) measurement and dose adjustment. The safety profile of BIIB093 observed in completed studies in participant with LHI and TBI is detailed in the Investigator's Brochure. Based on the safety profile and observed benefit in Phase 2 studies of BIIB093 for treatment of LHI and TBI, 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 and brain contusion.

4.4. Study Rationale

By understanding the biology of endothelial cells and capillary fragmentation, the expansion of cerebral contusions may be mitigated using pharmacologic means, in addition to control of coagulopathy, thrombocytopenia, and hemodynamics. Loss of microvascular integrity is thought to be due to the shearing forces of a brain trauma, as well as the upregulation of the sulfonylurea receptor 1-transient receptor potential melastatin 4 channel (known as SUR1-TRPM4) in endothelial cells. SUR1-TRPM4 is a cation channel that allows for harmful osmotic cell swelling under adenosine triphosphate-depleted conditions, which in turn leads to the lysis of endothelial cells and the loss of capillary structural integrity. This results in the extravasation of blood, and the resultant expansion of the initial contusion. Notably, deletion of ABCC8, the gene that encodes sulfonylurea receptor 1 (SUR1) reduces HPC and provides neuroprotection in animal models [Kurland 2012; Simard 2009b]. A recent review highlights the potential of BIIB093 to provide clinical benefit for brain contusion based on the totality of preclinical and preliminary clinical evidence [Jha 2020].

BIIB093 is being developed by Biogen for the treatment of patients with LHI and brain contusion. BIIB093 explicitly targets the SUR1-TRPM4 channel and mitigates HPC in animal models of brain and spinal cord contusion. Glibenclamide has also repeatedly demonstrated anti-perihematomal edema effects in nonclinical models. Specifically, glibenclamide reduces lesion volume and promotes recovery in experimental models of LHI, TBI, spinal cord injury, and subarachnoid hemorrhage [Ortega 2012; Simard 2006; Simard 2012a; Simard 2009a; Simard 2009b; Simard 2013; Simard 2010; Simard 2007; Simard 2012b; Simard 2008; Simard 2012c; Wali 2012; Zweckberger 2014]. Additionally, a multitude of clinical data obtained from biopsy samples from pericontusional tissue demonstrates upregulation of the SUR1-TRPM4 complex in astrocytes, as well as peri-contusional endothelium [Gerzanich 2018]. Lastly, upregulation of SUR1 in the cerebrospinal fluid of patients with TBI was recently demonstrated, with value as a biomarker of the evolution of cerebral edema [Jha 2017].

The proof of concept for BIIB093 was established in a Phase 2 study of LHI (Study 203, Section 4.3.2), a clinical entity with distinct pathophysiology (i.e., characterized by cytotoxic edema) from brain contusion, but similarly involving the SUR1-TRPM4 complex. As discussed, this study demonstrated a significant effect of BIIB093 on midline shift of the brain, a radiographic endpoint indicative of marked cerebral edema and increased intracranial pressure. The study provided evidence not only of proof of biology, but also confirmed the strong safety profile of BIIB093. Notably, these results were the impetus for the ongoing pivotal Phase 3 study, Study 301 (CHARM), investigating BIIB093 as a therapy for malignant cerebral edema in LHI [Sheth 2016].

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4.5. Dosing Rationale

4.5.1. Dosing Regimen

Dosing must be started within 10 hours of trauma/last known normal (LKN) and within 6 hours of arrival to the hospital. Dosing should be initiated within 1 hour of randomization, and continue for 96 hours (4 days). The dosing duration of 96 hours (4 days), spans the period during which patients are thought to be at highest risk for contusion expansion. Two BIIB093 dose levels will be administered (Table 1).

Table 1: BIIB093 Dosing Regimen

	IV bolus (slow IV push via syringe)	Infusion 1	Infusion 2
3 mg/day	0.13 mg (over approximately 2 minutes)	0.99 mg (0.1644 mg/h for 6 h)	10.21 mg (0.1134 mg/h for 90 h)
	Total dose: Day 1 (3.16 mg), Day 2 (2.72 mg), Day 3 (2.72 mg), Day 4 (2.72 mg) = 11.3 mg		
5 mg/day	0.21 mg (over approximately 2 minutes)	1.63 mg (0.2722 mg/h for 6 h)	16.84 mg (0.1871 mg/h for 90 h)
	Total dose: Day 1 (5.21 mg), Day 2 (4.49 mg), Day 3 (4.49 mg), Day 4 (4.49 mg) = 18.7 mg		

h = hour(s); IV = intravenous.
Note: 3 mg/day and 5 mg/day are approximate total daily doses.
Refer to the Directions for Handling and Administration (DHA) for corresponding mL/h rates and further information on windows for infusion timings.

The 2 BIIB093 dose levels (3 mg/day and 5 mg/day) selected for this study were determined based on clinical safety and pharmacokinetic (PK) data and preliminary exposure-response (efficacy/safety) analyses from the Phase 1 healthy volunteer studies (Study 101 and Study 102) and the Phase 2 LHI studies (Study 201 and Study 203).

4.5.1.1. Selection of 3 mg/day

The dosing recommendation for the investigation of brain contusion is guided by the clinical experience of BIIB093 in healthy volunteers and patients with LHI. Briefly, the IV infusion regimen for LHI in Phase 3 was refined based on dose escalation results from the Phase 1 study (Study 101: first-in-human study in healthy volunteers) and PK modeling, encompassing a 3stage IV infusion regimen (IV bolus followed by 2 infusion periods). The 3 mg/day dose was the highest dose tested in Study 101 in which severe hypoglycemia was not observed, and it had an acceptable safety profile and was well tolerated in the LHI Phase 2 studies. Additionally, this dosing regimen is selected to rapidly achieve and maintain the desired systemic steady-state concentration (approximately 25 ng/mL) of BIIB093 previously shown to be efficacious in patients with LHI. Efficacy of BIIB093 at 3 mg/day in brain contusion is also anticipated based on the similar pathophysiology between LHI and brain contusion. This is also supported by preclinical evidence (rat models of brain contusion), which demonstrated that glibenclamide significantly reduced progressive secondary hemorrhage with a dosing regimen identical to that used in LHI animal models [Simard 2010].

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4.5.1.2. Selection of 5 mg/day

In addition to 3 mg/day, this study will also evaluate a higher dose at 5 mg/day, on the basis of retrospective and exploratory exposure-response analyses, conducted by both Biogen and independent investigators, demonstrating increased efficacy of BIIB093 with higher exposures, as detailed below.

A retrospective analysis of Study 201, a pilot study of BIIB093 in LHI, dichotomized participants into low and high exposure cohorts. Analysis of efficacy data by exposure demonstrated improved mitigation of vasogenic edema (measured by T2 Flair MRI) with higher BIIB093 exposures (average concentration of 32 ng/mL) versus lower plasma levels (average concentration 16 ng/mL) [Kimberly 2014]. Notably, 25 ng/mL is the target concentration for 3 mg/day. Additionally, an exploratory analysis using data from Study 203 (pivotal Phase 2 LHI study) showed a consistent trend of higher BIIB093 exposure correlating with improved efficacy outcome (reduction of midline shift). A relationship between increasing BIIB093 exposure and decreasing matrix metalloprotease-9 (MMP-9) concentration was also observed, suggesting improved blood-brain- barrier integrity in the presence of higher BIIB093 drug exposure. Therefore, greater efficacy is anticipated for brain contusion at the higher dose of BIIB093.

The specific dose level at 5 mg/day was selected based on a totality of clinical safety (severe hypoglycemia) and pharmacodynamics (PD) data (blood glucose). Up to 10 mg/day has been previously evaluated in the first-in-human study in healthy participants (Study 101). Symptomatic severe hypoglycemia, or BG < 55 mg/dL (~3.1 mmol/L), was observed in 6 mg/day and 10 mg/day cohorts, and 3 mg/day was the highest dose studied that did not result in severe hypoglycemia. Doses between 3 and 6 mg/day have not been evaluated clinically. No apparent exposure-response relationship between BIIB093 plasma concentration and BG level was observed. As such, safety results from Study 101 were used to inform the clinical concentration threshold for severe hypoglycemia, which was 75 ng/mL. PK simulations of the anticipated exposures at 5 mg/day (mean plasma concentration at steady state: 40 ng/mL, 95% CI: 13.4, 61.8) showed the maximum predicted BIIB093 plasma concentration would remain below the threshold where severe hypoglycemia was observed.

Furthermore, the exposures of 5 mg/day dose level are covered within the safety margin established in BIIB093 preclinical studies. A 14-day toxicity study in adult rats was conducted to assess safety and tolerability of BIIB093. During the 14-day continuous infusion period, no BIIB093-related clinical observations were noted, but clinical chemistry results showed pharmacologic hypoglycemia in female rats. A sex difference was noted in rats as exposure to BIIB093 was generally higher in female rats compared with male rats; however, combined male and female rat exposure is used to generate exposure margins because a sex difference is not observed in humans. The no observed adverse effects level was considered to be 18.2 mg/kg, which provides exposure margins of 3-fold and 6-fold based on the maximum observed concentration and concentration at steady state (C_{ss}), respectively, at 5 mg/day. The exposure data at 5 mg/day are the result of simulations. A dose range of 3 mg/day to 5 mg/day has a limited dynamic range but, based on preclinical data, appears to balance safety and the opportunity to maximize efficacy.

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4.5.1.3. IV Infusion Duration

For the brain contusion program, the BIIB093 treatment period will be extended to 96 hours, as opposed to the 72-hour infusion period implemented in participants with LHI. An extended treatment period is believed to be of additional benefit to patients with brain contusion because intracranial pressure monitoring in the intensive care unit (ICU) is typically carried out for 4 to 5 days in these patients, and HPC and edema can occur as late as 3 to 4 days after head injury [Kurland 2012; Staykov 2011]. Dosing out to 96 hours will ensure that BIIB093 continues to affect the evolution of the hematoma and its surrounding edema, which tends to occur later in patients with brain contusion than in patients with a malignant infarction.

During the additional 24-hour infusion period, the same plasma $C_{ss,}$ will be maintained for BIIB093. While the overall drug exposure is increased, it is still within the safety margin established for BIIB093. It is also important to note that with the daily dose of 5 mg, the systemic exposure of BIIB093 acute treatment is significantly lower than that of the approved therapeutic oral glibenclamide (maximum dose of 20 mg/day approved for Micronase® or 12 mg/day approved for Glynase®) taken chronically by patients with diabetes.

Risk mitigation strategies will be applied for the occurrence of hypoglycemia (administration of IV dextrose or discontinuation/dose reduction/interruption of BIIB093, at the discretion of the Investigator) [see Section 11.4.1.1.1]. Based on the evidence available, the plasma C_{ss} is not expected to change; therefore, AEs are expected to be consistent with clinical studies to date, with hypoglycemia being the principal risk. Specific risk mitigation strategies are advised and for unmanageable hypoglycemia, discontinuation criteria are in place (see Section 10.1).

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5. SCHEDULE OF ACTIVITIES

Table 2: Schedule of Activities

	Screening/ Enrollment	Hours 0-12[1]	Hour 24 (±6 h)	Hour 48 (±12 h)	Hour 72 (±12 h)	Hour 96 (±12 h)[2]	Day 7 (±24 h)[3]	Hospital Discharge (±24 h)[4]	Day 30 (±7 d)[4]	Day 90 (±14 d)[4]	Day 180 (±14 d)[4]	NSx/Comfort Measures (if applicable)	ET Visit
Inclusion/ exclusion criteria	X												
Informed consent	X												
Demographics, medical history, physical examination (including weight and height)	X												
TT/LKN	X												
NCCT[5]	X[6]		X			X[7]						X	
GCS	X		X	X		X							
Pregnancy test (urine or serum)	X												
Blood alcohol level	X												
Blood sampling for coagulation panel (INR, PTT, fibrinogen)	X												
Blood sampling for hematology and blood chemistry	X						X						X[8]
Blood sampling for LFTs	X		X	X	X	X	X						
Vital signs[9]	X	X	X	X	X	X	X						X
Other assessments (ECG, [redacted])	(see Table 3 for ECG, [redacted] schedule of activities)												
Blood sampling for pharmacogenetics (optional)[10]		X											
Enrollment/randomization (TT/LKN < 10 h)	X												

	Screening/ Enrollment	Hours 0-12[1]	Hour 24 (±6 h)	Hour 48 (±12 h)	Hour 72 (±12 h)	Hour 96 (±12 h)[2]	Day 7 (±24 h)[3]	Hospital Discharge (±24 h)[4]	Day 30 (±7 d)[4]	Day 90 (±14 d)[4]	Day 180 (±14 d)[4]	NSx/Comfort Measures (if applicable)	ET Visit
Study treatment (TT/LKN < 10 h)		← 96-hour infusion → (see Section 4.5.1 for further details)											
Delayed intubation eCRF[11]			X	X	X	X							
BG measurement[12]	X	X	X	X	X	X	X						
Concomitant therapy	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant procedures[13]	X	X	X	X	X	X	X	X	X	X	X	X	X
Craniectomy/comfort care/ cranioplasty assessment form(s)												X	
MRI[14, 5]						X[15]						X	X[16]
GOS-E								X	X	X	X		X
[redacted]													
mRS										X	X		X
[redacted]													
Review safety data and record AEs/SAEs[17]	X	X	X	X	X	X	X	X	X	X	X		X
Brief suicide ideation/behavior assessment[18]	X								X	X	X		X

AE = adverse event; BG = blood glucose; CMO = comfort measures only; d = days; DC = decompressive craniectomy; ECG = electrocardiogram; eCRF = electronic case report form; ET = early termination; [redacted]; GCS = Glasgow Coma Scale; GOS-E = Glasgow Coma Scale-Extended; h = hours; INR = international normalized ratio; IPH = intraparenchymal hematoma; LFT = liver function test; LKN = last known normal; MRI = magnetic resonance imaging; mRS = modified Rankin Scale; NCCT = noncontrast computed tomography; NSx = neurosurgical intervention; [redacted] PTT = partial thromboplastin time; [redacted]; SAE = serious adverse event; SOC = standard of care; TT = time of trauma.

