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
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STATISTICAL ANALYSIS PLAN

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Study 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

Name of Study Treatment: BIIB093 (intravenous glibenclamide)

Protocol No.: 252BN201

Study Phase: 2

APPROVAL

This document has been reviewed and approved by:		
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SMT Medical Director	Signature	Date

VERSION HISTORY

SAP Version	Date	Primary Reasons for Amendment
1.0	03-MAR-2023	Not applicable
2.0	12-JUL-2023	To correct the derivation of the actual treatment for the 5mg/day group

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

Abbreviation	Definition
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
[redacted]	
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
[redacted]	
MRI	magnetic resonance imaging
mRS	modified Rankin Scale

NCCT	noncontrast computed tomography
NOAC	novel oral anticoagulants
NSx	neurosurgical intervention
OATP	organic anion transporting polypeptide
[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

1. Introduction

This statistical analysis plan (SAP) provides details of all pre-planned statistical analyses for Study 252BN201 (protocol version 3.0). Any deviation to this SAP will be described in the Clinical Study Report (CSR).

2. Study Overview

2.1. 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]

2.2. Study Design

The Study 252BN201 is a multicenter, double-blind, multidose, placebo-controlled, randomized, parallel-group, Phase 2 study to evaluate the efficacy and safety of BIIB093 (intravenous glibenclamide) in participants aged 18 to 85 years old (inclusive) who have a clinical diagnosis of brain contusion with lesions within the supratentorial brain parenchyma totaling > 3 mL at screening per investigator assessment of non-contrast computed tomography (NCCT) 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. Details of the study design and inclusion/exclusion criteria are described in Section 7 and 8 of the protocol, respectively; see Figure 1 for a schematic of the study design.

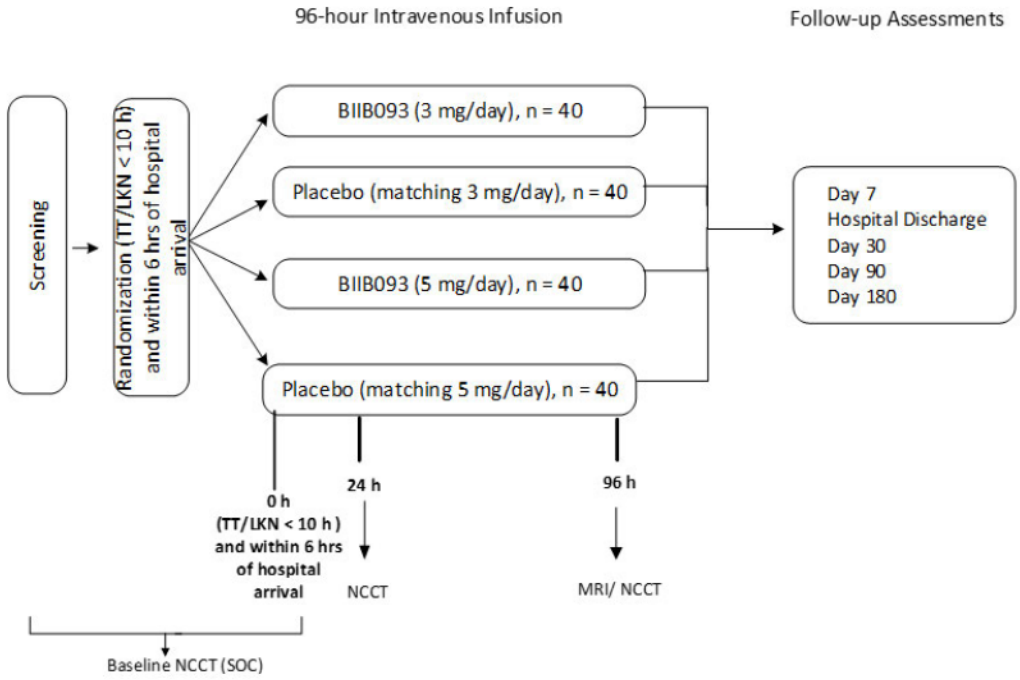
The total duration of study participation for each participant will be approximately 180 days; this consists of a concurrent screening and enrollment period, a treatment period of 96 hours, and a follow-up period up to Day 180.

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.

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

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).

2.3. 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%.

3. Definitions

3.1. Dates and Points of Reference

The first date of starting study drug infusion (BIIB093 3 mg/day, 5 mg/day or the matching placebo) is referred to as study Day 1. For all the dates in the study

- If a date is on or after study Day 1
  Study Day = (date of interest) – (study Day 1) + 1
- If a date is before study Day 1
  Study Day = (date of interest) – (study Day 1)

Study Hour 0 is defined as the start time of the study drug infusion. For all the times in the study before and during the study drug infusion

- Study Hour = (hour of interest) – (study Hour 0)

For efficacy data that are summarized or analyzed by visit, data collected on all scheduled visits and all unscheduled visits will be mapped to an appropriate analysis visit using the windowing scheme shown in Table 1. If there are 2 or more assessments available in the same analysis window for a subject, unless otherwise specified, the assessment that is closest to the target visit day/time will be used for analysis. If there are 2 or more assessments in the same analysis window with the same distance from the target visit day, the later assessment will be used.

Table 1. Visit Windows for Efficacy Endpoints

Volume Data		
Analysis visit	**Target timepoint in hr**	**Analysis visit window**
Screening	0	Most recent non-missing pre-dose value
Hour 24	24	[10, 38]
Hour 96	96	[76, 116]
GOS-E		
Analysis visit	**Target visit day**	**Analysis visit window**
Hospital discharge	7	(0, 23)
Day 30	30	[23, 60]
Day 90	90	(60, 135)

Day 180	180	>=135
mRS, [redacted]		
Analysis visit	**Target visit day**	**Analysis visit window**
Day 90	90	(45, 135)
Day 180	180	>=135
GCS		
Analysis visit	Target timepoint in hour	**Analysis visit window**
Screening	0	Most recent non-missing pre-dose value
Hour 24	24	(12, 36]
Hour 48	48	(36, 60]
Hour 96	96	(84, 120]

Study visits and associated visit windows for all remaining analyses are specified in Table 2, which are subject to change prior to the Day 4 administrative database lock. Study period in the table is defined in Section 3.3. Detailed protocol-specified schedule of activities and study visits in Table 2 of the protocol are attached in Appendix 1.

Table 2. Study periods, analysis visits and corresponding analysis visit windows.

