STATISTICAL ANALYSIS PLAN

BHR-100-301

A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Investigate the Efficacy and Safety of Progesterone in Patients with Severe Traumatic Brain Injury

Prepared for:

BHR Pharma, LLC

Version and Author details:

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SIGNATURES

The undersigned have approved this Statistical Analysis Plan for use in this study.

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TABLE OF CONTENTS

1 INTRODUCTION

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analysis of data collected under BHR Pharma Protocol BHR-100-301.

This SAP should be read in conjunction with the study protocol and electronic case report form (eCRF). This version of the plan has been developed using the protocol Amendment 3.0 dated November 15, 2011 and eCRF dated September 24, 2012. Changes to the SAP based on protocol and/or eCRF revisions are reflected in this final verion. This version is approved prior to unblinding and analysis of the global trial

The SAP has been developed in two stages. This amendment, SAP version 2.0, is is the final version prior to the global study database lock. Versions of the SAP up to initial sponsor approval were known as SAP1. PRA and the Sponsor (BHR Pharma) have agreed on the changes from version 1.0 to enable the final programming for the Clinical Study Report (CSR) and a potential New Drug Application (NDA). This final version of the SAP, version 2.0, has been approved by PRA and the sponsor prior to database lock.

1.1 Changes from the protocol

- The protocol states that the primary efficacy analysis will be conducted on all randomized subjects. BHR was advised by the Data and Safety Monitoring Board and the Steering Committee to redefine the intent-to-treat (ITT) population as all randomized subjects who received any amount of study drug treatment. This modified intent-to-treat (mITT) analysis was approved by the FDA in its Special Protocol Assessment Agreement Modification Letter dated April 4, 2013. This version of the SAP defines the mITT population, which will be used for all efficacy analyses.
- The protocol states that the Extended Glasgow Outcome Scale (GOS-E) will be analyzed using the 2-sided Wilcoxon Rank-Sum test. This version of the SAP states that the GOS-E will be analyzed similarly to the GOS, using a proportional odds model (POM) and sliding dichotomy (SD).

2 STUDY OBJECTIVES

The aim of this study is to determine the efficacy and safety of BHR-100 (intravenous (i.v.) progesterone lipid emulsion) compared to placebo infusion in the treatment of subjects with severe traumatic brain injury (TBI).

3 STUDY DESIGN

This trial is a multicenter, randomized, double-blind, placebo-controlled study, conducted in approximately 140 Level I (or equivalent) trauma centers in a number of geographical areas including North America, Europe, Asia and South America, to compare the efficacy and safety of i.v. BHR-100 with placebo in the treatment of subjects following severe TBI. Severe TBI is defined as a Glasgow Coma Scale (GCS) score at randomization of 3-8 (inclusive). During their involvement in the study, subjects will be managed in accordance with standard guidelines for

the management of severe TBI (Brain Trauma Foundation, American Brain Injury Consortium, and European Brain Injury Consortium).

The planned duration of the study will be 6 months for each subject, with the study consisting of the 3 phases:

- Screening,
- Treatment, and
- Follow-up.

During the screening period, subjects will be assessed for inclusion into the study and informed consent will be obtained. Medical and medication histories, physical exam including weight and pupil response, vital signs, ECG, laboratory tests (hematology, serum chemistry, urinalysis, and coagulation) and arterial blood gases (ABG: partial pressure of oxygen in arterial blood (PaO_2), partial pressure of carbon dioxide in arterial blood ($PaCO_2$), bicarbonate (HCO_3), pH, saturation of oxygen in arterial blood (SaO_2), and fraction of inspired oxygen (FiO_2)) will be performed prior to the initiation of study drug treatment. Intracranial pressure (ICP) and therapy intensity level (TIL) will be obtained prior to treatment initiation, if the ICP monitor is placed. Pre-treatment/baseline assessment of TBI will be recorded using GCS and computed tomography (CT) scan.

Once a subject is determined to be eligible for inclusion into the study, he/she will be randomized (1:1) to receive either i.v. BHR-100 or placebo, stratified by geographic region (North America, Europe, Asia and South America) using an Interactive Web-based Randomization System (IWRS).

During the treatment period, subjects will be administered continuous i.v. infusion of BHR-100 or matching placebo for 120 hours and the GCS and neuroworsening (defined as any one of the following: a decrease in GCS motor score ≥ 2, development of pupillary abnormalities, any other neurological deterioration, or progression of lesion on CT scan leading to a change in subject management) will be assessed daily. Vital signs, ABGs, ICP, and CPP will be recorded periodically, and TIL, concomitant medications, and adverse events (AEs) will be monitored continuously.

During the follow-up period, subjects will be assessed at the following post-injury timepoints:

- Day 6,
- Day 15 (or ICU discharge),
- Day 30 (Month 1),
- Day 90 (Month 3),
- Day 180 (Month 6).

See the protocol schedule of events for further details of the efficacy and safety assessments conducted at each timepoint.

An independent Data Safety Monitoring Board (DSMB) will monitor data periodically during the course of the study and will update the sponsor. Reviews will occur at approximately

100-subject intervals. A DSMB charter and Data Monitoring and Analysis Plan (DMAP) have been written to provide further details.

There will be one interim analysis conducted when 200 subjects in each treatment group (400 subjects total) have reached a study endpoint (completed the study and been assessed for 6-month Glasgow Outcome Scale (GOS), died, or lost to follow up). At the interim analysis, stopping for efficacy will be assessed using statistical methods for group sequential testing with the O'Brien Fleming method.

Additionally, stopping the study for futility will be assessed by review of the conditional power at the interim analysis.

3.1 Sample Size Considerations

The primary efficacy measurement for this study is GOS at 6 months after injury; see section 4.1.

For the purposes of the analysis and sample size calculation, the first 2 categories of the GOS (vegetative state and dead) will be combined. Based on the 6-month GOS outcome distribution from the head injury population with GCS 3-8 in the previous TBI Phase 3 trials in the International Mission for Prognosis and Analysis of Clinical Trials in TBI Project (IMPACT) Database, it is assumed that the following GOS responses will be observed at 6 months, in subjects treated with placebo: 31% good recovery, 21% moderate disability, 19% severe disability, and 29% vegetative state or dead (Lu, 2011).

A sample size of 1,180 subjects receiving study drug (590 in each treatment group) will be needed to detect a common odds ratio of 1.5, of improvement in GOS at 6 months in BHR-100 compared to placebo, at 90% power and a significance level of 0.01 (2-sided). This calculation used the sample size equation for comparing 2 groups of ordinal data using the technique of ordinal logistic regression proposed by Whitehead (1997).

3.2 Randomization

Subjects will be randomized to either BHR-100 or placebo on a 1:1 ratio, using an IWRS. The randomization will be stratified by geographic region of the site locations in order to avoid imbalance in the distribution of treatment groups within regions.

The following countries are planned to be involved in the study: Argentina, Austria, Belgium, China, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Malaysia, Netherlands, Romania, Russia, Singapore, Spain, Taiwan, Thailand, United Kingdom, and United States. Additional countries may be considered.

These countries will be grouped into the following regions: North America (US), Europe (Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Romania, Russia, Spain and UK), Asia (China, Malaysia, Singapore, Taiwan, and Thailand) and South America (Argentina).

4 STUDY VARIABLES AND COVARIATES

4.1 Primary Outcome Variable

The primary efficacy variable is the GOS at Month 6, post-injury assessment. The GOS is a 5-point scale used to assess the mortality and disability in TBI subjects and consists of the following 5 categories:

- Dead,
- Vegetative state,
- Severe disability,
- Moderate disability, and
- Good recovery.

For this study the first 2 categories of the GOS (dead and vegetative state) will be combined.

4.2 Secondary Outcome Variables

4.2.1 Efficacy

The secondary efficacy parameters for this study will be as follows:

- Mortality at Months 1 and 6,
- GOS at Month 3,
- Extended Glasgow Outcome Scale (GOS-E) at Months 3 and 6,
- Quality of Life Short Form-36 Health Survey (SF-36) at Months 3 and 6.

The exploratory efficacy parameters for this study will be as follows:

- Changes in intracranial pathology as assessed by admission and Day 6 (+/- 1 day) CT scans,
- Changes in ICP, CPP, and TIL.

4.2.2 Safety

In order to determine if i.v. BHR-100 is safe and well-tolerated, the following safety variables will be summarized:

- AEs,
- Vital signs,
- Laboratory data,
- Physical examinations,
- Electrocardiogram (ECG),
- ABG, and
- Neuroworsening.

4.3 Predetermined Covariates and Prognostic Factors

A number of predetermined prognostic covariates have been defined for consideration within this study:

- Age,
- Motor response component of GCS (1-2, 3, 4, or 5-6) used to determine eligibility,
- Pupillary response (bilateral, unilateral/no reactive pupils/not testable) used to determine eligibility,
- Presence of hypoxia (yes/suspected, no/unknown) any time prior to randomization,
- Presence of hypotension (yes/suspected, no/unknown) any time prior to randomization,
- CT result at baseline (Marshall's CT Classification I/II, III, IV, or evacuated/non-evacuated mass lesion),
- Presence of traumatic subarachnoid hemorrhage (yes, no), and
- Region (North America, Europe, Asia, South America).

All covariates will be measured at baseline, prior to randomization.

Randomization is expected to balance covariates amongst the treatment groups; consequently, no formal testing of baseline comparability will be conducted.

5 DEFINITIONS

Baseline and Change from Baseline, Repeated Observations

The baseline value for each assessment is defined as the last measurement taken prior to randomization.

For any parameter at a specific visit, change from baseline is calculated as the value of that parameter at that visit minus the baseline value of that parameter, as defined above.

For data with repeated observations at a given visit, for example, vital signs, the first collected value will be used in summaries, with repeat values being included in the data listings only.

Endpoint Completer

A subject is considered an endpoint completer if they provide a GOS assessment at Month 6 or die before Month 6.

Study Completer

A subject is considered a study completer if they complete a 6 month assessment.

Duration of study drug exposure (in hours)

The duration of study drug exposure (in hours) = date:hour of last study medication administered – date:hour of first study medication administered – sum of recorded durations of infusion rate interruptions.

Please note, date:hour is used since both the date and time of medication administration is recorded in the CRF. Only interruptions greater than 30 minutes are recorded on the eCRF and will be accounted for in the duration of study drug exposure derivation.

Total Dose (in mg/kg)

The total dose in mg for each study drug administration record will be calculated as:

*Infusion rate from eCRF (ml/hr) * total duration of study drug administration record (hr) * 2 (mg/ml).*

The total dose in mg will be summed across all study drug administration records for a subject and then divided by the weight in kg (from IWRS).

Relative Dose

The relative dose for a subject will be the total dose received in mg/kg divided by the total protocol expected dose of 60.21 mg/kg. Relative dose will only be summarized for subjects who receive study drug for 120 hours +/- 5%, i.e. 114-126 hours.

Study Medication Compliance (%)

The study medication percent compliance will be calculated as:

$$\frac{\textit{Number of hours of medication taken, as outlined in the protocol}}{\textit{120 (intended duration of medication intake)}} \times 100$$

Primary Endpoint: GOS at Month 6 assessment (6 months after injury), missing data imputation

When the primary efficacy endpoint is missing, the last observation carried forward (LOCF) principle will be used to populate the primary endpoint, i.e. the Month 3 GOS assessment will be carried forward. In the event that a subject is lost to follow-up and has neither the 3 nor the 6-month GOS, the missing values will be imputed based upon the primary proportional odds model (POM).

To obtain values for the missing responses using the POM the predicted response probabilities will be used. Specifying the PREDICTED option on the OUTPUT statement of PROC LOGISTIC, 3 (number of categories in response variable – 1) predicted probabilities will be provided for each subject; these are the ordered cumulative probability of each response category, i.e.

Probability($Y \leq 1$)=P($Y=1$)=Probability GOS=1
P($Y \leq 2$)=Probability that GOS is 1 or 2
P($Y \leq 3$)=Probability that GOS is 1, 2 or 3

Therefore, to obtain the predicted probability of each individual response, for example, the probability that the response was GOS=2, the following calculation is performed:

$P(Y=2)=P(Y \leq 2)-P(Y=1)$

Similarly,

$P(Y=3)=P(Y \leq 3)-P(Y \leq 2)$

and finally,

$P(Y=4)=1-[P(Y \leq 3)]$

since the individual probabilities must sum to one.

The missing GOS response will then be set to the most probable category, i.e. the response with the largest predicted probability.

It is anticipated that there will be minimal missing data, however sensitivity analyses will be carried out to confirm that the imputation method(s) did not have an impact on the primary efficacy analysis results. Therefore, the primary efficacy analyses will also be conducted on observed values only, without any imputation.

Covariates, missing data imputation

For the primary efficacy analyses, missing data for the following covariates will be imputed as the most commonly occurring value over subjects with non-missing data: motor response component of GCS, pupillary response, presence of hypoxia, presence of hypotension, CT classification, and presence of traumatic subarachnoid hemorrhage.

GOS assessment – Dead responses

Subjects without a GOS response assessment at Month 6 but who have a death date from the Death Report eCRF within 6 months + 28 days of their randomization date (calculated as death date – randomization date + 1 $\leq$ 208) will be assigned a Month 6 GOS response of Dead. Similarly, subjects without a GOS response assessment at Month 3 but who have a death date from the Death Report eCRF within 3 months + 28 days of their randomization date (calculated as death date – randomization date + 1 $\leq$ 118) will be assigned a Month 3 GOS response of Dead.

Secondary Endpoint: Mortality at Month 1

Survival status from the date of injury (Day 1 of the study) until Day 30 (Month 1) will be monitored and recorded as lost to follow-up, consent withdrawn, alive, dead or other. Only subjects with a mortality assessment post-injury of alive or dead will be used in the assessment of mortality.

Secondary Endpoint: Mortality at Month 6

Survival status from the date of injury (Day 1 of the study) until Day 180 (Month 6) will be monitored and recorded as lost to follow-up, consent withdrawn, alive, dead or other. Only subjects with a mortality assessment post-injury of alive or dead will be used in the assessment of mortality.

Time to death

The time to death (in days) will be defined as:

Date of death – date of TBI + 1

If a subject does not die during the conduct of the study, they will be censored at the earliest (minimum) of their Month 6 GOS assessment date and end of study date, and censor time (in days) will be defined as:

Minimum(month 6 GOS assessment date, end of study date) – date of TBI + 1

Since subjects were not followed for death after their Month 6 GOS assessment, subjects who have a death recorded after the assessment will be censored on the date of their Month 6 assessment.

Exploratory Endpoint: CPP

The following formulae are used to derive CPP:

Mean Arterial Pressure (MAP) = 2/3 diastolic BP + 1/3 systolic BP;

CPP = MAP – ICP.

MAP will be recorded as missing if either systolic BP and/or diastolic BP measurements are not recorded. CPP will be calculated where MAP and ICP have both been recorded; if either is missing the CPP will be recorded as missing.

Exploratory Endpoint: TIL

TIL will be monitored during Study Days 1 – 6 (inclusive). The administration of each of the following unique treatments will have a score of 1 and the maximum score (sum of the individual items) per assessment period (study day) is 10:

- Surgical decompression,
- Barbiturate induced coma,
- Hypothermia for ICP reduction,
- Hyperventilation ($pCO_2 < 30$),
- Pressor administration,
- Hypertonic saline,
- Mannitol,
- Ventricular drainage,
- Paralysis induction,
- Sedation.

Neuroworsening

Neuroworsening will be defined as the occurrence of any one of the following:

- A decrease in GCS motor score ≥ 2,
- Development of pupillary abnormalities,
- Any other neurological deterioration or progression of lesion on CT scan leading to a change in subject management.

Pupillary Response

Pupillary response will come from the assessment of right and left pupil reactivity as follows:

- If both right and left pupils react, pupillary response = bilateral,
- If only one of the right or left pupil reacts, pupillary response = unilateral, and
- If neither right nor left pupil reacts = no reactive pupils, or
- If the eyes are closed and reactivity is untestable = not testable.

Treatment-Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as events that start on or after the first dose of study medication. For this study it is intended that AEs will be collected for 15 days

after the initiation of study treatment; serious adverse events (SAEs) will be collected from the time of infusion start throughout the course of the subject's participation in the study (6 months).

All AE tables will be presented for TEAEs only, listings will present all AEs (including those not deemed to be TE).

6 ANALYSIS SETS

The following analysis populations will be defined for this study:

- Modified Intention-to-treat (mITT),
- Per Protocol (PP), and
- Safety.

The assignment of subjects to the study populations will occur at the blinded review meeting which will encompass discussion of major protocol violations.

6.1 Modified Intention-to-Treat

The mITT population will include all randomized subjects in whom treatment with i.v. study drug was initiated. Following the ITT principle, subjects will be analyzed according to the treatment they were assigned at randomization regardless of any randomization errors or amount of study drug infusion administered.

The mITT population will be the primary efficacy population, and all efficacy analyses and summaries will be performed using this population. All demographic and baseline summaries will also be summarized using the mITT population.

6.2 Per Protocol

The PP population will include all subjects in the mITT population who meet all the inclusion/exclusion criteria, received at least 96 hours over the course of 120 hours of study treatment (however, not excluding those subjects who die or are discontinued for an AE prior to receiving the full dose of 120 hours), and have a non-missing 6-month GOS score that was assessed at least 152 days from randomization. Subjects who initiate study drug infusion > 8 hours from time of injury but within 9 hours will be included in the PP population. The rationale for this is that the best available time of injury to the nearest hour is used at randomization, however a different time of injury may be determined later.

Study drug administration errors will be handled according to the following table when determining inclusion in the PP population:

Table 1
Handling of Study Drug Administration Errors in the Per Protocol Analysis

Medication Error Scenario		Inclusion in PP Population
Randomized to	**Study Drug of Erroneously Received Bottle**	
Placebo	Placebo	Included in placebo arm
Placebo	BHR-100	Not included
BHR-100	BHR-100	Included in BHR-100 arm
BHR-100	Placebo received as first administration of study drug or 2 or more bottles of placebo received at any time	Not included
BHR-100	1 placebo bottle received at any time except the first administration of study drug	Included in BHR-100 arm

Subjects at any site that is removed from the study for noncompliance with ABIC/EBIC/ Brain Trauma Foundation guidelines will be excluded from the PP population.

No imputation of the 6-month GOS score will occur in the PP analysis, but missing covariates will be imputed as described in Section 5.

The PP population will be used to perform confirmatory analyses of the primary efficacy evaluation.

6.3 Safety

The safety population will include all subjects who received any study drug. Subjects will be analyzed according to treatment received regardless of the randomization schedule. If a subject received *any* amount of BHR-100, they will be summarized according to treatment BHR-100 for the safety population.

The safety population will be used for all summaries of safety data and treatment exposure data.

7 INTERIM ANALYSIS

A formal interim analysis will be performed once the first 200 subjects in each treatment arm (total of 400 subjects) have reached a study endpoint (death, lost to follow up, or completed the study and assessed for the 6-month GOS). The database used for the interim analysis will only contain these 400 subjects.

At the planned interim analysis, the test statistic based on the effect size (common odds ratio) will be compared to the critical value shown below. If the test statistic exceeds the critical value, the unblinded study statisticians will discuss the continuation of the trial with the DSMB and the DSMB will inform the Sponsor. In order to stop the trial at the interim analysis, the significance level will need to be less than the critical p-value (i.e. $p < 0.0003$).

At the planned interim analysis, a 2-sided test will be performed to detect either an increase or decrease in the common odds ratio, as described in the section of this document on primary end point analysis, section 9.5.1. In order to preserve the over-all type I error rate at 1%, the critical value for the test statistic will be inflated above 2.575, the value that would be used if no repeated testing were used. The actual critical values and p-values will be computed using statistical methods for group sequential testing with the O'Brien Fleming method.

If the p-value from the test of the null hypothesis of no treatment difference is less than 0.0003 at the interim analysis, the study may be stopped for efficacy. Table 2 indicates the critical values, p-values and cumulative type I error for this study:

Table 2
Critical Values and p-Values of Interim and Final Analyses

Interim and final analyses	Total sample	Critical Value	p-value	Cumulative Type I Error
Interim (1)	400	3.65	0.0003	0.0003
Final (2)	1180	2.58	0.0098	0.0101

No formal stopping rule for futility will be established for this study. An assessment of conditional power at the interim analysis will be provided to the DSMB for consideration with the safety summaries in the evaluation of the overall risk/benefit of the study treatment.

Under the condition that the proportional odds model assumption holds, the statistical power to reject the null hypothesis of equal six-month GOS is shown below under a variety of scenarios (Table 3).

Conditional power is the estimate of the power to observe a difference in treatment groups different from that observed at the interim analysis. The conditional power is calculated based upon the observed critical value and measure of the completion of the trial. Methods for this calculation have been proposed by Lan, DeMets and Halperin and Lan, Simon and Halperin.

Table 3
Futility Analysis: Power to Reject Null hypothesis under Various Scenarios

Common odds ratio[1]		Power at interim and final analysis	
Placebo	BHR-100	Interim analysis[2]	Final analysis[3]
1.0	1.27	1.54%	39.36%
1.0	1.50	10.93%	90.66%
1.0	2.33	88.49%	99.99%

[1] A common odds ratio of 1.27, 1.5 and 2.33 is equivalent to a 5%, 10% and 20% effect size respectively.
[2] Interim analysis is based on the assessment of 400 completed subjects (200 in each arm).
[3] Final analysis is based on total study recruitment at 1180 treated subjects with 590 in each arm. This sample size is calculated based on the defined baseline outcome distribution (31% Good Recovery, 21% Moderate Disability, 19% Severe Disability and 29% Vegetative State/Death) to detect a common odds ratio of 1.5 of improvement in outcome with 90% power and 1% significance level (2-sided).

In the event that the *final* primary efficacy analysis does not show statistical significance at the study-wise 1% significance level (i.e. the final analysis p-value is not less than 0.0098) a final adjusted p-value will be calculated and the result considered statistically significant at the 5% level if the adjusted p-value is less than 0.05. The adjusted p-value will be calculated using EAST (Cytel Statistical Software, Cambridge, MA) or other appropriate statistical software package to adjust for the interim analysis.

8 DATA REVIEW

8.1 Data Handling and Transfer

For this study PRA International provides full Data Management services, including the development of the Data Management Plan (DMP) which outlines all Data Management activities to be undertaken. The DMP is a living document that evolves over the course of a trial and consists of the following documents:

- Data Management Process Summary,
- Annotated CRF,
- Data Management Quality Control Plan,
- Critical Variable List,
- Data Edit Specifications,
- Dictionary Coding Conventions,
- SAE/AE Reconciliation Plan,
- Electronic Clinical Data Handling Instructions, and
- Database Conversion Specifications.

For this study, PRA International defines and maintains the study database. The database will be provided to the PRA International Analysis and Reporting group in SAS dataset format.

Assessments will be conducted at the central bioanalytical laboratory for blood levels of progesterone.

8.2 Data Screening

Beyond the data screening built into the PRA DMP, programming of analysis datasets, tables, figures, and listings will be ongoing during the data management of the study. During this process potential data issues will be communicated to Data Management. Before the data are considered clean (as defined by PRA Data Management processes), blinded tables, figures, and listings will be run (using a dummy randomization) and distributed to the study team for review. Any data values requiring investigation or correction will be identified at that point, and protocol deviations will be reviewed and documented. Once all data issues have been resolved, the database will be locked, treatment codes unblinded, and the final run of outputs will take place.

Furthermore, during the conduct of the study, an independent DSMB will meet to conduct safety reviews of the data, at approximately 100-subject intervals. The duties, operational procedures, and frequency of meetings/teleconferences are described in the DSMB Charter. At each meeting, the DSMB can recommend early trial termination or study modification in response to safety concerns.

The DSMB can request additional, unplanned, unblinded analysis of primary outcome data in case of major safety issues from the safety analysis. Therefore, the DSMB will be able to monitor the study in its completeness by analyzing the overall risk/benefit of the trial results as necessitated by safety concerns that may arise.

9 STATISTICAL METHODS

All analyses and reporting of study results will be conducted using SAS V9.1.3 In addition EAST will be used to adjust for the interim analysis.

All variables will be presented using appropriate descriptive statistics according to the variable nature:

- Continuous variables: number of non-missing observations, mean, standard deviation , minimum, first quartile (Q1), median, third quartile (Q3), maximum,
- Categorical variables: number of non-missing observations, absolute and relative frequency (n and percentages (%)),
- Time-to-event variables: number of non-missing observations, number and percentage of censored observations, first quartile, median (and 95% CI), third quartile, and Kaplan-Meier survival curves.

The behavior over time of continuous variables will be analyzed by presenting descriptive statistics for each time point and the difference compared to baseline (actual values and change from baseline). The behavior over time of categorical data will be analyzed by presenting the descriptive statistics for each time point and the shift compared to baseline.

The decimal places for summary statistics and percentages will be as follows:

- Precision of data + 2 decimal places (dp) for standard deviations,
- Precision of data + 1 dp for means, medians and quartiles,
- Same precision as data for minimum and maximum,
- 1 dp for percentages except when the percentage is 100% in which case no dp would be presented, and

The primary and confirmatory efficacy analyses will be 2-sided and conducted at a 1% significance level. All secondary efficacy tests will be 2-sided and conducted at a 5% significance level.

The randomization will be stratified by region. This variable will be included as a covariate in the primary and secondary GOS efficacy analyses.

Secondary efficacy analyses will be conducted in ranked order as listed in Section 9.5.2 with the understanding that no confirmatory claims can be based on variables that have a rank lower than or equal to that variable whose null hypothesis was the first that could not be rejected at the $p<0.05$ significance level.

All exploratory analyses will be considered supportive in nature, and therefore no adjustment will be made for multiple testing of exploratory variables.

All data will be included in subject data listings for all subjects in the mITT population.

9.1 Subject Disposition

An enrollment summary will be presented overall and by site, showing the first date of consent, the date of the last subject randomized, duration (in days) (calculated as end date – start date +1), and number of subjects randomized and completed endpoint.

The number and percentage of subjects randomized in total, by site, by country and by region will be summarized for each treatment group and overall for the mITT population.

The number and percentage of subjects in each study population (mITT (randomized and treated with i.v. study drug), randomized but not treated, PP, Safety, Study Completers, Endpoint Completers (includes deaths prior to Month 6), and Early Terminations) and the reasons for early termination will be summarized by treatment group and overall for mITT subjects.

Subjects remaining in the study by time will also be summarized.

These details will also be listed.

9.2 Protocol Deviations and Violations

Subjects with protocol violations that result in exclusion from the PP population will be listed.