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[1] Hour 0 is defined as the start of study treatment infusion.
[2] In the event a participant is discharged from the hospital prior to Hour 96, every effort should be made to obtain neuroimaging (NCCT or MRI) prior to discharge.
[3] If a participant is due to be discharged from hospital prior to Day 7, every effort should be made to perform the Day 7 assessments at the time of discharge or just prior.
[4] All visits after hospital discharge can be conducted by telephone; however, the Day 90 and Day 180 Visits should be in person whenever possible. Should the follow-up visits at Day 90 and Day 180 be conducted remotely, [redacted].
[5] Scans (NCCT or MRI) obtained within 12 hours of IPH evacuation, DC, or CMO meet the requirement. Scans are not expected for other NSx interventions. If IPH evacuation, DC, or CMO are indicated prior to 96 hours, an NCCT or MRI scan in the 12 hours proceeding the procedure should be collected, and no further post procedural images are required beyond SOC.
[6] NCCT as SOC at Screening (prior to enrollment). If not eligible per SOC scan, a single, repeat, study-specific NCCT may be obtained to reassess contusion volume if feasible within the protocol-specified time window.
[7] Optional Hour 96 NCCT should be obtained in addition to the MRI whenever possible, after study treatment infusion is complete, within 18 hours of the Hour 96 timepoint.
[8] Only performed if participant has not yet been discharged from hospital.
[9] Vital signs include temperature, pulse rate, systolic and diastolic blood pressure, respiratory rate, and oxygen saturation. Measurements taken nearest to the assessment timepoint should be recorded.
[10] The optional blood sample for pharmacogenetic analysis requires a separate informed consent form to be administered between the start of study and hospital discharge. The pharmacogenetic sample should be collected as close to the consenting procedure as possible and preferably within 24 hours of the start of study treatment. The date and time of collection should be recorded.
[11] A delayed intubation eCRF must be completed if a participant is intubated for deteriorating neurologic status.
[12] Hourly (±30 minutes) for Hour 0 to Hour 24, every 2 hours (±30 minutes) for Hour 25 to Hour 48, and every 4 hours (±60 minutes) for Hour 49 to Hour 96. If treatment for low BG (< 70 mg/dL [~3.9 mmol/L]) is initiated, then BG monitoring is required every 15 minutes (±10 minutes) until BG is ≥ 80 mg/dL (~4.4 mmol/L) for 3 consecutive readings without exogenous bolus glucose supplementation. See Section 11.4.1.1.1 for details on BG monitoring and management.
[13] [redacted] A CMO eCRF must be completed for participants for whom care is withdrawn.
[14] An NCCT scan is sufficient for participants who cannot get an MRI.
[15] The 96 hour scan should be performed after study treatment infusion is complete, within 18 hours of the Hour 96 time point.
[16] Only required if ET occurs before the Hour 96 scan has been performed.
[17] Includes all AEs from the beginning of study treatment administration and all SAEs from the time of consent. AEs of special interest (hypoglycemia [BG < 55 mg/dL {~3.1 mmol/L}]) will be upgraded to an SAE. See Section 15.3 for further details on monitoring and recording AEs.
[18] A short suicidal ideation/behavior questionnaire will be conducted on participants who are alert and capable of providing answers at Screening (prior to dosing). For these participants, this questionnaire should be repeated at Days 30, 90, 180, and ET Visit. The questionnaire conducted at Screening will record "Life Time" events and subsequent visits (at Days 30, 90, 180, and ET Visit) will record "Since the Last Visit" events.

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Table 3: ECG, [redacted] Schedule of Activities

	12-lead ECG[1]	[redacted]
Predose	SOC ECG taken at Screening	
Minute 5	±5 minutes	
Hour 6	±5 minutes	
Hour 24	±5 minutes	
Hour 48	±5 minutes	
Hour 72	±5 minutes	
Hour 96	±5 minutes	

BG = blood glucose; ECG = electrocardiogram; [redacted]; SAE = serious adverse events; SOC = standard of care.

[1] After the start of study treatment infusion, ECG must be collected before blood sampling for [redacted]

6. STUDY OBJECTIVES AND ENDPOINTS

Primary Objective	Primary Endpoint
To determine if BIIB093 reduces brain contusion expansion by Hour 96 when compared to placebo. Measurements of contusion expansion are based on a comparison of the baseline images and the scans collected prior to and including 96-hour scan, or the scan obtained prior to DC, intraparenchymal hematoma (IPH) evacuation, or comfort measures only (CMO), if earlier.	Change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 96 hours or prior to DC, IPH evacuation, or CMO if these procedures occur before 96 hours per the central review.
Secondary Objectives	**Secondary Endpoints**
To evaluate the effects of BIIB093 on acute neurologic status, functional outcomes, and treatment requirements.	• Glasgow Outcome Scale – Extended (GOS-E) at Day 180 • Modified Rankin Scale at Day 90 • Proportion of participants requiring delayed intubation Note: delayed intubation is defined as participants requiring intubation (for neurologic deterioration only) at any time between 24 hours and 96 hours postinjury.
To further differentiate the mechanism of action of BIIB093 compared to placebo on contusion expansion by examining differential effects on hematoma and edema expansion.	• Change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 24 hours or prior to DC, IPH evacuation, or CMO if these procedures occur before 24 hours per the central review. • Change in absolute hematoma volume from baseline to 24 hours • Change in absolute edema volume from baseline to 96 hours

To determine if BIIB093 improves survival at Day 90 when compared to placebo.	Time to all-cause death, including neurological death, through Day 90.
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

7. STUDY DESIGN

7.1. Study Overview

This is a Phase 2, randomized, multicenter, double-blind, multidose, placebo-controlled study to assess the efficacy and safety of BIIB093 in inhibiting the progression of traumatic intracerebral contusions in participants aged 18 to 85 years.

Approximately 60 sites in 7 countries globally are planned. The study will randomize 160 participants.

Participants must be treated with BIIB093 within 10 hours of time of trauma/LKN and within 6 hours of hospital arrival. Dosing should be initiated within 1 hour of randomization and continue for 96 hours (4 days). For participants in the 3 mg/day dose arm, treatment will be initiated similarly to the regimen in an ongoing Phase 3 study targeting edema associated with LHI. Participants will receive a bolus IV dose of 0.13 mg (given over approximately 2 minutes), followed by 2 different infusion rates (a rapid IV infusion of 0.1644 mg/h for 6 hours followed by a slow IV infusion of 0.1134 mg/h for the remaining 90 hours). In the 5 mg/day dose arm, participants will receive a bolus IV dose of 0.21 mg (given over approximately 2 minutes), followed by 2 different infusion rates (a rapid IV infusion of 0.2722 mg/h for 6 hours followed by a slow IV infusion of 0.1871 mg/h for the remaining 90 hours). These treatment rates should be administered within the limitation of the device at the site. The treatment duration will be for 96 hours for both treatment groups.

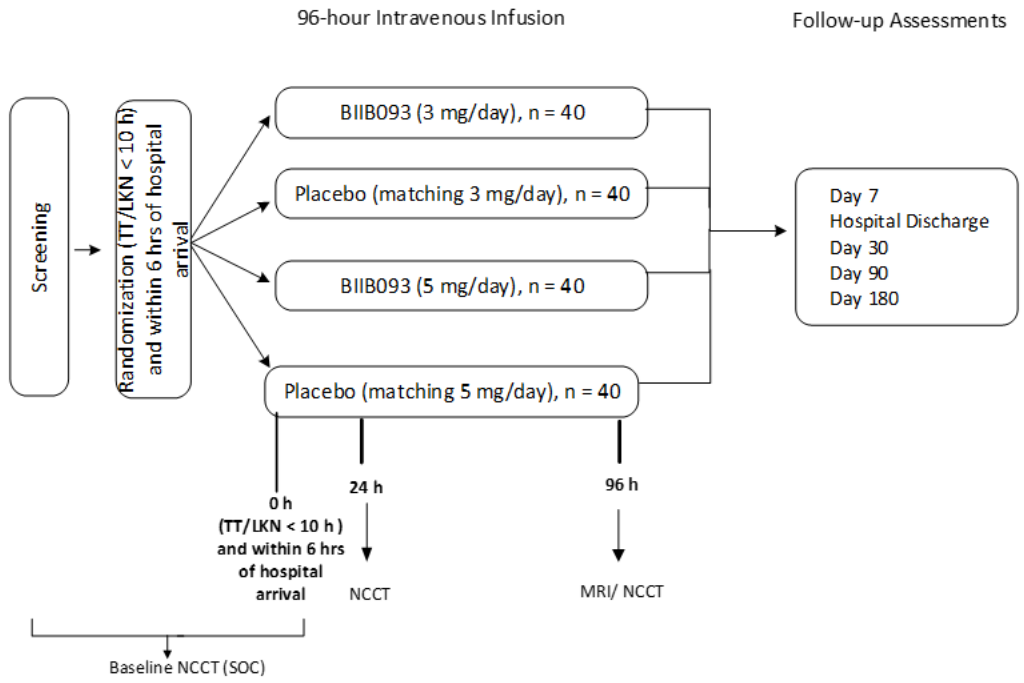
The primary endpoint of this study will be the change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 96 hours, or prior to DC, IPH evacuation, or CMO, if these procedures occur before 96 hours.

Participants will also have the functional assessments (i.e., GOS-E, [redacted], and mRS) performed at both Day 90 and Day 180 post trauma.

After the last participant completes their Day 4 (Hour 96) Visit, data for the primary endpoint and available data for the secondary endpoints will be locked for analysis. The final database lock will occur after the last participant completes their Day 180 Follow-up Visit, marking the end of the study.

See Figure 1 for a schematic of the study design.

Figure 1: Study Design



h = hours; MRI = magnetic resonance imaging; NCCT = noncontrast computed tomography; SOC = standard of care; TT/LKN = time of trauma/last known normal.
Dosing must be started within 10 hours from time of trauma/last known normal and within 6 hours of hospital arrival. Dosing should be initiated within 1 hour of randomization and continue for 96 hours (4 days).

7.2. Study Duration for Participants

The total duration of study participation for each participant will be approximately 180 days; this consists of a concurrent screening and enrollment period, a treatment period of 96 hours, and a follow-up period up to Day 180.

The primary endpoint for the study is at Hour 96. All randomized participants will be followed for 180 days unless consent is withdrawn.

The end of study for a participant is considered the final study assessment at Day 180 or the Early Termination (ET) Visit.

7.3. Responsibilities of Site Staff

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

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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 external independent 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. Details of the IDMC responsibilities will be provided in the IDMC charter.

7.5. End of Study

The end of the study is when the last participant completes the Day 180 Follow-up Visit or ET Visit.

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8. SELECTION OF PARTICIPANTS

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 regulations allow, and/or provision of informed consent by the participant'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. Aged 18 to 85 years old, inclusive, at the time of informed consent.

   Note: age 18 years at the time of informed consent or participant meets the minimum age of consent in accordance with national regulations (whichever is higher).

   Note: for countries where the minimum age of consent is over 18 years, participants may be enrolled provided a LAR is available, and if capable, the participant assents to treatment. The LAR must consider the participant's involvement in the study and provide informed consent for the participant.

3. A score of 5 to 15 on the GCS. Assessment should be made prior to medical intervention, where possible.

   Note: an enrollment cap on participants presenting with GCS 15 will be placed at 10% of total number of participants.

4. A clinical diagnosis of brain contusion with lesions within the supratentorial brain parenchyma totaling > 3 mL in volume on noncontrast computed tomography (NCCT) scan (allowing for multiple contusions) at Screening.

   Notes:

   a. Participants with multifocal contusions totaling > 3 mL in volume will be included. The sum total of contusion volumes should be calculated based on the baseline imaging.
   b. Contusion volume for a single contusion (hyperintense hematoma and hypointense edema on NCCT) must be determined and documented by the Investigator or his/her designee using study-specific methods detailed in the Imaging Manual.
   c. If more than 1 NCCT scan is performed prior to randomization, eligibility should be based on the most recent NCCT scan.

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d. In participants meeting all inclusion/exclusion criteria except for contusion volume totaling > 3 mL, a single repeat study-specific NCCT scan may be obtained to reassess contusion volume, if feasible, within the protocol-specified time window.

5. Mechanism of injury is defined.

   Note: emergency medical technicians, emergency physicians, or members of the study team can identify a likely or possible mechanism of head injury based on the clinical history and/or patient presentation.

6. Study drug (BIIB093) must be infused no more than 10 hours post trauma if known, or LKN (if time of trauma is unknown), and within 6 hours of hospital arrival. Dosing should be initiated within 1 hour of randomization and continue for 96 hours (4 days).

7. Functionally independent, in the opinion of the Investigator, prior to index head injury.

8. All women of childbearing potential and all men must practice highly effective contraception during the study and for 3 months after their last day of completing study treatment infusion.

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, patient is likely to have supportive care withdrawn within 24 hours.

2. Indication for immediate evacuation of IPH or DC.

3. Clinical signs of brainstem herniation, in the opinion of the Investigator.

4. NCCT or MRI evidence of penetrating brain injury impacting the brain parenchyma. Cerebrospinal fluid leak in isolation is not exclusionary unless evidence of parenchymal penetration by an external force (e.g., blunt object, bullet, or depressed skull fracture).

5. Any presence of midbrain or posterior fossa injury as assessed by imaging and clinical examination.

6. Symptoms and imaging suggestive of diffuse axonal injury as the predominant injury, in the opinion of the Investigator.

7. Intracranial hemorrhage due to causes other than TBI (e.g., spontaneous intracerebral hemorrhage, saccular/fusiform/infective aneurysm rupture), based on medical history of no trauma and location of the bleed.