Table 2: Study Period	Study Visit	Visit Number	Target Time	Visit Window
Pre-treatment	Pre-Treatment	1	0 h	< 0 h
On-treatment	Hour 0-12	2	12 h	0 - 12 h
	Hour 24	3	24 h	12 - 36 h
	Hour 48	4	48 h	36 - 60 h
	Hour 72	5	72 h	60 - 84 h
	Hour 96	6	96 h	84 - 120 h
	Hour 96 Ext	7	120 h	120 h – 72 h*
Follow-up	Day 30	8	30 d	> 72 h* – 60 d
	Day 90	9	90 d	60 – 150 d
	Day 180	10	180 d	150 – 210 d
	Day 180 Ext	11	270 d	> 210 d

h = hours, d = days. d* = days from the end of study drug infusion. The Hour 96 Ext visit window of each participant will end 72 hours after the end of study drug infusion, possibly including Day 7 or Discharge operation visits as defined in Table 2 of the protocol. The analysis visit window of Day 30 starts > 72 hours after the end of study drug infusion.

3.2. Study Treatment

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).

By-treatment-group analysis will be displayed as:

- Placebo
- BIIB093 3 mg/day

- BIIB093 5 mg/day
- BIIB093 combined
- Total, if applicable

The treatment groups are defined as follows.

3.2.1 Randomized Treatment Group

Randomized treatment refers to the treatment assigned to a participant at the initial randomization.

Accrual, study conduct, participant disposition, demographics, baseline disease characteristics, physical measurements, concomitant medications and non-drug therapies, efficacy and outcome research results will be analyzed and presented by randomized treatment group, unless otherwise specified.

3.2.2 Actual Treatment Group

Actual treatment refers to the actual study drug received by a participant.

- Randomized participants who are dosed but never receive any BIIB093 during study treatment administration will be assigned to placebo group.
- Randomized participants who receive any BIIB093 will be assigned to BIIB093 3 mg/day group, if the IV dose during bolus < 0.17 mg and the following IV infusion received by the participant < 11.31 mg for Infusion 1 and < 13.525 mg for Infusion 2; refer to Table 1 of the protocol.
- Randomized participants who receive any BIIB093 will be assigned to BIIB093 5 mg/day group, if the IV dose during bolus >= 0.17 mg or the following IV infusion received by the participant >= 11.31 mg for Infusion 1 or >= 13.525 mg for Infusion 2.
- Randomized participants who never receive any study drug (neither BIIB093 nor the matching placebo) will have missing actual treatment group and will be excluded in the analysis by actual treatment group.

Study results for safety (adverse events, serious adverse events, laboratory, vital signs, liver function test, electrocardiogram [ECG]), extent of exposure, [redacted] will be analyzed and presented by actual treatment group.

3.3. Study Periods

Pretreatment Period

The pretreatment period begins at the admission to hospital at the screening visit until start time of study drug infusion (Hour 0).

Measurements taken before the time of study drug infusion at Hour 0 are considered pretreatment for all data domains. If the time of measurement is missing, measurements taken on

Day 1 are considered pretreatment for the following data domains: demography, disease history, ECG, human genotyping, laboratory test results, medical history, physical examinations, participant status, and vital signs.

Baseline value is defined as the last non-missing value before the time of study drug infusion (Hour 0) or prior to or on Day 1 if the time of study drug infusion is missing.

On-Treatment Period

The on-treatment period begins at the time of study drug infusion (Hour 0) on Day 1 and ends 72 hours after the end of study drug infusion. The window of 72 hours is based on the half-life of study drug and allows the remaining study drug to clear from the participant's system.

Measurements taken after the time of the initiation of study drug infusion (Hour 0) on Day 1 through the end of study drug infusion plus 72 hours are considered on treatment for all data domains. In addition, if the time of measurement is missing, measurements taken on Day 1 are considered on-treatment for the following data domains: AEs, drug dispensation, exposure, non-study medications.

Follow-Up Period

The follow-up period begins at the end of study drug infusion plus > 72 hours and ends at the Day 180 visit or at the early termination (ET) visit, wherever applicable.

Measurements taken after the end of study drug infusion plus > 72 hours till the end of study for a participant are considered follow-up period for all data domains.

3.4. Key Derived Variables

Imaging data based on on-protocol images per the central review is described in Appendix 1. Imaging-based variables will be derived from the final read per image among on-protocol images (i.e., prior to NSx or CMO or early termination of study drug infusion) from the central review as follows for planned statistical analyses:

3.4.1. Change in Total Contusion Volume (hematoma plus perihematomal edema) from Baseline to 96 Hours

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. 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 central review, will be derived from available central reads, at baseline (before Hour 0) and closest to Hour 96. If multiple timepoints

are applicable, the read from the visit closer to Hour 96 will be used for analysis. If both MRI and NCCT have been carried out then the MRI read will be used.

3.4.2. Change in Total Contusion Volume (hematoma plus perihematomal edema) from Baseline to 24 Hours

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 central review, will be derived from available central reads, at baseline (before Hour 0) and closest to Hour 24. If multiple timepoints are applicable, the read closest to Hour 24 will be used for analysis.

3.4.3. Change in Absolute Hematoma Volume from Baseline to 24 Hours

Change in absolute hematoma volume from baseline to 24 hours will be derived from available central reads, at baseline (before Hour 0) and closest to Hour 24. If multiple timepoints are applicable, the read closest to Hour 24 will be used for analysis.

3.4.4. Change in Absolute Edema Volume from Baseline to 96 Hours

Change in absolute edema volume from baseline to 96 hours will be based on the edema volume measurements from the same follow-up visit for evaluating the total contusion volume.

[redacted]

3.5. Stratification Factors and Subgroup Variables

3.5.1. Stratification Factors

The randomization will be stratified by the follow risk factors:

- Baseline contusion volume per investigator assessment of NCCT scan or site local radiologic assessment
  - > 3 to 10 mL
  - > 10 mL
- Baseline Glasgow Coma Scale (GCS)
  - 5 to 8
  - 9 to 12
  - 13 to 15
- Age
  - ≤ 70 years old
  - > 70 years old
- Region
  - North America (United States)

- Rest of World (RoW)

3.5.2. Subgroup Variables

Subgroup variables will include stratification factors per IRT as described in Section 3.5.1 and following subgroup variables per Case Report Forms (CRFs):

- Age category at screening (≤ 70; > 70 years)
- Sex (Female; Male)
- Race category (White; Non-White)
- Ethnicity (Hispanic/Latino; Not Hispanic/Latino)
- Baseline brain contusion volume per investigator (≤ 10; >10 mL)
- Baseline brain contusion volume per the central review (≤ 10; >10 mL)
- Baseline hematoma volume per central review (≤ median; > median)
- Baseline edema volume per central review (≤ median; > median)
- Baseline Glasgow Coma Scale (GCS: 5 to 8; 9 to 12; 13 to 15)
- Baseline blood glucose (≤ median; > median)
- Baseline alcohol level (≤ median; > median)
- Baseline sodium (≤ median; > median)

By median in the above subgroup definitions is referred to the median of available measures of the variable in all treatment groups combined.