9.3 Treatments

9.3.1 Extent of Study Drug Exposure

The number of subjects in each of the following categories will be summarized for each treatment group and overall for the safety population:

- Who initiated study drug within 8 hours of injury,
- Who were treated for at least 96 hours,
- Who prematurely discontinued study drug (with the corresponding reason for discontinuation).

Duration of study drug exposure and total dose will also be summarized for the safety population. The duration of study drug exposure (in hours) will be summarized as both a continuous and categorical variable by treatment group and overall. Total dose (in mg/kg) will also be summarized as a continuous variable. Total dose received in milligrams will be adjusted by a subject's weight entered into IWRS at the time of randomization.

Continuous and categorical summaries of time since injury to study drug initiation will be presented.

Counts and percentages of subjects with any infusion rate modifications or interruptions, and the reasons for infusion rate modifications and interruptions, will be summarized by treatment group and overall for the safety population.

The percentage compliance with study medication will be summarized by treatment group and overall for the safety population as a continuous variable. See Section 5 for further details.

9.3.2 Concomitant Medications, Concomitant Procedures and Surgical Therapy

Prior medications are defined as medications with a start date before the first initiation of study medication. Concomitant medications are defined as medications which:

- Started after the initiation of study medication,
- Had a stop date on or after the first administration of study medication, or
- Are ongoing on Day 15.

It is possible for a medication to be both prior and concomitant. It should be noted that medications administered to or taken by the subject during the study will only be recorded from the time of informed consent through to Day 15 of the study.

Medications with partial start dates will be determined as prior and/or concomitant medications by using available non-missing information. Medications with completely missing start dates (i.e. missing information for medication start day, month, and year) will be assumed to be concomitant. If just the day is missing, and the month and year are the same as the month and year of study drug administration, the medication will be considered concomitant. If the day and month are missing and the year is present, and is the same as the year of study drug administration, the medication will be considered concomitant.

Medications will be coded using the WHO (World Health Organization) Drug Dictionary March 2010 version international thesaurus with no updates, adding WHO-DD preferred term for use in the relevant tabulation. Counts and percentages for prior and concomitant medications will be summarized by preferred term, treatment group and overall for the mITT population.

The number and percentage of subjects with intracranial and extracranial surgery will be summarized by surgery type, actual surgical procedure (for example, craniofacial surgery), treatment group and overall for the mITT Population.

9.4 Demographic and Baseline Characteristics

Demographic variables (age, sex, ethnicity and race), pregnancy testing, and baseline characteristics (geographical region, GCS motor score, pupillary response, presence of hypoxia, presence of hypotension, classification of CT scan, presence of traumatic subarachnoid hemorrhage) will be summarized for each treatment group and overall.

The cause of TBI and type of injuries (face, chest, abdomen, extremities, spine, head injury alone) will be summarized by treatment group and overall.

Medical histories will be coded using Medical Dictionary for Regulatory Activities (MedDRA) version 13.0 with no updates. The number and percentage of subjects reporting any medical history will be displayed together with the number and percentage of subjects having at least one medical history within each system organ class (SOC) and preferred term.

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Analysis

The primary efficacy variable is GOS evaluated at 6 months post injury. The primary analysis will be based on imputation of missing data as described in Section 5.

9.5.1.1 Proportional Odds Model

The primary efficacy variable of GOS at 6 months post injury will be compared between treatment groups using a POM. For the purposes of this analysis the first two categories of the GOS will be combined (vegetative state and dead). A POM will be fitted including the effect of treatment, geographic region (North America, Europe, Asia, and South America), age, GCS motor score, pupil response, and CT classification. With 4 categories in the response variable, GOS at 6 months following injury, the POM simultaneously fits 3 (number of categories – 1) binary logistic regression models as follows.

If Y = response = GOS at 6 months following injury.

Model 1
$Y_1 = 0$ (not event), if Y = vegetative state or dead
$Y_1 = 1$ (event), if Y = severe disability, moderate disability, good recovery

Model 2
$Y_2 = 0$ (not event), if Y = vegetative state or dead, severe disability
$Y_2 = 1$ (event), if Y = moderate disability, good recovery

Model 3
$Y_3 = 0$ (not event), if Y = vegetative state or dead, severe disability, moderate disability
$Y_3 = 1$ (event), if Y =good recovery

The dichotomous logistic regression models for Y_J (J=1, 2, 3) can be expressed as follows:

$$\ln (P_J/(1 - P_J)) = \alpha_J + \beta_1X_1 + \beta_2X_2 + \beta_3X_3 + \beta_4X_4 + \beta_5X_5 + \beta_6X_6,$$

where

- ln is the natural logarithm,
- P_J = Probability of an 'event' (for example, good recovery) = Probability that $Y_J = 1$,
- $P_J/(1 – P_J)$ = odds of an 'event',
- X_1 = treatment group,
- β_1 = effect of treatment,
- X_2 = region,
- β_2 = effect of region,
- X_3 = age,
- β_3 = effect of age,
- X_4 = GCS motor score,
- β_4 = effect of GCS motor score,
- X_5 = pupil response,
- β_5 = effect of pupil response, and
- X_6 = CT classification,
- β_6 = effect of CT classification.

With a POM, it is assumed that the effect of the explanatory variables, such as treatment, are identical for all possible dichotomies of the response variable, that is, β_1, etc. are the same for each model.

The fact that the effects of the explanatory variables (e.g. treatment (β_1), etc.) are the same for each model is referred to as the proportional odds assumption and needs to hold for this methodology to be appropriate. This assumption will be tested using the Score Test. A non-significant result (p-value > 0.05) supports the assumption of proportional odds. As the Score Test is known to be anti-conservative, additional graphical methods will be used to assess the proportional odds assumption in greater detail, if the Score Test is statistically significant.

The proportional odds assumption for an ordinal response implies that the curves on the various cumulative logits are parallel. This assumption can be assessed visually for a given predictor (e.g. region) by plotting it against the empirical logits.

For the 4 levels of the GOS there will be 3 cumulative logits which can be expressed as:

$Logit_1 = \log[\ p_1/(1-p_1)\ ] = \log[\ p_1/(p_2+p_3+p_4)\ ]$,
$Logit_2 = \log[\ (p_1+p_2)/(1-(p_1+p_2))\ ] = \log[\ (p_1+p_2)/(p_3+p_4)\ ]$,
$Logit_3 = \log[\ (p_1+p_2+p_3)/(1-(p_1+p_2+p_3))\ ] = \log[\ (p_1+p_2+p_3)/(p_4)\ ]$

where $p_i = P(Y=i)$, where Y (response, GOS at 6 months) = i and i=1, 2, 3 or 4.

By using the observed counts, y_i, in the study data empirical logits can be computed for use in plots as follows:

$EmpLogit_1 = \log[\ (y_1)/(y_2+y_3+y_4)\ ]$

where y_i=number of subjects with Y (response, GOS at 6 months) = i and i=1, 2, 3 or 4.

The empirical logits can then be calculated for each category of the predictor and plotted. If the resulting plotted lines are roughly parallel this can be considered a visual confirmation of the proportional odds assumption.

See Appendix 3 (Model Checking Figures) for plot specification details.

Provided that the proportional odds assumption is not rejected, the POM will then be used to test the null hypothesis that the odds of being "higher" or "lower" on the outcome variable, GOS at 6 months following injury, across the entire range of the outcome, adjusted for region, age, GCS motor score, pupil response, and CT classification (as defined in Section 4.3) is the same in both treatment groups, i.e.

Null Hypothesis: $H_0 : \beta_1 = 0$
Alternative Hypothesis: $H_1 : \beta_1 \neq 0$

If the p-value from the test of the null hypothesis of $\beta_1 = 0$ is less than 0.0003 (at the interim) or 0.0098 (at the final analysis), it will be concluded that BHR-100 is statistically significantly different from placebo with respect to the GOS at 6 months following injury. The odds of some degree of improvement in the GOS at 6 months will be modeled and the corresponding common odds ratio for treatment, e^{β_1}, can then be interpreted to determine the direction of the treatment difference as follows. With the placebo group being considered as the reference category, if the odds ratio ($OR_{BHR\text{-}100/placebo}$) is greater than 1, the odds of some improvement in the GOS at 6 months is greater in the BHR-100 treatment group compared to placebo.

In the event that the primary efficacy analysis does not show statistical significance at the study-wise 1% significance level, please refer to section 9.5.1.4 for further details on how the statistical significance of the primary efficacy analysis should be interpreted.

The POM will be fitted in SAS® using the PROC LOGISTIC procedure.

Goodness of fit of the model will be assessed using the Deviance and Pearson tests (add SCALE = NONE AGGREGATE to the MODEL statement of PROC LOGISTIC) to compare the fitted model with the saturated model. If these tests are not statistically significant it implies that the model fits the data adequately.

The score test for the proportional odds assumption and individual p-values associated with the tests of effects (treatment, geographic region, age, GCS motor score, pupil response, and CT classification) will be summarized for the POM of GOS at 6 months post injury.

The odds ratios and associated 95% CIs for the levels of the effects relative to a reference category will be presented for all factors and covariates included in the POM of GOS at 6 months post injury.

In addition to the results of the hypothesis tests from the statistical modeling, the number of non-missing observations, absolute and relative frequency (n and percentages), will be provided by treatment group for the GOS categories at 6 months post injury.

The analyses above will be repeated for the straight observed case analysis (no imputation of 6-month GOS or covariates) in the mITT population, the straight observed case analysis in the PP population (no imputation of 6-month GOS or covariates), and the analysis of imputed missing values in the mITT population for US subjects only.

In addition to the above POM for the primary analysis, the individual binary logistic regression models will be fitted for each possible dichotomization of the GOS at 6 months, as outlined above under model 1, 2 and 3. This will be done using missing value imputation for the mITT population. This will allow an assessment of the odds ratio for treatment within each possible dichotomization and a further assessment of the proportional odds assumption. If the parameter estimates obtained under each dichotomized model are similar then the proportional odds assumption would seem sensible.

A bar chart illustrating the percentage of responses in each GOS category for each treatment group will be produced for the GOS at 6 months for the mITT (observed values and missing values imputed) and PP populations (observed values).

9.5.1.2 Alternate Primary Efficacy Analysis (Sliding Dichotomy)

If the proportional odds assumption cannot be justified, a sliding dichotomy of the GOS outcome at 6 months following injury, following categorization of subjects into different prognosis groups (worst, intermediate, and best) based on baseline prognostic factors, will be the primary efficacy analysis. The primary sliding dichotomy analysis will be based on imputation of missing data (covariates and 6-month GOS assessments).

For each subject a baseline prognostic risk score (BPRS) will be calculated as a weighted linear function of baseline prognostic factors of age, age squared, GCS motor score, Marshall CT classification, pupillary reactivity, presence of hypoxia, presence of hypotension, and presence of traumatic subarachnoid hemorrhage. The weighting of the BPRS factors will be based on the prognostic model developed in Hukkelhoven et al (2005). The BPRS will be sorted from lowest to highest, noting that higher BPRS represent a worse prognosis, and split into tertiles which will represent best, intermediate and worst prognosis.

For the cohort predicted to have the worst outcome, the outcome of severe disability or better is considered a "favorable outcome," while for the cohort predicted to have the best outcome, only the outcome of good recovery is considered a "favorable outcome." For the middle cohort there is no difference from the dichotomized model, so that the outcomes of moderate disability and good recovery are pooled to define "favorable outcome."

The hypothesis that the proportion of favorable responses observed in each treatment group is the same will be tested using the Cochran-Mantel Haenszel (CMH) Chi-Square test, adjusted for region.

Null Hypothesis: $H_0: p_1 = p_2$
Alternative Hypothesis: $H_1: p_1 \neq p_2$

where p_1 = proportion of favorable responses in the BHR-100 treated group and p_2 = proportion of favorable responses in the placebo treated group. The Mantel-Haenszel estimate of the common odds ratio and corresponding 95% CI will also be presented.

If the p-value from the test of the null hypothesis of $p_1 = p_2$ is less than 0.0003 (at the interim) or 0.0098 (at the final analysis), it will be concluded that there is a statistically significantly difference in the proportion of favorable responses between the 2 treatment groups.

In addition to the formal inference testing discussed above, the difference in proportion of favorable outcomes and associated 2-sided 95% confidence interval between the BHR-100 and placebo treatment groups will be calculated.

In addition to the primary analysis that tests whether the overall proportion of favourable responses is the same in each treatment group, the CMH test results and odds ratios by baseline prognosis grouping (best, intermediate, worse) will also be presented. The Breslow-Day test will be computed to test whether the odds ratios are different across the prognostic groups. A significant test result will not affect the validity of the overall test of a difference between treatment groups, but will aid in the interpretation of the results.

The analyses above will be repeated for the straight observed case analysis (no imputation of 6-month GOS or covariates) in the mITT population, the observed case analysis in the PP population, and the analysis of imputed missing values in the mITT population for US subjects only.

9.5.1.3 Sensitivity Analysis (Dichotomized Model)

The GOS at 6 months post injury will be dichotomized into Good Recovery, Moderate Disability versus Severe Disability, Vegetative Status/Dead. As a supportive analysis, the binary outcome will be analyzed using logistic regression analysis. The logistic regression model will be fitted including the effect of treatment, geographic region (North America, Europe, Asia, and South America), age, GCS motor score, pupil response, and CT classification.

If Y = response = GOS at 6 months following injury.

Model
$Y_1 = 0$ (not event), if Y = vegetative state or dead, severe disability
$Y_1 = 1$ (event), if Y = moderate disability, good recovery

The dichotomous logistic regression model can be expressed as follows:

$$\ln (P/(1 - P)) = \alpha_J + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_4 + \beta_5 X_5 + \beta_6 X_6,$$

where

- ln is the natural logarithm,
- P = Probability of an 'event' (moderate disability, good recovery) = Probability that Y = 1,
- P/(1 – P) = odds of an 'event',
- X_1 = treatment group,
- β_1 = effect of treatment,
- X_2 = region,
- β_2 = effect of region,
- X_3 = age,
- β_3 = effect of age,
- X_4 = GCS motor score,
- β_4 = effect of GCS motor score,
- X_5 = pupil response,
- β_5 = effect of pupil response, and
- X_6 = CT classification,
- β_6 = effect of CT classification.

The logistic regression model will be used to test the null hypothesis that the odds of an 'event', i.e. observing a response of moderate disability or good recovery on the outcome variable, GOS at 6 months following injury, adjusted for region, age, GCS motor score, pupil response, and CT classification is the same in both treatment groups, i.e.

Null Hypothesis: $H_0 : \beta_1 = 0$
Alternative Hypothesis: $H_1 : \beta_1 \neq 0$

If the p-value from the test of the null hypothesis of $\beta_1 = 0$ is less than 0.05, it will be concluded that BHR-100 is statistically significantly different from placebo with respect to the GOS at 6 months following injury. The odds of an 'event' (moderate disability or good recovery) in the GOS at 6 months will be modeled and the corresponding common odds ratio for treatment, e^{β_1}, can then be interpreted to determine the direction of the treatment difference as follows. With the placebo group being considered as the reference category, if the odds ratio ($OR_{BHR\text{-}100/placebo}$) is greater than 1, the odds of a favorable outcome in the GOS at 6 months is greater in the BHR-100 treatment group compared to placebo.

The logistic regression analysis will be fitted in SAS® using the PROC LOGISTIC procedure.

Goodness of fit of the model will be assessed as outlined above for the Proportional Odds Model.

The individual p-values associated with the tests of effects (treatment, geographic region, age, GCS motor score, pupil response, and CT classification) will be summarized for the Logistic Regression Model of GOS at 6 months post injury.

The odds ratios and associated 95% CIs for the levels of effects relative to a reference category will be presented for all factors and covariates included in the Logistic Regression Model of GOS at 6 months post injury.

In addition to the results of the hypothesis tests from the statistical modeling, the number of non-missing observations, absolute and relative frequency (n and percentages), will be provided by treatment group for the dichotomized GOS categories at 6 months post injury.

The primary dichotomized analysis will be based on missing values of 6-month GOS and covariates imputed. It will also be repeated for the straight observed case analysis (no imputation of 6-month GOS or covariates) in the mITT population and the straight observed case analysis in the PP population.

A bar chart illustrating the percentage of responses in each of the dichotomized categories for each treatment group will be produced for the GOS at 6 months (observed values and missing values imputed) for the mITT population.

9.5.1.4 Interpretation of Statistical Significance of Primary Efficacy Analysis

In the event that the primary efficacy analysis does not show statistical significance at the study-wise 1% significance level, i.e. the final analysis p-value is not less than 0.0098, a final adjusted p-value will be calculated and the result considered statistically significant at the 5% level if the adjusted p-value is less than 0.05. The adjusted p-value will be calculated using EAST (Cytel Statistical Software, Cambridge, MA) or other appropriate statistical software

package to adjust for the interim analysis using the pre-specified boundaries discussed above and in section 7.

9.5.1.5 Handling of Missing Data

Please refer to section 5 for further details on the handling of missing data.

9.5.1.6 Exploratory Analysis

An exploratory analysis will be conducted to assess each of the following covariates of interest: treatment (BHR-100 vs. placebo), region (North America vs. Europe vs. Asia vs. South America), age, race (white vs. non-white), GCS motor score (1-2 vs. 3 vs. 4 vs. 5-6), pupil response (bilateral vs. unilateral/no reactive pupils/not testable), CT classification (I/II vs. III vs. IV vs. V/VI), presence of hypoxia (yes/suspected vs. no/unknown), presence of hypotension (yes/suspected vs. no/unknown), presence of traumatic subarachnoid hemorrhage (yes vs. no), gender (male vs. female), and time to first dose of study medication from TBI (0-4 vs. 4-6 vs. 4-8 vs. >8 hours), for inclusion into an expanded model. Each covariate, along with the corresponding interaction with treatment term, will be included in a simple model with treatment. A backward selection model will be fit beginning with all covariates. Factor by treatment interactions will be included in the backward elimination model if the p-value<0.10 in the corresponding simple model. A significance level of 0.05 may be too stringent and may exclude important variables from the model, so a significance level of 0.1 will be used for the backward selection process. If the interaction term is significant, an exploratory subgroup analysis will be performed for the corresponding covariate.

This analysis will be conducted for the POM based on imputation of missing data. Missing covariates will not be imputed for the exploratory analysis.

9.5.2 Secondary Variables

Secondary efficacy parameters will be ranked as follows:

1) GOS-E at Month 6,
2) Mortality at Month 6 in mITT population (comparison of incidence of death),
3) GOS at Month 3,
4) GOS-E at Month 3,
5) Mortality at Month 1 in mTT population (comparison of incidence of death),
6) SF-36 mental composite score at Month 6,
7) SF-36 physical composite score at Month 6
8) SF-36 mental composite score at Month 3, and
9) SF-36 physical composite score at Month 3.

No confirmatory claims can be based on variables that have a rank lower than or equal to the variable whose null hypothesis was the first that could not be rejected at the p<0.05 significance level.

9.5.2.1 Mortality at Month 1, Month 6

These efficacy variables are obtained by collecting the survival status from the date of injury (Day 1 of the study) until Day 30 (Month 1) and Day 180 (Month 6) respectively as lost to follow-up, consent withdrawn, alive, dead or other. Every effort will be made to ascertain the survival status of subjects with status other than dead or alive, but in the absence of further information these observations will be omitted from the analysis. The 1-month mortality rate will be defined as the proportion of subjects at risk in the mITT population (subjects for whom the survival status at Day 30 is known) who died on or before Study Day 30. Similarly, the 6-month mortality rate will be defined as the proportion of subjects at risk in the mITT population who died on or before Study Day 180.

The hypothesis that the mortality rate observed in each treatment group is the same will be tested using the Fisher's Exact test.

Null Hypothesis:	$H_0: p_1 = p_2$
Alternative Hypothesis:	$H_1: p_1 \neq p_2$

where p_1 = proportion of deaths in the BHR-100 treated group and p_2 = proportion of deaths in the placebo treated group.

A 2-sided, 5% significance level will be used to test the null hypothesis. If rejected ($p < 0.05$), it will be concluded that there is a statistically significant difference in the proportion of deaths between the 2 treatment groups.

In addition to the formal inference testing discussed above, 2-sided 95% confidence intervals for the difference in the proportion of deaths between BHR-100 and placebo treatment groups will be calculated.

Summaries of mortality at Months 1 and 6 will be presented for both the mITT and PP populations.

The mortality rate for each treatment group will also be plotted on a bar chart for mortality at 1 and 6 months for the mITT population.

9.5.2.2 GOS at Month 3

The GOS at Month 3 will be analyzed using the POM in the same way as the primary efficacy analysis of GOS at Month 6 outlined above for the observed values.

9.5.2.3 GOS-E at Month 3 and Month 6

The GOS-E at Month 3 and Month 6 will be analyzed using the POM, similar to the primary efficacy analysis of the GOS at Month 6 described above. The GOS-E is an 8-point scale with the following categories:

- Dead (D),
- Vegetative state (VS),
- Lower severe disability(SD LL),
- Upper severe disability (SD UL),
- Lower moderate disability (MD LL),

- Upper moderate disability (MD UL),
- Lower good recovery (GR LL),
- Upper good recovery (GR UL).

For the POM analysis, the first 2 categories will be combined (vegetative state and dead). With 7 categories in the response variable, the POM simultaneously fits 6 binary logistic regression models. If the proportional odds assumption cannot be justified, the GOS-E at Month 6 will be analyzed using the SD as described in Section 9.5.1.2. For each subject, a BPRS will be calculated as described in Section 9.5.1.2. Subjects will be sorted from lowest to highest based on BPRS, and split into 6 equal groups representing different prognosis groups. The first prognosis group, representing the lowest BPRS and therefore the best prognosis, will be Group 1. The definition of a favorable or unfavorable outcome for each group will be defined as in Table 4.

Table 4

Sliding Dichotomy Groupings for GOS-E

Group	Unfavorable Outcome	Favorable Outcome
1	D+VS+SD+MD+GR LL	GR UL
2	D+VS+SD+MD	GR
3	D+VS+SD+MD LL	MD UL+GR
4	D+VS+SD	MD+GR
5	D+VS+SD LL	SD UL+MD+GR
6	D+VS	SD+MD+GR

D= Dead, VS=Vegetative state, SD=Severe Disability, MD=Moderate Disability, GR=Good Recovery, SD LL=Lower severe disability, SD UL=Upper severe disability, MD LL=Lower moderate disability, MD UL=Upper moderate disability, GR LL=Lower good recovery, GR UL=Upper good recovery

The hypothesis that the proportion of favorable responses observed in each treatment group is the same will be tested using the CMH test as described above.

The analyses of the GOS-E at Month 3 and Month 6 will be done for the straight observed case analysis only.

9.5.2.4 Quality of Life: SF-36

During the conduct of the study, the SF-36 health survey will be administered at Months 3 and 6 to assess quality of life with respect to health status. Since a baseline SF-36 is not assessed prior to study treatment, the analyses of the SF-36 will compare mean SF-36 scores at Month 3 and 6 between treatment groups.

The SF-36 consists of 36 questions that are grouped into eight scaled scores. These scores are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight.

For each scale, a simple mean imputation of missing data with a restriction to cases where the subject has completed at least 50% of the items of that scale (the "half-scale" rule) will be used.

The eight sections are as follows:

- Vitality,
- Physical functioning,
- Bodily pain,
- General health perceptions,
- Physical role functioning,
- Emotional role functioning,
- Social role functioning, and
- Mental health.

Summary statistics for the 8 scales and the physical and mental composite summary scores will be presented for each treatment group.

In addition to summarizing the data, the physical and mental composite summary scores at Month 3 and 6 will be analyzed using an analysis of covariance (ANCOVA) model including treatment group.

The null hypothesis that the mean physical and mental summary scores are the same for both treatment groups (BHR-100 and placebo) will be tested against the 2-sided alternative hypothesis that the mean physical and mental summary scores are different in each treatment group, at the 0.05 significance level.

The least square means for the treatment groups, difference in least square means between the treatment groups, effect size calculated as the absolute difference in least square means between BHR-100 and placebo divided by the root mean square, and p-value for difference between treatment groups will be presented.

A 2-sided, 5% significance level will be used to test the null hypothesis. If rejected at the 5% level ($p < 0.05$), it will be concluded that there is a statistically significant difference in the relevant summary score between the 2 treatment groups. The magnitude of the summary statistics will be examined to determine the direction of the treatment difference.

Diagnostic residual plots will be evaluated to test for violations of normality. If the normality assumption for the model is not met, the null hypothesis that the mean physical and mental summary scores are the same in each treatment group will be tested using the 2-sided Wilcoxon Rank-Sum test, an unstratified non-parametric test, which can be obtained from the NPAR1WAY procedure in SAS®.

9.5.3 Exploratory Variables

9.5.3.1 Time to Death

The actual time to death will be analyzed for the mITT population.

If a subject does not die during the conduct of the study, they will be censored at their Month 6 GOS assessment or end of study date, whichever comes first.

The LIFETEST procedure in SAS® will be used to produce Kaplan-Meier plots and estimates of 25th, 50th, and 75th quartiles and corresponding 95% confidence limits of the median time to death. The 2 treatment groups will be compared using a 2-sided log-rank test. Examination of the point estimates will indicate the direction of the treatment difference. The cumulative percent mortality based on the Kaplan-Meier survival probability estimates will be plotted for each treatment group.

The time to death (in days) will be further analyzed using a Cox proportional hazard model. The comparison of the treatment effect on the time to death will be based on the hazard ratio (HR) from the Cox regression model using the PHREG procedure in SAS®. Estimates of HR and 95% confidence limits will be presented. The model will include the same terms as the primary efficacy analysis, namely treatment, region, age, GCS motor score, pupil response, and CT classification.

The Cox proportional hazards model is a standard model used in failure time analysis. Compared to parametric analyses, its assumptions are fairly unspecified and will therefore yield robust estimates of the treatment effect. The model will be applied using the Efron approach for handling ties, since this approach is known to give a reasonable approximation of the exact likelihood in the presence of ties and is computationally faster when large amounts of data are being analyzed.

9.5.3.2 Comparison of CT scans at admission and Day 6

A CT scan will be performed before randomization (Day 1) and once again at Day 6 ± 1 day post-injury to assess the progression of lesion volume and brain edema. The findings by the Central Reader will be classified in accordance with the Marshall classification:

- Diffuse injury I - no visible pathology (CT class I),
- Diffuse injury II (CT class II),
- Diffuse injury III – swelling (CT class III),
- Diffuse injury IV – shift (CT class IV),
- Evacuated mass lesion (CT class V),
- Non-evacuated mass lesion (CT class VI).

A shift summary of CT classification from Baseline to Day 6 will be presented by treatment group.