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8. Coagulopathy (international normalized ratio [INR] > 1.5, activated partial thromboplastin time [PTT] > 60 s, or fibrinogen < 1.0 g/L), severe anemia (hemoglobin < 85 g/L), or thrombocytopenia (platelets < 75,000 cells/mm^3) at Screening.

9. Symptoms, in the opinion of the Investigator, or electrocardiogram (ECG)-based signs (QT interval corrected for heartrate [QTc] > 520 ms) of myocardial ischemia or unstable angina at Screening, based on local assessment.

10. ECG evidence of second- or third-degree heart block or cardiac arrhythmia associated with hemodynamic instability.

11. Presence of concomitant spinal cord injury as assessed by imaging and clinical examination.

12. Injury to ascending aorta, carotid, or vertebral arteries.

13. Severe or unstable concomitant condition or disease (e.g., known significant neurologic deficit, cancer, sepsis, hematologic or coronary disease) that in the opinion of the Investigator may increase the risk of study participation or uninterpretable results, if known.

14. Patients with, in the opinion of the Investigator, life expectancy < 3 months not related to current brain contusion, or those unlikely to be compliant with follow-up.

15. Patients in whom a peripheral IV line cannot be placed.

16. Mentally incompetent (prior to trauma) patients and wards of the state, if known.

Medical History

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

18. Participants who are known to have taken oral glibenclamide within the past 10 hours.

19. A clinically significant severe form of renal or hepatic disorder in the Investigator's opinion from the patient's history (e.g., dialysis), if known.

20. Known history of G6PD deficiency.

21. Clinically significant hypoglycemia in the Investigator's opinion based on known medical history or screening laboratory assessments (i.e., screening BG < 70 mg/dL [~3.9 mmol/L]).

22. Patients who have or have ever had diabetic ketoacidosis or diabetic coma/precoma, if known.

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23. Uncontrolled hypertension (defined as systolic blood pressure > 200 mmHg continuously for over 60 minutes).

24. Hemodynamic instability (use of inotrope or vasopressor therapy or resuscitation requiring > 6 L crystalloid or colloid).

    Note: transient vasopressor used to support blood pressure during specific procedures (e.g., intubation or hypotension associated with sedation/analgesics) is permitted.

25. Diabetes controlled with sulfonylurea medication, if known.

26. Life-threatening or nonsurvivable polytrauma, per Investigator's judgment.

27. Cardiopulmonary resuscitation required at any point after injury or suspected anoxic brain injury based on clinical judgment.

28. History, within the past 6 months, of decompensated congestive heart failure (New York Heart Association heart failure Class III or IV – Class III: marked limitation in activity due to symptoms, even during less-than-ordinary activity, e.g., walking short distances [20 to 100 m]; class IV: severe limitations, experiences symptoms even while at rest. Mostly bedbound patients), if known.

29. Acute Coronary Syndrome within 3 months, if known.

30. Likely to be moved to CMO in the next 24 to 96 hours, in the opinion of the Investigator.

Medications

Every effort should be made to determine if patient was taking any of the following medications prior to randomization:

31. Use of potent organic anion transporting polypeptide (OATP) inhibitors (e.g., IV rifampin, cyclosporine) within 5 half-lives of the drug prior to enrollment, if known.

32. Use of novel oral anticoagulants [NOAC] (including direct thrombin inhibitors such as dabigatran, or Factor Xa inhibitors such as rivaroxaban or apixaban), in preceding 3 days prior to the injury, if known.

    Note: Patients in whom NOAC anticoagulation can be adequately reversed with Andexanet alfa may be enrolled after the Andexanet alfa infusion has been completed. This applies to the NOACs apixaban or rivaroxaban.

33. Use of antiplatelet therapy other than acetylsalicylic acid in the preceding 7 days prior to the injury, if known.

34. Use of vitamin K antagonists within 5 days prior to the injury, if known.

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Note: patients on vitamin K antagonists who are subtherapeutic with INR < 1.5 may be included. If a patient can be adequately reversed from vitamin K antagonism to a subtherapeutic INR in time for randomization, this is acceptable, and the patient should be screened for enrollment.

Other

35. Females who are pregnant or women of childbearing potential with a positive urine or serum pregnancy test at the time of admission.

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

37. Known current participation or known history of participation in any other investigational study that involved treatment with an investigational drug or device within 30 days prior to enrollment and for the duration of the current study participation.

38. Inability to comply with study requirements.

39. Other unspecified reasons that, in the opinion of the Investigator, make the participant unsuitable for enrollment.

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9. SCREENING AND RANDOMIZATION

9.1. Screening

Participants, their 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 participants arriving at the recruiting site with potential for dosing within the 10-hour window, and having a brain contusion due to a non-penetrating head injury should be considered for inclusion in this study.

A screen failure log will be maintained at each study site. Participants are eligible for rescreening (i.e., an additional study-specific imaging scan), provided they meet the protocol-specified time window and all inclusion/exclusion criteria. Screen failures are defined as participants who have been diagnosed with brain contusion, signed the informed consent form (ICF), but are not subsequently randomized. If a participant is considered a screen failure, the reasons for exclusion must be documented in the participant'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.

SAEs occurring during the screening period will be recorded on an SAE form; however, SAEs do not need to be recorded or followed once a participant is confirmed as a screen failure.

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

A short suicidal ideation/behavior questionnaire will be conducted on participants who are alert and capable of providing answers at Screening (prior to dosing). For these participants, this questionnaire should be repeated at Days 30, 90, 180, and ET Visit.

9.2. Randomization

Enrollment and randomization will be concurrent. Participants will be randomized/enrolled after all screening assessments have been completed and after the Investigator has verified that the participants are eligible per criteria in Section 8. Participants will be assigned a unique identification number that will be used on study-related documents pertaining to the participant.

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Any participant identification numbers that are assigned will not be reused even if the participant does not receive treatment or does not continue in the study.

Randomization will be performed using interactive response technology (IRT). Participants will be randomly assigned to 3 mg/day study treatment, 5 mg/day study treatment, 3 mg/day matching placebo, or 5 mg/day matching placebo in a 1:1:1:1 ratio, stratified by baseline contusion volume per Investigator assessment of NCCT scan or site local radiologic assessment (3 to 10 mL or > 10 mL), baseline GCS (5 to 8, 9 to 12, or 13 to 15 [an enrollment cap on participants presenting with GCS 15 will be placed at 10% of total number of participants]), age (≤ 70 or > 70 years), and region (North America [United States] or Rest of World).

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

9.3. Blinding Procedures

The Investigators, study site staff, participants, and caregivers will be blinded to the participant treatment assignments for the duration of the study. To maintain the study blind, it is imperative that subject treatment assignments are not shared with the subjects, their families, or any member of the blinded study team, both at the site and at Biogen. 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 (evaluators should not have participated in the treatment during the acute hospitalization phase of the study nor review the participant's hospital records from the acute hospitalization study period including BG levels, BG management, or carbohydrate intake [e.g., intravenous glucose or parenteral nutrition]).

The study Sponsor and CRO study management team will be fully blinded for the study. Interim analysis will be performed by an independent unblinded Sponsor team whose members are not part of the study management team for the continued data collection and study management. Full treatment assignment will only be available to this independent unblinded Sponsor team.

After the last participant completes their Day 4 Visit, data for the primary endpoint and available data for the secondary endpoints will be locked for analysis. An independent unblinded Sponsor team whose members are not part of the study management team for the continued data collection and study management will perform the primary and secondary efficacy analyses. The Sponsor and CRO study management team responsible for all site interactions and data entry will remain blinded to individual treatment assignments until the final database lock. The final database lock will occur after the last participant completes their Day 180 Follow-up Visit.

At the end of the study (i.e., once the clinical study report is finalized), if unblinding will not jeopardize the results of ongoing related studies, Biogen will provide the randomization codes to Investigators, who then can inform their participants about the treatment received.

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

10.1. Discontinuation of Study Treatment

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

- 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 participant, and the infusion rate has already been reduced to 0.0795 mg/h (refer to the Directions for Handling and Administration [DHA] for corresponding mL/h rate) for > 30 minutes.
- QT/QTc (formula not specified) of > 550 ms from local assessment, if the measurement is obtained and confirmed with a second ECG reading within 15 minutes.
- 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 participant has a positive pregnancy test during the 96-hour time window of treatment.
- The participant experiences an AE that necessitates permanent discontinuation of study treatment.
- The participant experiences a medical emergency that necessitates unblinding of the participant's treatment assignment.
- The participant experiences a hypersensitivity or suspected allergic reaction to study treatment, based on the Investigator's assessment.
- Informed consent withdrawal.
- At the discretion of the Investigator for medical reasons.

If the study treatment infusion is stopped as a result of low BG, please refer to the guidance in Section 11.4.1.1.1, Table 5. Investigators must also use their own medical judgment in conjunction with referencing the guidance. The primary reason for discontinuation of study treatment must be recorded in the participant's electronic case report form (eCRF). All participants who discontinue treatment, except for those who withdraw consent, will be followed to the end of study.

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

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Participants who discontinue treatment should be encouraged to remain in the study and continue protocol-required tests and assessments.

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 Measures

If a decision is made to move the participant to comfort care measures during the study, the Investigator should complete the comfort care eCRF and determine the GOS-E, when possible. If a brain imaging study has not been performed within the prior 12 hours to the decision, it should be obtained whenever possible.

10.2. Lost to Follow-Up

Potential sources of follow-up information will include participant medical records, the participant, 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. Participants will be considered lost to follow-up if all attempts to collect the follow-up assessments are unsuccessful. The participant 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 the participant with no response received within 30 days of sending the letter.

The following actions must be taken if a participant fails to appear for or respond to a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether the participant wishes to and/or should continue in the study.

- In cases in which the participant is deemed lost to follow-up, the Investigator or designee must make every effort to regain contact with the participant. These contact attempts should be documented in the participant's medical record.

- Should the participant continue to be unreachable, that participant will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

10.3. Withdrawal of Participants From Study

Participants must be withdrawn from the study if the participant or LAR withdraws consent for any reason.

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The primary reason for the participant's withdrawal from the study must be recorded in the participant's eCRF. If a participant is withdrawn due to pregnancy, ET study procedures will be performed. Participants must undergo ET assessments (see Section 5) unless withdrawal is due to death or withdrawal of consent. Participants who withdraw from the study may not be replaced.

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11. STUDY TREATMENT USE

11.1. Regimen

Refer to and follow the DHA for detailed information.

For participants in the 3 mg/day dose arm, study treatment administration will initiate with 0.13 mg administered as a bolus over approximately 2 minutes, followed by 0.1644 mg/h for 6 hours, followed by 0.1134 mg/h for the remaining 90 hours (or 0 mg in all cases for placebo) [refer to the DHA for corresponding mL/h rate].

For participants in the 5 mg/day dose arm, study treatment administration will initiate with 0.21 mg administered as a bolus over approximately 2 minutes, followed by 0.2722 mg/h for 6 hours, followed by 0.1871 mg/h for the remaining 90 hours (or 0 mg in all cases for placebo) [refer to the DHA for corresponding mL/h rate].

These treatment rates should be administered within the limitation of the device at the site. See the DHA for a summary of the study dosing.

The bolus will be administered by withdrawing the study treatment from the bag and injecting it by syringe through peripheral IV over an approximately 2-minute period.

BIIB093 cannot be administered with polymerizing vinyl chloride (PVC) bags and lines due to adsorption issues. Additionally, the drug adsorbs to inline filters. Refer to the DHA for additional information. The use of any IV components other than those specified per the DHA is strictly prohibited, unless permission to do so is provided by the Sponsor in writing (email).

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 AS THESE CONTAIN PVC AND MAY ABSORB THE DRUG**. 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.

Note: Study treatment administration does not need to occur in the ICU, provided that the appropriate BG monitoring can occur in the floor/unit where the participant is under care.

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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]). In the event of hypoglycemia, the study treatment infusion rate must be reduced as presented in Table 4.

Table 4: Dose Modification Schedule

If hypoglycemia occurs within the first 6 hours of infusion:	
For participants on high infusion rate (0.2722 mg/h)	The infusion rate must be reduced to 0.1644 mg/h. If hypoglycemia cannot be rectified or reoccurs, the infusion rate must be further reduced to 0.0795 mg/h and **must not** be uptitrated.
For participants on low infusion rate (0.1644 mg/h)	The infusion rate must be reduced to 0.0795 mg/h and **must not** be uptitrated.
If hypoglycemia occurs after the first 6 hours of infusion:	
For all study participants	The infusion rate must be reduced to 0.0795 mg/h. The infusion rate can be uptitrated to 0.1134 mg/h when blood glucose is > 80 mg/dL (~4.4 mmol/L) for 3 consecutive readings.

If, at the reduced rate (0.0795 mg/h), 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 participant, treatment should be discontinued (see Table 5 for further details).

If the study treatment needs to be temporarily stopped due to SOC ICU activities (e.g., transport of patient, IV-line changes or interstitial extravasation, etc.), the study treatment should be restarted as soon as possible per instructions in the DHA.

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

[redacted]

For mitigation strategies for hypoglycemia associated with dosing, please see Table 5.

11.3. Precautions

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

11.4. Concomitant Therapy and Procedures

11.4.1. Concomitant Therapy

A concomitant therapy is any medication administered between enrollment through Day 180 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 appropriate eCRF.

11.4.1.1. Allowed Concomitant Therapy

11.4.1.1.1. 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 studies 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; however, Investigators must use their own medical judgment in conjunction with referencing the guidance (Table 5).

Insulin

Insulin and other BG-lowering agents are not permitted during study treatment administration when BG < 140 mg/dL (~7.8 mmol/L).

Nutrition

Enteral nutrition is encouraged to be initiated within 24 hours of admission if consistent with SOC. Participants may need postpyloric administration of nutritional support.

