Clinical Study Protocol: SyNAPSe® Trial

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

Investigational Drug: BHR-100 (intravenous progesterone lipid emulsion)

Protocol Number: BHR-100-301

US IND Number: 104,330
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Amendment 1 April 15, 2010
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Amendment 3 November 15, 2011

Sponsor

BHR Pharma, LLC

[redacted]

Contract Research Organizations

[redacted]

[redacted]

PROTOCOL REVIEW AND SIGNATURE FORM

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

Protocol Number: BHR-100-301

BHR Pharma, LLC has reviewed the content and format of this protocol and approves Protocol No. BHR-100-301 for issuance.

BHR Pharma, LLC Representative

Name (print)

Signature **Date**

I agree to conduct the study as detailed herein and in compliance with ICH Guidelines for Good Clinical Practice and other applicable regulatory requirements, and to inform all who assist me in the conduct of this study of their responsibilities and obligations.

Principal Investigator

Name (print)

Signature **Date**

STUDY SYNOPSIS

Name of Sponsor	BHR Pharma, LLC
Name of Finished Product	BHR-100 (intravenous progesterone lipid emulsion)
Name of Active Ingredient	Progesterone
Title of Study	A Randomized, Double-Blind, Placebo-Controlled Phase 3 Study to Investigate the Efficacy and Safety of Progesterone in Patients with Severe Traumatic Brain Injury
Phase of Development	Phase 3
Study Centers	Multicenter study conducted in approximately 100 centers.
Indication	Severe (GCS 3-8) traumatic brain injury (TBI)
Study Duration	5 days infusion and 6 months total observation per subject

Study Objectives

The aim of the study is to determine the efficacy and safety of BHR-100 i.v. progesterone infusion compared to placebo infusion, utilizing the GOS in severe traumatic brain injury patients (GCS 3-8), with the treatment administered continuously over 5 days beginning within 8 hours after the injury. In addition, the safety and clinical benefit of BHR-100 treatment will be assessed through the secondary endpoints.

Study Endpoints

Primary Endpoint	GOS evaluated at 6 months post injury.
Secondary Endpoints	• Mortality assessment at 1 month and 6 months post TBI • Evaluation of GOS at 3 months • Evaluation of the GOS-E at 3 and 6 months • Quality of Life (SF-36) at 3 and 6 months • Impact of treatment on ICP, CPP, and TIL • Effect of treatment on the progression of intracranial pathology as assessed by admission (baseline) and end-infusion (Day 6 +/- 1 Day) CT scans

Study Design

Methodology	This trial will be a multicenter, randomized, double-blind, placebo-controlled study, conducted in approximately 140 Level I (or equivalent) trauma centers in various geographical areas including North America, Europe, Asia, and South America.

	The subjects will be managed in accordance with the standard guidelines for the management of severe TBI: BTF, ABIC, and EBIC (BTF, 2007; ABIC, 2003; Maas *et al.,* 1997, respectively). An independent DSMB will be appointed to have responsibility for safeguarding the interests of trial subjects, and assessing the safety and efficacy of the study treatments during the trial. Treatment allocation will be done using a centralized randomization system.
Number of Subjects	The planned total number of subjects will be 1180, randomized equally to BHR-100 or placebo.
Diagnosis and Main Criteria for Inclusion	1. Male or female patients, age between 16 and 70 years, inclusive (or other age limits as required by local regulations) 2. Weight from 45 to 135 kg, inclusive 3. Sustained a closed head trauma no more than 8 hours before initiation of study drug infusion (exposed dura mater is acceptable in the case of depressed skull fractures) 4. TBI diagnosed by history and clinical examination 5. GCS score between 3 and 8, inclusive 6. At least one reactive pupil (pinpoint pupils due to opioid pain treatment are considered reactive) 7. Evidence of TBI confirmed by abnormalities consistent with trauma on CT scan upon admission (Diffuse injury II-IV, evacuated and non-evacuated mass lesion, Marshall's CT Classification) 8. Indication for ICP monitoring
Exclusion Criteria	1. Life expectancy of less than 24 hours as determined by the Investigator 2. Prolonged and/or uncorrectable hypoxia (Pa02< 60 mmHg) or hypotension (systolic blood pressure < 90 mmHg) at the time of randomization 3. Any spinal cord injury 4. Pregnancy 5. Penetrating head injury 6. Bilaterally fixed dilated pupils at the time of randomization/ 7. Coma suspected to be primarily due to other causes (e.g. alcohol) 8. Pure epidural hematoma 9. Preexisting clinically significant disease or chronic condition that can be ascertained at the time of admission and could affect functional outcome 10. Severe cardiac or hemodynamic instability prior to randomization 11. Known treatment with another investigational drug, device, medical therapy or procedure within 30 days of injury

	12. A history of allergic reaction to progesterone and related drugs or any of the components of the infusion 13. Any disease, in the opinion of the Investigator, that is unstable or which could jeopardize the safety of the patient and his/her compliance in the study. 14. Subjects who, in the opinion of the Investigator, would not be able or willing to comply with the protocol through the final visit (6 months post-injury)
Test Product Dose and Mode of Administration	A loading dose of 0.71 mg/kg/hr of BHR-100 or placebo i.v. for the first hour will be followed by a continuous maintenance infusion of 0.5 mg/kg/hr for a total of 5 days/120 hours of treatment. The study drug treatment (BHR-100 or placebo) is administered by i.v. infusion via peristaltic pump and must be started within 8 hours after injury.
Duration of Treatment	A total of 5 days (120 hours) of continuous infusion treatment.
Criteria for Evaluation	
Efficacy	Primary: GOS assessment at Month 6 post-injury Secondary (all timepoints are at post-injury): • Mortality at Month 1 and Month 6 • GOS at Month 3 • GOS-E at Months 3 and 6 • SF-36 at Months 3 and 6 • ICP, CPP and TIL • CT scans at admission and end-infusionDay 6 (+/- 1 Day)
Safety	Safety assessments will include mortality, AEs, SAEs, vital signs, labs, and ECG. Additional secondary safety parameters (which also may constitute some aspects of efficacy) specific for this indication are: • Neuroworsening: defined as any one of the following relative to baseline: a decrease in GCS motor score $\geq$ 2, development of pupillary abnormalities, any other neurological deterioration or progression of lesion on CT scan leading to a change in patient management. • TIL for management of ICP and CPP, based on administration of the following treatments: ▪ none ▪ sedation/paralysis