9.5.3.3 ICP

Intracranial Pressure (ICP) will be collected for Days 1 – 6 of the study, at the investigators' discretion.

Descriptive summary statistics, categorical summaries (maximum daily ICP: 0 to <15, ≥15 to <25, ≥25 to <40 and ≥40 mmHg and maximum daily ICP: 0 to ≤20, >20 mmHg), and the number of subjects with maximum daily ICP ≥25 and maximum daily ICP >20 mmHg (cutpoints of particular interest) will be presented for the maximum ICP by treatment group and study day for the mITT population.

9.5.3.4 CPP

CPP is computed based upon simultaneously recorded ICP and blood pressure measurements, see Section 5 for formula. Summary statistics for the highest and lowest daily CPP values will be presented for each treatment group by Study Day.

CPP measurements in the following potentially clinically relevant categories will be presented for each treatment group: less than 50 mmHg, 50-<60 mmHg, 60-<70 mmHg and greater than or equal to 70 mmHg. The number and percentage of subjects within the various categories by Study Day will be summarized by treatment group.

Summary statistics will also be presented for the percentage of subjects with CPP measurements within the above specified categories at any time during treatment, where on-treatment will include all scheduled and unscheduled CPP measurements after the initiation of study medication.

9.5.3.5 TIL

TIL will be monitored during Study Days 1 – 6 (inclusive) while ICP is being monitored (i.e. up to 6 days).

Each of the unique treatments given on a study day used for ICP management will have a score of 1, and the maximum score (sum of the individual items) per assessment period (study day) is 10. It is assumed that there will be a stepwise progression of therapy (from sedation to surgical decompression). However, in the event that the most aggressive therapies are used, i.e. the subject has barbiturate administration or surgical decompression, this will result in a TIL score of 10 regardless of which of the other therapies have been administered.

The number of non-missing observations, absolute and relative frequency (n and percentage) of the subjects having at least one occurrence of the individual therapies (surgical decompression, barbiturate induced coma, hypothermia for ICP reduction, hyperventilation, pressor administration, hypertonic saline, mannitol, ventricular drainage, paralysis induction, and sedation) will be summarized for each treatment group. The most aggressive therapy received during Days 1-6, expressed as the highest stepwise level of the TIL, will also be summarized. Furthermore, the daily TIL score will be summarized as a continuous variable by Study Day and treatment group.

9.6 Safety Analyses

9.6.1 Adverse Events

For this study, it is intended to limit the collection of AEs to the window in which events are considered treatment-emergent. Treatment-emergent adverse events (TEAEs) are defined as events that start on or after the first dose of study medication and up to 15 days and 6 months after the initiation of study treatment, for AEs and SAEs respectively.

Partial start dates of AEs will be imputed in order to determine whether or not the AE is TE. If just the day is missing, and any date of dose administered is within the month of the AE, the AE will be treated as TE. If the month is missing and the year is present, and any date of dose administered is within the year of the AE, the AE will be treated as TE. If the year is missing,

the AE will be treated as TE. For the imputation, the day will be set to the first date of that month, or the first dose date, if the first dose date is within that month. Alternatively, if the month is missing the month will be set to January, or the first dose date, if the first dose date is within that year.

AEs will be coded using the MedDRA international thesaurus version 13.0 with no updates, adding system organ class (SOC) and preferred term. The AE summaries will be presented for TEAEs only. The total number of subjects reporting at least one AE and the number of AEs will be summarized by treatment group. The initial summary will also provide a breakdown of events that:

- Are treatment-related,
- Are serious,
- Are treatment-related and serious,
- Resulted in the study drug being prematurely discontinued,
- Are treatment-related and resulted in the study drug being prematurely discontinued,
- Resulted in death, and
- Are treatment-related and resulted in death.

Additionally, the overall summary of AEs will be summarized by treatment group for the subgroups of interest: gender, race group (white vs. non-white vs. not allowed to obtain), and age group (≤45 years vs. >45 years).

The number and percentage of subjects with at least one TEAE and the number of TEAEs will be presented by SOC, preferred term, and treatment group for the following summaries:

- All AEs,
- All AEs by gender,
- All AEs by race group,
- All AEs by age group,
- Treatment-related AEs,
- All AEs, by maximum severity,
- Treatment-related AEs, by maximum severity,
- All AEs, by maximum relationship,
- All AEs that resulted in the study drug being prematurely discontinued, and
- Treatment-related AEs that resulted in the study drug being prematurely discontinued.

Additionally, the following AEs of special interest will be presented by treatment group: serious thromboembolic events such as thrombotic myocardial infarction, pulmonary embolism, deep vein thrombosis, ischemic stroke; allergic reactions; marked liver function abnormalities; serious infections such as pneumonia, sepsis, meningitis. Preferred terms for each AE of special interest will be identified by medical review prior to unblinding for the primary analysis. Preferred terms related to the following events will also be grouped to ensure similar events that are coded to different terms using MedDRA are summarized together: electrolyte imbalance, anemia, infusion site reactions, thrombocyte disorders, and seizures. These events will also be listed.

9.6.2 Neuroworsening

See Section 5 for definition of neuroworsening. The incidence of any episode of neuroworsening occurring ≤ Day 6 and ≤Day 15 will be summarized.

Details of all neuroworsening events will also be listed.

9.6.3 Deaths and Serious Adverse Events

The number and percentage of subjects with at least one SAE and the number of events will be presented by SOC, preferred term and treatment group for the following summaries:

- All SAEs, and
- Treatment-related SAEs.

The primary cause of death as recorded on the death report will be summarized by treatment group and overall for the mITT population.

9.6.4 Laboratory Data

Laboratory data (coagulation, hematology, serum chemistry and urinalysis) will be collected at baseline, end of study treatment (Day 6), and Day 15 of the study.

The status of clinically significant (non AE) abnormalities (resolved, ongoing, or lost to follow-up) will be summarized for Day 15 by laboratory parameter and treatment group in the safety population.

Clinically significant (non-AE) abnormal lab results (coagulation, hematology, serum chemistry, and urinalysis) will be listed.

Coagulation, hematology, and serum chemistry laboratory assessments will also be summarized descriptively for baseline, Day 6, and Day 15. The change from baseline will be summarized for Day 6 and Day 15. All lab parameters will be summarized in standard SI units.

All lab results from Baseline, Day 6, and Day 15 will be listed.

9.6.5 Vital Signs

Vital signs will be collected for Days 1 – 6 of the study.

Descriptive summary statistics will be presented for the highest and lowest measurements by study day for each vital sign parameter: pulse rate (per minute), respiration rate (per minute), systolic and diastolic blood pressure (mm Hg), and temperature (°C). A descriptive summary of weight (kg) will also be presented. These tables will include the absolute values and the change from baseline. See Section 5 for the definition of baseline.

9.6.6 Physical Examinations, ECGs, and Other Observations Related to Safety

The number and percentage of subjects with normal or abnormal physical examination findings will be presented by visit, body system (e.g. skin, HEENT, etc.) and treatment group.

Post-baseline physical examination abnormalities will be listed to provide details of the noted abnormalities.

ECGs will be performed at Day 1 prior to the initiation of study treatment and at Day 6

(post-infusion).

Abnormal rhythm, conduction, and QRS complex findings will be summarized by study day and treatment group for the safety population. Subjects with abnormal and clinically significant, abnormal post-baseline results will be listed.

9.6.6.1 Arterial Blood Gases

Arterial blood gases (PaO_2, $PaCO_2$, HCO_3, pH, SaO_2 and FiO_2) will be recorded before randomization (Day 1 pre-dose) and once daily during Days 1 – 6.

Descriptive summary statistic tables will be presented for the worst daily ABG parameters by treatment group and measurement day. These tables will include the absolute values and the change from baseline. The worst value will be calculated as the lowest value of the day for PaO_2, HCO_3, pH, SaO_2, and FiO_2 and the highest value of the day for $PaCO_2$. See Section 5 for the definition of baseline and guidance on how to handle repeat observations at a given visit.

9.6.7 Progesterone Levels

A descriptive summary of Day 2 progesterone levels will be presented by treatment group.

10 VALIDATION

PRA Analysis and Reporting seeks to ensure the quality of the results provided for the study in the form of tables, figures, and listings (TFLs), and the derived datasets used in their creation, through the following processes:

- Derived datasets will be independently reprogrammed by a second programmer. The separate datasets produced by the two programmers must match 100%.
- Tables will be independently reprogrammed by a second programmer for numeric results. Statisticians will be involved in the process of programming and validating tables that include inferential statistical results.
- Figures will be checked for consistency against corresponding tables and listings, or independently reprogrammed if there are no corresponding tables or listings.
- Listings will be checked for consistency against corresponding tables, figures, and derived datasets.

The entire set of TFLs will be checked for completeness and consistency prior to its delivery to the sponsor by the lead analysis programmer, the lead statistician, and a senior level statistician, or above, who is not a member of the project team.

The PRA validation process will be repeated any time TFLs are redelivered using different data. Execution of this validation process will be documented through the study Table of Programs that will be provided to the sponsor at study conclusion.

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APPENDIX 1 GLOSSARY OF ABBREVIATIONS

ABG	Arterial Blood Gases
ABIC	American Brain Injury Consortium
AE	Adverse Event
ANCOVA	Analysis of Covariance
BHR-100	BHR Pharma, LLC's proprietary formulation of intravenous progesterone
BP	Blood Pressure
BPRS	Baseline Prognostic Risk Score
BTF	Brain Trauma Foundation
CI	Confidence Interval
CMH	Cochran-Mantel Haenszel
CPP	Cerebral Perfusion Pressure
CRF	Case Report Form (paper or other media)
CSR	Clinical Study Report
CT	Computed Tomography
DMAP	Data Monitoring and Analysis Plan
DMP	Data Management Plan
DP	Decimal Places
DSMB	Data Safety Monitoring Board
EBIC	European Brain Injury Consortium
ECG	Electrocardiogram
FDA	Food and Drug Administration
FiO_2	Fraction of Inspired Oxygen
GCS	Glasgow Coma Scale
GOS	Glasgow Outcome Scale
GOS-E	Extended Glasgow Outcome Scale
HCO_3	Bicarbonate
HR	Hazard Ratio
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use

ICP	Intracranial Pressure
ICU	Intensive Care Unit
IMPACT	International Mission for Prognosis and Analysis of Clinical Trials in TBI
ITT	Intent-to-treat
i.v.	Intravenous
IWRS	Interactive Web-based Randomization System
LOCF	Last Observation Carried Forward
MAP	Mean Arterial Pressure
MedDRA	Medical Dictionary for Regulatory Activities
mITT	Modified Intention-to-treat
OR	Odds Ratio
PaO_2	Partial Pressure of Oxygen
$PaCO_2$	Partial Pressure of Carbon Dioxide
POM	Proportional Odds Model
PP	Per Protocol
Q1	First Quartile
Q3	Third Quartile
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SaO_2	Saturation of Oxygen, arterial blood
SD	Sliding Dichotomy
SF-36	Short Form 36 Health Survey
SOC	System Organ Class
TBI	Traumatic Brain Injury
TEAE	Treatment-Emergent Adverse Events
TFL	Tables, Figures and Listings
TIL	Therapy Intensity Level
WHO-DD	World Health Organization-Drug Dictionary

APPENDIX 2 LIST OF POST-TEXT TABLES, FIGURES, LISTINGS, AND SUPPORTIVE SAS OUTPUT APPENDICES

Tables

Output	Title	Use Table Shell	DSMB*
Table 14.1.1.1	Summary of Investigational Sites' Enrollment Duration (mITT Population)		X
Table 14.1.1.2	Summary of Enrollment by Region, Country and Site (mITT Population)		X
Table 14.1.1.3	Summary of Subject Disposition (Randomized Subjects)		X
Table 14.1.1.4	Summary of Subject Status by Time (mITT Population)		
Table 14.1.1.5	Country Codes per ISO		
Table 14.1.2.1	Summary of Study Drug Exposure and Time From Injury (Safety Population)		X
Table 14.1.2.2	Drug Administration Summary (Safety Population)		
Table 14.1.2.3	Summary of Study Drug Compliance Rate (Safety Population)		
Table 14.1.3.1	Prior and Concomitant Medications by WHO Drug Dictionary Preferred Term (mITT Population)		
Table 14.1.3.2	Surgical Therapy (mITT Population)		
Table 14.1.4.1	Demographic Characteristics (mITT Population)		X
Table 14.1.4.2	Pregnancy Testing (mITT Population)		X
Table 14.1.4.3	Baseline Characteristics (mITT Population)		X
Table 14.1.4.4	Summary of Injury (mITT Population)		
Table 14.1.5	Summary of Medical History by System Organ Class and Preferred Term (Safety Population)		
Table 14.2.1.1	Summary of Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)		X
Table 14.2.1.2	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (mITT Population)		X
Table 14.2.1.3	ORs and 95% CIs of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (mITT Population)		X
Table 14.2.1.4	Summary of Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)	14.2.1.1	X
Table 14.2.1.5	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)	14.2.1.2	X

Output	Title	Use Table Shell	DSMB*
Table 14.2.1.6	ORs and 95% CIs of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)	14.2.1.3	X
Table 14.2.1.7	Summary of Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)	14.2.1.1	
Table 14.2.1.8	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (PP Population)	14.2.1.2	
Table 14.2.1.9	ORs and 95% CIs of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (PP Population)	14.2.1.3	
Table 14.2.1.10	Summary of Glasgow Outcome Scale at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)	14.2.1.1	
Table 14.2.1.11	Analysis of Glasgow Outcome Scale at 6 Months Post Injury for US Only – Proportional Odds Model - Missing Values Imputed (mITT Population)	14.2.1.2	
Table 14.2.1.12	ORs and 95% CIs of Glasgow Outcome Scale at 6 Months Post Injury for US Only – Proportional Odds Model - Missing Values Imputed (mITT Population)	14.2.1.3	
Table 14.2.1.13	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (Unadjusted Analysis) (mITT Population)	14.2.1.2	
Table 14.2.1.14	ORs and 95% CIs of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (Unadjusted Analysis) (mITT Population)	14.2.1.3	
Table 14.2.2.1	Summary of Sliding Dichotomy (Dichotomization) – Missing Values Imputed (mITT Population)		
Table 14.2.2.2	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Missing Values Imputed (mITT Population)		
Table 14.2.2.3	ORs and 95% CIs for Sliding Dichotomy at 6 Months Post Injury – Missing Values Imputed (mITT Population)		
Table 14.2.2.4	Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury – Observed Values (mITT Population)	14.2.2.1	
Table 14.2.2.5	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Observed Values (mITT Population)	14.2.2.2	
Table 14.2.2.6	ORs and 95% CIs for Sliding Dichotomy at 6 Months Post Injury – Observed Values (mITT Population)	14.2.2.3	
Table 14.2.2.7	Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury – Observed Values (PP Population)	14.2.2.1	
Table 14.2.2.8	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Observed Values (PP Population)	14.2.2.2	
Table 14.2.2.9	ORs and 95% CIs for Sliding Dichotomy at 6 Months Post Injury – Observed Values (PP Population)	14.2.2.3	

Output	Title	Use Table Shell	DSMB*
Table 14.2.2.10	Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)	14.2.2.1	
Table 14.2.2.11	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)	14.2.2.2	
Table 14.2.2.12	ORs and 95% CIs for Sliding Dichotomy at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)	14.2.2.3	
Table 14.2.3.1	Summary of Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)		X
Table 14.2.3.2	Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)		
Table 14.2.3.3	ORs and 95% CIs for Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)		
Table 14.2.3.4	Summary of Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)	14.2.3.1	
Table 14.2.3.5	Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)	14.2.3.2	
Table 14.2.3.6	ORs and 95% CIs for Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)	14.2.3.3	
Table 14.2.3.7	Summary of Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)	14.2.3.1	
Table 14.2.3.8	Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)	14.2.3.2	
Table 14.2.3.9	ORs and 95% CIs for Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)	14.2.3.3	
Table 14.2.3.10	Analysis of Dichotomized (GR vs. MD, SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)	14.2.3.2	
Table 14.2.3.11	ORs and 95% CIs for Dichotomized (GR vs. MD, SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)	14.2.3.3	
Table 14.2.3.12	Analysis of Dichotomized (GR, MD, SD vs. V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)	14.2.3.2	
Table 14.2.3.13	ORs and 95% CIs for Dichotomized (GR, MD, SD vs. V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)	14.2.3.3	
Table 14.2.4.1	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Exploratory Analysis – Missing Values Imputed (mITT Population)		

Output	Title	Use Table Shell	DSMB*
Table 14.2.4.2	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Region – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.3	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Region – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.4	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Age Group – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.5	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Age Group – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.6	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Race Group – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.7	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Race Group – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.8	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by GCS Motor Score – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.9	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by GCS Motor Score – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.10	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Pupil Response – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.11	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Pupil Response – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.12	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by CT Classification – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.13	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by CT Classification – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.14	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Presence of Hypoxia– Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.15	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Presence of Hypoxia – Exploratory Analysis – Missing Values Imputed (mITT Population)		

Output	Title	Use Table Shell	DSMB*
Table 14.2.4.16	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Presence of Hypotension– Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.17	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Presence of Hypotension – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.18	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Presence of Traumatic Subarachnoid Hemorrhage– Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.19	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Presence of Traumatic Subarachnoid Hemorrhage – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.20	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Gender – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.21	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Gender – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.22	Analysis of Glasgow Outcome Scale at 6 Months Post Injury by Time to First Dose – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.4.23	ORs and 95% CIs for Glasgow Outcome Scale at 6 Months Post Injury by Time to First Dose – Exploratory Analysis – Missing Values Imputed (mITT Population)		
Table 14.2.5.1	Summary and Analysis of Mortality at Month 6 (mITT Population)		X
Table 14.2.5.2	Summary and Analysis of Mortality at Month 1 (mITT Population)	14.2.5.1	X
Table 14.2.5.3	Summary and Analysis of Mortality at Month 6 (PP Population)	14.2.5.1	X
Table 14.2.5.4	Summary and Analysis of Mortality at Month 1 (PP Population)	14.2.5.1	X
Table 14.2.5.5	Summary and Kaplan-Meier Analysis of Time to Death (days) (mITT Population)		
Table 14.2.5.6	Summary of Cox Proportional Hazards Analysis of Time to Death (days) (mITT Population)		
Table 14.2.6.1	Summary of Glasgow Outcome Scale at 3 Months Post Injury – Observed Values (mITT Population)	14.2.1.1	
Table 14.2.6.2	Analysis of Glasgow Outcome Scale at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)	14.2.1.2	
Table 14.2.6.3	ORs and CIs of Glasgow Outcome Scale at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)	14.2.1.3	
Table 14.2.7.1	Summary of Glasgow Outcome Scale - Extended at 6 Months Post Injury – Observed Values (mITT Population)	14.2.1.1	

Output	Title	Use Table Shell	DSMB*
Table 14.2.7.2	Analysis of Glasgow Outcome Scale – Extended at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)	14.2.1.2	
Table 14.2.7.3	ORs and CIs of Glasgow Outcome Scale - Extended at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)	14.2.1.3	
Table 14.2.7.4	Summary of Sliding Dichotomy (Dichotomization) – Glasgow Outcome Scale – Extended at 6 Months Post Injury – Observed Values (mITT Population)		
Table 14.2.7.5	Summary and Analysis of Sliding Dichotomy – Glasgow Outcome Scale – Extended at 6 Months Post Injury – Observed Values (mITT Population)		
Table 14.2.7.6	ORs and 95% CIs for Sliding Dichotomy – Glasgow Outcome Scale – Extended at 6 Months Post Injury – Observed Values (mITT Population)		
Table 14.2.7.7	Summary of Glasgow Outcome Scale - Extended at 3 Months Post Injury – Observed Values (mITT Population)		
Table 14.2.7.8	Analysis of Glasgow Outcome Scale – Extended at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)		
Table 14.2.7.9	ORs and CIs of Glasgow Outcome Scale - Extended at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)		
Table 14.2.8.1	Summary of SF-36 by Visit (mITT Population)		
Table 14.2.8.2	Analysis of SF-36 by Visit (mITT Population)		
Table 14.2.9	Shift Summary of CT Classification (mITT Population)		
Table 14.2.10	Summary of Maximum Intracranial Pressure by Visit (mITT Population)		
Table 14.2.11.1	Summary of Cerebral Perfusion Pressure by Visit (mITT Population)		
Table 14.2.11.2	Potentially Clinically Important On-Treatment Cerebral Perfusion Pressure (mITT Population)		
Table 14.2.12.1	Summary of Therapy Intensity Level by Visit (mITT Population)		
Table 14.2.12.2	Summary of Individual TIL Therapies (mITT Population)		
Table 14.2.12.3	Summary of Maximum Therapy Intensity Level (mITT Population)		
Table 14.3.1.1	Overall Summary of Treatment Emergent Adverse Events (Safety Population)		X
Table 14.3.1.2	Overall Summary of Treatment Emergent Adverse Events by Gender (Safety Population)		
Table 14.3.1.3	Overall Summary of Treatment Emergent Adverse Events by Race Group (Safety Population)	14.3.1.2	

Output	Title	Use Table Shell	DSMB*
Table 14.3.1.4	Overall Summary of Treatment Emergent Adverse Events by Age Group (Safety Population)	14.3.1.2	
Table 14.3.1.5	Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)		X
Table 14.3.1.6	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Gender (Safety Population)		
Table 14.3.1.7	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Race Group (Safety Population)		
Table 14.3.1.8	Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Age Group (Safety Population)		
Table 14.3.1.9	Treatment-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)	14.3.1.5	X
Table 14.3.1.10	Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term (Safety Population)		
Table 14.3.1.11	Treatment-Related Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term (Safety Population)	14.3.1.9	
Table 14.3.1.12	Treatment Emergent Adverse Events by Maximum Relationship, System Organ Class and Preferred Term (Safety Population)		
Table 14.3.1.13	Treatment Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population)	14.3.1.5	
Table 14.3.1.14	Treatment-Related Treatment Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population)	14.3.1.5	
Table 14.3.1.15	Treatment Emergent Adverse Events of Special Interest (Safety Population)		X
Table 14.3.1.16	List of Adverse Events of Special Interest (Safety Population)		X
Table 14.3.2.1	Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)	14.3.1.5	X
Table 14.3.2.2	Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)	14.3.1.5	X
Table 14.3.2.3	Primary Cause of Death (mITT Population)		X
Table 14.3.4.1	Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Coagulation (Safety Population)		X
Table 14.3.4.2	Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Hematology (Safety Population)	14.3.4.1	X
Table 14.3.4.3	Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Serum Chemistry (Safety Population)	14.3.4.1	

Output	Title	Use Table Shell	DSMB*
Table 14.3.4.4	Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Urinalysis (Safety Population)		
Table 14.3.4.5	List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Coagulation (Safety Population)	14.3.4.9	X
Table 14.3.4.6	List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Hematology (Safety Population)		X
Table 14.3.4.7	List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Serum Chemistry (Safety Population)	14.3.4.9	X
Table 14.3.4.8	List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Urinalysis (Safety Population)	14.3.4.9	X
Table 14.3.4.9	Summary of Coagulation Laboratory Test Results (Safety Population)		
Table 14.3.4.10	Summary of Hematology Laboratory Test Results (Safety Population)	14.3.4.12	
Table 14.3.4.11	Summary of Serum Chemistry Laboratory Test Results (Safety Population)	14.3.4.12	
Table 14.3.5	Summary of Incidence of Neuroworsening (Safety Population)		
Table 14.3.6.1	Summary of Vital Signs Corresponding to Lowest Measurement (Safety Population)		X
Table 14.3.6.2	Summary of Vital Signs Corresponding to Highest Measurement (Safety Population)	14.3.5.1	X
Table 14.3.6.3	Summary of Vital Signs by Visit – Weight (kg) (Safety Population)		
Table 14.3.7.1	Summary of Physical Examination by Visit (Safety Population)		
Table 14.3.7.2	List of Physical Examination Abnormalities Post-Baseline (Safety Population)		
Table 14.3.8.1	Post-Baseline Abnormal ECG Results (Safety Population)		X
Table 14.3.8.2	List of Post-Baseline Abnormal ECG Results – Part 1 and Part 2 (Safety Population)		X
Table 14.3.9	Summary of Worst Arterial Blood Gas (ABG) Results by Visit (Safety Population)		X
14.3.10	Summary of Day 2 Progesterone Levels (Safety Population)		

*** Tables produced for DSMB**

Figures

Figure	Title	DSMB*
Figure 14.2.1.1	Glasgow Outcome Scale distribution at 6 Months Post Injury – Missing Values Imputed (mITT Population)	X

Figure	Title	DSMB*
Figure 14.2.1.2	Glasgow Outcome Scale distribution at 6 Months Post Injury – Observed Values (mITT Population)	X
Figure 14.2.1.3	Glasgow Outcome Scale distribution at 6 Months Post Injury – Observed Values (PP Population)	
Figure 14.2.2.1	Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)	
Figure 14.2.2.2	Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)	
Figure 14.2.3.1	Mortality at 6 Months (mITT Population)	X
Figure 14.2.3.2	Mortality at 1 Month (mITT Population)	X
Figure 14.2.3.3	Time to Death (mITT Population)	

*** Figures produced for DSMB**

Data Listings

Listing	Title	DSMB*
Listing 16.2.1.1	Study Completion/Discontinuation Details	
Listing 16.2.1.2	Eligibility/Randomization	
Listing 16.2.1.3	Exclusions from Per Protocol Population	
Listing 16.2.3.1	Subject General Information	X
Listing 16.2.3.2	Informed Consent	
Listing 16.2.4.1	Demographic Characteristics	X
Listing 16.2.4.2	Baseline Characteristics	X
Listing 16.2.4.3	Pre-injury Narrative – Baseline Status – Parts 1, 2 and 3	
Listing 16.2.4.4	Glasgow Coma Scale	
Listing 16.2.4.5	Medical History	
Listing 16.2.4.6	Prior, and Concomitant Medications	
Listing 16.2.4.7	Concomitant Procedures	
Listing 16.2.4.8	Surgical Therapy	
Listing 16.2.4.9	Study Admission	
Listing 16.2.4.10	Subject Transfer	
Listing 16.2.4.11	Facility Transfer	
Listing 16.2.4.12	Intubation	
Listing 16.2.4.13	Daily Fluid	
Listing 16.2.5.1	Study Drug Administration Parts 1 and 2	X
Listing 16.2.5.2	End of Treatment	X

Listing	Title	DSMB*
Listing 16.2.6.1.1	Glasgow Outcome Scale, Questions	X
Listing 16.2.6.1.2	Glasgow Outcome Scale, Explanation of Categories	X
Listing 16.2.6.1.3	Glasgow Outcome Scale – Extended, Explanation of Categories	
Listing 16.2.6.1.4	Glasgow Outcome Scale – Part 1	X
Listing 16.2.6.1.5	Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Parts 1-6	X
Listing 16.2.6.1.6	Primary Efficacy, Covariates, and Subgroup Variables (Observed Values)	X
Listing 16.2.6.1.7	Primary Efficacy, Covariates, and Subgroup Variables (Missing Values Imputed)	X
Listing 16.2.6.2	Sliding Dichotomy	
Listing 16.2.6.3	Mortality	X
Listing 16.2.6.4.1	SF-36, Explanation of Categories	
Listing 16.2.6.4.2	SF-36 (Individual Questions) - Parts 1, 2 and 3	
Listing 16.2.6.4.3	SF-36 (Scales and Summary Scores) - Parts 1 and 2	
Listing 16.2.6.5.1	CT Scan and Classification - Parts 1, 2 and 3	
Listing 16.2.6.5.2	CT Scan Comparison - Parts 1, 2 and 3	
Listing 16.2.6.6.1	Intracranial Pressure	
Listing 16.2.6.6.2	Intracranial Pressure Monitoring	
Listing 16.2.6.7	Cerebral Perfusion Pressure	
Listing 16.2.6.8.1	Therapy Intensity Level Parts 1 and 2	
Listing 16.2.7	Adverse Events	X
Listing 16.2.8.1.1	Laboratory (Coagulation) Results	
Listing 16.2.8.1.2	Laboratory (Hematology) Results	
Listing 16.2.8.1.3	Laboratory (Serum Chemistry) Results	
Listing 16.2.8.1.4	Laboratory (Urinalysis) Results	
Listing 16.2.8.1.5	Laboratory (Pregnancy Test) Results	
Listing 16.2.8.2	Vital Signs	X
Listing 16.2.8.3	Physical Examinations	
Listing 16.2.8.4	12-Lead Electrocardiogram (ECG) Parts 1 and 2	
Listing 16.2.8.5	Arterial Blood Gas	X
Listing 16.2.8.6	Neuroworsening Parts 1 and 2	

*** Listings produced for DSMB**

Note: Listings generated for all mITT subjects.