Maintenance Dextrose-Containing IV Solution

During the study treatment infusion period, BG monitoring is required as follows:

- Hour 0 to Hour 24, monitor hourly (±30 minutes)
- Hour 25 to Hour 48, monitor every 2 hours (±30 minutes)
- Hour 49 to Hour 96, monitor every 4 hours (±60 minutes)

See Section 5 for further details on timings of BG measurements. If treatment for hypoglycemia is initiated (for BG < 70 mg/dL [~3.9 mmol/L], then BG monitoring is required every 15 minutes (±10 minutes) until BG is ≥ 80 mg/dL (~4.4 mmol/L) for 3 consecutive readings without exogenous bolus glucose supplementation. BG monitoring may be performed more often at the discretion of the Investigator. Table 5 shows how BG should be monitored and managed according to inpatient BG levels.

Total fluid volume, inclusive of study treatment volume, infusion rate, infusion duration, sodium content, and percent of dextrose, should be guided by the clinical status of the subject and medical judgment.

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It is recommended that maintenance dextrose-containing IV solution be initiated when BG is < 120 mg/dL (~6.7 mmol/L) and maintained for the duration of the study treatment administration (up to 96 hours) with the new glycemic BG target in the range of 140 to < 180 mg/dL (~7.8-10 mmol/L).

Table 5: Blood Glucose Monitoring and Management

Inpatient BG Level	BG Monitoring and Management[1]
Initiation of dextrose-containing IV solution	
< 120 mg/dL (~6.7 mmol/L)	• It is recommended that D10NS at 35 to 50 mL/h be initiated as first-line management. Consider D5NS at a rate of 70 to 100 mL/h or other percent dextrose solutions as alternatives.
Maintenance of dextrose-containing IV solution after initiation	
≥ 180 mg/dL (~10 mmol/L)	• It is recommended that dextrose-containing IV solution be titrated downward or stopped temporarily until BG is ≥ 140 to < 180 mg/dL (~7.8 to ~10 mmol/L).
< 180 mg/dL (~10 mmol/L) but ≥140 mg/dL (~7.8 mmol/L)	• It is recommended that dextrose-containing IV solution be maintained or titrated to keep BG as ≥ 140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L).
< 140 mg/dL (~7.8 mmol/L) but ≥80 mg/dL (~4.4 mmol/L)	• Insulin and other BG-lowering agents are not permitted during study treatment administration when BG is < 140 mg/dL (~7.8 mmol/L). • It is recommended that dextrose- containing IV solution be maintained when BG is < 140 mg/dL (~7.8 mmol/L). Titrate up the IV infusion rate to keep BG ≥ 140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L)
< 80 mg/dL (~4.4 mmol/L)	• It is recommended that the infusion rate of the dextrose-containing IV solution be increased to keep BG ≥ 140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L).
< 70 mg/dL (~3.9 mmol/L)	• Test must be repeated to confirm level. • Must be treated with 50 mL of dextrose 50% in water or equivalent. • It is recommended that the infusion rate of the dextrose-containing IV solution be increased after the dextrose bolus.

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Inpatient BG Level	BG Monitoring and Management[1]
	• It is recommended that the infusion rate of the dextrose-containing IV solution be titrated up to keep BG ≥ 140 mg/dL (~7.8 mmol/L) to < 180 mg/dL (~10 mmol/L).
< 55 mg/dL (~3.0 mmol/L)	• Study treatment infusion rate must be reduced as follows: • If hypoglycemia occurs within the first 6 hours of infusion: – For participants on high infusion rate (0.2722 mg/h), the infusion rate must be reduced to 0.1644 mg/h. If hypoglycemia cannot be rectified or reoccurs, the infusion rate must be further reduced to 0.0795 mg/h and **must not** be uptitrated. – For participants on low infusion rate (0.1644 mg/h), the infusion rate must be reduced to 0.0795 mg/h and **must not** be uptitrated. • If hypoglycemia occurs after the first 6 hours of infusion, the infusion rate must be reduced to 0.0795 mg/h. The infusion rate can be uptitrated to 0.1134 mg/h when BG is > 80 mg/dL (~4.4 mmol/L) for 3 consecutive readings. • Study treatment should be discontinued if hypoglycemia cannot be rectified and is determined by the Investigator to be harmful to the participant

BG = blood glucose; D10NS = 10% dextrose in normal saline (or fluid containing 10% dextrose); D5NS = 5% dextrose in normal saline (or fluid containing 5% dextrose); IV = intravenous.
[1] Total fluid volume, inclusive of study treatment volume, should be consistent with site practice and guided by clinical status of the participant and medical judgment.

11.4.1.1.2. 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 participants 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 participant safety.

Participants 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.

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11.4.1.2. Disallowed Concomitant Therapy

Insulin and other BG-lowering agents are not permitted during study treatment administration when BG < 140 mg/dL (~7.8 mmol/L).

No other sulfonylurea agents may be administered during the hospital stay.

No other investigational drugs may be administered during the 180-day follow-up period.

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 participant is enrolled in the study and Day 180. The use of unapproved therapies and/or procedures is not permitted.

Concomitant procedures will be recorded through Day 180 or early discontinuation, whichever is earlier.

11.4.2.1. Neurosurgical Intervention

NSx procedures or interventions may be performed according to local SOC. Study treatment should not be stopped if the participant undergoes NSx. Participants should undergo follow-up assessments as per normal study procedures, where possible.

Information on the timing, type (craniotomy or DC), and reason for NSx (e.g., 1, radiographic changes; 2, change in symptoms and/or signs; 3, both radiographic changes and change in symptoms and/or signs; or 4, neither [i.e., prophylactic]) will be recorded in the eCRF. The evacuation of extra-axial hemorrhages and the placement of external ventricular drains using burr holes will also be collected in the eCRF. GCS should be recorded either at the time of decision to perform NSx or between such time and the intervention.

IPH evacuations and DC requires additional imaging. If a brain imaging scan was not performed in the prior 12 hours as part of the assessment to perform IPH evacuation or DC, a follow-up brain imaging study should be performed prior to these procedures (IPH evacuation, DC, and CMO) when possible.

Sites should be vigilant about intracranial pressure management and perform DC when it is clinically indicated as part of local SOC. The reasons for the DC should be recorded in the eCRF.

11.4.2.2. Intubation

Intubation may be performed according to local SOC. Timing of, and reasons for intubation, including whether the intubation was due to 1) change in level of alertness/consciousness, 2) respiratory distress 3) other (e.g., preparation for operative intervention) will be recorded in the eCRF. GCS should be recorded at the time of decision to intubate.

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The intubation eCRF should only be completed if the intubation occurs between 24 and 96 hours after the injury. Intubations performed in the emergency room, trauma bay, or upon immediate admission to the ICU need not be recorded. Participants should undergo follow-up assessments as per normal study procedures, where possible.

11.5. Continuation of Treatment

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

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12. STUDY TREATMENT MANAGEMENT

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

Site staff should follow the DHA for specific instructions on the handling, preparation, administration, and disposal of the study treatment. The DHA should align 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 participants enrolled in this study. Once study treatment is prepared for a participant, it can be administered only to that participant. Study treatment are for one-time use only; any study treatment remaining in the vial should not be used for another participant.

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 will 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% sodium chloride.

The study treatment in normal saline is stable at room temperature for 30 hours. A new vial is used for dosing on each day of the 4-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 adsorbs 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.

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Please refer to the DHA for detailed instructions regarding reconstitution of the study treatment.

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) 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. For additional information, please refer to the DHA.

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 (participant-by-participant 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. Please refer to the DHA for additional information. 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. 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.

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13. EFFICACY, [redacted] PHARMACOGENETIC, AND GENETIC ASSESSMENTS

See Section 5 for the timing of all assessments.

13.1. Clinical Efficacy Assessments

NOTE: the 90- and 180-Day efficacy outcomes will be performed by personnel who are blinded to on-treatment BG levels, BG-related AEs, and carbohydrate administration (e.g., intravenous glucose or parenteral nutrition). Such persons will not have access to the participant's medical record from the acute hospitalization study period but will instead be provided with participant/family/LAR contact details (if they are required to schedule the follow-up), the source documents for the assessments to be performed, and the list of unresolved AEs for the 30-, 90-, and 180-day follow ups.

The following clinical and imaging assessments will be performed to evaluate the efficacy of BIIB093:

- NCCT/MRI Assessments
  - Total contusion volume will be assessed by the central imaging core laboratory on baseline NCCT, 24-hour NCCT, and the 96-hour scan (MRI and/ or NCCT) and the scans obtained prior to DC, IPH evacuation, or CMO.
  - Absolute hematoma volume from baseline to 24 hours (the NCCT scan closest to the 24-hour timepoint will be used) unless DC, IPH evacuation, or CMO occurred prior to 24 hours, the scan acquired just prior to these procedures will be used.
  - Absolute edema volume from baseline to 96 hours (the MRI and/or NCCT scan closest to the 96-hour timepoint will be used) unless DC, IPH evacuation, or CMO occurred prior to 96 hours, in which case the scan acquired just prior to these procedures will be used.
  - [redacted]
  - NCCT and MRI will be acquired per specifications outlined in the Imaging Manual.
  - All imaging reads for efficacy will be performed by trained and certified central readers blinded to treatment assignment per procedures detailed in the Imaging Manual.
- Functional/Neurological Outcomes Assessments

- GCS and GOS-E

- mRS: 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 and Day 180 should be conducted in person where possible, and otherwise by telemedicine or telephone call, in order of preference. The same mRS rater should follow a participant for the duration of the study whenever possible. The Day 90 and Day 180 mRS assessments may be reviewed centrally and if so, queries will be issued in the event of discrepancies or inconsistencies.

[redacted]

13.4. Pharmacogenetic and Genetic Assessments

Where allowed by local, regional, and national regulatory authorities and ethics committees, participants will be offered the option to participate in genetic research related to brain contusion and metabolism of BIIB093. This is a 1-time optional blood draw. Participants, or the participant's LAR, will be required to sign a separate ICF between the start of study and hospital discharge. The pharmacogenetic sample should be collected as close to obtaining consent as possible and preferably within 24 hours of the start of study treatment to minimize the influence of participant outcomes on obtaining consent.

Genetic polymorphisms in genes associated with brain contusion or drug absorption, distribution, metabolism, and elimination (including but not limited to ABCC8, CYP2C9, OATP1B1, and G6PD) could influence the observed safety and efficacy of BIIB093. Genes of downstream pathways may also be explored. Despite continuing advances in genetic research and the

understanding of brain contusion, not all genetic factors relevant to BIIB093 have been identified.

The DNA samples will be coded with the participant's identification number and stored for 15 years or a duration dictated by local, national, or regional laws or regulations. No genotyping or genetic data will be provided to the participant. Details on genetic sample collection will be provided in a separate laboratory manual.

Other genetic tests for additional safety measures may be conducted where applicable (see Section 14.2).

13.5. Other Assessments: 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 participant whenever possible for the duration of the study.

[redacted]

14. SAFETY ASSESSMENTS

See 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 weight and height (may be estimated)
- Vital sign measurements: temperature, pulse 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 180 are to be recorded in the eCRF. Concomitant procedures will be recorded through Day 180.

  [redacted]

- AE and SAE recording
- Assessment of suicidal ideation/behavior at Screening and follow-up in patients whose level of consciousness is compatible with completion of the abbreviated suicidal ideation/behavior questionnaire. Investigators should use their best judgment to identify patients suitable for this assessment.

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 and platelet count, and absolute neutrophil count
- Blood chemistry: albumin, creatinine, blood urea nitrogen, glucose, calcium, phosphorus, bicarbonate (if available), chloride (if available), sodium, and potassium

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- Liver function test: bilirubin (total and indirect), alkaline phosphatase, ALT, AST, and gamma-glutamyl transferase
- Coagulation panel (INR, PTT, fibrinogen)
- Note that in any case of confirmed hemolytic anemia after randomization, the required local standard tests should be performed to confirm etiology of disease, including a G6PD genetic or enzymatic test (in accordance with local practice).

14.3. Product-Specific Safety Assessments

BG will be also measured to determine the safety of BIIB093. See Section 11.4.1.1.1 for full details of BG monitoring and management.

BG concentrations are to be measured by point-of-care (POC) testing of capillary blood (e.g., Accu-Chek). Alternatively, blood from an arterial or venous 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 versus arterial versus venous line) and whether the analysis was performed by POC or laboratory, must be recorded in the eCRF.

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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 participant. If necessary, appropriate medical intervention should be provided.

At the signing of the ICF, each participant or his/her LAR and/or main caregiver must be given the names and telephone numbers of 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 participant 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 participant 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 participant 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

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- Is a medically important event

A medically important event is an AE that, in the opinion of the Investigator, may jeopardize the participant 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 participant 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 participant'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 participant'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 participant 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 participant or does not make participant uncomfortable; does not influence performance or functioning; prescription drug not ordinarily needed for relief of symptoms but may be given because of personality of participant.
Moderate	Symptoms of a sufficient severity to make participant uncomfortable; performance of daily activity is influenced; participant is able to continue in study; treatment for symptoms may be needed.
Severe	Symptoms cause severe discomfort; symptoms cause incapacitation or significant impact on participant's daily life; severity may cause cessation of treatment with study treatment; treatment for symptoms may be given and/or participant hospitalized.

15.2.4. Expectedness of Events

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

15.3. Monitoring and Recording Events

15.3.1. Adverse Events

Any AE experienced by the participant between the time of first dose of study treatment and the participant's final clinic visit (including follow-up visit) is to be recorded on the eCRF, regardless of the severity of the event or its relationship to study treatment. At each study visit, the Investigator will assess the participant for AEs and will record any new AEs or updates to previously reported AEs on the eCRF. AEs that are ongoing when the participant completes or discontinues the study will be followed by the Investigator until the event has resolved, stabilized, or returned to baseline status. AEs ongoing at the time of the participant's study

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completion outcome will be recorded as ongoing on the eCRF. Serious AEs will be followed via ongoing Safety Report updates.

15.3.2. Adverse Events of Special Interest

An AE of special interest is an AE of scientific and medical concern specific to this study, for which ongoing monitoring and reporting are required.