3.6. Analysis Sets

The analysis sets include the full analysis set (the modified intention-to-treat participants), per-protocol analysis set, and the safety analysis set. All participants who have signed the informed consent form will be used for the enrollment summary. All randomized participants following the intention-to-treat principle will be used for time-to-event analysis (including the participants who are randomized but do not receive any study drug).

3.6.1. Full Analysis Set

The full analysis set, i.e., the modified intention-to-treat (mITT) participants, will include all the participants who are randomized, receive any study drug (BIIB093 3 mg/day, BIIB093 5 mg/day or the matching placebo), and have at least one final read per central review of contusion volume from an NCCT or MRI scan acquired between 10 hours after the initiation of study drug infusion and the Hour 96 visit or NSx or CMO (if earlier). In efficacy analyses performed on the full analysis set (mITT participants), participants will be analyzed according to the randomized treatment group (see Section 3.2.1 for the definition).

3.6.2. Per-Protocol Analysis Set

The per-protocol analysis set will include mITT participants who have no protocol violations described below. In analyses performed on the per-protocol analysis set, participants will be analyzed according to actual treatment group (see Section 3.2.2 for the definition). The detailed

definitions of protocol deviations, listed below, will be determined and documented prior to the Day 4 administrative database lock.

- Violation of eligibility criteria
  - Time to infusion post injury/last known normal (LKN) is more than 10 hours
  - Baseline contusion volume per investigator is ≤ 3 mL or missing
  - Baseline GCS is outside the range of 5-15
- Early discontinuation of treatment
  - Infusion is discontinued within 12 hours from the initiation of study drug infusion

3.6.3. Safety Analysis Set

The safety analysis of treated participants will include all randomized participants who received any infusion of study drug (BIIB093 3 mg/day, BIIB093 5 mg/day or the matching placebo). In analyses performed on the safety analysis set, participants will be analyzed according to their actual treatment groups (see Section 3.2.2 for the definition), unless otherwise specified.

[redacted]

4. List of Planned Study Analyses

4.1. Interim Analysis

An interim analysis will be performed by an internal, independent, unblinded team when approximately 90 subjects are dosed and completed Hour 96 visit or terminated early, for administration purposes. The interim analysis will include all subjects who are in the mITT or safety population as described in the SAP. The interim analysis will include the following analyses:

- Demographic and baseline
- Exposure

- Efficacy – to include:
  - Change in total contusion volume at hours 24 and 96
  - GOS-E at hospital discharge, Day 30, Day 90 and Day 180
  - Change in hematoma volume at hours 24
  - Change in edema volume at hours 96
  - Change in total contusion volume by GOS-E by visit
- Safety – to include:
  - AEs/SAEs
  - Hypoglycemia
  - Laboratory
  - ECG

4.2. Primary Analysis

The primary analysis will be performed after the Day 4 (Hour 96) administrative database lock when the last participant completes their study drug infusion at the Hour 96 visit. The primary analysis is used to formally evaluate the treatment effect of BIIB093 on imaging-based endpoints as well as the on-treatment safety compared with the matching placebo. It will include the analyses of primary endpoint (change in total contusion volume as defined in Section 3.4.1) and other imaging-based endpoints, and on-treatment safety data summaries. The primary efficacy and safety analyses will be performed on the full analysis set and the safety analysis set, respectively, as defined in Section 3.6, unless otherwise specified in Section 5.

4.3. Final Analysis

The final analysis will be performed after the Day 180 final database lock. The final analysis is to formally evaluate the treatment effect of BIIB093 on functional and survival endpoints compared with the matching placebo. It will include all the secondary [redacted] endpoints not analyzed in the primary analysis, including functional, patient survival, neurocognitive, and patient-reported [redacted], as well as treatment requirement and [redacted] The efficacy and safety analyses will be performed on the full analysis set and the safety analysis set, respectively, unless otherwise specified.

4.4. Independent Data Monitoring Committee

An independent data monitoring committee (IDMC) is established to assess the overall safety profile of BIIB093 during the study. The IDMC charter guides the overall governance plan for the IDMC. IDMC may recommend the Sponsor to terminate the study based on safety data. The IDMC will review the data every 3-5 months.

5. Statistical Methods for Planned Analyses

5.1. General Principles

Descriptive statistics will be provided for all efficacy endpoints. For continuous or numerical endpoints (change in volume, [redacted], GOS-E, etc.), number of participants with non-missing measures, mean, standard deviation (SD), median, quartiles (the 25th percentile or Q1, and the 75th percentile or Q3), and range (min, max) will be summarized. For categorical (nominal and ordinal) endpoints (GOS-E, mRS, etc.), number of participants with non-missing measures, number and percentage (%) of participants in each category of the endpoints will be summarized.

Treatment comparisons for the primary and secondary efficacy endpoints will be evaluated using 2-sided tests at the 0.05 level of significance. Point estimates of the treatment effect and 95% 2-sided confidence intervals (CIs) will be presented. The calculation of type I error will not adjust for multiple comparisons unless otherwise specified.

If more than 10% of data is missing for any baseline covariate, that covariate will not be used in the modeling described below.

All imaging efficacy endpoints including the primary endpoint will be evaluated by randomized treatment group using the full analysis set (the mITT participants; see Section 3.6), unless otherwise specified. The analyses performed on the full analysis set will be considered as the main analyses [ICH E9 (R1) Addendum, 2020].

The primary and secondary efficacy endpoints will also be analyzed based on the per-protocol analysis set as supplementary analyses. [redacted] The final model for each main analysis for the full analysis set will be used for the corresponding per-protocol analysis.

Subgroup analysis will be performed for primary and secondary efficacy endpoints and will present a point estimate of the treatment effect and 95% 2-sided CIs from unadjusted analyses, i.e., without including stratification factors or other covariates in the model other than the treatment group. These analyses will be performed on the full analysis set only. If the number of participants in a subgroup is too small (e.g. < 10% of mITT participants), the analysis in that subgroup may not be performed.

The software used for this analysis plan is SAS Studio.

5.1.1. Handling of Missing Date/time in Concomitant Medications

Missing start and/or stop date/time will be handled as follows for defining concomitant use of therapies. If study treatment start date/time is not available, the date/time of randomization will be used.

- If both start and stop date/time of a therapy are missing, that therapy is considered concomitant.