Statistical Output

Appendix	Title
Appendix 14.2.1.2	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)*
The above appendix will include the SAS output details relating to Table 14.2.1.2 and 14.2.1.3 (Analysis, ORs and CIs).	
Appendix 14.2.1.5	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.1.5 and 14.2.1.6 (Analysis, ORs and CIs).	
Appendix 14.2.1.8	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)
The above appendix will include the SAS output details relating to Table 14.2.1.8 and 14.2.1.9 (Analysis, ORs and CIs).	
Appendix 14.2.1.11	Analysis of Glasgow Outcome Scale at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.1.11 and 14.2.1.12 (Analysis, ORs and CIs).	
Appendix 14.2.1.13	Analysis of Glasgow Outcome Scale at 6 Months Post Injury– Missing Values Imputed (Unadjusted Analysis) (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.1.13 and 14.2.1.14 (Analysis, ORs and CIs).	
Appendix 14.2.2.2	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Missing Values Imputed (mITT Population)
Appendix 14.2.2.5	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Observed Values (mITT Population)
Appendix 14.2.2.8	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Observed Values (PP Population)
Appendix 14.2.2.11	Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)
Appendix 14.2.3.2	Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.3.2 and 14.2.3.3 (Analysis, ORs and CIs).	
Appendix 14.2.3.5	Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.3.5 and 14.2.3.6 (Analysis, ORs and CIs).	
Appendix 14.2.3.8	Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)
The above appendix will include the SAS output details relating to Table 14.2.3.8 and 14.2.3.9 (Analysis, ORs and CIs).	

Appendix	Title
Appendix 14.2.3.10	Analysis of Dichotomized (GR vs. MD, SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.3.10 and 14.2.3.11 (Analysis, ORs and CIs).	
Appendix 14.2.3.12	Analysis of Dichotomized (GR, MD, SD vs. V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.3.12 and 14.2.3.13 (Analysis, ORs and CIs).	
Appendix 14.2.4.1	Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Exploratory Analysis – Missing Values Imputed (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.4.1 (Analysis, ORs and CIs).	
Appendix 14.2.5.1	Summary and Analysis of Mortality at Month 6 (mITT Population)
Appendix 14.2.5.2	Summary and Analysis of Mortality at Month 1 (mITT Population)
Appendix 14.2.5.3	Summary and Analysis of Mortality at Month 6 (PP Population)
Appendix 14.2.5.4	Summary and Analysis of Mortality at Month 1 (PP Population)
Appendix 14.2.5.5	Summary and Kaplan-Meier Analysis of Time to Death (days) (mITT Population)
Appendix 14.2.5.6	Summary and Cox Proportional Hazards Analysis of Time to Death (days) (mITT Population)
Appendix 14.2.6.2	Analysis of Glasgow Outcome Scale at 3 months post injury – Observed Values (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.6.2 and 14.2.6.3 (Analysis, ORs and CIs).	
Appendix 14.2.7.2	Analysis of Glasgow Outcome Scale - Extended at 6 Months Post Injury – Observed Values (mITT Population)
The above appendix will include the SAS output details relating to Table 14.2.7.2 and 14.2.7.3 (Analysis, ORs and CIs).	
Appendix 14.2.7.5	Summary and Analysis of Sliding Dichotomy – Glasgow Outcome Scale – Extended at 6 Months Post Injury – Observed Values (mITT Population)
Appendix 14.2.7.8	Analysis of Glasgow Outcome Scale - Extended at 3 Months Post Injury – Observed Values (mITT Population)
Appendix 14.2.8.2	Analysis of SF-36 by Visit (mITT Population)

Model Checking Figures

Figure 14.2.1.1.1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months [Treatment Group] – Missing Values Imputed (mITT Population)
Figure 14.2.1.1.2	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months [Region] – Missing Values Imputed (mITT Population)
Figure 14.2.1.1.3	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months [Age] – Missing Values Imputed (mITT Population)
Figure 14.2.1.1.4	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months [GCS Motor Score] – Missing Values Imputed (mITT Population)
Figure 14.2.1.1.5	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months [Pupil Response] – Missing Values Imputed (mITT Population)
Figure 14.2.1.1.6	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months [CT Classification] – Missing Values Imputed (mITT Population)

Figure	14.2.1.1.1
Title 1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months – Missing Values Imputed [Treatment Group] (mITT Population)
Title 2	Predictor = Treatment Group
Type of graph	Line graph
y-axis	Empirical Cumulative Logit
y-axis (label)	Empirical Cumulative Logit
x-axis	Treatment Group
x-axis (label)	Treatment Group
Legend (if applicable)	A legend should be included to identify each empirical cumulative logit 1 = $EmpLogit_1 = \log[(y_1)/(y_2+ y_3+ y_4)]$, 2 = $EmpLogit_2 = \log[(y_1+ y_2)/(y_3+ y_4)]$ and 3 = $EmpLogit_3 = \log[(y_1+ y_2+ y_3)/(y_4)]$ And treatment group: BHR-100 and Placebo
Footnote 1	Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

Figure	14.2.1.1.2
Title 1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months Missing Values Imputed [Region] (mITT Population)
Title 2	Predictor = Region
Type of graph	Line graph
y-axis	Empirical Cumulative Logit
y-axis (label)	Empirical Cumulative Logit
x-axis	Region
x-axis (label)	Region
Legend (if applicable)	A legend should be included to identify each empirical cumulative logit 1 = $EmpLogit_1 = \log[(y_1)/(y_2+ y_3+ y_4)]$, 2 = $EmpLogit_2 = \log[(y_1+ y_2)/(y_3+ y_4)]$ and 3 = $EmpLogit_3 = \log[(y_1+ y_2+ y_3)/(y_4)]$ And region: North America, Europe, Asia and South America
Footnote 1	Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

Figure	14.2.1.1.3
Title 1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months Missing Values Imputed [Age] (mITT Population)
Title 2	Predictor = Age
Type of graph	Line graph
y-axis	Empirical Cumulative Logit
y-axis (label)	Empirical Cumulative Logit
x-axis	Age
x-axis (label)	Age
Legend (if applicable)	A legend should be included to identify each empirical cumulative logit 1 = $EmpLogit_1 = \log[(y_1)/(y_2+ y_3+ y_4)]$, 2 = $EmpLogit_2 = \log[(y_1+ y_2)/(y_3+ y_4)]$ and 3 = $EmpLogit_3 = \log[(y_1+ y_2+ y_3)/(y_4)]$
Footnote 1	Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

Figure	14.2.1.1.4
Title 1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months Missing Values Imputed [GCS Motor Score] (mITT Population)
Title 2	Predictor = GCS motor score
Type of graph	Line graph
y-axis	Empirical Cumulative Logit
y-axis (label)	Empirical Cumulative Logit
x-axis	GCS motor score
x-axis (label)	GCS motor score
Legend (if applicable)	A legend should be included to identify each empirical cumulative logit 1 = $EmpLogit_1 = \log[(y_1)/(y_2+ y_3+ y_4)]$, 2 = $EmpLogit_2 = \log[(y_1+ y_2)/(y_3+ y_4)]$ and 3 = $EmpLogit_3 = \log[(y_1+ y_2+ y_3)/(y_4)]$ And GCS motor score: $\leq$2 versus >2.
Footnote 1	Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

Figure	14.2.1.1.5
Title 1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months Missing Values Imputed [Pupil Response] (mITT Population)
Title 2	Predictor = Pupil Response
Type of graph	Line graph
y-axis	Empirical Cumulative Logit
y-axis (label)	Empirical Cumulative Logit
x-axis	Pupil Response
x-axis (label)	Pupil Response
Legend (if applicable)	A legend should be included to identify each empirical cumulative logit 1 = $EmpLogit_1 = \log[(y_1)/(y_2+ y_3+ y_4)]$, 2 = $EmpLogit_2 = \log[(y_1+ y_2)/(y_3+ y_4)]$ and 3 = $EmpLogit_3 = \log[(y_1+ y_2+ y_3)/(y_4)]$ And Pupil Response: bilateral, unilateral, no reactive pupils, or not testable
Footnote 1	Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

Figure	14.2.1.1.6
Title 1	Graphical Assessment of Proportional Odds Assumption for Proportional Odds Model of Glasgow Outcome Scale at 6 months Missing Values Imputed [CT Classification] (mITT Population)
Title 2	Predictor = CT Classification
Type of graph	Line graph
y-axis	Empirical Cumulative Logit
y-axis (label)	Empirical Cumulative Logit
x-axis	CT Classification
x-axis (label)	CT Classification
Legend (if applicable)	A legend should be included to identify each empirical cumulative logit 1 = $EmpLogit_1 = \log[(y_1)/(y_2+ y_3+ y_4)]$, 2 = $EmpLogit_2 = \log[(y_1+ y_2)/(y_3+ y_4)]$ and 3 = $EmpLogit_3 = \log[(y_1+ y_2+ y_3)/(y_4)]$ And CT Classification: Marshall's CT Classification II, III, IV, evacuated and non-evacuated mass lesion
Footnote 1	Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

APPENDIX 3 SHELLS FOR POST-TEXT TABLES, FIGURES, AND LISTINGS

Table 14.1.1.1 Summary of Investigational Sites' Enrollment Duration (mITT Population)

Region/Country[1]/ Site	Principal Investigator	Study			Number of Subjects	
		Start Date[2]	End Date[2]	Duration (days)[3]	Randomized	Completed Endpoint[4]
All Sites (N=xxx)		DDMONYYYY	DDMONYYYY	xx	xx	xx
Region 1/Country AR/						
01	xxxxxxxxxxxx	DDMONYYYY	DDMONYYYY	xx	xx	xx
02	xxxxxxxxxxxx	DDMONYYYY	DDMONYYYY	xx	xx	xx
03	xxxxxxxxxxxx	DDMONYYYY	DDMONYYYY	xx	xx	xx
…						

[1] See Table 14.1.1.6 for 2-letter country codes.
[2] Start Date and End Date are the date of the first consent and the last subject randomization at a specific site, respectively.
[3] Duration (days) = End Date – Start Date + 1.
[4] Subjects are endpoint completers if they provide a GOS assessment at Month 6 or die before Month 6.

Source: Listing 16.2.3.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.1.2 Summary of Enrollment by Region, Country, and Site (mITT Population)

Region[1]/Country[2]/Site	~~Statistic~~	BHR-100 (N=xx) n (%)	Placebo (N=xx) n (%)	Total (N=xx) n (%)
All Sites	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Region				
North America	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Europe	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Asia	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
South America	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Country				
AR	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
AU	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
BE	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…				
Region/Site				
North America	~~n (%)~~			
01	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
02	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Europe				
01		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
02		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…				

[1] North America=United States, Europe=Austria, Belgium, Czech Republic, Finland, France, Germany, Hungary, Israel, Italy, Netherlands, Romania, Russia, Spain, and United Kingdom, Asia=China, Malaysia, Singapore, Taiwan, and Thailand, South America=Argentina.
[2] See Table 14.1.1.6 for 2-letter country codes.
Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.

Source: Listing 16.2.4.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.1.3 Summary of Subject Disposition (Randomized Subjects)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Subjects Who Were				
Randomized but Not Treated	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Modified Intention-to-Treat[1]	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Safety Population[2]	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Per Protocol[3]	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Study Completers[4]	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Endpoint Completers[5]	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Early Termination	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Reason for Early Termination				
Death	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Adverse Event(s)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Withdrawal of Consent	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Protocol Violation	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Lost to Follow-up	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Discretion of the Investigator	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Discretion of the Sponsor	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

[1] Modified Intention-to-Treat (mITT) Population includes all subjects who were randomized and in whom treatment with i.v. study drug was initiated (analyzed according to randomized treatment).
[2] Safety Population includes all subjects who received any study medication (analyzed according to actual treatment received).
[3] Per Protocol Population includes all subjects in the mITT population who meet all inclusion/exclusion criteria, received at least 96 hours of study medication treatment, and have a non-missing 6-month GOS score.
[4] Subjects are completers if they complete 6 months involvement in the study.
[5] Subjects who provide a GOS at 6 months, including deaths carried forward to 6 months.
Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.

Source: Listings 16.2.1.1, 16.2.1.2, 16.2.3.1

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.1.4 Summary of Subject Status by Time (mITT Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Study Completers	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Early Termination	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Subjects Remaining in Study				
Day 1	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 2	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 3	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 4	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 5	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 6	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 15	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 30	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 90	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Day 180	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Subjects are completers if they completed a Month 6 visit. Early terminations include deaths.
Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.

Source: Listing 16.2.1.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.1.5 Country Codes per ISO

Code	Country
AR	Argentina
AT	Austria
BE	Belgium
CN	China
CZ	Czech Republic
DE	Germany
ES	Spain
FI	Finland
FR	France
GB	United Kingdom
HU	Hungary
IL	Israel
IT	Italy
MY	Malaysia
NL	Netherlands
RO	Romania
RU	Russia
SG	Singapore
TH	Thailand
TW	Taiwan
US	United States

Note: ISO=International Organization for Standardization.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.2.1 Summary of Study Drug Exposure and Time from Injury (Safety Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Trt[1] Initiated Within 8 Hours of Injury	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Treated for at Least 96 Hours	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Reason for Incomplete Drug Administration				
Adverse Event	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Death	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
PI Decision	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Sponsor Decision	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Consent Withdrawn	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Length of Exposure (hours)				
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx	xx , xx
Length of Exposure: Categorized (hours)				
>0-<=24	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>24-<=48	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>48-<=72	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>72-<=96	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>96-<=120	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>120	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Length of Exposure (in hours) = last dose date/time – first dose date/time – (sum of recorded durations of infusion rate interruptions).
Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.
[1] Trt = Treatment.
[2] Relative Dose is summarized for the subset of subjects who received drug for 114 to 126 hours (120 +/- 5%).

Source: Listing 16.2.5.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.2.1 Summary of Study Drug Exposure and Time from Injury (Safety Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Total Dose (mg/kg)				
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx	xx , xx
Relative Dose[2]				
0 < Relative Dose <=80%	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
80% < Relative Dose <=100%	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
100% < Relative Dose <=120%	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Relative Dose > 120%	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Time Since Injury to Study Drug (hours)				
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx	xx , xx
Time Since Injury to Study Drug: Categorized (hours)				
0-<=4	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>4-<=6	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>6-<=8	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>8-<=9	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
>9	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Length of Exposure (in hours) = last dose date/time - first dose date/time - (sum of recorded durations of infusion rate interruptions).
Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.
[1] Trt = Treatment.
[2] Relative Dose is summarized for the subset of subjects who received drug for 114 to 126 hours (120 +/- 5%).

Source: Listing 16.2.5.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.2.2 Drug Administration Summary (Safety Population)

Question	Response	~~Statistic~~	BHR-100 (N=xx) n (%)	Placebo (N=xx) n (%)	Total (N=xx) n (%)
Infusion Rate Modified on Any Day	Yes		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	No		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Reason for Modification	Adverse Event	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	IV Access Problem	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Subcutaneous Infusion	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Inappropriate/Non-Consistent Infusion Rate	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Other	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Infusion Interrupted >30 Minutes on Any Day	Yes		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	No		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Reason for Modification	Adverse Event	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	IV Access Problem	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Subcutaneous Infusion	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Inappropriate/Non-Consistent Infusion Rate	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Other	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.

Source: Listing 16.2.5.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Include loading dose and maintenance doses in same table.]

Table 14.1.2.3 Summary of Study Drug Compliance Rate (Safety Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Overall Compliance (%)	n	xx	xx	xx
	Mean (SD)	xx.xx (xx.xx)	xx.xx (xx.xx)	xx.xx (xx.xx)
	Median	xx.xx	xx.xx	xx.xx
	Q1, Q3	xx.xx , xx.xx	xx.xx , xx.xx	xx.xx , xx.xx
	Min, Max	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x

Note: Compliance rate is calculated by dividing the hours of study medication taken by the number of hours that should have been taken during the treatment period multiplied by 100.

Source: Listing 16.2.5.1 and 16.2.5.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Programmer Note: See section 5 and 9.3.1 for details about compliance calculation]

Table 14.1.3.1 Prior and Concomitant Medications by WHO Drug Dictionary Preferred Term (mITT Population)

		BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Any Prior or Concomitant Medication	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 1	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 2	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 3	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 4	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 5	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects in each treatment group and total in the population of interest.
Note: Subjects could have received more than one prior medication.
Note: Prior medications are defined as medications with a stop date before the first administration of study medication. Concomitant medications are defined as medications with a start or stop date after the first administration of study medication or ongoing on Day 15.

Source: Listing 16.2.4.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.3.2 Surgical Therapy (mITT Population)

Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Type of Surgery	N	xx	xx	xx
Intracranial	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extracranial	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Intracracranial Surgery Type	N	xx	xx	xx
Aneurysm (non trauma)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Acute Subdural Hematoma	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Contusion	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Craniofacial Surgery	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
CSF Shunt	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Chronic Subdural Hematoma	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Decompressive Craniectomy Injuries	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Depressed Skull Fracture	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Epidural Hematoma	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Intracerebral Hematoma	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Infection	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Optic Nerve Decompression	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Posterior Fossa Surgery	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Skull Base Fracture	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Ventriculostomy for CSG Drainage	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Debridement - Minimal for Penetrating Injuries	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Debridement - Extensive for Penetrating Injuries	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Foreign Body Removal	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Bone Flap Replacement	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects with data in each treatment group and total in the population of interest.

Source: Listing 16.2.4.8.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.3.2 Surgical Therapy (mITT Population)

Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Extracranial Surgery Type	N	xx	xx	xx
Maxillofacial	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extremity Fracture Lower Limb (Internal Fixation)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extremity Fracture Lower Limb (External Fixation)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extremity Fracture Upper Limb (Internal Fixation)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extremity Fracture Upper Limb (External Fixation)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Fasciotomy	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Laparotomy (Abdomen)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pelvic Fracture (Internal Fixation)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pelvic Fracture (External Fixation)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Placement of Chest Tube	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Placement of Gastric Tube (PEG)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Spinal Stabilization/Thoracic	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Spinal Stabilization/Lumbal	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Thoracotomy	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Tracheostomy	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Urinary Catheter	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Vascular (Operative)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Vascular (Endovascular Treatment)	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Wound Closure Graft	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects with data in each treatment group and total in the population of interest.

Source: Listing 16.2.4.8.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.4.1 Demographic Characteristics (mITT Population)

Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Age (years)	n	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx	xx , xx
Sex	N	xx	xx	xx
Male	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Female	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Ethnicity	N	xx	xx	xx
Hispanic or Latino	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Not Hispanic or Latino	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Not Allowed to Obtain	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Race	N	xx	xx	xx
White	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Black, African American or of African heritage	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Native Hawaiian or other Pacific Islander	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Asian	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
American Indian or Alaska Native	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Not Allowed to Obtain	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects with data in each treatment group and total in the population of interest.
Note: Age (years) = (date of informed consent – date of birth + 1)/365.25.

Source: Listing 16.2.4.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.4.2 Pregnancy Testing (mITT Population)

Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Female[1]	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Female of Child-Bearing Potential[2]	N	xx	xx	xx
Yes	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Missing	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Sample Collected for Pregnancy Test[3]	N	xx	xx	xx
Yes	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Missing	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pregnancy Test Result[4]	N	xx	xx	xx
Positive	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Negative	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Missing	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

[1] Percentages are calculated using the number of subjects with data as the numerator and the number of subjects in the mITT population as the denominator.
[2] Percentages are calculated using the number of subjects with data as the numerator and the number of female subjects as the denominator.
[3] Percentages are calculated using the number of subjects with data as the numerator and the number of female subjects of child-bearing potential as the denominator.
[4] Percentages are calculated using the number of subjects with data as the numerator and the number of samples collected for pregnancy testing as the denominator.

Source: Listing 16.2.8.1.5.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.4.3 Baseline Characteristics (mITT Population)

Characteristic	~~Statistic~~	BHR-100 (N=xx) n (%)	Placebo (N=xx) n (%)	Total (N=xx) n (%)
Region				
North America	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Europe	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Asia	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
South America	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
GCS Motor score				
1-2	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
3	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
4	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
5-6	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pupillary Response				
Bilateral	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Unilateral	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No Reactive Pupils	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Not Testable	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Hypoxia[1]				
Yes	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Suspected	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Unknown	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: GCS=Glasgow Coma Score.
Note: Percentages are based on the number of subjects with baseline data in each treatment group and overall.
[1] Hypoxia is defined as PaO_2 < 60 mmHg.
[2] Hypotension is defined as systolic blood pressure < 90 mmHg.
Source: Listing 16.2.6.1.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: The GCS motor score will come from the screening GCS, presence of hypoxia/hypotension comes from resuscitation CRF page, CT classification and presence of subarachnoid hemorrhage will come from the screening CT scan. Pupillary response will come from the assessment of right and left pupil reactivity. If both right and left pupils react = bilateral, if either right or left pupil reacts = unilateral , if neither pupil reacts = no reactivel pupils, or the eyes are closed (i.e. untestable) = not testable.]

Table 14.1.4.3 Baseline Characteristics (mITT Population)

Characteristic	~~Statistic~~	BHR-100 (N=xx) n (%)	Placebo (N=xx) n (%)	Total (N=xx) n (%)
Hypotension[2]				
Yes	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Suspected	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Unknown	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Marshall CT Classification				
I		xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
II	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
III	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
IV	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Evacuated/Non-Evacuated Mass Lesion	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Traumatic Subarachnoid Hemorrhage				
Yes	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
No	~~n (%)~~	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: GCS=Glasgow Coma Score.
Note: Percentages are based on the number of subjects with baseline data in each treatment group and overall.
[1] Hypoxia is defined as PaO_2 < 60 mmHg.
[2] Hypotension is defined as systolic blood pressure < 90 mmHg.

Source: Listing 16.2.6.1.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: The GCS motor score will come from the screening GCS, presence of hypoxia/hypotension comes from resuscitation CRF page, CT classification and presence of subarachnoid hemorrhage will come from the screening CT scan. Pupillary response will come from the assessment of right and left pupil reactivity. If both right and left pupils react = bilateral, if either right or left pupil reacts = unilateral , if neither pupil reacts = no reactivel pupils, or the eyes are closed (i.e. untestable) = not testable.]

Table 14.1.4.4 Summary of Injury (mITT Population)

Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Cause of Traumatic Brain Injury	n	xx	xx	xx
Motor Vehicle	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Motorcycle	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Fall	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Sports/Recreation	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pedestrian	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Diving	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Assault	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects in each treatment group and total in the population of interest.

Source: Listing 16.2.4.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.1.4.4 Summary of Injury (mITT Population)

Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Head Injury Alone	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Face	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Chest	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Abdomen	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extremities	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Spine	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects in each treatment group and total in the population of interest.

Source: Listing 16.2.4.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: The summaries of Face, Chest, Abdomen, Extremities, and Spine injuries will include subjects who had a severe or critical exam result for the given injury. Head injury alone summary will include subjects who did not have a severe or critical injury to one of the other body parts.]

Table 14.1.5 Summary of Medical History by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Any Medical History	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
System Organ Class 1	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 1	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 2	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 3	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 4	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 5	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
System Organ Class 2	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 1	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 2	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 3	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 4	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 5	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Percentages are based on the number of subjects in each treatment group and total in the population of interest.

Source: Listing 16.2.4.5.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.1.1 Summary of Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Glasgow Outcome Scale	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Good Recovery	n (%)	xx (xx.x %)	xx (xx.x %)
Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)
Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)
Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Percentages are based on the number of non-missing GOS at the month 6 assessment in each treatment group in the population of interest.

Source: Listing 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: For the "Observed Values" summaries, please add a Missing category to the table.]

Table 14.2.1.2 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (mITT Population)

Characteristic	DF[2]	Chi-Square[3]	P-Value[3]
Score Test for Proportional Odds Assumption[4]	xx	xx.xxx	x.xxx
Treatment	xx	xx.xxx	x.xxx
Region	xx	xx.xxx	x.xxx
Age	xx	xx.xxx	x.xxx
GCS Motor Score	xx	xx.xxx	x.xxx
Pupil Response	xx	xx.xxx	x.xxx
CT Classification	xx	xx.xxx	x.xxx

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.

[1] Response variable Glasgow Outcome Scale at 6 months post injury has 4 values (Good Recovery, Moderate Disability, Severe Disability and Vegetative State/Dead).

[2] DF=Degrees of Freedom.

[3] The score test is based on the Chi-Square test and the Type 3 analysis of effects are based on the Wald Chi-Square test from a Logistic Regression analysis (Proportional Odds Model). The POM will model the odds of a favorable outcome/higher GOS category and will be fitted including treatment, geographic region (North America, Europe, Asia, and South America), age, GCS motor score (1-2, 3, 4, 5-6), pupil response (unilateral, bilateral, no reactive pupils/not testable), and CT classification (I/II, III, IV, V/VI).