	▪ ventricular drainage ▪ hyperosmolar therapy ▪ blood pressure supportive agents ▪ hyperventilation • barbiturates • surgical decompression for refractory ICP control
Primary Efficacy Analysis	The primary efficacy variable is GOS evaluated at 6 months post injury. The proportional odds model (POM) (McCullagh, 1980) will be used to compare BHR-100 to placebo for the GOS outcome at six months (categories of good recovery, moderate disability, severe disability, and the combined vegetative state/death). A test for the proportional odds assumption will be conducted and if statistically significant, other polytomous logistic models will be investigated. The analyses will be conducted on an intent-to-treat (ITT) basis, and the 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. If the p-value from the test of the null hypothesis is less than 0.0003 (at the interim analysis) 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.
Sample Size Justification	A total sample size of 1180 patients is planned; patients will be randomized in a 1:1 ratio to BHR-100 or placebo. This sample size estimate was determined using a proportional odds model (Whitehead, 1993) of the 6-month GOS outcome distribution from the population with baseline GCS 3-8 in previous TBI Phase 3 trials in the IMPACT Database (Marmarou *et al.,* 2007). Randomization will be stratified by major geographical regions of the site locations in order to maintain overall equivalent treatment group size.
Baseline Data Analysis	Baseline comparability of the treatment groups for the most important prognostic factors (age, GCS motor score at baseline, pupillary response and CT classification) will be illustrated using appropriate descriptive statistics.
Safety Monitoring/DSMB	An independent DSMB will review safety and efficacy data from the trial in a blinded fashion. The data will be provided to the DSMB statistician at approximately 100-subject intervals, with precise intervals to be determined in consultation with the DSMB. The DSMB will determine the type of data and statistical comparisons required for review.

Interim Analysis	A formal interim analysis on the 6-month GOS will be performed once the first 200 subjects in each arm (400 total) have been assessed. At the planned interim analysis, a two-sided test will be conducted to detect either an increase or decrease in the common odds ratio. Any consideration to prematurely discontinue the trial will be discussed by the study statistician with the DSMB and the sponsor. In order to stop the trial at an interim analysis because of favorable outcome, the significance level will need to be less than the critical p-value of 0.0003.
Safety Analysis	All AEs and SAEs will be summarized by counts of subjects with AEs and individual occurrences according to the MedDRA coding. The following will be summarized both as the observed values and, where applicable, the changes from baseline of the values: ▪ Vital signs ▪ Safety labs ▪ ECG variables AE summaries will include abnormal, clinically significant lab results deemed by the Investigator as AEs. Counts and percentages of subjects with each symptom of neuroworsening will be described.

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LIST OF ABBREVIATIONS AND TERMS

ABIC	American Brain Injury Consortium
ABG	Arterial Blood Gases
AE	Adverse Event
BTF	Brain Trauma Foundation
CPP	Cerebral Perfusion Pressure
CRF	Case Report Form (paper or other media)
CT	Computed Tomography
DRS	Disability Rating Scale
DSMB	Data Safety Monitoring Board
EBIC	European Brain Injury Consortium
ECG	Electrocardiogram
EU	European Union
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GCS	Glasgow Coma Scale
GMP	Good Manufacturing Practice

GOS	Glasgow Outcome Scale
GOS-E	Glasgow Outcome Scale - Extended
HCO_3	Bicarbonate (in ABG)
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICP	Intracranial Pressure
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
i.m.	intramuscular
IMPACT	International Mission for Prognosis and Analysis of Clinical Trials in TBI
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-treat
i.v.	intravenous
IWRS	Interactive Web Response System
KPS	Karnofsky Performance Scale
LOCF	Last Observation Carried Forward
LAR	Legally Authorized Representative [per U.S. F.D.A. regulations 45 CFR 46.102(c) and 21 CFR 50.3(l)] and Legally Acceptable Representative [per ICH E6 CPMP/ICH/135/95]
MedDRA	Medical Dictionary for Regulatory Activities
NDA	New Drug Application
PIP	Progressive Intracranial Pathology
$PaCO_2$	Carbon Dioxide (in ABG)
PaO_2	Partial Pressure of Oxygen (in ABG)
POM	Proportional Odds Model
ProTECT^{TM}	Progesterone for Acute Traumatic Brain Injury Trial Experimental Clinical Treatment

QOL	Quality of Life
SAE	Serious Adverse Event
SaO_2	Arterial Oxygen Saturation (in ABG)
SAP	Statistical Analysis Plan
SD	Standard Deviation
SF-36	Short Form (36) Health Survey
TBI	Traumatic Brain Injury
TIL	Therapeutic Intensity Level
TNF	Tumor Necrosis Factor

1. INTRODUCTION AND RATIONALE

1.1 Background

Traumatic Brain Injury (TBI) is a leading cause of death and disability worldwide. In Europe, an overall average TBI incidence rate derived from estimates of hospitalized patients plus deaths is about 235 per 100,000 (Tagliaferri et al., 2006) and in China, severe TBI accounts for approximately 20% of brain injuries (Wu et al., 2008). The U.S. Centers for Disease Control and Prevention (CDC) estimate that more than 1.7 million Americans sustain TBI each year. Of these, approximately 1.36 million require emergency department visits, 275,000 are hospitalized, and 52,000 die (Faul et al., 2010). In the U.S. children aged 0 to 4 years, older adolescents aged 15 to 19 years, and adults aged 65 years and older are the age groups most likely to sustain a TBI (Faul et al., 2010)

TBI is graded as mild, moderate, or severe on the basis of the Glasgow Coma Scale (GCS). In severe injury (GCS 3-8) the subject is comatose, unable to open their eyes or follow commands (Teasdale and Jennett, 1974). Severe TBI accounts for more than 57,000 hospitalized patients in the U.S. each year, and mortality rates are highest in the severe category of TBI. Studies involving about 6000 severe TBI patients (GCS $\leq$ 8) observed mortality rates ranging from 20% to as high as 39%, translating into perhaps 11,000 – 22,000 deaths per year in this population (Marmarou et al., 2007). According to the CDC, 5.3 million Americans (2% of the population) are living with some degree of disability from a prior TBI (Brown et al. 2008; CDC, 2008). These patients have a long-term or lifelong need for help to perform activities of daily living as a result of TBI. In the US, the direct and indirect costs of TBI are estimated at $60 billion (Langlois et al., 2006).