Hypoglycemia defined as confirmed BG < 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 participant between the time of the signing of the ICF and the last follow-up visit 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.

Participants will be followed for all SAEs until the final study visit. 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 participant 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 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 participant has undergone study-related procedures
- Whether or not the participant 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

Participants should not become pregnant or impregnate their partners during the study treatment and for 3 months after their last day of completing study treatment infusion. If a female participant becomes pregnant, study treatment must be discontinued *immediately*.

The Investigator must report a pregnancy occurring in a female participant 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 participants should be reported as SAEs if conception occurred during the study or within 3 months after their last day of completing study treatment infusion.

15.4.2. Overdose

An overdose is any dose of study treatment administered to a participant or taken by a participant that exceeds the dose assigned to the participant 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.

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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 participant's treatment assignment may influence the participant's clinical care, the Investigator may access the participant's treatment assignment by IRT. The Investigator must document the reasons for unblinding in the participant's source documents. The Investigator is strongly advised not to divulge the participant'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 the study and for 3 months after their last day of completing study treatment infusion. In addition, participants 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 participant, can be considered an acceptable method of contraception based on the evaluation of the Investigator, who should also take into consideration the duration of the clinical study. Periodic abstinence (e.g., calendar, ovulation, symptothermal, postovulation methods) and withdrawal are not considered acceptable methods of contraception.

Pregnancy reporting is described in Section 15.4.1.

15.6. Safety Responsibilities

15.6.1. The Investigator

The Investigator's responsibilities include the following:

- Monitor and record all AEs, including SAEs, on the 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.

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- Ensure all AE and SAE reports are supported by documentation in the participants' 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 participants, the Clinical Monitor is responsible for reviewing with 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.

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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 primary endpoint of the study will be the change in total contusion volume (hematoma plus perihematomal edema), as measured by brain imaging from baseline to 96 hours, or prior to DC, IPH evacuation, or CMO, if these procedures occur before 96 hours, per the central review. The analysis of the primary endpoint and available data of the secondary endpoints will be performed after the last participant completes the Day 4 (Hour 96) Visit. The final analysis will be performed after the last participant complete the Day 180 Follow-up Visit.

A summary of demography, baseline disease characteristics, primary and secondary efficacy endpoints, [redacted] is provided in this section. Analyses of other supportive endpoints, including analyses of exposure-response relationships for clinical, imaging, and safety outcome measures, will be described in the Statistical Analysis Plan (SAP) prior to the database lock, 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, quartiles, and range) or with frequency distributions.

16.2. Efficacy

16.2.1. Analysis Population

The primary efficacy analyses will be conducted in the modified intent-to-treat population, which is defined as participants who are randomized and treated and have at least 1 centralized read of contusion volume from an NCCT or MRI scan acquired between 12 hours after the initiation of study treatment and by the Hour 96 Visit or prior to DC, IPH evacuation, or CMO, if performed before the Hour 96 visit.

16.2.2. Methods of Analysis

16.2.2.1. General Considerations

Summary statistics will be presented by treatment group. By-treatment-group analysis will be displayed as placebo, BIIB093 3 mg/day, BIIB093 5 mg/day, BIIB093 combined, and total (if applicable). For continuous endpoints, summary statistics will generally include the number of participants with data, mean, SD, median, quartiles, and range. For categorical endpoints, frequency and percentage of participants in each category will be presented. Statistical testing for efficacy endpoints will be performed between the BIIB093 (3 mg/day or 5 mg/day) and placebo groups. All tests will be 2-sided with a significance level equal to 0.05 (unless otherwise specified).

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Multiplicity will not be adjusted for the tests of the primary and secondary endpoints.

16.2.2.2. Analysis of the Primary Endpoint

Primary analysis of the primary endpoint will compare BIIB093 (3 mg/day or 5 mg/day) and placebo groups using an ANCOVA (analysis of covariance) model, adjusting for covariates including all the stratification factors at randomization, 96 hours imaging modality (MRI vs NCCT) and baseline contusion volume per the central read. Multiple imputation will be used to account for the missing values for Hour 96.

Sensitivity analyses for the assumptions will be performed to evaluate the impact of analysis sets, the impact of missing data, and the intercurrent event handling. Details will be specified in the SAP.

16.2.2.3. Analysis of the Secondary Endpoints

GOS-E at Day 180

GOS-E at Day180 will be analyzed as a 7-category ordinal scale (1/2, 3, 4, 5, 6, 7, and 8) using ordinal logistic regression, adjusting for covariates including all the stratification factors at randomization and baseline contusion volume per the central review and baseline GCS. Multiple imputation will be used to account for missing GOS-E at Day 180.

mRS at Day 90

mRS at Day 90 will be analyzed as a 5-category ordinal scale (0/1, 2, 3, 4, and 5/6) using ordinal logistic regression, adjusting for covariates including all the stratification factors at randomization, baseline contusion volume per the central review, and baseline GCS.

Proportion of participants requiring delayed intubation

The proportion of participants requiring delayed intubation at any time between 24 hours and 96 hours post injury or LKN will be analyzed at Day 4. The analysis will compare BIIB093 (3 mg/day or 5 mg/day) and placebo groups using a binary logistic regression, adjusting for covariates including all the stratification factors at randomization and baseline contusion volume per the central review and baseline GCS.

Change in total contusion volume (hematoma plus perihematomal edema) from baseline to 24 hours

An ANCOVA model will be used to compare BIIB093 (3 mg/day or 5 mg/day) and placebo groups, adjusting for covariates including all the stratification factors at randomization, and baseline contusion volume per the central read. This endpoint will be evaluated for all participants having a scan acquired between 12 hours after the initiation of study treatment and the end of the Hour 24 Visit. Summary statistics, including by-visit number of participants with data, mean, SD, median, quartiles, and range will be provided.

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Change in absolute hematoma volume from baseline to 24 hours

Analysis of covariance (ANCOVA) will be performed to compare the mean change from baseline between BIIB093 (3 mg/day or 5 mg/day combined) and placebo groups. This endpoint will be evaluated for all participants having a scan acquired between 12 hours after the initiation of study treatment and the end of the Hour 24 Visit. Summary statistics, including by-visit number of participants with data, mean, SD, median, quartiles, and range will be provided.

Change in absolute edema volume from baseline to 96 hours

ANCOVA will be performed to compare the mean change from baseline between BIIB093 (3 mg/day or 5 mg/day) and placebo groups. This endpoint will be evaluated for all participants having a scan acquired between 12 hours after the initiation of study treatment and the Hour 96 Visit. Multiple imputation will be used to account for missing values for the Hour 96. Summary statistics, including by-visit number of participants with data, mean, SD, median, quartiles, and range will be provided.

Time to all-cause death, including neurological death, through Day 90

Survival time will be analyzed for all randomized participants. Cox proportional hazards regression models will be used to assess the treatment effects on overall survival at Day 90 after adjusting for covariates including the stratification factors at randomization, baseline contusion volume per the central review, and baseline GCS. Kaplan-Meier curves will be presented for BIIB093 (3 mg/day or 5 mg/day) and placebo groups.

[redacted]

[redacted]

16.5. Pharmacogenetics

The exploration of pharmacogenetic markers will depend on the number of consenting participants, the observed degree of PK variability, and the progression of the study. Results from any genetic or pharmacogenetic research will be reported separately.

16.6. Safety

16.6.1. Analysis Population

The safety population is defined as all enrolled participants 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 participant 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 participant 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 and blood chemistry, including BG.

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 participants with shifts to categorical values (abnormal but not an AE, or abnormal AE) will be summarized by treatment group.

16.6.2.4. Vital Signs

Vital signs measures include oxygen saturation, pulse rate, 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 participants evaluated and the number and percentage of participants with clinically relevant postbaseline 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 rate, and blood pressure values are provided in Table 6.

Table 6: Criteria to Determine Clinically Relevant Vital Signs Abnormalities

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

16.7. Interim Analyses

An interim analysis may be performed by an internal, independent, unblinded team when approximately 90 subjects are dosed for administrative purposes. The interim analysis may include, but not be limited to the efficacy, safety, [redacted] analysis by treatment group. A clear process will be specified and implemented to ensure that the treatment blinding will be strictly maintained for investigators, subjects, and study personnel from the Sponsor and CRO throughout the study. The interim analysis will not inform the continued blinded data collection in the study. There is no Type I error adjustment for the proposed interim analysis. The interim analysis, if being conducted, will lead to one of the following actions:

1. Continue to complete the blinded study

2. Continue to complete the blinded study while accelerating Phase 3 study preparation after the interim analysis

The analysis of the primary and available data for the secondary endpoints will be performed after the last participant completes the Day 4 (Hour 96) Visit.

16.8. Sample Size Considerations

The study is planned to randomize approximately 160 participants. The primary endpoint for the study is the change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 96 hours, or prior to DC, IPH evacuation, or CMO, if these procedures occur before 96 hours. Assuming the common standard deviation of 29 mL in contusion volume change from baseline, a sample size of 160 participants (40 each in the 3 mg/day dose or matching placebo arms and 40 each in the 5 mg/day dose or matching placebo arms) will have approximately 90% power to detect assumed average difference of 15 mL between the pooled active treatment groups (n=80) and pooled placebo groups (n=80) using 2 group t-test at a 2-sided significance level of 5%.

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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 f or supervising those individuals and for implementing procedures to ensure the integrity of the tasks performed and any data generated.

17.1. Declaration of Helsinki

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

17.2. Ethics Committee

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

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

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

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

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

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

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17.3. Participant 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 participant, the participant'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 participant, must be explained to the participant (or the participant's LAR). The participant must be given sufficient time to consider whether to participate in the study.

Participants will be informed that their race and ethnicity will be collected (unless not permitted by local law or not approved by the governing ethics committee) and will be used during analysis of study results.

In addition, participants who have the capacity should provide their assent to participate in the study. The level of information provided to participants 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 participant or the participant'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 participant's medical record.

17.4. Participant 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, participants' 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 [redacted] 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 participant 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 participant'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 participant before the participant makes a decision to participate in the study.

17.7. Registration of Study and Disclosure of Study Results

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

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18. ADMINISTRATIVE PROCEDURES

18.1. Study Site Initiation

The Investigator must not screen any participants 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 eCRF 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 participants' 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 locations 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, or may perform monitoring activities remotely (where permitted by local regulations) only during the COVID-19 pandemic where onsite monitoring is not allowed per local/regional restrictions. A clinical site monitoring plan will detail who performs the monitoring, how often, and the extent of review. It also will provide the monitoring strategy, with emphasis on participant safety, data integrity, and 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 participant 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.

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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.

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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 participants are screened at each study site, the CRO will review study responsibilities with the Investigators and other site staff, as appropriate.

19.1.2. Interactive Response Technology

IRT will be used in this study. Before participants 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

Participant 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.

19.1.4. Central Laboratories for [redacted] Pharmacogenetic (as applicable) Assessments

A central laboratory has been selected by Biogen to collect and store laboratory samples ([redacted] genetic samples). Analyses will be performed at the central laboratory or by specialty laboratories based on assay availability.

19.1.5. Central Facility for Imaging Assessments

An independent imaging core laboratory (ICL) will collect, review, and analyze medical images acquired during this study. A study-specific Imaging Manual, developed by the Sponsor and the ICL, details the personnel, processes, and methods involved in managing and evaluating imaging data including the process for evaluating contusion volume by MRI and NCCT. The Imaging Manual provides standardized settings for imaging data acquisition and interpretation.

All imaging data, including screening scans from participants consented prior to screen failure and those scans acquired as part of SOC for enrolled participants, will be transferred to the ICL. The ICL will perform a quality review of the per-protocol imaging data.

The ICL will also evaluate the follow-up NCCT and MRI scans [redacted] to aid in interpretation of the study results. 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. The IDMC may recommend the Sponsor to change or terminate the study based on safety data.

19.3. Changes to Final Study Protocol

All protocol amendments must be submitted to the ethics committee and regulatory authorities if required by local law. Protocol modifications that affect participant 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 participant. 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.

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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 participant enrollment; or by other factors determined to be relevant by Biogen.

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

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APPENDIX 1. MEDICATIONS THAT MODULATE CYP2C9 AND CYP3A4

CYP2C9

Substrates	Inhibitors	Inducers
celecoxib	**Moderate**	**Moderate**
Glimepiride	amiodarone	rifampin
phenytoin	felbamate	enzalutamide
tolbutamide	fluconazole	aprepitan
warfarin	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	**Moderate**	**Moderate**
dronedarone	verapamil	bosentan
eletriptan	tofisopam	efavirenz
eplerenone	aprepitant	etravirine
felodipine	erythromycin	modafinil
indinavir	fluconazole	
lurasidone	cimetidine	
maraviroc	ciprofloxacin	
quetiapine	clotrimazole	
sildenafil	crizotinib	
ticagrelor	cyclosporine	
tolvaptan	dronedarone	
alprazolam	imatinib	
aprepitant	fluvoxamine	
atorvastatin	**Weak**	**Weak**
colchicine	ticagrelor	armodafinil
eliglustat	chlorzoxazone	rufinamide
pimozide	cilostazol	
rilpivirine	fosaprepitant	
rivaroxaban	istradefylline	
tadalafil	ivacaftor	
	lomitapide	
	ranitidine	
	ranolazine	
	tacrolimus	

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

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21. SIGNED AGREEMENT OF THE STUDY PROTOCOL

I have read the foregoing protocol, "A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients with Brain Contusion," 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 (*DD MMM YYYY*)

_____

Investigator's Name (Print)

_____

Study Site (Print)

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AMENDMENT SUMMARY

Biogen Protocol 252BN201

A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients with Brain Contusion

Version 3

Date: 14 November 2022

EUDRA CT Number: 2018-003858-24

Version 3 of the protocol has been prepared for this amendment, which supersedes Version 2.