- If the start date/time of a therapy is missing and the stop date/time of that therapy falls on or after the date/time of the study treatment start date/time, that therapy is considered concomitant.
- If the start date/time of a therapy is prior to the date/time of the study treatment start date/time and the stop date/time of that therapy is missing and the therapy is listed as continuing, that therapy is considered concomitant.
- If the start date/time of a therapy is prior to the date/time of the study treatment start date/time and the stop date/time of that therapy is missing and the therapy is listed as not continuing, that therapy is considered not concomitant.

5.1.2. Handling of Missing Date/Time in Adverse Events

Missing start/stop date/time will be handled as follows for defining treatment-emergent events. If study treatment start date/time is not available, the date/time of randomization will be used.

- If both the start and stop dates/time for an event are missing, then that event is considered treatment-emergent.
- If the start date/time for an event is missing and the stop date/time fall after the start date/time of the study treatment, then that event is considered treatment-emergent.
- If the start date was the same as the start date of the study treatment and the start time was missing, and the stop date/time is after the date/time of the study treatment or cannot be compared with the date/time of study treatment, then that event is considered treatment-emergent.

5.1.3. Handling of Partial Date/Time in Concomitant Medications and Adverse Events

For a therapy or an adverse event with a partial start and/or end date/time, the year/month/day of the therapy start and/or end will be compared to those of the first dosing date/time of the study treatment to determine the imputation rules. If a participant is not dosed, the date/time of randomization will be used.

The last date/time on study will be taken as the last visit/evaluation date/time from all available data for the participant. If a participant died during the study, the last date/time on study will be the date/time of death.

- For the start date/time of AEs or concomitant medications,
    - If only time is missing, and that the AE/concomitant medication starts on the same day as the treatment (or randomization if the participant is not dosed), then impute missing time using the treatment start time (study Hour 0); otherwise use the first (01) hour of that day as the hour.
    - If only day is missing, and that the AE/concomitant medication starts in the same month as the treatment (or randomization if the participant is not dosed), then impute missing day using the treatment start date (study Day 1); otherwise use the first (01) day of that month as the day.

- If both day and month are missing, and that the AE/concomitant mediation starts in the same year as the treatment (or randomization), then impute missing day and month using the treatment start date (Study Day 1); otherwise, use January 01 (01JAN) as the day and month.
- If the date/time for AE/concomitant medication is completely missing (no day, month or year), the start date/time of the study treatment will be used.

- For the stop date/time of AEs or concomitant medications,
  - If only time is missing, and that the AE/concomitant medication stops on the same day as the treatment, then impute missing time using the treatment end time; otherwise use the last (23) hour of that day as the hour.
  - If only day is missing, and that the AE/ concomitant medication stops in the same month as the treatment, then impute missing day using the treatment end date; otherwise use the last day of that month as the day.
  - If both day and month are missing, and that the AE/concomitant mediation stops in the same year as the treatment, then impute missing day and month using the treatment end date; otherwise, use December 31 (31DEC) as the day and month.
  - If the stop date is completely missing (no day, month or year), the study end date/time will be used.

5.1.4. Missing Values for GOS-E

GOS-E at [redacted] 180 will be analyzed as a 7-category ordinal scale (1/2, 3, 4, 5, 6, 7, 8). Multiple imputation will be used to account for missing values for GOS-E. Death and vegetative state are scored as 1 and 2 in GOS-E and therefore no missing GOS-E values are expected due to death or vegetative state. Missing GOS-E values due to reasons other than death or vegetative state will be imputed based on a linear model performed on the GOS-E scores leveraging the information of the patient at other time points as well as the time patterns of all other participants. The model will include treatment as a classification variable and other covariates: GOS-E score at the previous timepoint, region (North America and RoW), age (≤ 70, > 70 years), baseline GCS (5-8, 9-12, 13-15), baseline contusion volume per investigator ($>$ 3 to 10 mL vs >10 mL). Imputed values will be rounded to the closest valid GOS-E score, 100 imputations will be conducted with random seed pre-specified, and each imputation will result in a complete dataset for all mITT participants.

The missing data pattern will be evaluated including reasons for missingness, missing data by randomized treatment group and visit, and potential covariates associated with missingness. Sensitivity analyses will be planned to evaluate the robustness of the results from the main analysis of GOS-E.

5.1.5. Missing Values for mRS

The mRS [redacted] at Day 180 will be analyzed as a 5-category ordinal scale (0/1, 2, 3, 4, 5/6). No multiple imputation will be used to account for missing values for mRS.

5.2. Participant Accountability

The summaries in the end of treatment status section will be based on all randomized participants. Participant end-of-treatment status will be summarized in total and by randomized treatment group. The summary statistics include:

- Number (%) of participants randomized and dosed.
- Number (%) of participants who complete the treatment.
- Number (%) of participants who discontinue the treatment, and reason(s) for not completing the treatment will be summarized.

A participant listing of reasons for treatment discontinuation will be provided for all enrolled participants.

The summaries in the end of study status section will be based on the follow-up set. Participants end-of-study status will be summarized in total and by randomized treatment group. The summary statistics include:

- Number (%) of participants who enter 90-day (180-day) follow-up and have at least one assessment after the Day 90 visit.
- Number (%) of participants who complete the study.
- Number (%) of participants who withdraw from the study, and reason(s) for not completing the study.

A participant listing of reasons for study withdrawal will be provided for all enrolled participants.

5.3. Demographic and Baseline Characteristics

Demographic and baseline characteristics will be summarized by randomized treatment group for mITT and all randomized participants, respectively, unless specified otherwise. For continuous or numerical variables, the summary statistics will include number (%) of participants with non-missing measurements, mean, standard deviation (SD), median, quartiles (Q1, Q3), and range (min, max). For categorical (nominal or ordinal) variables, summary statistics include number (%) of participants in corresponding analysis population and number (%) of participants in each level of the categorical variable. The number (%) of participants with missing measurements will be provided for both continuous and categorical variables, if applicable.

5.3.1. Demographics per CRFs

- Age (years) at screening
- Age category at screening (≤ 60, 60 to 70, > 70 years)
- Sex (female, male, other)
- Race (White, African-American, Asian, Other)

- Ethnicity (Hispanic, Non-Hispanic)
- Geographic region (North America, RoW)

5.3.2. Baseline Disease Characteristics per CRFs

- Time (hours) to randomization post injury or LKN
- Time (hours) to initiation of study drug infusion post injury or LKN
- Time (hours) to NCCT for eligibility post injury or LKN
- Time (hours) to initiation of study drug infusion from NCCT for eligibility
- Injury types
- Baseline GCS before randomization
- Total injury severity scoring (ISS) score excluding head or face
- Baseline brain contusion volume (mL) per investigator
- Baseline brain contusion volume (mL) per the central review
- Baseline hematoma volume (mL) per the central review
- Baseline edema volume (mL) per the central review
- Baseline blood glucose
- Baseline alcohol level
- Baseline sodium

5.3.3. Stratification Factors per IRT

- Baseline contusion volume per investigator
  - > 3 to 10 mL
  - > 10 mL
- Baseline Glasgow Coma Scale (GCS)
  - 5 to 8
  - 9 to 12
  - 13 to 15
- Baseline age
  - ≤ 70 years old
  - > 70 years old
- Region
  - North America (United States and Canada)
  - Rest of World (RoW)
- Concordance rate of stratification factors per IRT and per CRFs by strata and overall

5.3.4. Physical Measurements at Baseline

The physical measurements will be captured for the participants during hospitalization.