1.2 Progesterone as a Neuroprotectant: Pre–Clinical Studies

Progesterone, primarily known as a gonadal hormone, is an important agent affecting many functions in the central nervous system, where it is also locally synthesized, and it may play an important role in promoting and enhancing repair after traumatic brain injury and stroke (Stein, 2005). A systematic review of experimental studies indicates that progesterone is neuroprotective, in terms of reducing lesion volume, following either cerebral ischemia or traumatic brain injury (Gibson *et al.,* 2008). Progesterone also has been shown to reduce post-injury edema in rats (Roof *et al.,* 1993) as well as improve cognitive recovery and secondary neuronal loss caused by contusion injury (Roof *et al.,* 1994). The protection against post-traumatic edema was seen in animals treated up to 24 hours post injury (Roof *et al.,* 1996). Progesterone also has been shown to protect against lipid peroxidation following TBI in rats (Roof *et al.,* 1997).

Progesterone has a membrane stabilizing effect that serves to reduce the damage caused by lipid peroxidation. In addition, it may provide neuroprotection by suppressing neuronal hyperexcitability (Sayeed *et al.,* 2007). Experimental studies by several investigators have documented the neuroprotective effects of progesterone in various models of traumatic brain injury and stroke (Cutler *et al.,* 2007; Cutler *et al.,* 2005; Cutler *et al.,* 2006; Djebaili *et al.,* 2005; Djebaili *et al.,* 2004; Duvdevani *et al.,* 1995; Galani *et al.,* 2001; Grossman *et al.,* 2004; Guo *et al.,* 2006; He *et al*., 2004; Pettus *et al*., 2005; Roof *et al.,* 1994; Roof *et al.,* 1996; Roof *et al.,* 2000; Sayeed *et al*., 2007; Shear *et al*., 2002; VanLandingham *et al*., 2007; Wright *et al*., 2001).

1.3 Progesterone as a Neuroprotectant: Clinical Studies in TBI

Based upon a large and growing body of preclinical evidence demonstrating the powerful neuroprotective properties of progesterone, the feasibility of progesterone therapy was studied to assess its applicability in patients with acute TBI. One pilot study (Xiao *et al.,* 2007) and two Phase 2 trials (Wright *et al.,* 2007; Xiao *et al.,* 2008) have been conducted with parenterally-administered progesterone, and the results have revealed an acceptable safety profile and promising efficacy outcomes to support further studies.

A Phase 2 randomized, double blind, placebo-controlled trial (the Progesterone for Acute Traumatic Brain Injury Trial Experimental Clinical Treatment (ProTECT™) study) was conducted by Wright *et al.* (2007) in 100 adult TBI patients arriving within 11 hours of injury and with a pre-resuscitation GCS ranging from 4 to 12. Patients were randomized on a 4:1 basis to receive either intravenous (i.v.) progesterone or placebo. Subjects were assessed daily for adverse events and signs of recovery. Safety and efficacy outcomes were assessed at 30 days post-injury. The primary safety measures were adverse event rates and mortality. The primary measure of benefit was the dichotomized Glasgow Outcome Scale Extended (GOS-E).

In the ProTECT™ study (Wright *et al.,* 2007), 77 subjects were randomized to progesterone and 23 to placebo. The mean time from injury to initiation of progesterone/placebo infusion was 6.3 hours. A progesterone alcohol solution was mixed with Intralipid® 20% (Fresenius Kabi, Clayton, NC), and the mixture infused at an initial rate of 14 mL/hr (0.71 mg/kg/h) for 1 hour followed by a decrease in infusion rate to 10 mL/hr (0.5mg/kg/hr) for overall treatment duration of 72 hours. Subjects treated with placebo received the same infusion regimen minus the progesterone. The treatment groups had similar baseline demographic and clinical characteristics. Laboratory and physiologic values were similar throughout treatment.

No serious adverse events were attributed to progesterone. Adverse and serious adverse event rates were similar in both groups, except that subjects treated with progesterone had a lower 30-day mortality rate than those in the placebo group (Relative Risk [RR] 0.43; 95% confidence interval 0.18 to 0.99). The majority of severe (GCS 4-8) TBI survivors in both groups had relatively poor GOS-E and Disability Rating Scale (DRS) scores. However, moderate TBI (GCS 9-12) survivors who received progesterone were more likely to have a moderate-to-good outcome than those randomized to placebo. It was concluded that, in this small study, progesterone caused no discernible harm and showed possible signs of benefit.

The pharmacokinetics of progesterone intravenous infusion were examined in the above trial in 33 subjects (Wright *et al.,* 2005). Multiple blood samples were obtained from 11 female and 21 male subjects receiving progesterone infusions and 1 female and 3 males receiving placebo infusions for 72 hours. Analyses demonstrated that stable progesterone concentrations can be rapidly achieved via progesterone infusion following TBI.

In a pilot randomized trial (Xiao *et al.,* 2007), the therapeutic effects of intramuscular (i.m.) progesterone were studied in 56 TBI patients with baseline GCS of 5 to 8. Twenty six were treated with progesterone and 30 subjects received placebo. Neurologic outcome was assessed using the Glasgow Outcome Scale (GOS) and the Karnofsky Performance Scale (KPS). Three-month follow up indicated that GOS, KPS, and the degree of verbal impairment were better in the progesterone-treated group than in the control group ($p < 0.05$); however there was no

significant difference in mortality. Serum 15-F(2t)-isoprostane and tumor necrosis factor (TNF)-alpha levels were reduced significantly in the progesterone-treated group on the 5th and 10th day after injury (p<0.05), supporting the notion that the positive effects of progesterone may be due to its alleviating inflammatory and lipid peroxidation response .

Following the above study, Xiao *et al*. conducted a prospective, randomized, placebo-controlled trial of progesterone in 159 severe TBI patients with a GCS 3-8 who arrived within 8 hours of injury (Xiao *et al.,* 2008). Patients were randomized to receive intramuscularly either progesterone (n=82) or placebo (n=77). At 3 months and 6 months after treatment, subjects given progesterone had significantly more favorable functional outcomes and decreased mortality compared with placebo-treated subjects (mortality at 6 months $p < 0.05$).

In summary, studies have shown that administering relatively large doses of progesterone during the first few hours to days after injury significantly limits central nervous system damage, reduces loss of neural tissue, and improves functional recovery. Although the research published to date has focused primarily on progesterone's effects on blunt TBI, there is evidence that the hormone affords protection from several forms of acute central nervous system injury, including penetrating brain trauma, stroke, anoxic brain injury, and spinal cord injury. Progesterone appears to exert its protective effects by protecting or restoring the blood-brain barrier, attenuating cerebral edema, down-regulating the inflammatory cascade, and limiting cellular necrosis and apoptosis. All are plausible mechanisms of neuroprotection (Stein, 2008).