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PRIMARY REASON FOR AMENDMENT

The primary reasons for this amendment to Protocol 252BN201 is to expand the patient population to reflect the more common clinical presentation of TBI patients with contusion, update the primary endpoint analysis to consider contusion volume as a continuous variable, and include an interim analysis to facilitate an early opportunity to begin Phase 3 planning. The study population will be expanded to include those indicated for surgery and those with survivable polytrauma which will also be facilitated by the removal of midline shift and injury severity score thresholds. The dosing time window will be extended to 10 hours to allow for additional patients to be treated including inter-hospital transfers. An interim analysis, conducted by a separate unblinded team, will facilitate an earlier start to Phase 3 planning while continuing the Phase 2 as a blinded study.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 8.1, Inclusion Criteria

Now reads:

6. ~~Randomization~~ **Study drug (BIIB093) must be infused** ~~must occur within~~ ~~6~~ **no more than 10 hours post trauma**, if known, or **LKN** ~~last known normal~~ (if time of trauma is unknown), **and within 6 hours of hospital arrival**. **Dosing should be initiated within 1 hour of randomization and continue for 96 hours (4 days).**

Rationale: Inclusion criterion 6 was updated to expand the treatment time window, which would allow for inclusion of late presenters and to ensure that dosing of early patients is not delayed. This update would address the highest rate of recruitment failures, thereby accelerating recruitment in the process. The impact of dosing time on treatment effect will be explored.

This change also affects Sections 1, Synopsis; 4.5.1, Dosing Regimen; 5, Schedule of Activities (Table 2); 7.1, Study Overview, including Figure 1, Study Design; and 9.1, Screening.

Section 8.1, Inclusion Criteria

Now reads:

~~8. Absence of immediate indication for intracranial surgery to decompress or evacuate hematoma.~~

~~Note: presence of other injuries within the cranial vault will be allowed provided they do not require immediate operative intervention (including rim subdural, epidural, subarachnoid, or intraventricular hemorrhage). Previous or planned insertion of external ventricular drains or drilling of burr holes are permitted.~~

Rationale: Inclusion criterion 8 was removed to allow operative intervention for extra-axial injuries and new exclusion 8.2.

Section 8.2, Exclusion Criteria

Now reads:

2. **Indication for immediate evacuation of IPH or DC.**

Rationale: Exclusion criterion 2 was updated to allow operative intervention for extra-axial injuries.

This change also affects Section 5, Schedule of Activities, Table 2 (renumbered footnote 7).

Section 8.2, Exclusion Criteria

Now reads:

~~8. Midline Shift >5 mm on baseline NCCT or MRI~~

Rationale: Exclusion criterion 8 was removed because midline shift at baseline is often a function of extra-axial injuries, and the study now allows for operative management that could affect such injuries.

Section 8.2, Exclusion Criteria

Now reads:

26. **Life-threatening or nonsurvivable p~~P~~olytrauma per Investigator's judgement**.~~(intra-abdominal or orthopedic trauma) requiring operative surgical management, if known. Minor fractures requiring splinting or reduction of dislocations are permitted, as are non-operative intra-abdominal injuries or placement of noninvasive external fixation devices.~~

    ~~Note: as per the Investigator's discretion, radiology procedures for embolization are allowed, provided they are minor and not associated with large-volume bleeding.~~

Rationale: Exclusion criterion 26 was reworded to specify life-threatening or nonsurvivable polytrauma, based on site feedback that many patients with contusions have polytrauma. Patients with non-life threatening/survivable polytrauma may benefit from the drug, and enrollment of these patients would increase generalizability of results. Polytrauma that is normally survivable will have minimal impact to the primary endpoint of change in total contusion volume (hematoma plus perihematomal edema) for the following reasons:

a. Polytraumas that lead to significant hematologic derangements will be excluded through laboratory exclusion criteria. Hematologic derangements would likely affect hematoma expansion.

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b. Polytraumas that are likely nonsurvivable would likely lead to significant volume of fluid to resuscitate the patient which would likely lead to some effect on our primary outcome.
c. Current TBI outcome predictors (IMPACT, CRASH) do not utilize the degree of polytrauma in their functional outcomes.

Section 16.7, Interim Analysis

Change: An interim analysis was added to the protocol.

Now reads:

~~No formal interim analysis was planned for the study.~~ **An interim analysis may be performed by an internal, independent, unblinded team, when approximately 90 subjects are dosed for administrative purposes. The interim analysis may include, but not be limited to the efficacy, safety, [redacted] analysis by treatment group. A clear process will be specified and implemented to ensure that the treatment blinding will be strictly maintained for investigators, subjects, and study personnel from the Sponsor and CRO throughout the study. The interim analysis will not inform the continued blinded data collection in the study. There is no Type I error adjustment for the proposed interim analysis. The interim analysis, if being conducted, will lead to one of the following actions:**

2. **Continue to complete the blinded study.**

3. **Continue to complete the blinded study while accelerating Phase 3 study preparation after the interim analysis.**

Rationale: The Sponsor plans to conduct an interim analysis in order to support internal decision making to enable pivotal study planning. Introduction of an interim analysis at N=90 would allow for an early signal to facilitate an earlier Phase 3 start. The final decision to start the Phase 3 study will also depend on feedback from regulatory agencies and the continued data collection in the Phase 2 study.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 4.5.1.2, Selection of 5 mg/day

Change: Clarified that exposure data from the 5 mg/day dose was the result of simulations.

Now Reads:

The no observed adverse effects level was considered to be 18.2 mg/kg, which provides exposure margins of 3-fold and 6-fold based on the maximum observed concentration and concentration at steady state (C_{ss}), respectively, at 5 mg/day. **The exposure data at 5 mg/day are the result of simulations.**

Rationale: This change was made to ensure accurate reporting, and to meet a regulatory commitment to the French Regulatory Agency.

Section 5, Schedule of Activities, Table 2

Change: A new footnote pertaining to scans in relation to IPH evacuation, DC, or CMO was added to the NCCT and MRI row in Table 2.

Now reads:

[5]Scans (NCCT or MRI) obtained within 12 hours of IPH evacuation, DC, or CMO meet the requirement. Scans are not expected for other NSx interventions. If IPH evacuation, DC, or CMO are indicated prior to 96 hours, an NCCT or MRI scan in the 12 hours proceeding the procedure should be collected, and no further post-procedural images are required beyond SOC.

This change also affects Section 6, Study Objectives and Endpoints (Primary Objectives and Endpoints, [redacted]), and Section 13.1, Clinical Efficacy Assessments.

Rationale: These changes were made to ensure that all scans are acquired as part of SOC and to allow use of them in cases of CMO or surgery involving IPH evacuation or DC. It also clarifies that subsequent scans after IPH evacuation, DC, or CMO are not required.

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Section 5, Schedule of Activities, Table 2

Change: A new footnote pertaining to optional NCCT scans was added.

Now Reads:

[7]Optional Hour 96 NCCT should be obtained in addition to the MRI whenever possible, after study treatment infusion is complete, within 18 hours of the Hour 96 timepoint.

Rationale: Measurement of contusion volume changes based on 96-hour MRI, and baseline NCCT may be influenced by the difference in sensitivity of the 2 imaging modalities. An optional 96-hour NCCT is being added to the assessment schedule to collect evidence on both NCCT and MRI in a subset of patients to allow for comparison of contusion volume between modalities. This additional NCCT is per investigator judgment and not expected to replace the existing MRI in cases where MRI is feasible.

This change also affects Section 13.1, Clinical Efficacy Assessments.

Section 5, Schedule of Activities, Table 2

Change: Changed assessment language regarding MRI/NCCT, and this change was also reflected in the footnote.

Now reads: ~~MRI (if not possible NCCT is acceptable)~~**MRI**[5, 14]

[14] ~~If~~ **An NCCT scan is sufficient for participants who cannot get an MRI**. ~~A participant cannot get an MRI due to the participant's clinical condition, contraindication to MRI, or MRI technician/MRI unavailability, the participant is to get an NCCT scan.~~

Rationale: This change was made to support the flexibility to use NCCT instead of MRI if MRI is contraindicated.

Section 6, Study Objectives and Endpoints

Change: The primary endpoint was amended to increase statistical power to detect a meaningful treatment effect while recognizing any reduction in contusion volume is desirable to detect. The GOS-E at Day 180 was [redacted] added as one of the secondary endpoints. [redacted] Change in total contusion volume (hematoma plus perihematomal edema) from baseline to 24 hours was added as one of the secondary endpoints.

Now reads:

Primary Endpoint:

Change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 96 hours or prior to DC, IPH evacuation, or CMO if these procedures occur before 96 hours per the central review.

~~Proportion of participants with contusion (hematoma plus perihematomal edema) expansion by Hour 96 (or prior to NSx or CMO).~~

~~Note: to meet criteria for expansion of total contusion volume per the central review, a participant must have the following:~~

- ~~≥ 50% increase from baseline contusion volume, and~~
- ~~≥ 4.0 mL absolute increase from baseline~~

  ~~OR~~

- ~~≥ 10.0 mL total expansion from baseline~~

Secondary Endpoint:

- Glasgow Outcome Scale-Extended (GOS-E) at Day-[redacted]-**180**.
- **Change in total contusion volume (hematoma plus perihematomal edema) as measured by brain imaging from baseline to 24 hours or prior to DC, IPH evacuation, or CMO if these procedures occur before 24 hours per the central review.**
- Change in absolute hematoma volume from baseline to 24 hours
- Change in absolute edema volume from baseline to 96 hours

Rationale: According to the current protocol definition of expansion, the pooled blinded proportion of patients meeting the contusion expansion criteria appeared to be very high, particularly for participants with MRI scans at 96 hours. This high proportion was significantly greater than the assumed 50% proportion in the placebo arm used to justify sample size. The revised primary endpoint analysis will treat contusion volume as a continuous variable and assess the change in volume from baseline as a continuous variable; adjusted by imaging modality. Change in contusion volume at 24 hours was added as a secondary endpoint which will involve NCCT to NCCT comparison. The Day 180 GOS-E assessment will be favored over its Day [redacted] measurement as it is the registrational endpoint in TBI studies.

This change also affects Section 7.1, Study Overview; Section 11.4.2.1, Neurosurgical Intervention; Section 13.1, Clinical Efficacy Assessments; Section 16, Statistical Methods and Determination of Sample Size; Section 16.2.1, Analysis Population; Section 16.2.2.2, Analysis of the Primary Endpoint; Section 16.2.2.3, Analysis of the Secondary Endpoints; and Section 16.8, Sample Size Considerations.

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Section 6, Study Objectives and Endpoints

Change: [redacted] GOS-E at Day [redacted] replaced GOS-E at Day 180.

Now reads:

[redacted]

Rationale: [redacted]

Section 7.1, Study Overview

Change: The database-lock language was changed to remove the Day 90 lock

Now reads:

~~The study database will first be locked after the last participant finishes their Day 4 Visit and the primary and imaging based endpoints will be analyzed. A final study database lock will occur when the last participant completes their Day 90 Follow-up Visit to analyze key functional outcomes. The long term follow-up database will be locked for evaluation of long term safety and efficacy after the last participant completes the Day 180 Follow-up Visit. The end of the study is when the last participant completes their Day 180 assessments.~~

After the last participant completes their Day 4 (Hour 96) Visit, data for the primary endpoint and available data for the secondary endpoints will be locked for analysis. The final database lock will occur after the last participant completes their Day 180 Follow-up Visit, marking the end of the study.

Rationale: The 90 Day database lock did not add significant value to accelerate study interpretation. This change is consistent with the greater importance of the Day 180 GOS-E over Day [redacted] GOS-E.

This change also affects Section 9.3, Blinding Procedures, and Section 16, Statistical Methods and Determination of Sample Size.

Section 8.2, Exclusion Criteria

Change: Exclusion criterion 14 was removed.

Now reads:

~~14. Injury Severity Score (not including head or face) >12.~~

Rationale: This criterion was removed to be consistent with allowance of polytrauma patients.

Section 11.4.1.1.1, Interventions Related to Blood Glucose

Change: More detailed guidance for managing BG while on treatment was added.

Now Reads:

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 studies 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**; however, Investigators must use their own medical judgment in conjunction with referencing the guidance (Table 5).**

Insulin

Insulin and other BG-lowering agents are not permitted during study treatment administration when BG is < ~~120~~ **140** mg/dL (~~6.7~~ **7.8 mmol/L**).

Maintenance ~~Fluids~~ **Dextrose-Containing IV Solution**

During the study treatment infusion period, BG monitoring is required **as follows**:

- **Hour 0 to Hour 24, monitor** hourly (±30 minutes) ~~for~~
- Hour ~~0~~ **25** to Hour ~~24~~ **48, monitor** every 2 hours (±30 minutes) ~~for~~
- Hour ~~25~~ **49** to Hour ~~48~~ **96,** ~~and~~ **monitor** every 4 hours (±60 minutes) ~~for Hour 49 to Hour 96~~

~~(s~~ **S**ee Section 5 for further details on timings of BG measurements~~)~~. If treatment for hypoglycemia is initiated (**for BG <70mg/dL [~3.9 mmol/L]),** then BG monitoring is required every 15 minutes (±10 minutes) until BG is ≥ 80 mg/dL (~4.4 mmol/L) for 3 consecutive

readings without exogenous bolus glucose supplementation. BG monitoring may be performed more often at the discretion of the Investigator. Table 5 shows how BG should be monitored and managed according to inpatient BG levels.

Total fluid volume, inclusive of study treatment volume, infusion rate, infusion duration, sodium content, and percent of dextrose, should be guided by the clinical status of the subject and medical judgment.

It is recommended that maintenance dextrose-containing IV solution be initiated when BG is < 120 mg/dL (~6.7 mmol/L) and maintained for the duration of the study treatment administration (up to 96 hours) with the new glycemic BG target in the range of 140 to < 180 mg/dL (~7.8-10 mmol/L).