[4] A non-significant result supports the proportional odds assumption.

Source: Listing 16.2.6.1.4 and 16.2.6.1.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.1.3 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model – Missing Values Imputed (mITT Population)

Effect[3]	Odds Ratio	95% CI[2]
Treatment (BHR-100 vs. Placebo)	x.xx	(x.xx, x.xx)
Region (North America vs. Europe)	x.xx	(x.xx, x.xx)
Region (Asia vs. Europe)	x.xx	(x.xx, x.xx)
Region (South America vs. Europe)	x.xx	(x.xx, x.xx)
Age	x.xx	(x.xx, x.xx)
GCS Motor Score (3 vs. 1/2)	x.xx	(x.xx, x.xx)
GCS Motor Score (4 vs. 1/2)	x.xx	(x.xx, x.xx)
GCS Motor Score (5/6 vs. 1/2)	x.xx	(x.xx, x.xx)
Pupil Response (Bilateral vs. Unilateral/No Reactive Pupils/Not Testable)	x.xx	(x.xx, x.xx)
CT Classification (I/II vs. V/VI)	x.xx	(x.xx, x.xx)
CT Classification (III vs. V/VI)	x.xx	(x.xx, x.xx)
CT Classification (IV vs. V/VI)	x.xx	(x.xx, x.xx)

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.

[1] OR=Odds Ratio.

[2] CI=Confidence Interval.

[3] The OR and CIs come from a Logistic Regression analysis (Proportional Odds Model). The POM will model the odds of a favorable outcome/higher GOS category and will be fitted including treatment, geographic region (North America, Europe, Asia, and South America), age, GCS motor score (1-2, 3, 4, 5-6), pupil response (unilateral, bilateral, no reactive pupils/not testable), and CT classification (I/II, III, IV, V/VI). For factors, the last level is taken as the reference level. For example, CT classification with 5 levels (II-V/VI), level V/VI is taken as the reference level. Marshall CT Score classification was used.

Source: Listing 16.2.6.1.4 and 16.2.6.1.6.

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Table 14.2.1.4 Summary of Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)
Table 14.2.1.5 Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)
Table 14.2.1.6 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)

Table 14.2.1.7 Summary of Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)
Table 14.2.1.8 Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (PP Population)
Table 14.2.1.9 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Observed Values (PP Population)

Table 14.2.1.10 Summary of Glasgow Outcome Scale at 6 Months Post Injury for US Only – Missing Values Imputed (mITT Population)
Table 14.2.1.11 Analysis of Glasgow Outcome Scale at 6 Months Post Injury for US Only – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.1.12 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury for US Only – Proportional Odds Model - Missing Values Imputed (mITT Population)

Table 14.2.1.13 Analysis of Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (Unadjusted Analysis) (mITT Population)
Table 14.2.1.14 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury – Proportional Odds Model - Missing Values Imputed (Unadjusted Analysis) (mITT Population)

Note: Tables 14.2.1.13 and 14.2.1.14 will only have a row for Treatment, as other covariates will not be included in the model.

Table 14.2.2.1 Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Prognosis	Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Best	n	n	xx	xx	xx
	Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Intermediate	n	n	xx	xx	xx
	Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Moderate Disability	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Worst	n	n	xx	xx	xx
	Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Moderate Disability	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Severe Disability	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Overall	n	n	xx	xx	xx
	Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Moderate Disability	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.
Percentages are based on the number of subjects in each treatment group in the population of interest.

Source: Listing 16.2.6.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Is there a way to indicate with a different font or making the font bold the Glasgow Outcome Scale outcomes that respond to a favorable outcome, i.e. split the overall column into approximately 50:50 within each prognosis group?]

Table 14.2.2.2 Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Prognosis	Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	P-Value[1] BHR-100 vs. Placebo	Difference (95% CI)[2] BHR-100 - Placebo
Overall	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
Best	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
Intermediate	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
Worst	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects. Percentages are based on the number of subjects in each treatment group in the population of interest.
[1] P-value is based on Cochran-Mantel Haenszel Chi-Square test adjusted for region.
[2] Difference is in proportion of favourable outcomes. The confidence interval for the difference is the standard Wald asymptotic confidence interval based on the normal approximation to the binomial distribution.

Source: Listing 16.2.6.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.2.4 Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury **– Observed Values (mITT Population)**
Table 14.2.2.5 Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury **– Observed Values (mITT Population)**
Table 14.2.2.6 ORs[1] and 95% CIs[2] for Sliding Dichotomy at 6 Months Post Injury **– Observed Values (mITT Population)**

Table 14.2.2.7 Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury **– Observed Values (PP Population)**
Table 14.2.2.8 Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury **– Observed Values (PP Population)**
Table 14.2.2.9 ORs[1] and 95% CIs[2] for Sliding Dichotomy at 6 Months Post Injury **– Observed Values (PP Population)**

Table 14.2.2.10 Summary of Sliding Dichotomy (Dichotomization) at 6 Months Post Injury **for US Only – Missing Values Imputed (mITT Population)**
Table 14.2.2.11 Summary and Analysis of Sliding Dichotomy at 6 Months Post Injury **for US Only – Missing Values Imputed (mITT Population)**
Table 14.2.2.12 ORs[1] and 95% CIs[2] for Sliding Dichotomy at 6 Months Post Injury **for US Only – Missing Values Imputed (mITT Population)**

Table 14.2.2.3 ORs[1] and 95% CIs[2] for Sliding Dichotomy at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Characteristic	Prognosis	p-value	OR[3] (95% CI)
Breslow-Day Test for Homogeneity of Odds Ratios		x.xxx	
Prognosis	Overall		x.xx (xx.x, xx.x)
	Best		x.xx (xx.x, xx.x)
	Intermediate		x.xx (xx.x, xx.x)
	Wost		x.xx (xx.x, xx.x)

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.
[1] OR=Odds Ratio.
[2] CI=Confidence Interval.
[3] OR for BHR-100 vs. Placebo is based on Cochran-Mantel Haenszel Chi-Square test adjusted for region.

Source: Listing 16.2.6.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.3.1 Summary of Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Glasgow Outcome Scale[1]	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
N	n	xx	xx
GR	n (%)	xx (xx.x %)	xx (xx.x %)
MD, SD, V/D	n (%)	xx (xx.x %)	xx (xx.x %)
N	n	xx	xx
GR, MD	n (%)	xx (xx.x %)	xx (xx.x %)
SD, V/D	n (%)	xx (xx.x %)	xx (xx.x %)
N	n	xx	xx
GR, MD, SD	n (%)	xx (xx.x %)	xx (xx.x %)
V/D	n (%)	xx (xx.x %)	xx (xx.x %)

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects. Percentages are based on the number of subjects with data at the month 6 assessment in each treatment group in the population of interest.

[1] GR=Good Recovery, MD=Moderate Disability, SD=Severe Disability, V/D=Vegetative State/Dead. Vegetative state and dead categories are combined for analysis.

Source: Listing 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.3.2 Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale[1] at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Variable	DF[2]	Chi-Square[3]	P-Value[3]
Treatment	xx	xx.xxx	x.xxx
Region	xx	xx.xxx	x.xxx
Age	xx	xx.xxx	x.xxx
GCS Motor Score	xx	xx.xxx	x.xxx
Pupil Response	xx	xx.xxx	x.xxx
CT Classification	xx	xx.xxx	x.xxx

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.

[1] Response variable Glasgow Outcome Scale at 6 months post injury has 2 values (Good Recovery, Moderate Disability vs. Severe Disability, Vegetative State/Dead).

[2] DF=Degrees of Freedom.

[3] The Type 3 analysis of effects are based on the Wald Chi-Square test from a Logistic Regression analysis. The odds of a favorable outcome (GR, MD) will be modeled and will be fitted including treatment, geographic region (North America, Europe, Asia, and South America), age, GCS motor score (1-2, 3, 4, 5-6), pupil response (unilateral, bilateral, no reactive pupils/not testable), and CT classification (I/II, III, IV, V/VI).[4]

Source: Listing 16.2.6.1.4 and 16.2.6.1.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.3.3 ORs[1] and 95% CIs[2] for Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Effect[3]	Odds Ratio	95% CI[2]
Treatment (BHR-100 vs. Placebo)	x.xx	(x.xx, x.xx)
Region (North America vs. Europe)	x.xx	(x.xx, x.xx)
Region (Asia vs. Europe)	x.xx	(x.xx, x.xx)
Region (South America vs. Europe)	x.xx	(x.xx, x.xx)
Age	x.xx	(x.xx, x.xx)
GCS Motor Score (3 vs. 1/2)	x.xx	(x.xx, x.xx)
GCS Motor Score (4 vs. 1/2)	x.xx	(x.xx, x.xx)
GCS Motor Score (5/6 vs. 1/2)	x.xx	(x.xx, x.xx)
Pupil Response (Bilateral vs. Unilateral/No Reactive Pupils/Not Testable)	x.xx	(x.xx, x.xx)
CT Classification (I/II vs. V/VI)	x.xx	(x.xx, x.xx)
CT Classification (III vs. V/VI)	x.xx	(x.xx, x.xx)
CT Classification (IV vs. V/VI)	x.xx	(x.xx, x.xx)

Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.

[1] OR=Odds Ratio.

[2] CI=Confidence Interval.

[3] The OR and CIs come from a Logistic Regression analysis. The odds of a favorable outcome (GR, MD) will be modeled and will be fitted including treatment, geographic region (North America, Europe, Asia, and South America), age, GCS motor score (1-2, 3, 4, 5-6), pupil response (unilateral, bilateral, no reactive pupils/not testable), and CT classification (I/II, III, IV, V/VI).
For factors, the last level is taken as the reference level. For example, CT classification with 4 levels (II-V/VI), level V/VI is taken as the reference level. Marshall CT classification was used.

Source: Listing 16.2.6.1.4 and 16.2.6.1.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.3.4 Summary of Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)

Glasgow Outcome Scale[1]	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
n	n	xx	xx
GR, MD	n (%)	xx (xx.x %)	xx (xx.x %)
SD, V/D	n (%)	xx (xx.x %)	xx (xx.x %)

[1] GR=Good Recovery, MD=Moderate Disability, SD=Severe Disability, V/D=Vegetative/Dead. Vegetative state and dead categories are combined.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Source: Listing 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Note to Programmer: Missing value imputation ONLY done for GR, MD vs. SD, V/D dichotomization.

Table 14.2.3.5 Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale[1] at 6 Months Post Injury – Observed Values (mITT Population)
Table 14.2.3.6 ORs[1] and 95% CIs[2] for Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)

Table 14.2.3.7 Summary of Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)
Table 14.2.3.8 Analysis of Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale[1] at 6 Months Post Injury – Observed Values (PP Population)
Table 14.2.3.9 ORs[1] and 95% CIs[2] for Dichotomized (GR, MD vs. SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (PP Population)

Table 14.2.3.10 Analysis of Dichotomized (GR vs. MD, SD, V/D) Glasgow Outcome Scale[1] at 6 Months Post Injury – Missing Values Imputed (mITT Population)
Table 14.2.3.11 ORs[1] and 95% CIs[2] for Dichotomized (GR vs. MD, SD, V/D) Glasgow Outcome Scale at 6 Months Post Injury –Missing Values Imputed (mITT Population)

Table 14.2.3.12 Analysis of Dichotomized (GR, MD, SD vs. V/D) Glasgow Outcome Scale[1] at 6 Months Post Injury – Missing Values Imputed (mITT Population)
Table 14.2.3.13 ORs[1] and 95% CIs[2] for Dichotomized (GR, MD, SD vs. V/D) Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)

Table 14.2.4.1 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury – Exploratory Analysis – Missing Values Imputed (mITT Population) – **EXAMPLE SHELL***

Effect	DF[4]	Wald Chi-Square[5]	P-Value[5]	Interaction Wald Chi-Square[5]	Interaction with Treatment P-value
Simple Model[2]					
Treatment	xx	xx.xxx	x.xxx	xx.xxx	
Region	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Age	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Race	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
GCS Motor Score	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Pupil Response	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
CT Classification	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Hypoxia	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Hypotension	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Subarachnoid Hemorrhage	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Gender	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Time to first dose	xx	xx.xxx	x.xxx	xx.xxx	x.xxx
Backward Elimination Model[3]					
Treatment	xx	xx.xxx	x.xxx		
Region	xx	xx.xxx	x.xxx		
Age	xx	xx.xxx	x.xxx		
…					

[1] Response variable Glasgow Outcome Scale at 6 months post injury has 4 values (Good Recovery, Moderate Disability, Severe Disability and Vegetative State/Dead).
[2] Each factor is included in a model with treatment and the factor by treatment interaction and run individually.
[3] The backward elimination model begins with all factors in the model. Factor by treatment interactions with p<0.10 in the simple model are included in the Backward Elimination Model. Factors must have a significance level of p<0.10 to remain in the model. Only the final model is shown.
[4] DF=Degrees of Freedom.
[5] The Type 3 analysis of effects are based on the Wald Chi-Square test.

Source: Listing 16.2.6.1.4 and 16.2.6.1.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[* The above template is an example. ONLY the final exploratory model will be presented, so not all the terms indicated above may be included.]
If any of the interaction terms in the exploratory analysis are significant, the following subgroup analyses will be presented:

Table 14.2.4.2 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Region – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.3 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Region – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.4 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Age Group – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.5 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Age Group – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.6 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Race Group – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.7 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Race Group – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.8 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by GCS Motor Score – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.9 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by GCS Motor Score – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.10 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Pupil Response – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.11 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Pupil Response – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.12 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by CT Classification – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.13 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by CT Classification – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.14 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Presence of Hypoxia – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.15 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Presence of Hypoxia – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.16 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Presence of Hypotension – Proportional Odds Model – Missing Values Imputed (mITT Population)
Table 14.2.4.17 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Presence of Hypotension – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.18 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Presence of Traumatic Subarachnoid Hemorrhage – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.19 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Traumatic Subarachnoid Hemorrhage – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.20 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Gender – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.21 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Gender – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.4.22 Analysis of Glasgow Outcome Scale[1] at 6 Months Post Injury by Time to First Dose – Proportional Odds Model - Missing Values Imputed (mITT Population)
Table 14.2.4.23 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 6 Months Post Injury by Time to First Dose – Proportional Odds Model – Missing Values Imputed (mITT Population)

Table 14.2.5.1 Summary and Analysis of Mortality at Month 6 (mITT Population)

Mortality	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	P-Value[1] BHR-100 vs. Placebo	Difference (BHR-100 - Placebo) (95% CI[2])
N[3]	n	xx	xx		
Lost to Follow-up	n (%)	xx (xx.x %)	xx (xx.x %)		
Consent Withdrawn	n (%)	xx (xx.x %)	xx (xx.x %)		
Alive	n (%)	xx (xx.x %)	xx (xx.x %)		
Dead	n (%)	xx (xx.x %)	xx (xx.x %)		
Other	n (%)	xx (xx.x %)	xx (xx.x %)		
N[4]	n	xx	xx		
Alive	n (%)	xx (xx.x %)	xx (xx.x %)	0.xxx	x.xx (x.xx, x.xx)
Dead	n (%)	xx (xx.x %)	xx (xx.x %)		

[1] P-value is based on Fishers Exact test. Only subjects who were either alive or dead at Month 6 will be included in the analysis.
[2] 2-sided 95% confidence interval for the difference in percentage of deaths between BHR-100 and placebo.
[3] Percentages are based on the number of subjects in the mITT population.
[4] Percentages are based on the number of subjects with status=alive or dead, Month 6 within the mITT Population.

Source: Listing 16.2.6.3.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Add a missing category if not all mITT subjects provide details on Month 6 mortality.]

Table 14.2.5.2 Summary and Analysis of Mortality at Month 1 (mITT Population)
[Update the footnotes to reflect Month 1 timepoint.]

Table 14.2.5.3 Summary and Analysis of Mortality at Month 6 (PP Population)
Table 14.2.5.4 Summary and Analysis of Mortality at Month 1 (PP Population)

Table 14.2.5.5 Summary and Kaplan-Meier Analysis of Time to Death[1] (days) (mITT Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Kaplan-Meier Estimates	Total Deaths	xx	xx
	Total Censored	xx	xx
	25th percentile	xx	xx
	Median (95% CI)	xx (xx , xx)	xx (xx , xx)
	75th percentile	xx	xx
Treatment Difference from Placebo[2]		p=0.xxx	

[1] Time to Death (in days) = Date of death/date of last contact (for censored records) – date of TBI + 1.
[2] P-value is based on Log-Rank test.

Source: Listing 16.2.6.3.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: The K-M estimates are those obtained from PROC LIFETEST.

The log-rank test is fitted in SAS using the following syntax:

```
PROC LIFETEST DATA=<dataset name>;
     TIME WKS*CENS(1 – censoring indicator);
     STRATA TREATMENT;
RUN;]
```

Table 14.2.5.6 Summary of Cox Proportional Hazards Analysis of Time to Death (days) (mITT Population)

Factor/Covariate[1]	Hazard Ratio[1]	95% Confidence Limits	P-value
Treatment Group (BHR-100 vs. Placebo)	x.xxx	(x.xxx, x.xxx)	0.xxx
Region (North America vs. Europe)	x.xxx	(x.xxx, x.xxx)	0.xxx
Region (Asia vs. Europe)	x.xxx	(x.xxx, x.xxx)	0.xxx
Region (South America vs. Europe)	x.xxx	(x.xxx, x.xxx)	0.xxx
Age	x.xxx	(x.xxx, x.xxx)	0.xxx
GCS Motor Score (3 vs. 1/2)	x.xxx	(x.xxx, x.xxx)	0.xxx
GCS Motor Score (4 vs. 1/2)	x.xxx	(x.xxx, x.xxx)	0.xxx
GCS Motor Score (5/6 vs. 1/2)	x.xxx	(x.xxx, x.xxx)	0.xxx
Pupil Response (Bilateral vs. Unilateral/No Reactive Pupils/Not Testable)	x.xxx	(x.xxx, x.xxx)	0.xxx
CT Classification (I/II vs. V/VI)	x.xxx	(x.xxx, x.xxx)	0.xxx
CT Classification (III vs. V/VI)	x.xxx	(x.xxx, x.xxx)	0.xxx
CT Classification (IV vs. V/VI)	x.xxx	(x.xxx, x.xxx)	0.xxx

[1] For factors the last level is taken as the reference level. Marshall CT classification was used.

Source: Listings 16.2.6.1.6 and 16.2.6.3.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Indicator variables or PROC TPHREG (which has a CLASS statement) will need to be created for the factors with more than 2 levels (Region, GCS motor score, Pupil Response and CT classification).

```
proc tphreg data=<dataset>;
 class treatment region gcs_motor pupil ct_class;
 model time_to_death*censoring(0-censoring indicator)=treatment region age gcs_motor pupil ct_class/ties=efron;
run;
proc phreg data=<dataset>;
 treatment gcs_motor pupil ct_class;
 model time_to_death*censoring(0-censoring indicator)=treatment region1 4 region2 4 region3 4 age gcs_motor pupil1 3 pupil2 3
ct class2 6 ct class3 6 ct class4 6 ct class5 6/ties=efron; NB. Underlined terms are indicator variables.
run;
```

NB. Using EFRON method for ties.]

Table 14.2.6.1 Summary of Glasgow Outcome Scale at 3 Months Post Injury – Observed Values (mITT Population)
Table 14.2.6.2 Analysis of Glasgow Outcome Scale at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)

Table 14.2.6.3 ORs[1] and 95% CIs[2] for Glasgow Outcome Scale at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)

Table 14.2.7.1 Summary of Glasgow Outcome Scale – Extended at 6 Months Post Injury – Observed Values (mITT Population)

Glasgow Outcome Scale-Extended	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Dead	n (%)	xx (xx.x %)	xx (xx.x %)
Vegetative State	n (%)	xx (xx.x %)	xx (xx.x %)
Lower Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)
Upper Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)
Lower Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)
Upper Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)
Lower Good Recovery	n (%)	xx (xx.x %)	xx (xx.x %)
Upper Good Recovery	n (%)	xx (xx.x %)	xx (xx.x %)
Missing	n	xx	xx

Note: Percentages are based on the number of non-missing GOS-E at the month 6 assessment in each treatment group within the population of interest.

Source: Listings 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.7.2 Analysis of Glasgow Outcome Scale – Extended at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)
[See shell for 14.2.1.2.]

Table 14.2.7.3 ORs and CIs of Glasgow Outcome Scale - Extended at 6 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)
[See shell for 14.2.1.3.]

Table 14.2.7.4 Summary of Sliding Dichotomy (Dichotomization) – Glasgow Outcome Scale – Extended at 6 Months Post Injury - Observed Values (mITT Population)

Prognosis	Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Overall (N=xx)
Group 1 (Best)	n	n	xx	xx	xx
	Upper Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Lower Good Recovery	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Upper Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Lower Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Upper Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Lower Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Group 2	n	n	xx	xx	xx
	Upper Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Lower Good Recovery	**n (%)**	**xx (xx.x %)**	**xx (xx.x %)**	**xx (xx.x %)**
	Upper Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Lower Moderate Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Upper Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Lower Severe Disability	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Vegetative State/Dead	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
…					
Group 6 (Worst)					
…					
Overall					
…					

Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Source: Listing 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Include all 6 prognosis groups and an overall summary. Please make the font bold for the responses in each prognosis group that correspond to a favorable outcome (see SAP text above in Section 9.5.2.3.]

Table 14.2.7.5 Summary and Analysis of Sliding Dichotomy – Glasgow Outcome Scale – Extended at 6 Months Post Injury - Observed Values (mITT Population)

Prognosis	Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	P-Value[1] BHR-100 vs. Placebo	Difference (95% CI)[2] BHR-100 - Placebo
Overall	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
Group 1 (Best)	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
Group 2	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
Group 3	n	n	xx	xx	0.xxx	xx.x (xx.x, xx.x)
	Favorable	n (%)	xx (xx.x %)	xx (xx.x %)		
	Unfavorable	n (%)	xx (xx.x %)	xx (xx.x %)		
…						

Note: Percentages are based on the number of subjects in each treatment group in the population of interest.
[1] P-value is based on Cochran-Mantel Haenszel Chi-Square test adjusted for region.
[2] Difference is in proportion of favourable outcomes. The confidence interval for the difference is the standard Wald asymptotic confidence interval based on the normal approximation to the binomial distribution.
Source: Listing 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.7.6 ORs[1] and 95% CIs[2] for Sliding Dichotomy – Glasgow Outcome Scale – Extended at 6 Months Post Injury - Observed Values (mITT Population)

Characteristic	Prognosis	p-value	OR[3] (95% CI)
Breslow-Day Test for Homogeneity of Odds Ratios		x.xxx	
Prognosis	Overall		x.xx (xx.x, xx.x)
	Group 1 (Best)		x.xx (xx.x, xx.x)
	Group 2		x.xx (xx.x, xx.x)
	Group 3		x.xx (xx.x, xx.x)
	Group 4		x.xx (xx.x, xx.x)
	Group 5		x.xx (xx.x, xx.x)
	Group 6 (Worst)		x.xx (xx.x, xx.x)

[1] OR=Odds Ratio.
[2] CI=Confidence Interval.
[3] OR for BHR-100 vs. Placebo is based on Cochran-Mantel Haenszel Chi-Square test adjusted for region.

Source: Listing 16.2.6.1.4.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.7.7 Summary of Glasgow Outcome Scale – Extended at 3 Months Post Injury – Observed Values (mITT Population)
Table 14.2.7.8 Analysis of Glasgow Outcome Scale – Extended at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)
[See shell for 14.2.1.2.]

Table 14.2.7.9 ORs and CIs of Glasgow Outcome Scale - Extended at 3 Months Post Injury – Proportional Odds Model - Observed Values (mITT Population)
[See shell for 14.2.1.3.]

Table 14.2.8.1 Summary of SF-36[1] by Visit (mITT Population)

Scale Visit	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Vitality			
Month 3	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx
Month 6	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx
Physical Functioning			
Month 3	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx
Month 6	n	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Q1, Q3	xx.x , xx.x	xx.x , xx.x
	Min, Max	xx , xx	xx , xx
…			

[1] SF-36=Short Form (36) Health Survey.

Source: Listing 16.2.6.4.3.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Month 3 and Month 6 for vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health & physical and mental composite summary scores.]

Table 14.2.8.2 Analysis of SF-36 by Visit (mITT Population)

Summary Scores	Visit	Comparison	LS Mean BHR-100	LS Mean Placebo	Difference in LS Mean BHR-100 – Placebo (95% CI)[1]	Effect Size[1]	P-Value[1]
Physical Composite	Month 3	BHR-100 vs. Placebo	xx.x	xx.x	xx.x (xx.x, xx.x)	x.xxx	0.xxx
	Month 6	BHR-100 vs. Placebo	xx.x	xx.x	xx.x (xx.x, xx.x)	x.xxx	0.xxx
Mental Composite	Month 3	BHR-100 vs. Placebo	xx.x	xx.x	xx.x (xx.x, xx.x)	x.xxx	0.xxx
	Month 6	BHR-100 vs. Placebo	xx.x	xx.x	xx.x (xx.x, xx.x)	x.xxx	0.xxx

[1] LS Mean, Effect Size and P-Value are based on type III sum of squares from an ANCOVA model for the SF-36 composite summary scores at Month 3 and Month 6, including treatment group.
The SF-36 scores are calculated so that a higher score indicates better health.
A positive difference in LS Mean (BHR-100 – Placebo) indicates a positive effect of BHR-100 over placebo.

Source: Listing 16.2.6.4.3.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.9 Shift Summary of CT[1] Classification (mITT Population)

Treatment Group	Baseline[2]	Day 6[2]							
		I	II	III	IV	Evacuated Mass Lesion	Non-Evacuated Mass Lesion	Missing	Dead
BHR-100 (N=xx)	I	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	II	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	III	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	IV	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Evacuated Mass Lesion	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Non-Evacuated Mass Lesion	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
	Missing	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

[1] CT=Computed Tomography.
[2] The Baseline scan was obtained pre-randomization. The second CT was obtained post-infusion on Day 6 +/- 1 day (Post-Injury).
CT scans were assessed and compared by the Central Reader, and classified as follows: I=Diffuse Injury No Visible Pathologic Change, II=Diffuse Injury – Cisterns present, III=Diffuse Injury with Swelling, IV=Diffuse Injury with Shift, V=Evacuated Mass Lesion and VI=Non-Evacuated Mass Lesion.

Source: Listing 16.2.6.5.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Placebo.]