1.4 Rationale for Timing of Drug Administration

The start of infusion in this clinical trial must occur within 8 hours of the time of injury, preferably as soon as possible, in accordance with the "Golden Hour" principle of emergency medicine that earlier treatment is better. While one animal model of TBI suggests progesterone has a therapeutic window that continues out to 24 hours post-injury (Roof *et al.,* 1996), efficacy seemed to diminish as a function of time prior to treatment. Moreover, the presumed mechanisms of action for progesterone in TBI argue for earlier intervention. While progesterone has many pro-trophic effects that affect damage repair and could be responsible for the large observed treatment window, an ideal neuroprotective agent should ***prevent*** damage, and the pathogenesis of TBI begins very early post-injury.

Although the mechanistic and preclinical considerations drive earlier treatment, there are practical obstacles of informed consent and study treatment preparation that must be considered. Patients are unable to provide consent due to level of consciousness, therefore consent must be sought from a relative or other authorized representative, as permitted by local regulations. Feasibility research indicates that obtaining informed consent will be rate-limiting and if, for example, only 6 hours are allowed for treatment initiation, timely enrollment becomes problematic. The 8-hour window required in this protocol strikes the appropriate balance between the need for early initiation of treatment and the requirement to obtain appropriate informed consent.

2. STUDY OBJECTIVES

2.1 Primary Objective

The aim of the study is to determine the efficacy and safety of BHR-100 utilizing the 6-month GOS in severe TBI patients (GCS 3-8) following 120 hours of study treatment.

2.2 Secondary Objectives

In addition, the clinical benefit of progesterone treatment will be further assessed through the evaluation of:

1. mortality at 1 month and 6 months post injury
2. GOS at 3 months
3. GOS-E at 3 and 6 months
4. Quality of Life using Short Form (36) Health Survey (SF-36) at 3 and 6 months
5. the effect on Intracranial Pressure (ICP), Cerebral Perfusion Pressure (CPP), and Therapeutic Intensity Level (TIL)
6. the effect on the progression of intracranial pathology as assessed by the admission and the Day 6 (+/- 1 Day) computed tomography (CT) scans

3. STUDY DESIGN

3.1 Description of Overall Study Design

This is a multi-center, randomized, double blind, placebo controlled study conducted on 1180 severe TBI patients at 100 or more international trauma centers (sites). All subjects will be managed in accordance with standard guidelines for TBI from the Brain Trauma Foundation (BTF), American Brain Injury Consortium (ABIC) and European Brain Injury Consortium (EBIC) (BTF, 2007; ABIC, 2003; Maas et al., 1997).

Randomization will be implemented using Interactive Web-based Response System (IWRS) technology. Randomization will be stratified by major geographical regions. The post-stabilization GCS of 3 to 8, assessed at the study center, will serve as the index (randomization) GCS. If a true index GCS at arrival is not feasible due to medically indicated measures (i.e., GCS is 3 due to sedation and paralysis), the Investigator needs to obtain a reliable GCS assessment obtained by the Emergency Team at the scene of injury (field GCS) and/or other transferring medical facility. The score must include each component of the score (eye opening, verbal and motor responses), and must total 3-8. Any reliable GCS of 3 to 8, inclusive, qualifies the patient for study enrollment. To maintain the blind, all study procedures are to be performed by site personnel blind to treatment assignment.

Subjects will be intensively monitored during the five-day infusion period and their Intensive Care Unit (ICU) stay. The start and duration of ICP monitoring will be at the discretion of the site based on the subject's clinical condition. If the ICP monitor is placed, ICP and TIL will be recorded for a period of up to six days. The baseline CT scan used for randomization and a second CT scan obtained on Day 6 (+/- 1 day) will be centrally analyzed for progressive intracranial pathology (PIP).

Adverse events (AEs) will be collected beginning at the start of study drug infusion and through Day 10 post-infusion (Days 1-15). Serious adverse events (SAEs) will be collected beginning at the start of study drug infusion, continuing throughout the six-month subject duration in the study.

The GOS will be collected at three and six months as well as the GOS-E.

The Schedule of Events is shown in Appendix A.

3.2 Study Endpoints

3.2.1 Primary Endpoint

GOS evaluated at Month 6 post-injury.

3.2.2 Secondary Endpoints

Secondary endpoints will be assessed by the following measures:

- Mortality assessment at 1 month and 6 months post TBI
- Evaluation of GOS at 3 months

- Evaluation of the GOS-E at Months 3 and 6
- SF-36 at Months 3 and 6
- Changes in ICP, CPP, and TIL
- Changes in intracranial pathology as assessed by the admission and end-infusion Day 6 (+/-1 Day) CT scans.

4. SELECTION OF STUDY POPULATION

One thousand one hundred and eighty subjects (1180) will be enrolled in this trial. Patients who have severe TBI and who meet the following inclusion/exclusion criteria will be eligible.

4.1 Inclusion Criteria

1. Male or female patients, age between 16 and 70 years, inclusive (or other age limit as required by local regulations)
2. Weight from 45 to 135 kg, inclusive
3. Sustained a closed head trauma no more than 8 hours before initiation of study drug infusion (exposed dura mater is acceptable in the case of depressed skull fractures)
4. TBI diagnosed by history and clinical examination
5. GCS score between 3 and 8, inclusive
6. At least one reactive pupil (pinpoint pupils due to opioid pain treatment are considered reactive)
7. Evidence of TBI confirmed by abnormalities consistent with trauma on CT scan upon admission (diffuse injury II-IV, evacuated and non-evacuated mass lesion, Marshall's CT Classification)
8. Indication for ICP monitoring

4.2 Exclusion Criteria

1. Life expectancy of less than 24 hours as determined by the Investigator
2. Prolonged and/or uncorrectable hypoxia (Pa02< 60 mmHg) or hypotension (systolic blood pressure < 90 mmHg) at the time of randomization
3. Any spinal cord injury
4. Pregnancy
5. Patients with penetrating head injury
6. Bilaterally fixed dilated pupils at the time of randomization
7. Coma suspected to be primarily due to other causes (e.g. alcohol)
8. Pure epidural hematoma
9. Preexisting clinically significant disease or chronic condition that can be ascertained at the time of admission and could affect functional outcome
10. Severe cardiac or hemodynamic instability prior to randomization
11. Known treatment with another investigational drug, device, medical therapy or procedure within 30 days of injury
12. A history of allergic reaction to progesterone and related drugs or any of the components of the infusion
13. Any disease, in the opinion of the Investigator, that is unstable or which could jeopardize the safety of the patient and his/her compliance in the study.
14. Patients who, in the opinion of the Investigator, would not be able or willing to comply with the protocol through the final visit (6 months post-injury)