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Table 5: Blood Glucose Monitoring and Management

Inpatient BG Level	BG Monitoring and Management[1]
~~>120 mg/dL (~6.7 mmol/L)[2]~~	~~It is recommended that neither D5NS nor D10NS are administered.~~
Initiation of dextrose-containing IV solution	
< 120 mg/dL (~6.7 mmol/L)[2]	• It is recommended that ~~D5NS~~ **D10NS at 35 to 50 mL/h be initiated as first-line management**. **Consider D5NS** at a rate of 70 to 100 mL/h **or other percent dextrose solutions as alternatives.** ~~is administered.~~ • ~~Insulin and other BG lower agents are not permitted during study treatment administration when BG < 120 mg/dL (~6.7 mmol/L).~~
Maintenance of dextrose-containing IV solution after initiation	
≥180 mg/dL (~10 mmol/L)	• **It is recommended that dextrose-containing IV solution be titrated downward or stopped temporarily until BG is ≥ 140 to < 180 mg/dL (~7.8 to ~10 mmol/L).**
<180 mg/dL (~10 mmol/L) but ≥140 mg/dL (~7.8 mmol/L)	• **It is recommended that dextrose containing IV solution be maintained or titrated to keep BG as ≥140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L).**
<140 mg/dL (~7.8 mmol/L) but ≥ 80 mg/dL (~4.4 mmol/L)	• **Insulin and other BG lowering agents are not permitted during study treatment administration when BG is < 140 mg/dL (~7.8 mmol/L).** • **It is recommended that dextrose-containing IV solution be maintained when BG is < 140 mg/dL (~7.8 mmol/L). Titrate up the IV infusion rate to keep BG ≥ 140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L).**
~~< 100 mg/dL (~5.6 mmol/L)[2]~~	~~• It is recommended that D5NS is started at 70 to 100 mL/hr.~~ • ~~It is recommended that the IV fluid rate is titrated up or down to maintain BG > 80 mg/dL (~4.4 mmol/L).~~
< 80 mg/dL (~4.4 mmol/L)[2]	~~• D5NS must be started or, if D5NS is already being administered , the participants must be switched to D10NS.~~ • **It is recommended that the infusion rate of the dextrose-containing IV solution be increased to keep BG ≥ 140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L).**
< 70 mg/dL (~3.9 mmol/L)	• **It is recommended that the infusion rate of the dextrose-containing IV solution be increased after the dextrose bolus.** • **It is recommended that the infusion rate of the dextrose-containing IV solution be titrated up to keep BG ≥ 140 mg/dL (~7.8 mmol/L) but < 180 mg/dL (~10 mmol/L)**

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Inpatient BG Level	BG Monitoring and Management[1]
< 55 mg/dL (~3.0 mmol/L)	• Study treatment infusion rate must be reduced as follows: o If hypoglycemia occurs within the first 6 hours of infusion: ▪ For participants on high infusion rate (0.2722 mg/h), the infusion rate must be reduced to 0.1644 mg/h. If hypoglycemia cannot be rectified or reoccurs, the infusion rate must be further reduced to 0.0795 mg/h and must not be uptitrated. ▪ For participants on low infusion rate (0.1644 mg/h), the infusion rate must be reduced to 0.0795 mg/h and must not be uptitrated. o If hypoglycemia occurs after the first 6 hours of infusion, the infusion rate must be reduced to 0.0795 mg/h. The infusion rate can be uptitrated to 0.1134 mg/h when BG is > 80 mg/dL (~4.4 mmol/L) for 3 consecutive readings. • Study treatment should be discontinued if hypoglycemia cannot be rectified and is determined by the Investigator to be harmful to the participant.

BG = blood glucose; D10NS = 10% dextrose in normal saline (or fluid containing 10% dextrose); D5NS = 5% dextrose in normal saline (or fluid containing 5% dextrose); IV = intravenous.

[1] Total fluid volume, inclusive of study treatment volume, should be consistent with site practice and **guided by** clinical status of the participant **and medical judgment**.

~~[2] Participants with a BG level greater than 70 mg/dL (~ 3.9 mmol/L) are not required to receive dextrose if they have cardiac or renal issues necessitating reduced fluid intake.~~

Rationale: Protocol guidelines are updated to optimize blood- and dextrose-containing maintenance IV solution management to prevent or reduce the occurrence of hypoglycemia and to minimize fluid or sodium overload.

This change also affects Section 10.1, Discontinuation of Study Treatment, and Section 11.4.1.2, Disallowed Concomitant Therapy.

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Section 18.3, Monitoring of the Study

Change: Language added regarding the remote monitoring of study sites.

Now Reads:

The Clinical Monitor will visit the study site at regular intervals during the study and after the study has completed, as appropriate, **or may perform monitoring activities remotely (where permitted by local regulations) only during the COVID-19 pandemic where on-site monitoring is not allowed per local/regional restrictions.**

Rationale: Accommodate remote clinical study site visits in the context of possible disruptions related to COVID-19.

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SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- Heart rate was replaced with pulse rate when referencing vital signs for harmonization with the CDISC CDASH industry standards.
- The Sponsor Signatory name and credentials were updated.
- It was specified that analysis of the primary and available data for the secondary endpoints will be performed after the last participant completes the Day 4 (Hour 96) Visit.
- Section 2, List of Abbreviations, was updated.
- In Section 4.5.1, Dosing Regimen, language was rephrased to start with the strictest dosing requirements, and in Table 1 (BIIB093 Dosing Regimen), the bolus infusion volume of study treatment was removed for the 3- and 5-mg dose due to anticipated changes in saline bag volume and concentration. The bolus infusion volume was also removed in Section 11.1, Regimen.
- In Section 5, Schedule of Activities, Table 2, the following updates were made:
  - "Craniectomy" was removed from the column header and replaced with "NSx."
  - "Comfort Care" was replaced with "Comfort Measures" in the column header for consistency.
  - Weight and height were specified as part of the physical examination.
  - Footnote 4 was updated to specify that if follow-up visits at Day 90 and 180 were conducted remotely, [redacted]. (This was also reflected in Section 13.1, Clinical Efficacy Assessments.)
  - Footnotes were renumbered due to the addition of footnotes 5 and 7.
  - Footnote 13 was updated to say that [redacted] eCRFs, not a DC eCRF, should be completed for participants who receive [redacted].
- In Section 6, Study Objective and Endpoints, It was clarified in the Primary Objective that scans be obtained prior to DC, IPH evacuation, or CMO if these procedures occur before Hour 96.

- In Section 8.2, Exclusion Criteria, criterion 32 was updated to allow enrollment of patients for whom anticoagulation from NOACs can be adequately reversed with Andexanet alfa.

- In Section 9.3, Blinding Procedures, a paragraph describing how the interim analysis will be performed by an independent unblinded team was added.

- In Section 10.1, Discontinuation of Study Treatment, the phrase "study treatment must be discontinued" was removed from the first bullet to avoid repetition.

- In Section 11.4.1, Concomitant Therapy, it was clarified that all concomitant therapy will be recorded in the appropriate eCRF.

- In Section 11.4.2, Concomitant Procedures, a sentence was added stating that the use of unapproved therapies and/or procedures is not permitted.

- In Section 11.4.2.2, Intubation, the first sentence in the second paragraph was reworded from "after the start of infusion" to "after the injury."

- In Section 12, Study Treatment Management, language was changed to state that the DHA should align with all other reference documents instead of superseding all other documents. This revision is in response to a minor finding from an MHRA inspection. In addition, references to Pharmacy Manual were changed to DHA.

- In Section 15.3.1, Adverse Events, clarifying language was added with regard to recording of ongoing AEs in the eCRF after study completion.

- In Section 16.2.2.2, Analysis of the Primary Endpoint, and Section 16.2.2.3, Analysis of the Secondary Endpoint, it was stated that multiple imputation would be used to account for missing values at Hour 96.

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LIST OF ABBREVIATIONS

BG	blood glucose
CDISC	Clinical Data Interchange Standards Consortium
CDASH	Clinical Data Acquisition Standards Harmonization
CMO	comfort measures only
COVID-19	Coronavirus disease 2019
DC	decompressive craniectomy
DHA	Directions for Handling and Administration
eCRF	electronic case report form
GOS-E	Glasgow Outcome Scale – Extended
IPH	intraparenchymal hematoma
IV	intravenous
LKN	last known normal
MHRA	Medicines and Healthcare products Regulatory Agency
MRI	magnetic resonance imaging
NCCT	noncontrast computed tomography
NOAC	novel oral anticoagulants
NSx	neurosurgical intervention
[redacted]	
SOC	standard of care

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AMENDMENT SUMMARY

Biogen Protocol 252BN201

A Multicenter, Double-Blind, Multidose, Placebo-Controlled, Randomized, Parallel-Group, Phase 2 Study to Evaluate the Efficacy and Safety of Intravenous BIIB093 for Patients with Brain Contusion

Version 2

Date: 18 February 2020

EUDRA CT Number: 2018-003858-24

Version 2.0 of the protocol has been prepared for this amendment, which supersedes Version 1.

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PRIMARY REASON FOR AMENDMENT

The primary reason for this amendment to Protocol 252BN201 is to expand the population base for treatment with BIIB093. The age range for study inclusion was increased from up to 80 years old to up to 85 years old. In addition, the Glasgow Coma Scale (GCS) score range for study inclusion was increased from up to 14 to up to 15.

New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 8.1, Inclusion Criteria

Now reads:

2. Aged 18 to ~~80~~**85** years old, inclusive, at the time of informed consent.

Note: age 18 years at the time of informed consent or participant meets the minimum age of consent in accordance with national regulations (whichever is higher).

Note: for countries where the minimum age of consent is over 18 years, participants may be enrolled provided a LAR is available, and if capable, the participant assents to treatment. The LAR must consider the participant's involvement in the study and provide informed consent for the participant.

3. A score of 5 to ~~14~~**15** on the GCS. Assessment should be made prior to medical intervention, where possible.

Note: an enrollment cap of participants presenting with GCS 15 will be placed at 10% of total number of participants.

Rationale: This development program is intended to benefit as many participants as is feasible as well as scientifically-justified. The liberalization of enrollment criteria is intended to achieve a wider range of participants who might benefit from potential treatment with BIIB093. The first change related to age was based on review of prescreening data. Age range was increased based on data demonstrating participants > 80 but < 85 years of age are presenting with contusions and undergoing active medical care with good prognosis based on presenting GCS scores.

Secondly, many participants with contusions > 3 cc are presenting with unaltered neurologic status (GCS 15) and given the propensity for contusions to expand and clinical deterioration to occur as a result, these participants may benefit from treatment with BIIB093. With the inclusion of participants with GCS 15, an enrollment cap at 10% was placed to ensure that the study population is well-balanced amongst presenting GCS participants and to prevent excessive enrollment of participants with mild complicated traumatic brain injury. This change also affects Section 1, Synopsis; Section 7.1, Study Overview; and Section 9.2, Randomization.

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SUMMARY OF MAJOR CHANGES TO THE PROTOCOL

Changes to the protocol are presented chronologically. New text is shown in **bold** type; deleted text is shown with a ~~strikethrough~~.

Section 1, Synopsis

The synopsis was revised to reflect changes made throughout the protocol.

Section 5, Schedule of Activities, Table 2

Change: Footnote 2 was updated to clarify that if a participant is discharged from the hospital prior to Hour 96, sites should still obtain neuroimaging prior to the participant departing the hospital.

Footnote 11 was updated to clarify the definition of low blood glucose (BG).

Footnote 13 was updated to clarify that participants can get a noncontrast computed tomography (NCCT) scan if a magnetic resonance imaging (MRI) is not possible due to the participant's clinical condition, contraindication to MRI, or MRI technician/MRI unavailability.

Footnote 14 was updated to clarify that Hour 96 MRI scan should be performed within 18 hours of the Hour 96 time point.

Now reads:

[2] In the event ~~that~~ a participant ~~rapidly improves and~~ is discharged from the ~~intensive care unit before~~ **hospital prior to Hour** 96 ~~hours~~, every effort should be made to obtain ~~the~~**neuroimaging (**NCCT~~/~~ **or** MRI ~~scans)~~ **prior to discharge**.

[11] Hourly (±30 minutes) for Hour 0 to Hour 24, every 2 hours (±30 minutes) for Hour 25 to Hour 48, and every 4 hours (±60 minutes) for Hour 49 to Hour 96. If treatment for ~~hypoglycemia~~ **low BG (< 70 mg/dL [~3.9 mmol/L])** is initiated, then BG monitoring is required every 15 minutes (±10 minutes) until BG is ≥ 80 mg/dL **(~4.4 mmol/L)** for 3 consecutive readings without exogenous bolus glucose supplementation. See Section 11.4.1.1.1 for details on BG monitoring and management.

[13] If a participant cannot get an MRI ~~for any reason (e.g.,~~ **due to the participant's** clinical condition, contraindication to MRI, or ~~equipment unavailable),~~**MRI technician/MRI unavailability,** the participant is to get an NCCT scan.

[14] The 96−hour scan should be performed after study treatment infusion is complete**, within 18 hours of the Hour 96 time point**.

Rationale: Footnote 2 was updated to clarify that neuroimaging needs to be obtained prior to participant discharge in the event the participant is due to be discharged from hospital prior to Hour 96 due to clinical improvement.

Footnote 11 was updated to clarify that frequent BG monitoring every 15 minutes is required when BG < 70 mg/dL and not when BG < 55 mg/dL (per protocol definition of hypoglycemia).

Footnote 13 was updated to clarify that NCCT scan should still be obtained in the event an MRI is untenable due to participant's clinical deterioration, contraindication to MRI, or equipment/technician unavailability.

Footnote 14 was updated to extend the time window for Hour 96 MRI and be consistent with the MRI to be acquired post treatment infusion. The extended time window reflects feedback from sites on the availability of MRI and need for extra time to conduct this assessment, given the possibility of participant presentation during off-hours (11 pm to 6 am).

Section 6, Study Objectives and Endpoints

Change: [redacted] Objectives related to evaluation of BIIB093 was updated.