- Height (cm)
- Weight (kg)
- Body mass index (BMI; kg/m^2)

5.3.5. Medical History

Medical history (medical condition or surgical procedure) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA), if applicable.

- The number (%) of participants with medical history (including ongoing and stopped conditions) will be summarized.
- A participant listing of medical history will be provided.

5.4. Protocol Deviations

Protocol deviations identified during site monitoring will be captured in the Protocol Deviation Log and categorized as major or minor deviations.

- Number (%) of participants with any major protocol deviations will be summarized by randomized treatment group for mITT participants.
- A listing of major and minor protocol deviations for all randomized participants will be provided.

5.5. Study Treatment Exposure and Concomitant Medications

5.5.1. Study Treatment Exposure

The extent of study treatment exposure will be summarized by actual treatment group for the safety analysis set in the Day 4 database. The total amount (mg) of study drug received via infusion is calculated from the infusion rate with start and stop date/time and volume administered (bolus and re-bolus only). The duration of study drug administration (hours) is calculated from the first bolus date/time to the last infusion date/time. The duration of study drug infusion (hours) is calculated from start/stop date/time of each bolus or infusion (the duration of study drug administration minus the dose interruption intervals).

- Total amount of study drug will be summarized by treatment group.
- Duration of study drug administration will be summarized by treatment group.
- Duration of study drug infusion will be summarized by treatment group.
- Number (%) of participants with any infusion interruptions and reason for the first interruption for a participant will be summarized by treatment group.
- Number (%) of participants with any rate changes and reason for the first change for a participant will be summarized by treatment group.
- Listing of reasons for interruption, rate change and dose reduction will be provided.
- Listing of kit numbers will be provided.

5.5.2. Concomitant Medications

All concomitant medications will be coded using the World Health Organization (WHO) medication dictionary.

- Number (%) of participants taking any concomitant medications will be summarized by randomized treatment group and total and by indication for mITT participants.
- A listing of concomitant medications for randomized participants will be presented.

5.5.3. Non-drug Therapies

A concomitant therapy (including medication or non-drug therapy) is defined as any therapy that is taken on or after the start date/time of study drug infusion. This includes therapies that are started prior to start of study drug infusion if their use continues after study drug infusion. If a participant never receives study drug, date of randomization will be used, if applicable. Handling of partial or missing start/stop date/time is described in Section 5.1. Concomitant non-drug therapies will be coded using MedDRA.

The following non-drug therapies will be summarized by randomized treatment group and total and by indication for mITT participants:

- Number (%) of participants taking any non-drug therapies.
- Number (%) of participants requiring NSx including craniotomy and DC, time and the reasons of DC.
- Number (%) of participants with decision of CMO, time and reasons of CMO.
- Number (%) of participants requiring delayed intubation, time and reasons of delayed intubation.

A listing of non-drug therapies for randomized participants will be provided.

5.6. Efficacy Endpoints

All efficacy endpoints will be analyzed by randomized treatment group for all mITT participants in the full analysis set, unless otherwise specified.

5.6.1. General Analysis Methods for Efficacy Endpoints

All endpoint models (binary logistic regression, ordinal logistic regression, Cox model, and analysis of covariance) below will regress the outcome on the randomized treatment group, comparing the BIIB093 combined with placebo groups, adjusting for all the IRT stratification factors at randomization (see Section 3.5.1), baseline contusion volume per the central review and baseline GCS.

Analysis of covariance (ANCOVA) will be performed to compare the change in total contusion volume (primary analysis), change in absolute hematoma volume, the change in absolute edema volume, [redacted] from baseline in the main analysis comparing the BIIB093 combined with placebo groups. The least square (LS) mean difference with the corresponding 2-sided 95% CI and p-values for the treatment group will be provided.

Binary logistic regression will be used for binary outcomes comparing the BIIB093 combined with placebo groups. Odds ratio, the corresponding 2-sided 95% confidence interval (CI) and p-value will be reported for the treatment group.

Ordinal logistic regression (proportional odds model) will be used for GOS-E as a 7-category ordinal scale (1/2, 3, 4, 5, 6, 7, 8) and for mRS as a 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90 and 180. Odds ratio, the corresponding 2-sided 95% CI and p-value for the treatment group will be reported.

The proportional odds ratio assumption will be tested using likelihood ratio test based on observed data. In the case the assumption does not hold (p-value < 0.05) or non-convergence, the Mann-Whitney test will be used as the primary inference and the source of non-proportionality or non-convergence will be investigated. Following the Mann-Whitney test, dichotomized analysis will be conducted to assess the treatment effects.

The Cox proportional hazard model will be used to assess the treatment effect on overall survival at Day 90 for all randomized participants. Hazard ratio, 2-sided 95% CI as well as the p-value for the treatment group will be reported. Kaplan-Meier curves will be presented by randomized treatment group, and Greenwood's formula will be used to calculate the standard error of the Kaplan-Meier estimates.

Multiplicity will be not be adjusted for the tests of the primary and secondary endpoints, since the current study sample size is not powered for a moderate treatment effect on GOS-E.

To explore the exposure-response relation of different BIIB093 doses, similar efficacy endpoint models will be used for analyzing the two active dose arms separately (BIIB093 3 mg/day vs. BIIB093 5 mg/day vs. placebo). The results of the exposure-response analysis will report point estimate of the treatment effect (odds ratio, hazard ratio, or least-square mean difference) and the corresponding 2-sided 95% CIs. No p-values for the exposure-response analysis will be reported.