Table 14.2.10 Summary of Maximum Intracranial Pressure by Visit (mITT Population)

Visit[1]	Characteristic[2]	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Baseline	Missing ICP	n	xx	xx
	Maximum ICP (continuous)	n	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x , xx.x	xx.x , xx.x
		Min, Max	xx , xx	xx , xx
	Maximum ICP (categorical)			
	0 to < 15 mmHg	n (%)	xx (xx.x %)	xx (xx.x)
	>=15 to < 25 mmHg	n (%)	xx (xx.x %)	xx (xx.x)
	>=25 to < 40 mmHg	n (%)	xx (xx.x %)	xx (xx.x)
	>=40 mmHg	n (%)	xx (xx.x %)	xx (xx.x)
	Maximum ICP (categorical)			
	0 to <= 20 mmHg	n (%)	xx (xx.x %)	xx (xx.x)
	>20 mmHg	n (%)	xx (xx.x %)	xx (xx.x)
	Maximum ICP >= 25mmHg			
	Yes	n (%)	xx (xx.xx %)	xx (xx.xx %)
	No	n (%)	xx (xx.xx %)	xx (xx.xx %)
	Maximum ICP > 20mmHg			
	Yes	n (%)	xx (xx.xx %)	xx (xx.xx %)
	No	n (%)	xx (xx.xx %)	xx (xx.xx %)
…				

[1] The baseline value is defined as the last measurement taken prior to first administration of study drug.
[2] ICP=Intracranial Pressure.
Note: Percentages are calculated using the number of subjects with data as the numerator and the number of subjects with a non-missing ICP result as the denominator.

Source: Listing 16.2.6.6.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Day 1-6 (scheduled visits only).]

Table 14.2.11.1 Summary of Cerebral Perfusion Pressure by Visit (mITT Population)

Visit[1]	Characteristic[2]	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Baseline	Missing CPP	n	xx	xx
	Lowest CPP (continuous)	n	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x , xx.x	xx.x , xx.x
		Min, Max	xx , xx	xx , xx
	Lowest CPP (categorical)	n	xx	xx
	< 50mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
	>=50 - <60mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
	>=60 - <70mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
	>=70mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
	Highest CPP (continuous)	n	xx	xx
		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x , xx.x	xx.x , xx.x
		Min, Max	xx , xx	xx , xx
	Highest CPP (categorical)	n	xx	xx
	< 50mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
	>=50 - <60mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
	>=60 - <70mmHg	n (%)	xx (xx.x %)	xx (xx.x %)
…	>=70mmHg	n (%)	xx (xx.x %)	xx (xx.x %)

[1] The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).
[2] CPP=Cerebral Perfusion Pressure.

Source: Listing 16.2.6.7.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Day 1-6.]

Table 14.2.11.2 Potentially Clinically Important On-Treatment[1] Cerebral Perfusion Pressure (mITT Population)

Characteristic[2]	Response	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Subjects with any On-treatment CPP Measurement		n	xx	xx
Any CPP value < 50mmHg	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
	No	n (%)	xx (xx.x %)	xx (xx.x %)
Any CPP value >=50 - <60mmHg	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
	No	n (%)	xx (xx.x %)	xx (xx.x %)
Any CPP value >=60 - <70mmHg	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
	No	n (%)	xx (xx.x %)	xx (xx.x %)
Any CPP value >=70mmHg	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
	No	n (%)	xx (xx.x %)	xx (xx.x %)

[1] On-treatment includes all scheduled and unscheduled CPP measurements taken during Days 1-6 after initiation of study medication.
[2] CPP=Cerebral Perfusion Pressure.

Source: Listing 16.2.6.7.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.12.1 Summary of Therapy Intensity Level by Visit (mITT Population)

Visit[1] Characteristic[2]	Response	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Baseline		n	xx	xx
TIL (continuous)		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x , xx.x	xx.x , xx.x
		Min, Max	xx , xx	xx , xx
Day 1		n	xx	xx
TIL (continuous)		Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
		Median	xx.x	xx.x
		Q1, Q3	xx.x , xx.x	xx.x , xx.x
		Min, Max	xx , xx	xx , xx
…				

[1] The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).
[2] TIL=Therapy Intensity Level. TIL is recorded for up to 6 days while ICP is being monitored. Each of the listed treatments will have a score of 1 with a maximum score of 10 per subject.

Source: Listing 16.2.6.8.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Day 2-6.]

Table 14.2.12.2 Summary of Individual TIL Therapies (mITT Population)

Therapy	BHR-100 (N=xx)	Placebo (N=xx)
Surgical Decompression	xx (xx.x %)	xx (xx.x %)
Barbiturate Induced Coma	xx (xx.x %)	xx (xx.x %)
Hypothermia	xx (xx.x %)	xx (xx.x %)
Hyperventilation (pCO_2<30)	xx (xx.x %)	xx (xx.x %)
Pressor Administration (to keep CPP>60)	xx (xx.x %)	xx (xx.x %)
Hypertonic Saline	xx (xx.x %)	xx (xx.x %)
Mannitol	xx (xx.x %)	xx (xx.x %)
Ventricular Drainage	xx (xx.x %)	xx (xx.x %)
Paralysis Induction	xx (xx.x %)	xx (xx.x %)
Sedation	xx (xx.x %)	xx (xx.x %)

Subjects may have received multiple therapies, and therefore may be counted in multiple rows.
Source: Listing 16.2.6.8.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.2.12.3 Summary of Maximum Therapy Intensity Level (mITT Population)

Therapy	~~Response~~	~~Statistic~~	BHR-100 (N=xx)	Placebo (N=xx)
Surgical Decompression			xx (xx.x %)	xx (xx.x %)
Barbiturate Induced Coma			xx (xx.x %)	xx (xx.x %)
Hypothermia			xx (xx.x %)	xx (xx.x %)
Hyperventilation (pCO_2<30)			xx (xx.x %)	xx (xx.x %)
Pressor Administration (to keep CPP>60)			xx (xx.x %)	xx (xx.x %)
Hypertonic Saline			xx (xx.x %)	xx (xx.x %)
Mannitol			xx (xx.x %)	xx (xx.x %)
Ventricular Drainage			xx (xx.x %)	xx (xx.x %)
Paralysis Induction			xx (xx.x %)	xx (xx.x %)
Sedation			xx (xx.x %)	xx (xx.x %)
No Intervention			xx (xx.x %)	xx (xx.x %)

Note: Subjects are summarized according to the maximum therapy received on Days 1-6.

Source: Listing 16.2.6.8.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.3.1.1 Overall Summary of Treatment Emergent Adverse Events (Safety Population)

	BHR-100 (N=xx)		Placebo (N=xx)	
Adverse Event Category	# (%) Subj	# AEs	# (%) Subj	# AEs
Any	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Serious AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related Serious AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any AE Leading to Premature Discontinuation of Study Drug	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE Leading to Premature Discontinuation of Study Drug	xx (xx.x %)	xx	xx (xx.x %)	xx
Any AE Which Resulted in Death	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE Which Resulted in Death	xx (xx.x %)	xx	xx (xx.x %)	xx

Note: Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: For each category, subjects are included only once, even if they experienced multiple events in that category.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: An event is considered related to study medication if it has a relationship other than not related. An event is considered serious, if "Is this a serious adverse event (SAE)"=Yes, an event leads to premature discontinuation of study drug if action taken with study drug due to the AE is drug withdrawn and an event which resulted in death has "If SAE is Yes, Results in death?"=Yes.]

Table 14.3.1.2 Overall Summary of Treatment Emergent Adverse Events by Gender (Safety Population)
Gender: Male

	BHR-100 (N=xx)		Placebo (N=xx)	
Adverse Event Category	# (%) Subj	# AEs	# (%) Subj	# AEs
Any	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Serious AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related Serious AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any AE Leading to Premature Discontinuation of Study Drug	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE Leading to Premature Discontinuation of Study Drug	xx (xx.x %)	xx	xx (xx.x %)	xx
Any AE Which Resulted in Death	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE Which Resulted in Death	xx (xx.x %)	xx	xx (xx.x %)	xx

Note: Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: For each category, subjects are included only once, even if they experienced multiple events in that category.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: An event is considered related to study medication if it has a relationship other than not related. An event is considered serious, if "Is this a serious adverse event (SAE)"=Yes, an event leads to premature discontinuation of study drug if action taken with study drug due to the AE is drug withdrawn and an event which resulted in death has "If SAE is Yes, Results in death?"=Yes.]

Table 14.3.1.2 Overall Summary of Treatment Emergent Adverse Events by Gender (Safety Population)
Gender: Female

	BHR-100 (N=xx)		Placebo (N=xx)	
Adverse Event Category	# (%) Subj	# AEs	# (%) Subj	# AEs
Any	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Serious AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related Serious AE	xx (xx.x %)	xx	xx (xx.x %)	xx
Any AE Leading to Premature Discontinuation of Study Drug	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE Leading to Premature Discontinuation of Study Drug	xx (xx.x %)	xx	xx (xx.x %)	xx
Any AE Which Resulted in Death	xx (xx.x %)	xx	xx (xx.x %)	xx
Any Treatment-Related AE Which Resulted in Death	xx (xx.x %)	xx	xx (xx.x %)	xx

Note: Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: For each category, subjects are included only once, even if they experienced multiple events in that category.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: An event is considered related to study medication if it has a relationship other than not related. An event is considered serious, if "Is this a serious adverse event (SAE)"=Yes, an event leads to premature discontinuation of study drug if action taken with study drug due to the AE is drug withdrawn and an event which resulted in death has "If SAE is Yes, Results in death?"=Yes.]

Table 14.3.1.3 Overall Summary of Treatment Emergent Adverse Events by Race Group(Safety Population)
[Repeat the table for each Race group: white, non-white, not allowed to obtain]
Table 14.3.1.4 Overall Summary of Treatment Emergent Adverse Events by Age Group (Safety Population)
[Repeat the table for each Age group: ≤45 years, >45 years]

Table 14.3.1.5 Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	BHR-100 (N=xx) # (%) Subj	 # AEs	Placebo (N=xx) # (%) Subj	 # AEs
Any Adverse Event	xx (xx.x %)	xx	xx (xx.x %)	xx
System Organ Class 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 4	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 5	xx (xx.x %)	xx	xx (xx.x %)	xx
System Organ Class 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 4	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 5	xx (xx.x %)	xx	xx (xx.x %)	xx
System Organ Class 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 4	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 5	xx (xx.x %)	xx	xx (xx.x %)	xx

Note: Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: Adverse events are coded by MedDRA Version 13.0.
Note: For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Sort in decreasing order of frequency in the BHR-100 column by SOC and by preferred term within SOC.]

Table 14.3.1.9 Treatment-Related Treatment Emergent Adverse Events by System Organ Class and Preferred Term (Safety Population)
[Repeat above table for treatment-related AEs.]

Table 14.3.1.6 Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Gender (Safety Population)
Gender=Male

	BHR-100 (N=xx)		Placebo (N=xx)	
Subgroup System Organ Class Preferred Term	# (%) Subj	# AEs	# (%) Subj	# AEs
Any Adverse Event	xx (xx.x %)	xx	xx (xx.x %)	xx
System Organ Class 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 4	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 5	xx (xx.x %)	xx	xx (xx.x %)	xx
System Organ Class 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 4	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 5	xx (xx.x %)	xx	xx (xx.x %)	xx
System Organ Class 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 3	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 4	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 5	xx (xx.x %)	xx	xx (xx.x %)	xx

Note: Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: Adverse events are coded by MedDRA Version 13.0.
Note: For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Gender=Female. Sort in decreasing order of frequency in the BHR-100 column by SOC and by preferred term within SOC.]

Table 14.3.1.7 Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Race Group (Safety Population)
[Repeat above table for race groups White, Non-white, and Not allowed to obtain.]
Table 14.3.1.8 Treatment Emergent Adverse Events by System Organ Class, Preferred Term, and Age Group (Safety Population)

[Repeat above table for age groups ≤45 years and >45 years.]

Table 14.3.1.10 Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	BHR-100 (N=xx)			Placebo (N=xx)		
	Mild n (%)	Moderate n (%)	Severe n (%)	Mild n (%)	Moderate n (%)	Severe n (%)
All Adverse Events	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
System Organ Class 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 1	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 2	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 3	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 4	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)
Preferred Term 5	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)	xx (xx.x%)

Note: Treatment-Emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: Adverse Events are coded by MedDRA Version 13.0.
Note: For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.
Note: If the severity of an Adverse Event is missing, then it is considered to be severe.

Source: Listing 16.2.7.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Each subject is counted only once in the particular AE class, under the highest intensity they experienced for that class of AE.]

Table 14.3.1.11 Treatment-Related Treatment Emergent Adverse Events by Maximum Severity, System Organ Class and Preferred Term (Safety Population)

Table 14.3.1.12 Treatment Emergent Adverse Events by Maximum Relationship and System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	BHR-100 (N=xx)				Placebo (N=xx)			
	Not Related n (%)	Possibly n (%)	Probably n (%)	Related n (%)	Not Related n (%)	Possibly n (%)	Probably n (%)	Related n (%)
All Adverse Events	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
System Organ Class 1	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 1	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 2	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 3	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 4	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 5	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
System Organ Class 2	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 1	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 2	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 3	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 4	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Preferred Term 5	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Treatment-Emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: Adverse Events are coded by MedDRA Version 13.0.
Note: For each system organ class and preferred term, subjects are included only once, even if they experienced multiple events in that system organ class or preferred term.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.
Note: If the relationship of an Adverse Event is missing, then it is considered to be related to study medication.

Source: Listing 16.2.7.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Each subject is counted only once in the particular AE class, under the most related category they experienced for that class of AE. If the AE relationship to study medication is missing, then it is considered to be related.]

Table 14.3.1.13 Treatment Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population)
Table 14.3.1.14 Treatment-Related Treatment Emergent Adverse Events Leading to Premature Discontinuation of Study Drug by System Organ Class and Preferred Term (Safety Population)
[Use shell for Table 14.3.1.7, change footnotes accordingly.]

Table 14.3.1.15 Treatment Emergent Adverse Events of Special Interest (Safety Population)

AE of Special Interest Preferred Term	BHR-100 (N=xx) # (%) Subj	 # AEs	Placebo (N=xx) # (%) Subj	 # AEs
Any Adverse Event of Special Interest	xx (xx.x %)	xx	xx (xx.x %)	xx
Serious Thromboembolic Events	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 1	xx (xx.x %)	xx	xx (xx.x %)	xx
Preferred Term 2	xx (xx.x %)	xx	xx (xx.x %)	xx
…				
Thrombotic Myocardial Infarction	xx (xx.x %)	xx	xx (xx.x %)	xx
Pulmonary Embolism	xx (xx.x %)	xx	xx (xx.x %)	xx
Deep Vein Thrombosis	xx (xx.x %)	xx	xx (xx.x %)	xx
Ischemic Stroke	xx (xx.x %)	xx	xx (xx.x %)	xx
Allergic Reactions	xx (xx.x %)	xx	xx (xx.x %)	xx
Marked Liver Function Abnormalities	xx (xx.x %)	xx	xx (xx.x %)	xx
Serious Infections	xx (xx.x %)	xx	xx (xx.x %)	xx
Pneumonia	xx (xx.x %)	xx	xx (xx.x %)	xx
Pneumonia Streptococcal	xx (xx.x %)	xx	xx (xx.x %)	xx
Sepsis	xx (xx.x %)	xx	xx (xx.x %)	xx
Meningitis	xx (xx.x %)	xx	xx (xx.x %)	xx

Note: Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication.
Note: Adverse events are coded by MedDRA Version 13.0.
Note: For each preferred term, subjects are included only once, even if they experienced multiple events in that preferred term.
Note: Percentages are based on the number of subjects in each treatment group in the population of interest.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Sort in decreasing order of frequency in the BHR-100 column by preferred term. Need to identify the MedDRA preferred terms that relate to these events of special interest (see page 28 of protocol for events of special interest details).]

Table 14.3.1.16 List of Adverse Events of Special Interest (Safety Population)

Treat-ment Group	Subject No.	Sex/ Age/ Race[1]	Adverse Event/ Preferred Term/ SOC	Start Date/ Day[2]	Stop Date	Length of Exposure (days)[3]	Duration[4]	Intensity	Relation-ship/ Outcome	Action Taken with Study Drug	Serious?/ Treatment Emergent?[5]
BHR-100	xx-xxx	M/10/W	xxxxxxxxxxxxxx / xxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxx	DDMONYYYY/ xx	DDMONYYYY	xx	xx	Mild, Moderate, Severe	Not Related, Possibly Related, Probably Related, Related/Recovered/resolved, Recovering/Resolving, …	Dose not changed, drug withdrawn, …	Yes/ Yes

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] Day is relative to the start date of study medication, event start date – administration start date + 1 if event start date if on or after the date of the start of study medication administration or event start date – administration start date if event date if before the date of the start of study medication administration.
[3] Length of exposure is based on administration start date and administration end date during the study (end date – start date + 1).
[4] Duration = AE end date – AE start date + 1.
[5] Treatment emergent adverse events are defined as events that start on or after the first dose of study medication.
Events of special interest are defined as one of the following dictionary defined terms: Serious Thromboembolic Events, Thrombotic Myocardial Infarction, Pulmonary Embolism, Deep Vein Thrombosis, Ischemic Stroke, Allergic Reactions, Marked Liver Function Abnormalities, Serious Infections, Pneumonia, Pneumonia Streptococcal, Sepsis, or Meningitis.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.3.2.1 Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)
Table 14.3.2.2 Treatment-Related Serious Adverse Events by System Organ Class and Preferred Term (Safety Population)
[Use shell for Table 14.3.1.7, change footnotes accordingly.]

Table 14.3.2.3 Primary Cause of Death (mITT Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Any Death	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Increased Intracranial Pressure	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Increase in Hematoma Size	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
New Hematoma/Re-accumulation	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Cerebral Edema	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Herniation	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Cerebral Infarct	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Cerebral Vasospasm	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Meningitis	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Extracranial Injury	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Myocardial Infarction	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pulmonary Embolus	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Multiple Organ Failure	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Pneumonia	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Adult Respiratory Distress Syndrome	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Sepsis	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Unknown/Undetermined	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Other	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.3.4.1 Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Coagulation (Safety Population)

	BHR-100		Placebo	
Outcome	Day 6 n (%)	Day 15 n (%)	Day 6 n (%)	Day 15 n (%)
Number of Abnormal, Clinically Significant (non-AE) lab results	xx	xx	xx	xx
Resolved		xx (xx.x %)		xx (xx.x %)
Ongoing		xx (xx.x %)		xx (xx.x %)
Lost to Follow-up		xx (xx.x %)		xx (xx.x %)
Missing		xx (xx.x %)		xx (xx.x %)

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: If there are no results with a Missing outcome, do not include the Missing row.]

Table 14.3.4.2 Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Hematology (Safety Population)

Parameter Outcome	BHR-100 Day 6 n (%)	BHR-100 Day 15 n (%)	Placebo Day 6 n (%)	Placebo Day 15 n (%)
White blood cell count				
Number of Abnormal, Clinically Significant (non-AE) lab results	xx	xx	xx	xx
Resolved		xx (xx.x %)		xx (xx.x %)
Ongoing		xx (xx.x %)		xx (xx.x %)
Lost to Follow-up		xx (xx.x %)		xx (xx.x %)
Missing		xx (xx.x %)		xx (xx.x %)
…				

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat **for remaining hematology lab tests: Differential WBC, Red blood cell count (RBC), Hemoglobin, Hematocrit, Reticulocyte count, and Platelets.** If there are no results with a Missing outcome, do not include the Missing row.]

Table 14.3.4.3 Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Serum Chemistry (Safety Population)
(Use Table 14.3.4.2 shell, Subset off details for serum chemistry lab tests: AST, ALT, Alkaline Phosphatase, GGT, Total Protein, Total Cholesterol, Triglycerides, Glucose, Sodium, Potassium, Chloride)

Table 14.3.4.4 Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Urinalysis (Safety Population)
(Use Table 14.3.4.2 shell, Subset off details for all urinalysis tests)

Table 14.3.4.5 List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Coagulation (Safety Population)
(Produce for INR)
[Use shell below for Table 14.3.4.6]

Table 14.3.4.6 List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Test Results: Hematology (Safety Population)

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Test Name	Visit	Sample Date	Result (Unit)	Range Flag[2]	Reference Range Low	Reference Range High	Outcome	Other, specify
BHR-100	xx-xxx	M/35/W	Hemoglobin	Screening	DDMONYYYY	xx.x g/L	L	xx.x	xx.x	Ongoing	
				UN	DDMONYYYY	xx.x g/L	L	xx.x	xx.x	Resolved	
				Day 6	DDMONYYYY	xx.x g/L	L	xx.x	xx.x	Ongoing	
				Day 15	DDMONYYYY	xx.x g/L	L	xx.x	xx.x	Other	xxxxxxxxxx
…											

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] N = Normal, L = Low, H = High.
UN = Unscheduled.

[Note to Programmer: Produce for clinically significant abnormalities only. Produce for Hemoglobin, Hematocrit, RBC, Reticulocyte Count, Platelet Count, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils.]

Table 14.3.4.7 List of Post-Baseline Abnormal, Clinically Significant (non-AE) Laboratory Tests: Serum Chemistry (Safety Population)
(Produce for Sodium, Potassium, Chloride, Total Cholesterol, Triglycerides, ALT, AST, GGT, Alkaline Phosphatase, Total Protein, Glucose.)
Table 14.3.4.8 List of Post-Baseline Abnormal, Clinically Signficant (non-AE) Laboratory Tests: Urinalysis (Safety Population)
(Produce for pH, Specific Gravity, Protein, Glucose, Blood, WBC, RBC, Casts, Epithelial Cells, Bacteria.)
[Use shell for table 14.3.4.6]

Table 14.3.4.9 Summary of Coagulation Laboratory Test Results (Safety Population)

		BHR-100 (N=xx)		Placebo (N=xx)	
Parameter/Visit	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline
INR (ratio)					
Baseline	n	xx		xx	
	Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
	Median	xx.x		xx.x	
	Min, Max	xx , xx		xx , xx	
	Q1, Q3	xx , xx		xx , xx	
Day 6	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx , xx	xx , xx	xx , xx	xx , xx
	Q1, Q3	xx , xx	xx , xx	xx , xx	xx , xx
Day 15	n	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx , xx	xx , xx	xx , xx	xx , xx
	Q1, Q3	xx , xx	xx , xx	xx , xx	xx , xx
…					

Note: The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).

Source: Listing 16.2.8.1.1.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.3.4.10 Summary of Hematology Laboratory Test Results (Safety Population)
(Produce for Hemoglobin, Hematocrit, RBC, Reticulocyte Count, Platelets, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, and Basophils. Sort parameters alphabetically. Summarize parameters in standard SI units.)

Table 14.3.4.11 Summary of Serum Chemistry Laboratory Test Results (Safety Population)
(Produce for Sodium, Potassium, Chloride, Total Cholesterol, Triglycerides, ALT, AST, GGT, Alkaline phosphatase, Total Protein, Glucose. Sort parameters alphabetically. Summarize parameters in standard SI units.)

Table 14.3.5 Summary of Incidence of Neuroworsening (Safety Population)

	Statistic	BHR-100 (N=xx)	Placebo (N=xx)	Total (N=xx)
Subjects Experiencing Neuroworsening Event ≤ Day 6	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)
Subjects Experiencing Neuroworsening Event ≤ Day 15	n (%)	xx (xx.x %)	xx (xx.x %)	xx (xx.x %)

Note: Neuroworsening is defined as any one of the following: a decrease in GCS motor score ≥ 2 , development of pupillary abnormalities, any other neurological deterioration or progression of lesion on CT scan leading to a change in subject management.
Note: Percentages are based on the number of subjects in each treatment group and overall in the population of interest.

Source: Listing 16.2.8.6.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.3.6.1 Summary of Vital Signs Corresponding to Lowest Measurement by Visit (Safety Population)

		BHR-100 (N=xx)		Placebo (N=xx)	
Variable/Visit	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Pulse (per min)					
Baseline	n	xx		xx	
	Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
	Median	xx.x		xx.x	
	Min, Max	xx , xx		xx , xx	
	Q1, Q3	xx , xx		xx , xx	
Day 1	N	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx , xx	xx , xx	xx , xx	xx , xx
	Q1, Q3	xx , xx	xx , xx	xx , xx	xx , xx
Day 2	N	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx , xx	xx , xx	xx , xx	xx , xx
	Q1, Q3	xx , xx	xx , xx	xx , xx	xx , xx
…					

Note: The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).

Source: Listing 16.2.8.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Day 3-6. Repeat for other vital sign parameters – respiration rate (bpm, breaths per minute), systolic pressure (mmHg), diastolic blood pressure (mmHg), and temperature (C). The vital signs are reported which correspond to the lowest and highest measurements per study day.]

Table 14.3.6.2 Summary of Vital Signs Corresponding to Highest Measurement by Visit (Safety Population)

Table 14.3.6.3 Summary of Vital Signs by Visit – Weight (kg) (Safety Population)

		BHR-100 (N=xx)		Placebo (N=xx)	
Variable/Visit	Statistic	Actual Value	Change from Baseline	Actual Value	Change from Baseline
Weight (kg)					
Baseline	n	xx		xx	
	Mean (SD)	xx.x (xx.xx)		xx.x (xx.xx)	
	Median	xx.x		xx.x	
	Min, Max	xx , xx		xx , xx	
	Q1, Q3	xx , xx		xx , xx	
Day 6	N	xx	xx	xx	xx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x	xx.x	xx.x
	Min, Max	xx , xx	xx , xx	xx , xx	xx , xx
	Q1, Q3	xx , xx	xx , xx	xx , xx	xx , xx

Note: The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).

Source: Listing 16.2.8.2.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Table 14.3.7.1 Summary of Physical Examination by Visit (Safety Population)

Body System/ Visit	Characteristic	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Skin		N	xx	xx
Baseline	Normal	n (%)	xx (xx.x%)	xx (xx.x%)
	Abnormal	n (%)	xx (xx.x%)	xx (xx.x%)
	Not Done	n	xx (xx.x%)	xx (xx.x%)
		N	xx	xx
Day 6	Normal	n (%)	xx (xx.x%)	xx (xx.x%)
	Abnormal	n (%)	xx (xx.x%)	xx (xx.x%)
	Not Done	n	xx (xx.x%)	xx (xx.x%)
HEENT		N	xx	xx
Baseline	Normal	n (%)	xx (xx.x%)	xx (xx.x%)
	Abnormal	n (%)	xx (xx.x%)	xx (xx.x%)
	Not Done	n	xx (xx.x%)	xx (xx.x%)
		N	xx	xx
Day 6	Normal	n (%)	xx (xx.x%)	xx (xx.x%)
	Abnormal	n (%)	xx (xx.x%)	xx (xx.x%)
	Not Done	n	xx (xx.x%)	xx (xx.x%)
Respiratory		N	xx	xx
Screening	Normal	n (%)	xx (xx.x%)	xx (xx.x%)
	Abnormal	n (%)	xx (xx.x%)	xx (xx.x%)
	Not Done	n	xx (xx.x%)	xx (xx.x%)
…				

Note: The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1). For physical examination assessments this will be the screening visit.
Note: Percentages are based on the number of subjects with data at the visit within the population of interest.