4.3 Withdrawal of Subjects from the Study

A good faith effort will be made to ensure that subjects complete the study through the 6-month assessments, consistent with the provisions of informed consent and good clinical judgment with respect to safety. The following are potential reasons to terminate the participation of a subject in the study:

- The subject's health would be jeopardized by continued participation.
- Lost to follow-up: subject fails to return to the study site for scheduled visits and does not respond to multiple telephone or written attempts to contact. (Note: if subject cannot return to the study site due to relocation, but moves to an area near another participating site, all efforts should be made to continue study participation at that site).
- Withdrawal of consent: subject or the subject's legally authorized representative or legally acceptable representative (LAR), as applicable in the region where the study is conducted, decides to stop participation in the study for any reason other than an AE, or is unable to complete the study as described in the study protocol. Although a subject or LAR is not obliged to give his/her reason for withdrawing prematurely, the Investigator will make a reasonable effort to obtain the reason while fully respecting the subject's rights. Every effort will be made to contact a subject or LAR who fails to attend any follow-up appointments/contacts in order to complete study assessments.
- Administrative: the Sponsor decides to terminate or discontinue the study (either at the study site or the entire study).

The reason for withdrawal will be captured on the appropriate electronic case report form (eCRF). The Study Termination form must be completed for all randomized subjects, including subjects discontinuing prior to any study drug administration. The Medical Monitor will be informed of early withdrawal of a subject from the study.

4.3.1 Subject Replacement

Subjects who do not complete the study for any reason will not be replaced.

5. STUDY MEDICATION

Study drug will only be shipped to Investigators who have provided the Sponsor (or an authorized representative) all required study documents, including Institutional Review Board (IRB)/Independent Ethics Committee (IEC) approval, have signed a final study agreement, and have been approved by the Sponsor to begin the study. Study drug will be provided by the Sponsor (or authorized representative) as blind-labeled ready-to-use bottles containing an i.v. formulation of BHR-100 or placebo ready for infusion.

5.1 Blinding and Unblinding

All site personnel will be blinded to study treatment assignment. The Investigator or designee will be responsible for drug accountability and dispensing of the study treatment infusions.

In the case of an AE or SAE for which the Investigator must know a specific treatment allocation to ensure the subject's safety, the Investigator will utilize the IWRS according to the study instructions provided. It should be stressed that unblinding the treatment allocation is only allowed for safety concerns in an emergency situation. If unblinding is required in the interest of safety and time allows, the Investigator is encouraged to discuss the matter with the study Medical Monitor whenever possible.

Whenever possible, the Investigator is to assess the relationship of the AE to the study drug before the treatment code is broken. In all cases, the Medical Monitor must be notified within 24 hours after the code has been broken.

In the case a randomization code is unblinded, a subject already undergoing study drug infusion may have the treatment discontinued at the investigator's discretion. All attempts should be made to continue all study procedures and evaluations through Month 6, unless the subject or subject's authorized representative refuses further follow-up.

5.2 Formulation, Packaging, and Labeling

BHR-100 [redacted]

The placebo drug product is a sterile lipid emulsion preparation of the same ingredients as BHR-100, but without the progesterone.

Both drug products are provided ready-to-use, packaged in 250 ml clear glass bottles, labeled 'For Investigational Use Only'.

5.3 Storage

All study drug must be stored in a secure limited-access area, at controlled room temperature (13 – 30° C) and **protected from light,** in accordance with labeled storage requirements. Room temperature must be monitored and recorded.

5.4 Dispensing

The Investigator (or designee) will dispense only the specific numbered bottles of the study treatment according to IWRS assignment.

5.5 Dosage and Administration

Subjects will be administered either BHR-100 or placebo infusion utilizing a peristaltic infusion pump. An i.v. loading dose of BHR-100 or placebo for the first hour at 0.71 mg/kg/hr will be followed by a 119-hr continuous maintenance infusion of 0.5 mg/kg/hr, for a total of 120 hours of treatment. The IWRS calculates the loading and maintenance infusion rates according to the subject's weight entered into the IWRS. The rates assigned for the subject (loading dose, followed by maintenance infusion) must be used to administer the study drug.

Study drug infusion treatment must be started within 8 hours after injury using a dedicated i.v. line (central or peripheral line).

5.6 Drug Accountability

The Investigator will maintain accurate records of the disposition of all clinical drug supplies received during the study and the dates on which drug supplies were received from the Sponsor or authorized representative.

5.7 Assessment of Compliance

Study drug will be administered by qualified clinical personnel. At the end of the study drug administration a clinical research staff member will verify that the entire dose (120 total hours from start to finish) has been administered to the subject. All details of the study drug infusion will be recorded, including any interruption and the reason. Any dose interruptions greater (>) than 30 minutes will be recorded as a protocol deviation.

5.8 Concomitant Medications

All other medications administered to or taken by the subject during the study (from time of consent through Study Day 15) are to be recorded on the eCRF. Information should be recorded for: name of drug, dose, route of administration, start and end dates and time (for i.v. drugs), and indication, including medications used for ICP management.

5.8.1 Allowed Concomitant Medications/Procedures

All medications and procedures required to treat the subject's TBI should be administered as recommended in the standard guidelines for the management of severe TBI (BTF, ABIC, and EBIC). Any therapeutic or surgical procedure performed for concurrent conditions from the time of informed consent through Study Day 15 should be recorded, including the date, description of the procedure, and clinical findings. The nature and volume of i.v. fluids will be measured on a daily basis and any other fluid/blood/blood product replacement will be documented.

5.8.2 Concomitant Medications/Therapies to be Avoided

Investigational drugs, devices, procedures or therapies should not be used at any time during the subject's 6-month participation in the study because of their potential to confound the results. Subjects participating in this clinical trial should not also be enrolled in another trial utilizing any investigational drug, device, procedure or therapy. Enrollment into a strictly observational trial is permitted, as long as the study assessments in this trial are not compromised.

6. STUDY PROCEDURES

The Schedule of Events (Appendix A) summarizes the frequency and timing of the required study assessments.

The subject should be managed for TBI as recommended in the BTF, ABIC, and EBIC guidelines for the management of severe TBI.