Table 3: Main Analyses for Efficacy Endpoints

Endpoints	**Analysis method**	**Analysis Population**	**SAP Section**
Primary endpoint			
Change in total contusion volume 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	Analysis of Variance (ANCOVA)	mITT per-protocol	5.6.2

Secondary endpoints			
GOS-E at Day 180	Ordinal logistic regression with multiple imputation	mITT per-protocol	5.6.3
mRS as 5-category ordinal scale (0/1, 2, 3, 4, 5/6) at Day 90	Ordinal logistic regression	mITT per-protocol	5.6.3
mRS as 2-category ordinal scal (0-2 vs 3-6) at Day 90	Binary logistic regression	mITT per-protocol	5.6.3
Proportion of participants requiring delayed intubation	Binary logistic regression	mITT per-protocol	5.6.3
Change in total contusion volume from baseline to 24 hours or prior to DC, IPH evacuation or CMO if these procedures occur before 24 hours per the central review	Analysis of Variance (ANCOVA)	mITT per-protocol	5.6.3
Change in absolute hematoma volume from baseline to 24 hours	Analysis of Variance (ANCOVA)	mITT per-protocol	5.6.3
Change in absolute edema volume from baseline to 96 hours	Analysis of Variance (ANCOVA)	mITT per-protocol	5.6.3
Time to all-cause death through day 90	Cox proportional hazards regression model	mITT per-protocol	5.6.3

5.6.2. Primary Efficacy Endpoint

Primary endpoint is the change in total contusion volume (hematoma plus perihematomal edema) as measure 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 definition of main estimand follows a white-on-treatment strategy [ICH E9 (R1) Addendum, 2020], i.e., all the central reads between 12 hours after the initiation of study drug infusion and Hour 96 or prior to DC, IPH evacuation or CMO if these procedures occur before 96 hours will be used; see details in Section 3.4.1.

Main Analysis

The analysis of the primary endpoint will consist in testing the null hypothesis H0: $p1 = p2$ versus the alternative hypothesis H1: $p1 \neq p2$, where p1 is the change from baseline of total contusion volume in the placebo group and p2 that in the BIIB093 combined group according to the randomized treatment group for the full analysis set.

- The hypothesis will be tested using ANCOVA, adjusted for covariates specified in Section 5.6.1, at a 2-sided significance level of 0.05 with the Day 4 database.
- The estimated of least squared mean difference for treatment group, the corresponding 95% confidence interval and the p-value will be reported.
- In case that the ANCOVA does not converge numerically due to perfect separation of the responses by some stratification factor, the stratification factor that causes it will be excluded from the model.

Sensitivity Analysis and Supplementary Analysis

- A supplementary analysis on the primary endpoint will be performed on the mITT population and excluding all DC, IPH evacuation or CMO.
- A sensitivity analysis on the primary endpoint will be performed on the PP population.
- A sensitivity analysis on the primary endpoint will be performed on the mITT population using the eCRF data as covariates rather than IRT stratification data.

5.6.3. Secondary Efficacy Endpoints

GOS-E at Day 180

GOS-E will be assessed as a 7-category ordinal scale (1/2, 3, 4, 5, 6, 7, 8) at discharge, Day 30, Day 90, and Day 180.

- GOS-E at Day 180 will be analyzed by randomized treatment based on observed data for the full analysis set using ordinal logistic regression adjusting for covariates specified in Section 5.6.1.

- Dichotomized GOS-E (0-4 versus 5-8) at Day 180 will be analyzed using binary logistic regression adjusting for covariates specified in Section 5.6.1.
- Multiple imputation for missing GOS-E values at Day 180 will be conducted as specified in Section 5.1. The analysis results from imputed datasets will be combined for inference using Rubin's rule.
- Descriptive statistics for GOS-E scores will be summarized by visit (see Section 5.1).

mRS at Day 90

mRS will be assessed at Day 90 and Day 180 as a 5-category ordinal scale (0/1, 2, 3, 4, 5/6).

- mRS at Day 90 will be analyzed in the final database for the full analysis set using ordinal logistic regression based on observed data adjusting for covariates specified in Section 5.6.1.
- Dichotomized mRS (0-2 versus 3-6) at Day 90 will be analyzed using binary logistic regression adjusting for covariates specified in Section 5.6.1.

Proportion of Participants Requiring Delayed Intubation

Proportion of participants who required delayed intubation for neurologic deterioration at any time between 24 hours and 96 hours postinjury or LKN will be analyzed for the full analysis set in the Day 4 database.

- The proportion of participants requiring delayed intubation will be analyzed using binary logistic regression adjusting for covariates specified in Section 5.6.1.

Change in Total Contusion Volume from Baseline to 24 Hours

Change in total contusion volume from baseline to 24 hours or prior to DC, IPH evacuation or CMO if these procedures occur before 24 hours per central review will be analyzed in the Day 4 database for the full analysis set.

- ANCOVA will be performed to compare the mean change between BIIB093 combined and placebo groups based on the observed data.
- By-visit mean and change in total contusion volume from baseline will be summarized.

Change in Absolute Hematoma Volume from Baseline to 24 Hours

Change in absolute hematoma volume from baseline to 24 hours will be analyzed in the Day 4 database for the full analysis set.

- ANCOVA will be performed to compare the mean change between BIIB093 combined and placebo groups based on the observed data.
- By-visit mean and change in absolute hematoma volume from baseline will be summarized.

Change in Absolute Edema Volume from Baseline to 96 Hours

Change in absolute edema volume from baseline to 96 hours will be analyzed in the Day 4 database.

- ANCOVA will be performed to compare the mean change between BIIB093 combined and placebo groups based on the observed data.
- By-visit mean and change in absolute edema volume from baseline will be summarized.

Time to All-cause Death, Including Neurological Death, through Day 90

Survival time in days through Day 90 is defined as the time from randomization to death, including all-cause death and neurological death. For a participant who discontinues and is not known to have died during the study, survival time will be censored at the time when the participant is last known to be alive of the study. Survival time will be analyzed in the Day 90 database for all randomized participants.

- Survival time will be analyzed using Cox proportional hazards regression models of overall survival after adjusting for covariates specified in Section 5.6.1.
- Kaplan Meier curves of survival will be presented for BIIB093 3mg/day, BIIB093 5 mg/day, BIIB093 combined and placebo groups.

[redacted]

[redacted]

5.7. Safety [redacted]

Adverse events (AEs) will be collected throughout the study and coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse events will be summarized based on the principle of treatment emergence.

A treatment-emergent adverse event is defined as 1) any adverse event that has onset on or after start of study drug infusion, or 2) any pre-existing condition that has worsened after start of study drug infusion. On-treatment events are treatment-emergent events that occurred within 3 days after end of study drug infusion. Similarly, on-treatment laboratory data are those from the samples taken from start of study drug infusion to 3 days after the end of study drug infusion. Handling of missing or partial date/time for adverse events and laboratory data is described in Section 5.1.

5.7.1 Adverse Events

The incidence of treatment-emergent adverse events will be summarized by actual treatment group and for the safety analysis set overall, by severity, and by relationship to study treatment.