Now reads:

To evaluate the [redacted] of BIIB093 up to Day ~~7/Discharge.~~**4 (Hour 96).**

Rationale: The infusion is discontinued at Day 4, the timing of the primary endpoint. Exposure to BIIB093 will rapidly decline from this point onward.

Section 7.1, Study Overview

Change: Schedule of study database lock and timing of endpoint analyses were clarified.

Now reads:

The study database will first be locked after the last participant finishes their Day ~~90 follow-up visit~~**4 Visit** and the primary and ~~secondary~~**imaging-based** endpoints will be analyzed ~~in the primary and secondary efficacy analyses~~. A final study database lock will occur when the last participant completes their Day ~~180 follow~~**90 Follow-**up ~~visit~~**Visit** to analyze **key functional outcomes. The long-term follow-up database will be locked for evaluation of long-term safety and efficacy after the last participant completes** the ~~remaining endpoints.~~**Day 180 Follow-up Visit.** The end of the study is when the last participant completes their Day 180 assessments.

Rationale: The schedule of the first study database lock was updated from after Day 90 to after Day 4. This change is consistent with the analysis of the primary endpoint which will be performed on Day 4 (Hour 96). Further clarification was added to specify that the final study database will be locked at Day 90 and the long-term follow-up database will be locked at

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Day 180. These changes are also consistent with the analyses of key functional outcomes on Day 90 and long-term safety and efficacy endpoints on Day 180.

This change also affects Section 9.3, Blinding Procedures, and Section 16, Statistical Methods and Determination of Sample Size.

Section 8.1, Inclusion Criteria

Change: The mechanism of injury for study inclusion was clarified.

A note was added to inclusion criterion 8.

Now reads:

5. Mechanism of injury is ~~well~~ defined**.**

~~First-responders/~~**Note:** emergency medical~~-staff report identifies~~**technicians, emergency physicians, or members of the study team can identify** a ~~clear~~**likely or possible** mechanism of **head** injury~~, i.e., motor vehicle accidents, assault, pedestrian struck, fall, or sports injuries, etc~~ **based on the clinical history and/or patient presentation**.

~~a. Presence of other injuries within the cranial vault will be allowed provided they do not require operative intervention (including rim subdural, epidural, subarachnoid, or intraventricular hemorrhage).~~

8. Absence of immediate indication for intracranial surgery to decompress or evacuate hematoma.

Note: presence of other injuries within the cranial vault will be allowed provided they do not require immediate operative intervention (including rim subdural, epidural, subarachnoid, or intraventricular hemorrhage). Previous or planned insertion of external ventricular drains or drilling of burr holes are permitted.

Rationale: The change in inclusion criterion 5 was based on site feedback in which an exact mechanism of trauma was unknown. Liberalization of this wording is to allow for enrollment of participants whose injury-circumstances are not entirely clear but who may benefit from treatment nonetheless, so long as they remain within the treatment window.

The change in inclusion criterion 8 was made to clarify the meaning of "intracranial surgery" and that burr hole placement or external ventricular drain insertion are not exclusionary.

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Section 8.2, Exclusion Criteria

Change: The exclusion criterion for NCCT or MRI was clarified.

The use of transient vasopressor was clarified.

The use of interventional radiology procedures for embolization was clarified.

The use of vitamin K antagonists in the study was clarified.

Now reads:

3. NCCT or MRI evidence of penetrating brain injury~~.~~ **impacting the brain parenchyma. Cerebrospinal fluid leak in isolation is not exclusionary unless evidence of parenchymal penetration by an external force (e.g., blunt object, bullet, or depressed skull fracture).**

25. Hemodynamic instability (use of inotrope or vasopressor therapy or resuscitation requiring > 6 L crystalloid or colloid).

Note: transient vasopressor used to support blood pressure during specific procedures (e.g., intubation or hypotension associated with sedation/analgesics) is permitted.

27. Polytrauma (intra-abdominal or orthopedic trauma) requiring operative/surgical management, if known. Minor fractures requiring splinting or reduction of dislocations ~~is~~**are** permitted, as are nonoperative intra-abdominal injuries **or placement of noninvasive external fixation devices**.

Note: as per the Investigator's discretion, interventional radiology procedures for embolization are allowed, provided they are minor and not associated with large-volume bleeding.

35. Use of vitamin K antagonists within 5 days prior to the injury, if known.

Note: patients on vitamin K antagonists who are subtherapeutic with INR < 1.5 may be included. **If a patient can be adequately reversed from vitamin K antagonism to a subtherapeutic INR in time for randomization, this is acceptable, and the patient should be screened for enrollment.**

Rationale: The change in exclusion criterion 3 was made to clarify that cerebrospinal fluid leaks are not exclusionary and provide further clarity on the meaning of "penetrating brain injury".

The change in exclusion criterion 25 was based on the Investigator's feedback at the Investigator's meeting, vasopressors are often transiently used for blood pressure support during

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procedures. This is to clarify that this does not reflect a hemodynamically unstable participant and that these participants are eligible for enrollment.

The change in exclusion criterion 27 was based on the Investigator's feedback at the Investigator's meeting, trauma participants may undergo noninvasive endovascular repair of small-volume bleeding unlikely to affect volume status or the primary endpoint. These participants should be included.

The change in exclusion criterion 35 was made to provide additional clarity that reversal of vitamin K antagonists is acceptable.

Section 9.1, Screening

Change: Suicidal ideation assessment was added to the schedule of activities at Baseline and follow-up.

Now reads:

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

A short suicidal ideation/behavior questionnaire will be conducted on participants who are alert and capable of providing answers at Screening (prior to dosing). For these participants, this questionnaire should be repeated at Days 30, 90, 180, and ET Visit.

Rationale: This change was made to comply with regulatory draft guidance stipulating that prospective suicidal ideation and behavior assessments should be carried out in all clinical trials involving any drug being developed for CNS activity. This assessment will only be carried out in participants deemed capable of understanding and appreciating the content of the questionnaire. In addition, this change was made to understand any possible association between BIIB093 and suicidal ideation in participants with brain contusion.

This change also affects Section 5, Schedule of Activities (Table 2) and Section 14.1, Clinical Safety Assessments.

Section 9.3, Blinding Procedures

Change: The blinding procedure was clarified.

Now reads:

The study Sponsor and CRO study management team will be fully blinded for the study. ~~When~~**After** the last participant completes their Day ~~90~~**4** ~~visit~~**Visit**, the clinical study database will be locked and designated personnel at the Sponsor will be unblinded for the purposes of evaluating the primary and secondary efficacy analyses. The final database lock will occur

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~~when~~**after** the last participant completes their Day **90 Visit and the long-term follow-up database will be locked after the last participant completes the Day** 180 **Follow-up** Visit. The Sponsor and CRO study management teams responsible for all site interactions and data entry will remain blinded **through Day 180** to individual treatment assignments ~~during the study~~.

Rationale: This change was made to clarify that blinding will be maintained until the End of Study for data integrity of long-term functional outcomes.

[redacted]

Change: [redacted]

Now reads:

[redacted]

[redacted]

~~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.~~

Sites should be vigilant about intracranial pressure management and perform DC when it is clinically indicated as part of local SOC. The reasons for the DC should be recorded in the eCRF.

Rationale: This change was made to clarify the acceptability of minimally invasive procedures such as burr hole placement and external ventricular drain insertion, and that these procedures are not exclusionary for enrollment since these procedures have minimal impact on the primary

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endpoint. Clarification was also added to ensure standard of care (SOC) is followed by all sites regarding the need for surgical decompression.

Section 12.1.2, BIIB093 Storage

Change: Storage requirement of BIIB093 was clarified.

Now reads:

All vials of BIIB093 are to be stored at ~~room temperature (≤~~**1°C to ≤** 25°C ~~or~~ **(34°F to** ≤ 77°F~~),~~**)** **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.

Rationale: This change was made to clarify specifications with more detail surrounding light sensitivity of BIIB093 and parameters for storage.

This change also affects Section 12.2, Placebo.

Section 14.2, Laboratory Safety Assessments

Change: laboratory tests for safety assessments were clarified.

Now reads:

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 ~~with differential~~ and platelet count, and absolute neutrophil count
- Blood chemistry: ~~total protein~~, albumin, creatinine, blood urea nitrogen, ~~uric acid,~~ **glucose, calcium, phosphorus, bicarbonate (if available), chloride (if available), sodium, and potassium**
- **Liver function test:** bilirubin (total and ~~direct~~**indirect**), alkaline phosphatase, ALT, AST, **and** gamma-glutamyl transferase~~, glucose, calcium, phosphorus, bicarbonate, chloride, sodium, and potassium~~
- Coagulation panel (INR, PTT, fibrinogen)
- Note that in any case of confirmed hemolytic anemia~~,~~ **after randomization, the required local standard tests should be performed to confirm etiology of disease, including** a G6PD genetic or enzymatic test ~~should be performed~~ (in accordance with local practice).

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Rationale: Laboratory assessments in this study will be conducted at local laboratories and per the sites SOC. Required investigational parameters are adjusted to adopt sites SOC without compromising participants' safety assessments and follow-up.

Section 16.2.2.2, Analysis of the Primary Endpoint

Change: The images that will be used to determine the primary endpoint and the timing of scans for contusion volume were clarified.

Now reads:

The primary endpoint ~~of~~**,** the proportion of participants with contusion expansion**,** will be determined by **final** centralized readings of contusion volume from **baseline and all on-protocol** images collected ~~at baseline and 96~~ **between 12** hours **after the initiation of study treatment up to the Hour 96 visit or the time of NSx or CMO (if earlier)**. Primary analysis of the primary endpoint will compare BIIB093 (3 mg/day or 5 mg/day) and placebo groups using a binary logistic regression, adjusting for covariates including all the stratification factors at randomization and baseline contusion volume per the central read and baseline GCS.

Sensitivity analyses **for the assumptions** will be performed to evaluate the impact of **analysis sets, the impact of** missing data, and the ~~missing data~~**intercurrent event** handling**. Details** will be specified in the SAP.

Rationale: It is necessary to delineate the admissible images which will be used to determine contusion expansion. This change was made to clarify that the postbaseline images used for defining contusion expansion should be collected after 12 hours and before the time of NSx or CMO if that happens before Hour 96. This change also makes the definition of contusion expansion consistent with that of the modified intend-to-treat population. Furthermore, changes to sensitivity analyses were made to clarify the scope of the analyses.

This change also affects Section 16.2.1, Analysis Population.

Section 16.2.2.3, Analysis of the Secondary Endpoints

Change: The timing for the analysis of participants requiring delayed intubation was clarified.

The analysis population for survival time (all randomized participants) was clarified.

Now reads:

Proportion of participants requiring delayed intubation

The proportion of participants requiring delayed intubation **at any time between 24 hours and 96 hours postinjury or last known normal will be analyzed at Day 4. The analysis** will compare BIIB093 (3 mg/day or 5 mg/day) and placebo groups using a binary logistic regression,

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adjusting for covariates including all the stratification factors at randomization and baseline contusion volume per the central review and baseline GCS.

Time to all-cause death, including neurological death, through Day 90

Survival time will be analyzed for all randomized participants. Cox proportional hazards regression models will be used to assess the treatment effects on overall survival at Day 90 after adjusting for covariates including the stratification factors at randomization, baseline contusion volume per the central review, and baseline GCS. Kaplan Meier curves will be presented for BIIB093 (3 mg/day or 5 mg/day) and placebo groups.

Rationale: The change in the timing for the analysis of delayed intubation was made to clarify the definition of delayed intubation in relation to the note found in Section 6, Secondary Endpoints.

The change related to analysis population for survival time was made to clarify the analysis population for time-to-event endpoint since it is different from the rest of the endpoint analyses, where the modified intend-to-treat set is used. All randomized participants are used to capture as much survival information as possible regardless of whether the participants have admissible images collected after randomization.

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SUMMARY OF MINOR CHANGES TO THE PROTOCOL

The following minor changes were made to the protocol, as appropriate:

- The version number and date were updated throughout the protocol.
- The number of countries participating in the study was changed from 5 to 7. Study sites in Canada were also removed from the study.
- The equivalent unit of BG in mmol/L was added throughout the protocol.
- New text and citation were added in Section 4.4, Study Rationale.
- New text in the footnote was added in Section 4.5.1, Dosing Regimen, Table 1.
- A new row for other assessments (ECG, [redacted]) and additional information on timing/dosing windows for infusion were added in Section 5, Schedule of Activities, Table 2.
- The statement related to database lock was removed in Section 7.5, End of Study.
- In Section 8.2, Exclusion Criteria, other reasons for study exclusion was clarified to specify that the final decision on the exclusion of a participant from the study must be made by the Investigator without interference by the Sponsor.
- In Section 11.1, Regimen, the delivery method of study treatment through central line or peripherally inserted central catheter line was further clarified. A note was also added to clarify that study treatment administration does not need to occur in the ICU.
- Dose modification during the study was clarified in Section 11.2 by revising the text and adding Table 4. The other succeeding tables were renumbered due to the addition of Table 4.
- In Section 11.4, Concomitant Therapy and Procedures, the description of treatment guidelines provided in the Study Reference Guide was removed.
- Table 5 in Section 11.4.1.1.2, Interventions Related to Blood Glucose was updated to reflect the information presented in Table 4.
- Normal saline was changed to sodium chloride in Section 12.1, BIIB093.
- Clarification was added in Section 14.3, Product-Specific Safety Assessments to note that venous line can also be used as a source of blood for BG measurement.

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- The definition of hypoglycemia was revised in Section 15.3.2, Adverse Events of Special Interest.

- The presentation of data by treatment group was clarified in Section 16.2.2, Methods of Analysis. By-treatment-group analysis will be displayed as placebo, BIIB093 3 mg/day, BIIB093 5 mg/day, BIIB093 combined, and total (if applicable). Continuous endpoints will also be presented in quartiles.

- Typographical errors and formatting were corrected.

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