In order not to interfere with the standard of medical care and to minimize additional study-specific procedures, some of the subject's baseline characteristics will be recorded from procedures performed routinely for the management of severe TBI. Except where otherwise specified below, the last available values prior to study randomization will be recorded. These may include general (physical and neurological) examination findings. These data may even be obtained in another hospital, and are acceptable to record in the eCRF.

6.1 Screening

The following assessments will be conducted after arrival of the patient at the study hospital.

- Demographic data
- Review of inclusion/exclusion criteria
- Review of relevant medical history
- Review of medication history
- Informed Consent
- Full physical examination including:
  - Body weight
  - Right and left pupil response must be recorded
  - Injury Cause and Severity Assessment
- Vital signs
- Obtain blood samples for local lab assessments (see Appendix B for details)
- Serum or urine pregnancy test for women of child-bearing potential
- ECG
- GCS (all components: Eye opening, Verbal Response, and Motor Response)
- Baseline CT scan
- If the ICP monitor is placed, monitoring of:
  - ICP
  - TIL
- Arterial Blood Gases (ABG): While the subject is intubated, the highest value of the day for the $PaCO_2$ and the lowest value of the day for PaO_2, pH, HCO_3 and SaO_2, along with the accompanying Fio_2 setting, will be recorded.
- Concomitant medications/procedures

6.2 Screening and Randomization Process (IWRS)

Subjects will be randomized to either placebo or active drug on a 1:1 ratio. Randomization is stratified by region (North America, South America, Europe, and Asia). Once a subject is determined eligible for the study and informed consent has been obtained, the Investigator or designee will access the web-based randomization system (IWRS), and will reply to the system questions as prompted. All subjects (or the subject's LAR) from whom informed consent is obtained should be entered into IWRS. Screening information will be entered into the IWRS for the screened subject:

- Date and time of injury, date and time of informed consent, date of birth
- GCS
- Subject initials, gender, and weight

The IWRS will assign the Subject identification (ID) number. This assigned ID number will be used throughout the subject's participation in the study.

All screening procedures should be completed and inclusion/exclusion criteria confirmed prior to the randomization in the IWRS. Once the subject is ready to be randomized into the study, the Investigator or designee will log into IWRS, select the screened subject number and confirm inclusion/exclusion criteria. Upon confirmation, IWRS will provide a Randomization Notification including the following information:

- Assigned bottle numbers for the five day infusion;
- The loading dose infusion rate in milliliters per hour for the first hour;
- The maintenance dose infusion rate in milliliters per hour for the remaining 119 hours of administration.

Careful attention should be paid to correctly administering the assigned study drug as well as administering the assigned loading and maintenance dose infusion rates as these are calculated according to the subject's weight (see Section 5.5).

6.3 Study Drug Infusion Period: Days 1-5

The study treatment infusion MUST be initiated no later than 8 hours after the documented time of injury.

The following evaluations and assessments will be performed:

- Start and stop times of each infusion; record bottle changes
- Recording of any deviation [greater than 30 minutes] from the specified dosing times (1-hour loading dose, then 119-hour maintenance infusion) and assigned infusion rates
- Progesterone level sampling (all subjects on Day 2 (48 +/- 6 hours after initiation of the study drug infusion); additional sampling on PK subjects only)
- Daily GCS (best), if possible to assess without interfering with the subject's condition (if sedation is deemed necessary for medical reasons it should not be (temporarily) halted just to assess GCS)

- ICP, TIL for ICP management, and vital signs: The ICP, TIL and vital signs [heart rate (bpm), respiration rate (per min), systolic and diastolic blood pressure (mm Hg), temperature (Cº) and pupil response] will be recorded at 00:00, 06:00, 12:00 and 18:00 hrs (+/- 30 minutes). In addition ICP, TIL and vital signs will be recorded whenever ICP management changes. If the ICP monitor is not placed, vital signs will still be collected.
- ABGs: Daily while the subject is intubated, as described in Section 6.1
- Daily fluid balance
- Neuroworsening assessment, if applicable
- Concomitant medications and procedures
- AEs
- SAEs
- Pre-injury narrative for GOS assessment: complete no later than 14 days post-randomization

6.4 Day 6: End-of-Infusion Evaluations

- GCS (best), if possible to assess (see Section 6.3)
- End-infusion CT scan (+/- 1 day scheduled at the discretion of the Investigator). It is recommended that the CT scan be completed at or near the end of the infusion; however, if the Investigator deems it necessary to obtain the CT scan on Day 5, this is acceptable.
- Full physical examination including body weight
- ICP, TIL, and vital signs, including pupil responses
- Local lab assessments (see Appendix B for details) within 1 hour after study drug infusion is completed (A pregnancy test for women of child-bearing potential is not required on Day 6)
- ABGs: While the subject is intubated, as described in Section 6.1
- ECG
- Daily fluid balance
- Concomitant medications and procedures
- Neuroworsening assessment, if applicable
- AEs (to be collected through Day 15)
- SAEs

6.5 Day 15: Post-Infusion Evaluations/Discharge

Day 15 assessments must be completed 15 days post-injury, ± 5 days or at ICU discharge, whichever occurs earlier.

- GCS (best), if possible to assess (see Section 6.3)
- Local lab assessments (see Appendix B for details) (A pregnancy test for women of child-bearing potential is not required on Day 15)
- Concomitant medications and procedures

- Dates of ICU discharge and hospital discharge
- Neuroworsening assessment, if applicable
- AEs
- SAEs

6.6 Day 30 (Month 1) Assessments

Day 30 assessments must be completed 30 days post-injury, ± 2 days.

- Subject status, including mortality and dates of ICU discharge and hospital discharge
- SAEs

6.7 Day 90 (Month 3) Assessments

Day 90/Month 3 assessments should be completed 90 days post-injury, ± 14 days, during an in-person visit.

- Subject status, including dates of ICU discharge and hospital discharge
- GOS and GOS-E
- SF-36 (must be completed by the subject)
- SAEs

6.8 Day 180 (Month 6) Assessments

Day 180/Month 6 assessments should be completed at 180 days post-injury ± 28 days, during an in-person visit.

- Subject status, including mortality and dates of ICU discharge and hospital discharge
- GOS and GOS-E
- SF-36 (must be completed by the subject)
- SAEs

6.9 Progesterone Blood Sample Collection

Blood will be collected by venipuncture on Day 2 (48 +/- 6 hours after initiation of the study drug infusion) for each subject for determination of progesterone levels by the Central Bioanalytical Laboratory.