For the analysis of AE incidence by severity, the occurrence of the AE with the greatest severity will be used, and a participant will be counted only once and only in the category of the greatest severity for each event.

For the analysis of AE incidence by relationship to study treatment, the occurrence of the AE with the strongest relationship to study treatment will be used and a participant is counted only once and only in the category of the strongest relationship to study treatment for each event.

AEs during on-treatment period will be provided for the safety analysis set of the Day 4 database and summarized for CSR in the Day 180 database.

- AEs during on-treatment period will be summarized by actual treatment group and
  - by system organ class (SOC) and preferred term (PT).
  - with ≥ 5% higher in incidence for BIIB093 combined compared to placebo by SOC and PT.
  - with ≥ 5% higher in incidence for BIIB093 combined or placebo by SOC and PT.
  - with ≥ 5% in incidence for BIIB093 combined or placebo by PT.
- Related AEs (see Section 15.2.2 of the protocol) during on-treatment period by SOC and PT will be summarized by treatment group.
- AEs and related adverse event during on-treatment period by maximum severity, SOC and PT will be summarized by actual treatment group, respectively.
- Serious adverse events (SAEs) and related SAEs during on-treatment period by SOC and PT will be summarized by actual treatment group, respectively.
- AEs leading to the following events by maximum severity, SOC and PT will be summarized by actual treatment group, respectively.
  - AEs leading to early termination of study drug infusion.
  - AEs leading to infusion interruption.

- AEs leading to infusion rate change.
- AEs leading to infusion dose reduction.

AEs during the study will be summarized for the safety analysis set when applicable:

- AEs and related AEs during the study by SOC and PT will be summarized by actual treatment group, respectively.
- AEs and related AEs during the study by maximum severity, SOC and PT will be summarized by actual treatment group, respectively.
- SAEs and related SAEs during the study SOC and PT will be summarized by actual treatment group, respectively.
- AEs leading to withdrawal from study by maximum severity, SOC and PT will be summarized by actual treatment group, respectively.

The following listings will be provided, when applicable:

- Listing of AEs during the study.
- Listing of SAEs during the study.
- Listing of AEs leading to early termination of study drug infusion.
- Listing of AEs leading to infusion interruption.
- Listing of AEs leading to rate change and dose reduction.
- Listing of AEs leading to withdrawal from study.

5.7.2 Adverse Events of Special Interest (AESI)

The adverse event of special interest (AESI) categories may include but are not limited to hypoglycemia (BG < 55 mg/dl).

- AESI during on-treatment and during the study will be summarized by actual treatment group for the safety analysis set, respectively.

In addition, the following listings will be provided:

- Listing of adverse events of special interest during the study.
- Listing of hypoglycemia events during the study.
- Listing of adverse events for participants with any hypoglycemia events.

5.7.3 Death

All-cause deaths and deaths by the neurological criteria will be summarized for all randomized participants.

- Number (%) of deaths during on-treatment will be summarized by actual treatment group.
- Number (%) of deaths before Discharge, Day 30, Day 90 and Day 180 will be summarized by actual treatment group.

- Listing of deaths during the study will be provided, including timing of the death relative to study treatment and the investigator assessment of the cause of death.

5.7.4 Clinical Laboratory Results

Clinical laboratory evaluations include hematology and blood chemistry will be summarized by actual treatment group for the safety analysis set.

Hematology, including but not limited to the following parameters:

- White blood cells (leukocytes)
- Absolute neutrophil counts
- Red blood cells
- Hemoglobin
- Hematocrit
- Platelet count

Blood chemistry, including but not limited to the following parameters:

- Liver: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP), total bilirubin, and direct bilirubin
- Renal: blood urea nitrogen (BUN) and creatinine
- Electrolytes: sodium, potassium, and bicarbonate
- Other: glucose, calcium, phosphorus and albumin

Shift Analyses

Laboratory abnormalities will be summarized with shift tables. Tables will present changes relative to each parameter's normal ranges. Each participant's hematology and blood chemistry values will be flagged as "low", "normal", or "high" relative to the normal ranges of the local laboratory or as "unknown" if no result is available.

Shifts from baseline to high/low status for hematology and blood chemistry parameters will be presented. In each summary, the denominator for the percentage is the number of participants at risk for the shift. The number at risk for shift to low is the number of participants whose baseline value was not low and who had at least one post-baseline value. The number at risk for shift to high is the number of participants whose baseline value was not high and who had at least one post-baseline value. Participants will be counted only once for each parameter and each type of shift regardless of how many post-dosing assessments had that type of shift. Participants with shift to low or high will be listed by laboratory parameter and shift type.

Potentially Clinically Significant Laboratory Abnormalities Analyses

For hematology and blood chemistry, the number of participants with potentially clinically significant laboratory abnormalities post-baseline will be summarized for the parameters provided in Table 4. Participants need to have at least one post-baseline evaluation and a baseline

value not potentially clinically significant (including missing) in order to be included in the analysis.

Table 4. Criteria to Potentially Clinically Significant (PCS) Laboratory Abnormalities

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
HEMATOLOGY		
White blood cells	$< 3.0 \times 10^9$/L	$> 16 \times 10^9$/L
Neutrophils	$< 1.5 \times 10^9$/L	$> 13.5 \times 10^9$/L
Red blood cells	$\leq 3.5 \times 10^{12}$/L	$\geq 6.4 \times 10^{12}$/L
Hemoglobin - Females	≤ 95 g/L	≥ 175 g/L
Hemoglobin - Males	≤ 115 g/L	≥ 190 g/L
Hematocrit - Females	$\leq 32\%$	$\geq 54\%$
Hematocrit - Males	$\leq 37\%$	$\geq 60\%$
Platelet count	$\leq 75 \times 10^9$/L	$\geq 700 \times 10^9$/L
BLOOD CHEMISTRY		
Alanine aminotransferase (ALT)	N/A	$> 3 \times$ ULN
Aspartate aminotransferase (AST)	N/A	$> 3 \times$ ULN
Alkaline phosphatase (ALP)	N/A	$> 3 \times$ ULN
Total bilirubin	N/A	$> 1.5 \times$ ULN
Blood urea nitrogen (BUN)	N/A	≥ 10.7 mmol/L
Creatinine	N/A	≥ 176.8 µmol/L
Sodium	≤ 126 mmol/L	≥ 156 mmol/L
Potassium	≤ 3 mmol/L	≥ 6 mmol/L
Bicarbonate	≤ 16 mmol/L	≥ 35 mmol/L
Glucose	≤ 2.2 mmol/L	≥ 9.7 mmol/L

Clinical Laboratory Outlier Criteria		
Parameter name	**PCS Low**	**PCS High**
Calcium	≤ 2 mmol/L	≥ 3 mmol/L
Phosphorus	≤ 0.6 mmol/L	≥ 1.7 mmol/L
Albumin	≤ 25 g/L	≥ 625 g/L
ULN = upper limit of normal		

By-visit Summaries

- For numerical laboratory parameters, actual values, change from baseline and percent change from baseline will be summarized by visit.
- Number of evaluable participants, mean, standard deviation, quartiles, min and max values will be presented at each visit.
- Plots of mean values (with standard error) for numeric laboratory parameters at each visit will be provided.
- Listings of individual laboratory measurements for all the parameters will be provided.