Source: Listing 16.2.8.3.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Physical examination is only conducted at screening and Day 6 visit.
Repeat for all Body systems: Skin, HEENT, Respiratory, Cardiovascular, Abdomen (including liver and kidneys), Neurological, Gastrointestinal, Genitourinary, Endocrine, Lymph Nodes.]

Table 14.3.7.2 List of Physical Examination Abnormalities Post-Baseline (Safety Population)

Treatment Group	Subject No.	Sex/Age/ Race[1]	Body System	Baseline[2]	Visit[3]	Describe Abnormality
BHR-100	xx-xxx	M/35/W	(Skin, HEENT, Respiratory, Cardiovascular, Abdomen (including liver and kidneys), Neurological, Gastrointestinal, Genitourinary, Endocrine, Lymph Nodes.)	Normal	(Day 6, UN)	xxxxxxxxxxxxxxxxx
…						

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1). For physical examination assessments this will be the screening visit.
[3] UN = Unscheduled.

[Note to Programmer: Only produce for records which record the physical examination post-baseline as abnormal.]

14.3.8.1 Post-baseline Abnormal ECG Results (Safety Population)

Visit[1]	Characteristic[2]	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Baseline	Abnormal Rhythm	n	xx	xx
	Sinus Arrhythmia	n (%)	xx (xx.x %)	xx (xx.x %)
	Atrial Fibrillation	n (%)	xx (xx.x %)	xx (xx.x %)
	Atrial Flutter	n (%)	xx (xx.x %)	xx (xx.x %)
	Premature Ventricular Contraction	n (%)	xx (xx.x %)	xx (xx.x %)
	Other Arrhythmia	n (%)	xx (xx.x %)	xx (xx.x %)
	Abnormal Rhythm – Clin Sig	n	xx	xx
	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
	No	n (%)	xx (xx.x %)	xx (xx.x %)
	Abnormal Conduction	n	xx	xx
	LBBB	n (%)	xx (xx.x %)	xx (xx.x %)
	RBBB	n (%)	xx (xx.x %)	xx (xx.x %)
	AV Block	n (%)	xx (xx.x %)	xx (xx.x %)
	QT Prolongation	n (%)	xx (xx.x %)	xx (xx.x %)
	Other	n (%)	xx (xx.x %)	xx (xx.x %)
	Abnormal Conduction – Clin Sig	n	xx	xx
	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
	No	n (%)	xx (xx.x %)	xx (xx.x %)

[1] The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).
[2] Clin Sig = Clinically Significant.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Baseline and Day 6.]

14.3.8.1 Post-baseline Abnormal ECG Results (Safety Population)

Visit[1]	Characteristic[2]	Statistic	BHR-100 (N=xx)	Placebo (N=xx)
Baseline	Abnormal QRS Complex	n	xx	xx
	Non-specific ST Changes	n (%)	xx (xx.x %)	xx (xx.x %)
	Old MI	n (%)	xx (xx.x %)	xx (xx.x %)
	Myocardial Ischemia	n (%)	xx (xx.x %)	xx (xx.x %)
	Acute Myocardial Infarction	n (%)	xx (xx.x %)	xx (xx.x %)
	Other	n (%)	xx (xx.x %)	xx (xx.x %)
	Abnormal QRS Complex - Clin Sig	n	xx	xx
	Yes	n (%)	xx (xx.x %)	xx (xx.x %)
…	No	n (%)	xx (xx.x %)	xx (xx.x %)

[1] The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1).
[2] Clin Sig = Clinically Significant.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for Screening and Day 6.]

Table 14.3.8.2 List of Post-Baseline Abnormal ECG Results – Part 1 (Safety Population)

				Rhythm			Conduction			
Treatment Group	Subject No.	Sex/Age/ Race[1]	Visit[2]	Result	Specify#	Clin. Sig.[3]	Result	Specify#	QTC Prolongation (ms)	Clin. Sig.[3]
BHR-100	xx-xxx	M/35/W	Day 6	Abnormal	Sinus Arrhythmia	No	Normal			
			UN	Abnormal	Other: xxxxxxxxxxxxx	Yes	Abnormal	QT Prolongation	xxx	No
…										

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] UN = Unscheduled.
[3] Clin. Sig. = Clinically Significant.
If specify=other include details from the other specify comment here.

[Note to Programmer: Only produce for records which record the ECG post-baseline as abnormal.]

Table 14.3.8.2 List of Post-Baseline Abnormal ECG Results – Part 2 (Safety Population)

				QRS Complex			
Treatment Group	Subject No.	Sex/Age/ Race[1]	Visit[2]	Result	Specify#	Clin. Sig.[3]	Comments
BHR-100	xx-xxx	M/35/W	Day 6	Abnormal	Non-specific ST Changes	Yes	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
			UN	Normal			
…							

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] UN = Unscheduled.
[3] Clin. Sig. = Clinically Significant.
If specify=other include details from the other specify comment here.

[Note to Programmer: Only produce for records which record the ECG post-baseline as abnormal.]

14.3.9 Summary of Worst Arterial Blood Gas (ABG) Results by Visit (Safety Population)

ABG Parameter Timepoint	BHR-100 (N = XXX) Value	BHR-100 (N = XXX) Change from Baseline	Placebo (N = XXX) Value	Placebo (N = XXX) Change From Baseline
PaO_2				
Baseline				
n	xx		xx	
Mean (std)	xx.xx (xx.xxx)		xx.xx (xx.xxx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx.x, xx.x		xx.x, xx.x	
Day 1				
n	xx	xx	xx	xx
Mean (std)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)	xx.xx (xx.xxx)
Median	xx.x	xx.x	xx.x	xx.x
Q1, Q3	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Min, Max	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x	xx.x, xx.x
Day 2				
n	xx		xx	
Mean (std)	xx.xx (xx.xxx)		xx.xx (xx.xxx)	
Median	xx.x		xx.x	
Q1, Q3	xx.x, xx.x		xx.x, xx.x	
Min, Max	xx.x, xx.x		xx.x, xx.x	
…				

Note: The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1). Worst result is calculated as lowest value of the day for PaO_2, HCO_3, pH, SaO_2, and FiO_2 and the highest value of the day for $PaCO_2$.

Source: Listing 16.2.8.5.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Repeat for all ABG parameters: PaO_2, $PaCO_2$, HCO_3, pH, SaO_2 (%) and FiO_2 (%) and all visits (Day1-6). Values should be the worst ABG result recorded that day.]

Table 14.3.10 Summary of Day 2 Progesterone Levels (Safety Population)

Parameter	Statistic	BHR-100 (N = XXX)	Placebo (N = XXX)
Day 2			
Baseline	n	xxx	xxx
	Mean (SD)	xx.x (xx.xx)	xx.x (xx.xx)
	Median	xx.x	xx.x
	Min, Max	xx , xx	xx , xx
	Q1, Q3	xx , xx	xx , xx

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Figure	14.2.1.1
Title 1	Glasgow Outcome Scale distribution at 6 Months Post Injury – Missing Values Imputed (mITT Population)
Title 2	
Type of graph	Bar Chart
y-axis	% response
y-axis (label)	% response
x-axis	Glasgow Outcome Scale response
x-axis (label)	Glasgow Outcome Scale response
Legend (if applicable)	Treatment Group: BHR-100 and Placebo. Different bar color for each treatment group. Glasgow Outcome Scale response: D/VS=Dead, Vegetative State, SD=Severe Disability, MD=Moderate Disability, GR=Good Recovery
Footnote 1	Note: Percentages are based on the number of GOS at the month 6 assessment in each treatment group in the population of interest, after imputation. Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.1.

Figure	14.2.1.2
Title 1	Glasgow Outcome Scale distribution at 6 Months Post Injury – Observed Values (mITT Population)
Title 2	
Type of graph	Bar Chart
y-axis	% response
y-axis (label)	% response
x-axis	Glasgow Outcome Scale response
x-axis (label)	Glasgow Outcome Scale response
Legend (if applicable)	Treatment Group: BHR-100 and Placebo. Different bar color for each treatment group. Glasgow Outcome Scale response: D/VS=Dead, Vegetative State, SD=Severe Disability, MD=Moderate Disability, GR=Good Recovery
Footnote 1	Note: Percentages are based on the number of non-missing GOS at the month 6 assessment in each treatment group in the population of interest. Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.4.

Figure	14.2.1.3
Title 1	Glasgow Outcome Scale distribution at 6 Months Post Injury – Observed Values (PP Population)
Title 2	
Type of graph	Bar Chart
y-axis	% response
y-axis (label)	% response
x-axis	Glasgow Outcome Scale response
x-axis (label)	Glasgow Outcome Scale response
Legend (if applicable)	Treatment Group: BHR-100 and Placebo. Different bar color for each treatment group. Glasgow Outcome Scale response: D/VS=Dead, Vegetative State, SD=Severe Disability, MD=Moderate Disability, GR=Good Recovery
Footnote 1	Note: Percentages are based on the number of non-missing GOS at the month 6 assessment in each treatment group in the population of interest. Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.1.7.

Figure	14.2.2.1
Title 1	Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Missing Values Imputed (mITT Population)
Title 2	
Type of graph	Bar Chart
y-axis	% response
y-axis (label)	% response
x-axis	Dichotomized Glasgow Outcome Scale response (favorable, unfavorable)
x-axis (label)	Dichotomized Glasgow Outcome Scale response (favorable, unfavorable)
Legend (if applicable)	
Footnote 1	Favorable response = GR,MD; Unfavorable response = SD, VS/D. Note: Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model.
Additional information	Corresponds to table 14.2.3.1.

Figure	14.2.2.2
Title 1	Dichotomized Glasgow Outcome Scale at 6 Months Post Injury – Observed Values (mITT Population)
Title 2	
Type of graph	Bar Chart
y-axis	% response
y-axis (label)	% response
x-axis	Dichotomized Glasgow Outcome Scale response (favorable, unfavorable)
x-axis (label)	Dichotomized Glasgow Outcome Scale response (favorable, unfavorable)
Legend (if applicable)	
Footnote 1	Favorable response = GR,MD; Unfavorable response = SD, VS/D.
Additional information	Corresponds to table 14.2.3.4.

Figure	14.2.3.1
Title 1	Mortality at 6 months (mITT Population)
Title 2	
Type of graph	Bar Chart
y-axis	% mortality
y-axis (label)	% mortality
x-axis	Treatment Group
x-axis (label)	Treatment Group
Legend (if applicable)	Treatment Group: BHR-100 and Placebo. Different bar color/pattern for each treatment group.
Footnote 1	Note: Fishers Exact test p=0.xxx. Only subjects who were either alive or dead at Month 6 will be included in the analysis. Note: Percentages are based on the number of subjects with status=alive or dead at Month 6 within the mITT population. Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.5.1.

Figure	14.2.3.2
Title 1	Mortality at 1 month (mITT Population)
Title 2	
Type of graph	Bar Chart
y-axis	% mortality
y-axis (label)	% mortality
x-axis	Treatment Group
x-axis (label)	Treatment Group
Legend (if applicable)	Treatment Group: BHR-100 and Placebo. Different bar color/pattern for each treatment group.
Footnote 1	Note: Fishers Exact test p=0.xxx. Only subjects who were either alive or dead at Month 1 will be included in the analysis. Note: Percentages are based on the number of subjects with status=alive or dead at Month 1 within the mITT population. Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Corresponds to table 14.2.5.2.

Figure	14.2.3.3
Title 1	Time to Death (mITT Population)
Title 2	
Type of graph	Line graph
y-axis	1 - Kaplan-Meier survival estimates x 100
y-axis (label)	Cumulative Percent Dead
x-axis	Time (0-6/7 months)
x-axis (label)	Time (in months)
Legend (if applicable)	BHR-100, Placebo (different line type for each treatment group)
Footnote 1	Time to death = (Date of death or date of last contact (if censored) – date of TBI + 1)/30.4. Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x
Additional information	Censored observations should be identified. Output K-M survival estimates using OUTSURV on PROC LIFETEST statement or SURVIVAL statement. Then calculate 1-K-M survival estimates as want to calculate probability of death over time. Then multiply by 100 to obtain the percentage. Figure will run from 0% (no deaths) to 100% (all subjects have died) as the x-axis of time progresses from the left to the right. Figure corresponds with Table 14.2.5.5.

LISTINGS

Listing 16.2.1.1 Study Completion/Discontinuation Details

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Infusion Administration Start Date/Time	Infusion Completion Date/Time	Completion Status	Reason for Early Termination (Specify)	Date of Study Completion/ Early Termination
BHR-100	xx-xxx	M/35/W		DDMONYYYY/ XX:XX	Completed	(Death, Adverse Event(s), Withdrawal of Consent, Protocol Violation, Lost to Follow-up, Discretion of the Investigator, Discretion of the Sponsor, other) (provide details when reason for termination is other)	DDMONYYYY
	xx-xxx	F/33/B		DDMONYYYY/ XX:XX	Withdrew	Other (xxxxxxxxxxxxxxxxxxxxxxxxxxxxx)	DDMONYYYY
…							

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.1.2 Eligibility/Randomization

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date/Time of Written Informed Consent	Subject met all entry criteria?	Inclusion/Exclusion Criteria Not Met	Subject Randomized?	Date/Time of Randomization
BHR-100	xx-xxx	M/35/W	DDMONYYYY/ XX:XX	(Yes, No)	Inclusion Criteria 1	(Yes,No)	DDMONYYYY/ XX:XX

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: All inc/exc criteria met comes from has the subject met all eligibility criteria?
If date of randomization provided, subject is randomized set to Yes]

Listing 16.2.1.3 Exclusions from Per Protocol Population

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Violation Code	Violation Description
BHR-100	xx-xxx	M/35/W	xxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Include violations with an NE (not evaluable) designation.]

Listing 16.2.3.1 Subject General Information

Treatment Group	Subject No.	Sex/ Age/ Race[1]	mITT[2]	Safety/ Act Tmt	PP[2]	Date or Date/Time							Exit Day[3]	Treatment Duration (hours)[4]	Compliance Rate[5]
						Screened	Informed Consent	Randomization	First Dose	Last Dose	Study Exit	Study Outcome			
BHR-100	xx-xxx	M/35/W	Yes	Yes	Yes	DDMONYYYY	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	DDMONYYYY	Completed	182	120	xxx.x
		F/33/B	Yes	Yes	Yes	DDMONYYYY	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	DDMONYYYY	Withdrew	24	121	xxx.x
…															

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] mITT=Modified Intention-to-Treat, PP=Per Protocol.
[3] Exit day = exit date (date of completion/date of early termination) – date of randomization + 1.
[4] Treatment duration (hours) = (end of administration date/time – start of administration date/time + 1) – duration of any interruptions.
[5] Compliance rate is calculated by dividing the hours of study medication taken by the number of hours that should have been taken during the treatment period multiplied by 100.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: List for BHR-100 and Placebo. Sort by subject number within treatment group. This note relates to all listings.]

Listing 16.2.3.2 Informed Consent

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date/Time of Written Informed Consent	Did Subject Sign Informed Consent when he/she regained consciousness?		
				Response	If Yes, Date Subject Signed Informed Consent	If No or N/A, Specify
BHR-100	xx-xxx	M/35/W	DDMONYYYY/ XX:XX	(yes, no, N/A)	DDMONYYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.1 Demographic Characteristics

Treatment Group	Subject No.	Date of Birth	Date of Screening Visit	Age (years)[1]	Sex	Ethnicity[2]	Race[3] If other, Specify	Weight (kg)	Region/Country[4]/Site
BHR-100	xx-xxx	DDMONYYYY	DDMONYYYY	xx	(Male, Female)	(HL, NHL, NAL)	(W, B, P, A, N, Z, O) (xxxxxxxxxxxxxxx)	xx.x	xxxxxx/xx/xxxxxx (Region is North America, Europe, or Asia and South America)
…									

[1] Age is defined as (date of informed consent – date of birth + 1)/365.25.
[2] HL= Hispanic or Latino, NHL=Not Hispanic or Latino, NAL=Not Allowed to Obtain.
[3] W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[4] This is the two letter country code: US=United States, AT=Austria, BE=Belgium, CZ=Czech Republic, FI=Finland, FR=France, DE=Germany, HU=Hungary, IL=Israel,IT=Italy, NL=Netherlands, RO=Romania, RU=Russia, GB=United Kingdom, ES=Spain, CN=China, MY=Malaysia, TW=Taiwan, Province of China, SG=Singapore, TH=Thailand, AR=Argentina.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Weight is obtained from IWRS upload.]

Listing 16.2.4.2 Baseline Characteristics

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date of Screening Visit	Date/Time of Injury	Start Date/Time of Study Medication	Injury to medication intake (hours)[2]	Cause of TBI[3] (If Other, Specify)	Exam	Status[4]
BHR-100	xx-xxx	M/35/W	DDMONYYYY	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	7	Motor Vehicle	Head	Critical
	xx-xxx	F/33/W	DDMONYYYY	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	8.5*	Other (xxxxxxxxxxxxxxxxx)	Abdomen	Serious
	xx-xxx	F/39/B	DDMONYYYY	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	7	(Motor Vehicle, Motorcycle, Fall, Sports/ Recreation, Pedestrian, Diving, Assault, Other)	(Head, Face, Chest, Abdomen, Extremities, Spine)	(None, Minor, Moderate, Serious, Severe, Critical)
…									

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] Injury to medication intake (hours) = start date/time of study medication – date/time of injury. A star (*) will be added to indicate that the intake of study medication was greater than 8 hours after injury.
[3] TBI=Traumatic Brain Injury.
[4] None=no treatment, moderate=requires only outpatient treatment, serious=requires non-ICU hospital admission, severe=requires ICU observation and/or basic treatment, critical=requires intubation, mechanical ventilation or vasopressors for blood.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.3 Pre-Injury Narrative – Baseline Status – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Interview Date/Time	Occupational Status	Social Skills
BHR-100	xx-xxx	M/35/W	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.3 Pre-Injury Narrative – Baseline Status – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Interview Date/Time	Activities of Daily Living	Mode of Transportation
BHR-100	xx-xxx	M/35/W	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.3 Pre-Injury Narrative – Baseline Status – Part 3

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Interview Date/Time	General	Source of Information
BHR-100	xx-xxx	M/35/W	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	(Patient alone, Relative/Friend/Caretaker Alone, Patient plus Relative/Friend/Caretaker, Medical Personnel)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.4 Glasgow Coma Scale

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Study Day	Date/ Time of Assessment	~~Stop Date/ Time~~	Not Done?	Eye Opening[2] (none due to severe facial swelling/damage)	Verbal Response[3] (none due to intubation)	Motor Response[4]	GCS Score	Assessed By? If Other, Specify	~~Did Neurological Worsening Occur?~~
BHR-100	xx-xxx	M/30/W	(Screening Post-Resuscitation, Day 1, Day 2, Day 3, Day 4, Day 5, Day 6 Day 15)	DDMONYYYY/ XX:XX	~~DDMONYYYY/ XX:XX~~	(yes, no)	(SPON, SPEECH, PAIN, NONE) (no, yes)	(O, C, INAPP, INCOMP, NONE) (yes, no)	(OC, LP, WNF, ABF, ABE, NONE)	xx	(Neurosurgeon, ER Physician, Intensivist, Other (specify))	~~(yes, no)~~

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] SPON=Spontaneous, SPEECH=In response to speech, PAIN=In response to pain, NONE=None.
[3] O=Oriented, C=Confused, INAPP=Inappropriate words, INCOM=Incomprehensible sounds, NONE=None.
[4] OC=Obeys Commands, LP=Localizes Pain, WNF=Withdrawal/Normal flexion, ABF=Abnormal flexion, ABE=Abnormal Extension, NONE=None.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.5 Medical History

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date of Diagnosis	System	Diagnosis or Abnormality	Diagnosis Active?	End Date
BHR-100	xx-xxx	M/35/W	DDMONYYYY	(Skin, HEENT, Respiratory, …)	xxxxxxxxxxxxx	(Yes, No)	(DDMONYYYY, or missing if diagnosis is active)
…							

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Listing 16.2.4.6 Prior and Concomitant Medications

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Preferred Drug Name/ Medication Name	Dose Per Frequency	Units	Frequency	Route	Start Date	Ongoing?	Stop Date	Indication	P/ C[2]
BHR-100	xx-xxx	M/35/W	xxxxxxxxxxxxxxxxxx/ xxxxxxxxxxxxxxxxxx	xx	(mg, g, …, Other)	(Day, Week, Month, As needed, One time)	(PO, SC, IM, IV, … Other)	DDMONYYYY	(Yes, No)	DDMONYYYY (Stop date will be missing if medication ongoing.)	xxxxxxxxxxx	C

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] P=Prior Medication, C=Concomitant Medication, P&C=Prior and Concomitant Medication.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.7 Concomitant Procedures

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Procedure Date	Procedure	Indication/Reason
BHR-100	xx-xxx	M/35/W	DDMONYYYY Procedure Date	xxxxxxxxxxxxxxxxx	xxxxxxxxxxxxxxxx

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.8 Surgical Therapy

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date of Surgery	Type of Surgery	Specify	Repeat Procedure?
BHR-100	xx-xxx	M/35/W	DDMONYYYY	(Intracranial Surgery, Extracranial Surgery)	((Aneurysm…) if Intracranial Surgery, (Maxillofacial …) if Extracranial Surgery, or Specify if Other) (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)	(Yes, No)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.9 Study Admission

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Was Subject Transferred from Another Facility?	Admission to First Facility Date/Time	Admission at Study Center Date/Time
BHR-100	xx-xxx	M/35/W	(yes, no)	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.10 Subject Transfer

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Initial Site Number	Initial Subject Number	New Site Number	New Subject Number	Date Subject First Seen at New Site	Type of Visit (Specify)
BHR-100	xx-xxx	M/35/W	xx	xx-xxx	xx	xx-xxx	DDMONYYYY	(Day, 15, Day 30, Day 90, Day 180, Other) (xxxxxxxxxxxxxxxxxxxxxxx)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.11 Facility Transfer

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Subject Discharged/Transferred From		Subject Discharged/Transferred to/Admitted To	
			Specify	Date	Specify	Date
BHR-100	xx-xxx	M/35/W	(ICU, General Ward, Nursing Home/Long-Term Care, Other ICU, Other Hospital, Rehabilitation Unit, Home, Other) (xxxxxxxxxxxxxxxxxxxxxx)	DDMONYYYY	(ICU, General Ward, Nursing Home/Long-Term Care, Other ICU, Other Hospital, Rehabilitation Unit, Home, Other) (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)	DDMONYYYY

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.12 Intubation

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date/Time of Intubation	Date/Time of Extubation
BHR-100	xx-xxx	M/35/W	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.4.13 Daily Fluid

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Collection Period Start Date/Time	Collection Period Stop Date/Time	Total Fluid Administered (ml)	Total Fluid Excreted (ml)
BHR-100	xx-xxx	M/35/W	Day 1	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	xxxxx.x	xxxxx.x

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.5.1 Study Drug Administration – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Dose/ Day/ Bottle/ Record	Start Date/ Time	Stop Date/ Time	Route	Infusion Rate (ml/hr)
BHR-100	xx-xxx	M/35/W	(Loading, Maintenance)/1 /1/1	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	(Central line, Peripheral line)	xxxxx.x

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.5.1 Study Drug Administration – Part 2

				Infusion Rate		Infusion Rate Interrupted		
Treat-ment Group	Subject No.	Sex/ Age/ Race[1]	Dose/ Day/ Bottle/ Record	Modified?	Reason If Other, Specify	For more than 30 mins?	Reason If Other, specify	Duration (mins)
BHR-100	xx-xxx	M/35/ W	(Loading, Maintenance)/1/1/1	(Yes, No)	(Adverse Event, I.V. access problem, …, Other) (xxxxxxxxxxxxxxxxxxxxxxxxx)	(Yes, No)	(Adverse Event, I.V. access problem, …, Other) (xxxxxxxxxxxxxxxx)	xxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.5.2 End of Treatment

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Did the Subject Complete 5 Days of Treatment?	Date/Time Infusion Completed	If No, Reason for Discontinuation of Study Drug (If Other, Specify)	Treatment Duration (hours)[2]
BHR-100	xx-xxx	M/35/W	(Yes, No)	DDMONYYYY	(Adverse Event, Death, PI Decision, Sponsor Decision, Consent Withdrawn, Other) (xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)	xxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

[2] Duration of study drug exposure (in hours) = date:hour of last study medication administered – date:hour of first study medication administered + 1 – sum of recorded durations of infusion rate interruptions.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.1 Glasgow Outcome Scale, Questions

Question	Details and Possible Responses
1	Has the subject resumed pre-injury occupational status? Yes/No. [If subject resumed pre-injury occupational status is "Yes"] Check one box on the right A, B, C or D, that is most specific to the subject : A: Subject has resumed pre-injury employment: (e.g. executive or skilled laborer that has returned to the same level of responsibility at the same number of hours worked each week at the same performance level equivalent to that of their pre-injury status, with or without the use of compensatory mechanisms.) B: Subject could have resumed pre-injury occupational status, but currently has a reduction in performance level due to outlying circumstances that are not brain related: (e.g. previous work place out of business so they are unemployed and job hunting or a physical injury such as leg amputation that prevents them from returning to work - these are not "Brain Related Injuries" and should not be rated as a No for these types of reasons.) C: Subject has resumed academic pursuits: (e.g. a student has resumed the same number of hours/classes at the same performance level equivalent to that of their pre-injury abilities - independently, without the need for special accommodations such as tutors, if they were not necessary prior to the injury.) D: Subject has resumed household responsibilities: (e.g. a subject that was previously a housewife, househusband, unemployed and/or volunteer that has returned to the same level of responsibility, same number of hours involved at the same performance level equivalent to that of pre-injury.)
2	Has the subject resumed at least half as often as the pre-injury level of social activities? Yes/No.
3	Has the subject resumed pre-injury level of independence in activities of daily living? Yes/No.
4	Is the subject able to be left alone at home and is able to care for her/himself at the same level of pre-injury? Yes/No.
5	Has the subject resumed independence in transportation? Yes/No.
6	Does the subject respond to verbal communication and/or obey commands? Yes/No.