At selected sites (10-15 US-based sites) ten (10) serial blood samples for pharmacokinetics (PK) analysis will be collected at the following times relative to the beginning of the infusion: 1, 8, 24, 48, 56, 72, 96, 104, 120, and 138 hours.

The blood samples will be taken from the arm not used for the study drug infusion. Guidelines for sample preparation, storage, packaging, and shipping will be provided to the Investigator by the Central Bioanalytical Laboratory.

7. ASSESSMENTS OF EFFICACY AND SAFETY

7.1 Efficacy Parameters

The following primary and secondary efficacy parameters will be assessed in this trial. These endpoints are described in detail in Section 7.3.

Primary: GOS assessment at Month 6 post- injury

Secondary (all timepoints are post-injury):

- Mortality at Month 1 and 6
- GOS at Month 3
- GOS-E at Months 3 and 6
- SF-36 at Months 3 and 6
- ICP, CPP and TIL
- Comparison of CT scans at admission and end-infusion Day 6 (+/-1 Day)

7.2 Safety Parameters

Safety and tolerability will be determined by AEs, ECGs, safety labs, vital signs, fluid balance, ABGs, and neuroworsening.

7.2.1 Adverse Events and Serious Adverse Events

Adverse events whether reported, observed, or elicited by indirect questioning will be captured from the time of infusion start through 10 days post-infusion (Days 1-15). SAEs will be captured from the time of infusion start throughout the course of the subject's participation in the study (6 months). The AE/SAE relationship to the study treatment will be judged as not related, possibly related, probably related, or related. Ongoing AEs will be followed to resolution, whenever possible.

Particular attention should be paid to the following potential risks previously identified as associated with administration of progesterone: 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.

All SAEs will be reported by telephone or written report within 24 hours of being notified of the event to the Sponsor's Medical Monitor and then reported to each site's IRB/IEC according to the local regulations. Serious adverse events that persist at Month 6 post-injury will be documented as to their final status.

7.2.2 ECG

The ECGs will be analyzed at the site and documented on the CRF by the Investigator. All clinically significant abnormal ECGs, assessed for clinical relevance by the Investigator, must be documented as an AE on the CRF.

7.2.3 Laboratory Safety Tests

Standard clinical safety labs will be measured locally at the sites and recorded for the specified time points (see Appendix B for details). The Investigator will assess all abnormal lab values at these time points for clinical significance; if categorized as adverse events, they will be collected and recorded similarly to other AEs. All clinically significant abnormal lab values will be followed until resolution, whether or not they are deemed AEs by the investigator. If resolution is not seen, a justification as to the cause for such an abnormality, such as if due to an underlying pre-existing condition, associated co-morbidity, etc, will be recorded.

7.2.4 Vital Signs

Vital signs (heart rate (bpm), respiration rate (per min), systolic and diastolic blood pressure (mm Hg), and temperature (C°), and pupil response) will be monitored in parallel with and per the same timing as ICP and TIL (Sections 7.3.4 and 7.3.5 below).

7.2.5 Daily Fluid Balance

The total amount of fluids administered and the total excreted once per 24 hour period will be recorded during Day 1 through Day 6.

7.2.6 Arterial Blood Gases

While the subject is intubated, the highest value of the day for the $PaCO_2$ and the lowest value of the day for PaO_2, pH, HCO_3 and SaO_2 along with the accompanying Fio_2 setting will be recorded before randomization (Day 1 pre-dose) and daily during Day 1 through Day 6.

7.2.7 Neuroworsening

Instances of neuroworsening will be recorded daily from Day 1 through Day 15. 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 patient management.

7.3 Selection of Efficacy Measurements Related To Management of TBI

7.3.1 Glasgow Outcome Scale (GOS)

The GOS (Jennett and Bond, 1975) is the primary endpoint of this study and assesses mortality and disability in TBI patients according to the designation Good Recovery, Moderate Disability, Severe Disability, Vegetative State or Dead. The GOS will be administered using a standard questionnaire and accompanying narratives at 3 and 6 months post-injury. A baseline narrative will also be recorded by the Investigator. A central review will be performed of all GOS recordings.

7.3.2 Glasgow Outcome Scale - Extended (GOS-E)

The GOS-E will be administered at 3 months and 6 months post injury. A standardized questionnaire structuring the interview will be used, as well as the narrative completed by the Investigator. A central review will be performed of all GOS-E recordings.

The GOS-E assessment of mortality and disability in TBI patients extends the original five GOS categories of functional outcome to eight categories (Jennett *et al.,* 1981; Wilson *et al.,* 1998; Teasdale *et al.,* 1998):

- Dead
- Vegetative State
- Lower Severe Disability
- Upper Severe Disability
- Lower Moderate Disability
- Upper Moderate Disability
- Lower Good Recovery
- Upper Good Recovery

7.3.3 Mortality

Any SAE which results in death at any time during the study will be recorded both as an SAE and a Death Report. The Death Report will include the primary cause of death, secondary cause if any, and the date and time of death. If an autopsy is performed, the report should be collected and provided in a de-identified manner.

7.3.4 Intracranial Pressure/Cerebral Perfusion Pressure

If an ICP monitor is placed, ICP measures will be recorded as early as before randomization (Day 1 pre-dose, or as soon as the monitor is placed) and for up to 6 days while ICP is being monitored. The ICP will be recorded daily at the specific times of: 00:00, 06:00, 12:00 and 18:00 hour (+/- 30 minutes), along with vital signs [heart rate (bpm), respiration rate (per min), systolic and diastolic blood pressure (mmHg), temperature (C^{o}) and pupil response]. In addition to the 4 daily timepoints, ICP and vital signs will be recorded whenever ICP management changes. If the ICP monitor is not placed, vital signs will still be collected at these four timepoints per day.

ICP will be monitored preferentially using a catheter connected to an external strain gauge (intraparenchymal ICP device or ventricular catheter for the ICP measurement). If placement of an intraventricular catheter is not possible, an intraparenchymal catheter placed away from the lesion may be used. The timing and duration of ICP monitoring will be at the discretion of the Investigator.

The CPP will be calculated automatically as the difference of mean arterial pressure and ICP, based on the blood pressure and ICP readings recorded in the eCRF.

7.3.5 Therapeutic Intensity Level (TIL)

TIL data will be recorded for up to 6 days or while ICP is being monitored. TIL scores will be automatically calculated based on the medications and procedures used to manage the subject's ICP, as recorded into the eCRF. Table 1 lists the specific known treatments commonly used to manage ICP and CPP and the corresponding scoring system (modified from Maset *et al.,* 1987). If no therapies were utilized, then the scoring is zero during a given time period.