Analysis of Blood Glucose

The blood glucose from local laboratory are collected at screening, Hours 0-12, Hour 24, Hour 48, Hour 72, Hour 96 and Day 7 with the normal ranges. Additionally, the Point-of-Care (POC) blood glucose is collected pre-dose, hourly up to Hour 96 without normal ranges. The normal range for POC blood glucose data are assigned as between 70 mg/dL and 139 mg/dL, according to the reference range recommended by the American Diabetes Association for random blood glucose measurements. For all analyses, the two sources of data (local laboratory and POC) will be combined and analyzed together.

Summary of lowest post-baseline value of blood glucose will be provided. The number (%) of participants with post-baseline blood glucose abnormalities (<55 mg/dL, <80 mg/dL, <120 mg/dL) will be summarized by actual treatment group. Blood glucose values for participants with post-baseline blood glucose <55 mg/dL will be listed.

Analysis of Liver Function Tests

Potential serious hepatotoxicity is defined as alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >= 3 × upper limit of normal (ULN) and total bilirubin > 2 × ULN at any time post-baseline, not necessarily concurrent (i.e., on the same day).

A scatterplot of the maximum post-baseline ALT or AST value relative to ULN and maximum post-baseline total bilirubin value relative to ULN (not necessarily concurrent) for each

participant will be provided. A line plot of ALT, AST, alkaline phosphatase (ALP) and total bilirubin values over time for participants with potential serious hepatotoxicity will be provided.

In addition, the number (%) of participants meeting the laboratory abnormality criteria listed below will be summarized, respectively:

- ALT > 3 × ULN
- ALT > 5 × ULN
- AST > 3 × ULN
- AST > 5 × ULN
- AST or ALT > 3 × ULN
- AST or ALT > 5 × ULN
- Total Bilirubin > 2 × ULN
- ALP >1.5 × ULN
- AST or ALT > 3 × ULN and Total Bilirubin > 2 × ULN

Concurrent is defined as on the same day. A listing of participants with potential serious hepatotoxicity will be provided.

5.7.5 Electrocardiogram (ECG)

The number (%) of participants with shifts to categorical values (abnormal not AE, or abnormal AE) will be summarized by actual treatment group. ECG parameters include heart rate, PR Interval, RR Interval, QRS Duration, QT Interval, QTcF, and QTcB, where QTcB is calculated as $QT/(RR/1000)^{1/2}$. The actual values and change from baseline for each of the ECG parameters will be summarized by actual treatment group and by visit summary. If there are multiple records fall into the same visit windows, the worst record will be presented in the summary.

5.7.6 Vital Signs

Vital signs measures include oxygen saturation, heart rate (pulse), respiratory rate, temperature, and systolic and diastolic blood pressure. The analysis of vital signs will focus on the incidence of clinically relevant abnormalities for participants in safety analysis set. The abnormalities for temperature, heart rate, systolic blood pressure, and diastolic blood pressure are provided in Table 6 of the protocol.

- The number of participants evaluated and the number (%) of participants with clinically relevant post-baseline abnormalities will be presented by actual treatment group.
- Summary statistics for actual values and change from baseline will also be presented by actual treatment group.
- Participant listing of vital signs will be provided.

[redacted]

5.10. <Additional> Patient Reported Outcomes (PROs)

Not applicable

5.11. <e.g., Antigenicity/Immunogenicity> Endpoints

Not applicable

5.12. <Other Analyses>

Not applicable

5.13. Statistical Considerations for Interim Analysis

The interim analysis will not inform the continued blinded data collection in the study. There is no Type I error adjustment for 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.

6. Changes from Protocol-Specified Analyses

Not applicable for this version.

7. Summary of Changes from the Previous Version of the SAP

Not applicable for this version.

8. References

Machamer, J., Temkin, N. R., Manley, G. T., & Dikmen, S. (2018). Functional Status Examination in patients with moderate-to-severe traumatic brain injuries. *Journal of Neurotrauma*, 1132-1137.

Wilkes, S., McCormack, E., & Kenney, K. (2018). Evolution of Traumatic Parenchymal Intracranial Hematomas (ICHs): Comparison of Hematoma and Edema Components. *Front Neurol, 9*, 527.

APPENDICES

APPENDIX 1. IMAGING DATA PER THE CENTRAL REVIEW

On-Protocol Images for the Central Review

MR and NCCT images will be used to assess changes in brain contusion, hemorrhage and edema volume, [redacted]. Eligible participants will undergo NCCT at baseline and Hour 24 and MRI/NCCT at Hour 96.

- Screening NCCT will be the one closest to the randomization, which is assessed for eligibility with a brain contusion volume of > 3mL per investigator review and used for stratification at randomization
- All NCCT/MRI brain images collected by the imaging CRO up to the Hour 96 visit (or NSx or CMO, if earlier) will be considered on-protocol images and will be submitted for central review

Imaging Data per the Central Review

Key reading process and imaging data per the central review will be provided as follows:

- Image quality control (QC) personnel will review all received imaging data to ensure accuracy of labeling and appropriateness for reads of all on-protocol imaging
- Two independent neuroradiologist readers trained on the study will read each participant case once all on-protocol images are available. Initial reads (i.e., 2 records per image) will be locked and provided for all available time points
- Following completion of initial reading, a single final read per participant-time point is determined through averaging of the two independent reads or by reader consensus per procedure outlined in the brain MRI/NCCT worksheet (BMCW) Completion Guidelines version 2.0

[redacted]

APPENDIX 2. SCHEDULE OF ACTIVITIES

The schedule of activities is described in Section 5 of the protocol.

Table 3: 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

	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
Other assessments (ECG, [redacted])	(see Protocol Table 3 for ECG, [redacted] schedule of activities)												
Blood sampling for pharmacogenetics (optional)[10]		X											
Enrollment/randomization (TT/LKN < 10 h)	X												
Study treatment (TT/LKN < 10 h)		← 96-hour infusion → (see Protocol 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

	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
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.

[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 Protocol 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 Protocol 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.

Table 4: 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].

[redacted]

Signature Page

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