Listing 16.2.6.1.2 Glasgow Outcome Scale, Explanation of Categories

Rating	Explanation
Good Recovery	If you answered YES to ALL questions (1-6).
Moderate Disability	If you answered NO to questions 1 and 2 and YES to 3, 4, 5 & 6.
Severe Disability	If you answered NO to questions 3, 4, or 5 and YES to 6.
Vegetative State	If you answered NO to Question 6.
Dead	

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.3 Glasgow Outcome Scale – Extended, Explanation of Categories

GOS-E Rating	Explanation
Upper Good	Return to normal life and NO current problems relating to the injury that affect daily life (dizziness, headache, and sensitivity to noise or light, slowness, memory failure, concentration problems).
Lower Good	Return to normal life BUT current problems relating to the injury that affect daily life (dizziness, headache, and sensitivity to noise or light, slowness, memory failure, concentration problems). Social Activities: Resumed at least half as often as pre-injury. Disruption or Strain: Occasional (less than once per week).
Upper Moderate	Work capacity: Reduced Social Activities: Resumed less than half as often as pre-injury Disruption or Strain: Frequent (once a week or more but tolerable)
Lower Moderate	Work capacity: Unable to work or only able to work in sheltered workshop Social Activities: Unable or rarely able to participate Disruption or Strain: Constant (daily and intolerable)
Upper Severe	Care: Does not require someone to be around at home most of the time (for at least 8 hours during the day, if necessary) Travel: Unable to travel locally without assistance Shopping: Unable to shop without assistance
Lower Severe	Care: Requires frequent help of someone to be around at home most of the time

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.4 Glasgow Outcome Scale

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	Source of Information	Q1	Q2	Q3	Q4	Q5	Q6	GOS Rating	GOS – Extended Rating
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	(Patient Alone, Relative/Friend/ Caretaker Alone, …)	(Yes: (A,B,C,D) or No)	(Yes, No)	(Yes, No)	(Yes, No)	(Yes, No)	(Yes, No)	(Good Recovery, Moderate Disability, Severe Disability, Vegetative State, Dead)	(Upper Good, Lower Good, Upper Moderate, Lower Moderate, Upper Severe, Lower Severe)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

[Note to Programmer: Dead is not an option on the GOS CRF page. This information can be read from the mortality or date of death details (for premature terminations due to death). This information should be combined for the derived datasets.]

Listing 16.2.6.1.5 Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	Occupational Status	Summarize Subjects Work Capacity
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	(Returned to normal level, Reduced, Only able to work in sheltered work shop or unable to work)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.5 Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	Social Skills	Has the subject resumed pre-injury level of social activities?
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	(At least half as often, Less than half as often, Unable to or rarely participate)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.5 Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Part 3

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	Disruption or Strain	Summarize the subject's extent of disruption or strain:
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	(Occasional (less than once per week), Frequent (once per week or more but tolerable), Constant (daily and intolerable))

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.5 Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Part 4

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	Activities of Daily Living	Are the family able to leave subject home alone for >= 8 hours/day, if necessary?
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	(yes, no)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.5 Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Part 5

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	Mode of Transportation	Is subject able to drive or use public transport without assistance?	Is subject able to shop without assistance?
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxx	(yes, no)	(yes, no)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.5 Glasgow Outcome Scale, Glasgow Outcome Scale-Extended Narrative – Part 6

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Month	Interview Date	General	Are there any problems e.g. dizziness, that affect daily life after the head injury?
BHR-100	xx-xxx	M/35/W	(3,6)	DDMONYYY	xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx	(yes, no)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.1.6 Primary Efficacy, Covariates, and Subgroup Variables (Observed Values)

Treatment Group	Subject No.	Sex/ Age/ Race[1]	GOS Rating at Month 6	Region	GCS Motor Score	Pupil Response	CT Classification	Time to First Dose Relative to TBI (Hours)	Baseline Hypoxia	Baseline Hypo-tension	Traumatic Sub-arachnoid Hemorrhage
BHR-100	xx-xxx	M/35/W	(Good Recovery, Moderate Disability, Severe Disability, Vegetative State)	(North America, Europe, Asia and South America)	(1-2, 3, 4, 5-6)	(Bilateral, Unilateral, No Reactive Pupils, Not Testable)	(II, III, IV, evacuated/ non-evacuated mass lesion)	(0-<=4, >4-<=8, >8)	(Yes, No)	(Yes, No)	(Yes, No)

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Repeat this shell for
Listing 16.2.6.1.7 Primary Efficacy, Covariates, and Subgroup Variables (Missing Values Imputed)
Add
Note:Missing values are first imputed by carrying forward the Month 3 GOS assessment. If a subject has neither the 3 nor the 6 month GOS, the missing value is imputed based upon the primary proportional odds model. Missing covariates are imputed as the most common level over all subjects.

Listing 16.2.6.2 Sliding Dichotomy

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Prognosis Group	GOS Group (4-level)	GOS Group (2-level)
BHR-100	xx-xxx	M/30/W	Month 6	(Best, Intermediate, Worst)	(Good Recovery, Moderate Disability, Severe Disability, Vegetative State/Dead)	(Favorable, Unfavorable)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.3 Mortality

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Status (If Other, Specify)	Patient Residence	Date of Death or Date of Last Contact	Time to Death or Last Contact (days)[2]
BHR-100	xx-xxx	M/30/W	Month 1	(Lost to Follow-up, Consent Withdrawn, Alive, Dead, Other [specify])	(At Home, Hospital, Rehab Unit, Nursing Home/Long-Term Care, Other[Specify])	DDMONYYY	XX*
			Month 6				

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] If subject has not died, they will be censored on their last date of contact for the Kaplan-Meier survival analysis.
* Indicates that time to death or last contact is censored.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.4.1 SF-36, Explanation of Categories

Question	Explanation
1. In general, would you say your health is:	1=Excellent, 2=Very Good, 3=Good, 4=Fair, 5=Poor.
2. Compared to one year ago, how would you rate your health in general now?	1=Much better now than one year ago, 2=Somewhat better now than one year ago, 3=About the same as one year ago, 4=Somewhat worse now than one year ago, 5=Much worse now than one year ago.
3. The following questions are about activities you might do during a typical day. Does your health now limit you in these activities? If so, how much?	
a. Vigorous activities	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
b. Moderate activities	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
c. Lifting or carrying groceries	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
d. Climbing several flights of stairs	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
e. Climbing one flight of stairs	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
f. Bending, kneeling, or stooping	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
g. Walking more than one mile	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
h. Walking several hundred yards	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
i. Walking one hundred yards	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
j. Bathing or dressing yourself	1=Yes, limited a lot, 2=Yes, limited a little, 3=No, not limited at all
4. During the past 4 weeks, have you had any of the following problems with your work or other regular daily activities as a result of your physical health?	
a.	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time
b.	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time
c.	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time
d.	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time

Listing 16.2.6.4.1 SF-36, Explanation of Categories

Question	Explanation
5. During the past 4 weeks, how much of the time have you had any of the following problems with your work or other regular daily activities as a result of any emotional problems (such as feeling depressed or anxious)?	
a. Cut down on the amount of time spent on work or other activities.	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time
b. Accomplished less than you would like	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time
c. Did work or other activities less carefully than usual	1=All of the time, 2=Most of the time, 3=Some of the time, 4=A little of the time, 5=None of the time
6. During the past 4 weeks, to what extent has your physical health or emotional problems interfered with your normal social activities with family, friends, neighbors, or groups?	1=Not at all, 2=Slightly, 3=Moderately, 4=Quite a bit, 5=Extremely
7. How much bodily pain have you had during the past 4 weeks?	1=None, 2=Very mild, 3=Mild, 4=Moderate, 5=Severe, 6=Very severe
8. During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?	1=Not at all, 2=Slightly, 3=Moderately, 4=Quite a bit, 5=Extremely

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.4.1 SF-36, Explanation of Categories

Question	Explanation
9. These questions are about how you feel and how things have been with you during the past 4 weeks. For each question, please give the one answer that comes closest to the way you have been feeling. How much of the time during the past 4 weeks...	
a. Did you feel full of life?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
b. Have you been very nervous?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
c. Have you felt so down in the dumps that nothing could cheer you up?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
d. Have you felt calm and peaceful?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
e. Did you have a lot of energy?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
f. Have you felt downhearted and depressed?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
g. Did you feel worn out?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
h. Have you been happy?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
i. Did you feel tired?	1 = All of the time, 2 = Most of the time, 3 = Some of the time, 4 = A little of the time, 5 = None of the time
10. During the past 4 weeks, how much of the time has your physical health or emotional problems interfered with your social activities (like visiting friends, relatives, etc.)?	
11. How TRUE or FALSE is each of the following statements for you?	
a. I seem to get sick a little easier than other people	1 = Definitely true, 2 = Mostly true, 3 = Don't know, 4 = Mostly false, 5 = Definitely false
b. I am as healthy as anybody I know	1 = Definitely true, 2 = Mostly true, 3 = Don't know, 4 = Mostly false, 5 = Definitely false
c. I expect my health to get worse	1 = Definitely true, 2 = Mostly true, 3 = Don't know, 4 = Mostly false, 5 = Definitely false
d. My health is excellent	1 = Definitely true, 2 = Mostly true, 3 = Don't know, 4 = Mostly false, 5 = Definitely false

Listing 16.2.6.4.2 SF-36 (Individual Questions) – Part 1

					Q1	Q2	Q3									
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Interview Date			a	b	c	d	e	f	g	h	i	j
BHR-100	xx-xxx	M/39/W	Month 3	DDMONYYYY	(1-5)	(1-5)						(1-3)				
			Month 6													

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.4.2 SF-36 (Individual Questions) – Part 2

					Q4				Q5			Q6	Q7	Q8
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Interview Date	a	b	c	d	a	b	c			
BHR-100	xx-xxx	M/39/W	Month 3	DDMONYYYY			(1-5)				(1-5)	(1-5)	(1-5)	(1-5)
			Month 6											

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.4.2 SF-36 (Individual Questions) – Part 3

					Q9									Q10	Q11			
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Interview Date	a	b	c	d	e	f	g	h	i		a	b	c	d
BHR-100	xx-xxx	M/39/W	Month 3	DDMONYYYY					(1-5)					(1-5)			(1-5)	
			Month 6															

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.4.3 SF-36 (Scales and Summary Scores) – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Interview Date	Vitality	Physical Functioning	Bodily Pain	General Health Perceptions	Physical Role Functioning
BHR-100	xx-xxx	M/30/W	Month 3	DDMONYYYY	xxx	xxx	xxx	xxx	xxx
			Month 6						

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.4.3 SF-36 (Scales and Summary Scores) – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Interview Date	Emotional Role Functioning	Social Role Functioning	Mental Health	Physical Composite	Mental Composite
BHR-100	xx-xxx	M/30/W	Month 3	DDMONYYYY	xxx	xxx	xxx	xxx	xxx
			Month 6						

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.5.1 CT Scan and Classification – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit/ Date/ Time	Admission CT Scan / If No, Study Day	Number of Parenchymal Hemorrhage Lesions	Subarachnoid Hemorrhage/ If Yes, Specify	Basal Cisterns	Midline Shift Size (mm)	Total Volume of Largest Lesion (ml)	Parenchymal Hemorrhage/ If Yes, ≥ 25 ml?
BHR-100	xx-xxx	M/30/W	Screen-Ing DDMONYYYY/ XX:XX Day 6 DDMONYYYY/ XX:XX	(Yes, No) / x	xx	(Yes, No)/ (Basal, Convexity)	(Present, Compressed, Absent)	xx	xxxx.xx	(Yes,No)/ (Yes,No)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.5.1 CT Scan and Classification – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit/ Date/ Time	Cerebral Contusion / If Yes, ≥ 25 ml?	Subdural Hemorrhage/ If Yes, ≥ 25 ml?	Epidural Hemorrhage/ If Yes, ≥ 25 ml?	Intraventricular Hemorrhage/ If Yes, ≥ 25 ml?	Small Slit Ventricles	Cerebral Edema	Pneumocephalus
BHR-100	xx-xxx	M/30/W	Screen-Ing DDMONYYYY/ XX:XX Day 6 DDMONYYYY/ XX:XX	(Yes,No)/ (Yes,No)	(Yes,No)/ (Yes,No)	(Yes,No)/ (Yes,No)	(Yes,No)/ (Yes,No)	(Yes, No)	(Yes, No)	(Yes, No)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.5.1 CT Scan and Classification – Part 3

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit/ Date/ Time	Other Intracranial Findings/ Specify	Skull Fracture, Depressed	Skull Fracture, Basilar	Skull Fracture, Other / Specify	Evacuated Mass or Plans to Evacuate	CT Classification
BHR-100	xx-xxx	M/30/W	Screen-Ing DDMONYYYY/ XX:XX Day 6 DDMONYYYY/ XX:XX	(Yes,No)/ xxxxxxxx	(Yes, No)	(Yes, No)	(Yes, No) / xxxxxxxxxx	(Yes, No)	(1,2 … 6)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.5.2 CT Scan Comparison – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date of Comparison[2]	Parenchymal Hemorrhage	Cerebral Contusion	Subdural Hematoma	Epidural Hematoma	Subarachnoid Hematoma	Intraventricular Hemorrhage	Progressive Intracranial Pathology (PIP)
BHR-100	xx-xxx	M/30/W	DDMONYYYY	(Not Applicable, Improved, Worsened, New Findings, No Change)						(Not Applicable, Same, Worsened, Improved)
			DDMONYYYY							

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] CT scans will be compared to the screening CT scan.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.5.2 CT Scan Comparison – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date of Comparison[2]	Small Slit Ventricles	Cerebral Edema	Midline Shift	Pneumo-cephalus	Other Intracranial Findings (specify)
BHR-100	xx-xxx	M/30/W	DDMONYYYY	(Not Applicable, Improved, Worsened, New Findings, No Change)				(Not Applicable, Improved, Worsened, New Findings, No Change) (xxxxxxxxxxxxxxxxxxxxxxx)
BHR-100	xx-xxx	M/31/W	DDMONYYYY					

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] CT scans will be compared to the screening CT scan.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.5.2 CT Scan Comparison – Part 3

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date of Comparison[2]	Skull Fracture, Depressed	Skull Fracture, Basilar	Skull Fracture, Other
BHR-100	xx-xxx	M/30/W	DDMONYYYY	(Not Applicable, Improved, Worsened, New Findings, No Change)		
BHR-100	xx-xxx	M/31/W	DDMONYYYY			

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] CT scans will be compared to the screening CT scan.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.6.1 Intracranial Pressure

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date	Time	Value
BHR-100	xx-xxx	M/30/W	Screening	DDMONYYYY	xx.xx	xxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.6.2 Intracranial Pressure Monitoring

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Date/Time ICP Monitor Placed	Device Used (If Other, Specify)	End Date/Time ICP Monitoring	Reason for Ending ICP Monitoring (If Other, Specify)
BHR-100	xx-xxx	M/30/W	DDMONYYYY/ XX:XX	(Ventriculostomy, Intraparenchymal, Epidural, Subdural, Other)	DDMONYYYY/ XX:XX	(Clinically no longer required, Monitor/catheter failure, Patient considered unsalvageable, Patient died, Other)
				(xxxxxxxxxxxxxxx)		(xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.7 Cerebral Perfusion Pressure

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date	ICP (mmHg)	Highest/ Lowest ICP?	Pulse Rate (bpm)	Systolic Blood Pressure (mmHg)	Diastolic Blood Pressure (mmHg)	CPP (mmHg)
BHR-100	xx-xxx	M/30/W	Screen-ing	DDMONYYYY	xxx	(H, L)	xxx	xxx	xxx	xxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.8.1 Therapy Intensity Level – Part 1

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date/ Time/ ICP[2]	Sedation	Paralysis Induction	Ventricular Drainage	Mannitol	Hypertonic Saline
BHR-100	xx-xxx	M/30/W	Screening	DDMONYYYY/ XX:XX/ (H, L, UNK)	(Yes, No)	(Yes, No)	(Yes, No)	(Yes, No)	(Yes, No)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] Was TIL recorded at highest (H), lowest (L) or unknown (UNK) ICP value. The therapies taken each study day through to day 6 can continue to be monitored after the ICP monitor is removed. For such cases the ICP measurement would be unknown.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.6.8.1 Therapy Intensity Level – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date/ Time/ ICP[2]	Pressor Administration	Hyper-ventilation	Hypothermia for ICP Reduction	Barbiturate Induced Coma	Surgical Decompression	TIL Score
BHR-100	xx-xxx	M/30/W	Screening	DDMONYYYY/ XX:XX/ (H, L, UNK)	(Yes, No)	(Yes, No)	(Yes, No)	(Yes, No)	(Yes, No)	x

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] Was TIL recorded at highest (H), lowest (L) or unknown (UNK) ICP value. The therapies taken each study day through to day 6 can continue to be monitored after the ICP monitor is removed. For such cases the ICP measurement would be unknown.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.7 Adverse Events

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Adverse Event/ Preferred Term/ SOC	Start Date/ Stop Date/ Day[2] /	Duration[3]/ Length of Exposure (hours)[4]	Intensity/ Relationship/ Outcome[5]	Action Taken with Study Drug[6]	Treatment for AE? (specify)[7]	Serious?/ (Reason for Seriousness[8])/ Treatment Emergent?[9]
BHR-100	xx-xxx	M/30/W	xxxxxxxxxxxxxxx/ Xxxxxxxxxxxxxx/ xxxxxxxxxxxxxx	DDMONYYYY/ DDMONYYYY/ xx	x/ x.xx	xxxxxxxx/ x/ x	x	xxx/ (x)	xxx (xxx)/ xx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] Day is relative to the start date of study medication, event start date – administration start date + 1 if event start date is on or after the date of the start of study medication administration or event start date – administration start date if event date is before the date of the start of study medication administration.
[3] Length of exposure is based on administration start date and administration end date during the study (end date – start date + 1).
[4] Duration = AE end date – AE start date + 1.
[5] Relationship: 1=Not related, 2=Possibly related, 3=Probably related, 4=Related.
Outcome: 1=Recovered/resolved, 2=Recovering/resolving, 3=Not recovered/not resolved, 4=Recovered/resolved with sequelae, 5=Fatal, 6=Unknown.
[6] 1=Dose not changed, 2=Drug withdrawn, 3=Drug interrupted, 4=Dose reduced, 5=Dose increased, 6=Unknown, 7=Not applicable.
[7] 1=none, 2=Change in therapy intensity level, 3=procedure/surgery, 4=other (specify).
[8] 1=Results in death, 2=Life threatening, 3=Results in persistent or significant disability/incapacity, 4=Requires or prolongs hospitalization, 5=Congenital abnormality/birth defect, 6=Other medically important event.
[9] Treatment-emergent adverse events are defined as events that start on or after the first dose of study medication and up to 15 days and 6 months after the initiation of study treatment, for adverse events and serious adverse events respectively.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.1.1 Laboratory (Coagulation) Results

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Test Name	Visit	Sample Date/ Time	Result (Unit)	Change from Baseline	Range Flag[2]	Reference Range Low	Reference Range High	Clin Sig?	Is this an AE?
BHR-100	xx-xxx	M/35/W	INR	Screening	DDMONYYYY/ XX:XX	xx.x g/L	xx.x	L	xx.x	xx.x	(Yes, No)	(Yes, No)
				Day 6	DDMONYYYY/ XX:XX	xx.x g/L	xx.x	L	xx.x	xx.x		
				Day 15	DDMONYYYY/ XX:XX	xx.x g/L	xx.x	L	xx.x	xx.x		
…												

Note: The baseline value is defined as the last measurement taken prior to first administration of study drug (Day 1). For laboratory assessments this will be the screening visit.

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.
[2] N = Normal, L = Low, H = High.

[Note to Programmer: Do not include unscheduled results in this listing.]

Listing 16.2.8.1.2 Laboratory (Hematology) Results
(Produce for Hemoglobin, Hematocrit, RBC, Reticulocyte Count, Platelet Count, WBC, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)
Listing 16.2.8.1.3 Laboratory (Serum Chemistry) Results
(Produce for Sodium, Potassium, Chloride, Cholesterol, total, Triglycerides, ALT, AST, GGT, Alkaline Phosphatase, Total Protein, Glucose)
Listing 16.2.8.1.4 Laboratory (Urinalysis) Results
(Produce for pH, Specific Gravity, Protein, Glucose, Blood, WBC, RBC, Casts, Epithelial Cells, Bacteria)
[Use shell for Listing 16.2.8.1.1]

Listing 16.2.8.1.5 Laboratory (Pregnancy Test) Results

				If, Yes			
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Is Subject Female of Child-bearing Potential?	Was Sample Collected for Pregnancy Test?	Pregnancy Test Type	Date of Collection	Pregnancy Test Result
BHR-100	xx-xxx	M/35/W	(yes, no)	(yes, no)	(Serum, Urine)	DDMONYYYY	(Positive, Negative)
…							

[1] M = Male, F = Female; W = White, B = Black, African American or of African Heritage, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, Z=Not Allowed to Obtain, O = Other.

Listing 16.2.8.2 Vital Signs

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date/Time	Pulse Rate (bpm)	Resp Rate (bpm)	SBP (mmHg)	DBP (mmHg)	Temp (°C)	Weight (kg)	Right Pupil[2]	Left Pupil[2]
BHR-100	xx-xxx	M/30/W	Screen-ing	DDMONYYYY/ XX:XX	xxx	xx	xxx	xxx	xx.x	xx	(R, NR, UN)	(R, NR, UN)

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] R=Reacts, NR=No Reaction, UN=Eyes Closed/Untestable.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.3 Physical Examinations

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date Exam Performed	Body System	Status	Abnormalities
BHR-100	xx-xxx	M/30/W	Screen-ing	DDMONYYYY	Skin	Normal	
					HEENT	Abnormal	xxxxxxxxxxxxxxxxxx
					Respiratory	Not Done	
					Cardiovascular	Not Done	
					Abdomen	Normal	
					Musculoskeletal	Normal	
					Neurological	Normal	
					Gastrointestinal	Normal	
					Genitourinary	Normal	
					Endocrine		
			...	...	Lymph Nodes	...	...
					. . .		

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.4 12-Lead Electrocardiogram (ECG) – Part 1

					Rhythm			Conduction			
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Heart Rate bpm)	Result	Specify	Clin Sig	Result	Specify	Clin Sig	QT Prolongation Interval
BHR-100	xxx-xxxx	M/30/W	Screening	xx	(Normal, Abnormal)	(Sinus Arrhythmia, …, Other Arrhythmia [xxxxxxx])	(Yes, No)	(Normal, Abnormal)	(LBBB, …, Other [xxxxxx])	(Yes, No)	xxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.4 12-Lead Electrocardiogram (ECG) – Part 2

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	QRS Complex			Comments
				Result	Specify	Clin Sig	
BHR-100	xxx-xxxx	M/30/W	Screening	(Normal, Abnormal)	(Non-specific ST changes, …, other [xxxxx])	(Yes, No)	xxxxxxxxxxxxxxxxxxxxxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.5 Arterial Blood Gas

Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Date/ Time	Line	pH	$PaCO_2$ (mmHg)	HCO_3 (mmol/L)	SaO_2 (%)	PaO_2 (mmHg)	FiO_2 (%)
BHR-100	xx-xxx	M/30/W	Screening	DDMONYYYY/ XX:XX	(1.1, 2.2, 3.3, 4.4, 5.5, 6.6)	x.xx	xxx.x*	xxx.x	xxx.x	xxx.x	xx.xx*

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
* Indicates the worst value of the day for a given parameter.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.6 Neuroworsening – Part 1

				Neuroworsening?			Prior Neurologic Worsening					
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Visit	Start Date/ Time	Stop Date/ Time	Contin-uing?	Eye Opening[2] (none due to severe facial swelling/damage)	Verbal Response[3] (none due to intubation)	Motor Response[4]	Right Pupil React-ivity[5]	Left Pupil React-ivity[5]	ICP(mmHg)/ SBP (mmHg)/ DBP (mmHg)
BHR-100	xx-xxx	M/30/W	Day 1	DDMONYYYY/ XX:XX	DDMONYYYY/ XX:XX	(yes, no) If no, a stop date should be provided in the previous column.	(SPON, SPEECH, PAIN, NONE) (no, yes)	(O, C, INAPP, INCOMP, NONE) (yes, no)	(OC, LP, WNF, ABF, ABE, NONE)	(R, NR, UN)	(R, NR, UN)	xxx/ xxx/ xxx

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] SPON=Spontaneous, SPEECH=In response to speech, PAIN=In response to pain, NONE=None.
[3] O=Oriented, C=Confused, INAPP=Inappropriate words, INCOM=Incomprehensible sounds, NONE=None.
[4] OC=Obeys Commands, LP=Localizes Pain, WNF=Withdrawal/Normal flexion, ABF=Abnormal flexion, ABE=Abnormal Extension, NONE=None.
[5] R=Reacts, NR=No Reaction, UN=Untestable.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x

Listing 16.2.8.6 Neuroworsening – Part 2

				At Time of Neurologic Worsening						
Treatment Group	Subject No.	Sex/ Age/ Race[1]	Start Date/ Time	Eye Opening[2] (none due to severe facial swelling/damage)	Verbal Response[3] (none due to intubation)	Motor Response[4]	Right Pupil React-ivity	Left Pupil React-ivity	ICP(mmHg)/ SBP (mmHg)/ DBP (mmHg)	Primary Reason for Deterioration (If Other, Specify)
BHR-100	xx-xxx	M/30/W	DDMONYYYY/ XX:XX	(SPON, SPEECH, PAIN, NONE) (no, yes)	(O, C, INAPP, INCOMP, NONE) (yes, no)	(OC, LP, WNF, ABF, ABE, NONE)	(R, NR, UN)	(R, NR, UN)	xxx/ xxx/ xxx	(Increased Intracranial Volume, Cerebral Ischemia, Seizures, Systemic Complication, Other [xxxxxxxxxxxxxxxx])

[1] M = Male, F = Female; W = White, B = Black or African American, P = Native Hawaiian or Other Pacific Islander, A = Asian, N = American Indian or Alaska Native, O = Other.
[2] SPON=Spontaneous, SPEECH=In response to speech, PAIN=In response to pain, NONE=None.
[3] O=Oriented, C=Confused, INAPP=Inappropriate words, INCOM=Incomprehensible sounds, NONE=None.
[4] OC=Obeys Commands, LP=Localizes Pain, WNF=Withdrawal/Normal flexion, ABF=Abnormal flexion, ABE=Abnormal Extension, NONE=None.
[5] R=Reacts, NR=No Reaction, UN=Untestable.

Program: xxxxxxx.sas, Output: xxxxxxx.rtf, Generated on: DDMONYYYY xx:xx, Page x of x