Table 1
Therapeutic Intensity Level Grading System

Therapy	Score

Surgical Decompression	1
Barbiturate Induced Coma	1
Hypothermia for ICP reduction	1
Hyperventilation (pCO_2<30)	1
Pressor Administration (to keep CPP 60)	1
Hypertonic Saline	1
Mannitol	1
Ventricular Drainage	1
Paralysis Induction	1
Sedation	1
Maximum Total Score	**10**
TIL scores will be analyzed based on the therapies recorded. Because of the stepwise progression of therapy (from sedation to barbiturate use), barbiturate administration or surgical decompression constitutes a total score of 10 when performed. Modified from Maset et al., 1987	

7.3.6 CT Scans

A baseline CT scan will be performed before randomization as part of eligibility assessment. A follow-up CT scan will be performed end-infusion on Day 6 (+/- 1 day) post-injury to assess the progression of lesion volume and brain edema. The findings will be classified in accordance with the Marshall criteria (Marshall *et al.,* 1992). Baseline and Day 6 (+/- 1 Day) CT scans will be sent to the central reader, who will evaluate them for study analysis purposes only.

7.3.7 QOL SF-36

The Quality of Life (QOL) SF-36 questionnaire will be assessed at 3 and 6 months post injury. The SF-36 is a validated generic, easily administered survey of patient health consisting of eight scaled scores, which are the sums of the responses to questions in each section (Ware and Sherbourne, 1992; McHorney et al., 1993). Each scale is directly transformed into a 1-100 scale on the assumption that each question carries equal weight. The eight sections are:

- Vitality
- physical functioning
- bodily pain
- general health perceptions
- role physical
- role emotional
- role mental
- mental health

The 8 scales can also be summarized into two summary scores for physical and mental health, respectively. The SF-36 must be completed by the subject.

7.3.8 Glasgow Coma Scale

The Glasgow Coma Scale (Teasdale and Jennett, 1974) will be performed before randomization and once daily (best) during Days 1 to 6 and on Day 15. The GCS is a neurological scale which aims to give a reliable, objective way of recording the conscious state of a person. A patient is assessed against each of three criteria, eye, verbal and motor responses, and the resulting values are summed for the total GCS score. The lowest possible total GCS is 3 (deep coma or death), while the highest is 15 (fully awake person).

8. STATISTICAL PLAN

8.1 Sample Size Justification

It is planned to recruit a total of 1180 patients randomized in a 1:1 ratio to BHR-100 or placebo (590 in each treatment group). This sample size estimation is based on the use of a proportional odds model (Whitehead, 1993) to analyze the primary outcome variable, namely the conventional 5-point GOS at six months after injury. Assuming approximately 31% good outcome, 21% moderate disability, 19% severe disability and 29% combined vegetative state and death, the total sample size of 1180 subjects will give 90% power to detect a common odds ratio of 1.5 of improvement in outcome (i.e. 10% effect size) at the 1% significance level (two-sided). The baseline outcome distribution used is based on the six-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 (Marmarou *et al.,* 2007).

8.2 Baseline Data

Baseline comparability of the randomized groups will be illustrated using appropriate descriptive statistics.

8.3 Primary Efficacy Analysis

The primary efficacy variable is GOS evaluated at 6 months post injury.

The proportional odds model (POM) (McCullagh, 1980) will be used to compare BHR-100 to placebo for the GOS outcome at six months (categories of good recovery, moderate disability, severe disability, and the combined vegetative state/death). A test for the proportional odds assumption will be conducted and if statistically significant, other polytomous logistic models will be investigated. The analyses will be conducted on an intent-to-treat (ITT, i.e. all randomized subjects) basis, and the 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.

If the p-value from the test of the null hypothesis is less than 0.0003 (at the interim analysis) 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.

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.

8.3.1 Alternate Primary Efficacy Analysis: Sliding Dichotomy Model

If the proportional odds assumption cannot be justified, an analysis will be conducted using a sliding dichotomy (Maas et al., 2006; Murray et al., 2005) of the GOS outcome at 6 months following injury, following categorization of patients into different prognosis groups (worst,

intermediate, and best) based on baseline prognostic factors. The hypothesis that the proportion of favorable responses observed in each treatment group is the same will be tested both within the baseline prognosis grouping (best, intermediate and worst) and overall using the Cochran-Mantel Haenszel Chi-Square test, adjusted for region.

If the p-value from the test of the null hypothesis of no difference in the proportion of favorable responses observed in each treatment group 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.

If this analysis is not required as an alternate analysis to the Proportional Odds Model analysis, it will still be performed as an additional sensitivity analysis.

8.3.2 Sensitivity Analysis: Dichotomized Model

In addition, the GOS at 6 months post injury will be dichotomized into Good Recovery, Moderate Disability versus Severe Disability, Vegetative Status/Dead.

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.

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.

8.3.3 Handling of Missing Primary Efficacy Endpoint Data

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 has neither the 3 nor the 6-month GOS, the missing values would be imputed based upon the proportional odds model. It is anticipated that there will be minimal missing data, however sensitivity analyses will be carried out, if necessary, to confirm that the imputation method(s) did not have an impact on the primary efficacy analysis results.

8.4 Secondary Endpoints and Exploratory Endpoints

Secondary efficacy parameters include:

1. Mortality at Month 6
2. Mortality at Month 1
3. GOS at Month 3
4. GOS-E at Month 6
5. GOS-E at Month 3
6. SF-36 at Month 6
7. SF-36 at Month 3

Exploratory parameters include:

1. Assessment of CT scans (admission vs. end-infusion Day 6 +/-1 Day)
2. ICP
3. CPP
4. TIL

These parameters are described briefly in the sections that follow.

8.4.1 Mortality Assessment at One and Six Months Post-injury

The mortality rate at one and six months will be compared between the two treatment groups. The hypothesis that the mortality rate at one month (and at 6 months) observed in each treatment group is the same will be tested using the Fisher's Exact test. A two-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.

The time from injury to death will be analyzed using Kaplan-Meier analysis and Cox Proportional Hazard Modeling.

8.4.2 Secondary Analyses of GOS at Three Months Post-injury

The GOS at three months will be analyzed following the same analyses and procedures for the primary efficacy analysis described in Section 8.3. This will provide a measure of functional improvement between BHR-100 and placebo.

8.4.3 GOS-E at Three and Six Months Post-injury

The extended GOS is an 8-point scale with the following categories: Dead, Vegetative State, Lower Severe Disability, Upper Severe Disability, Lower Moderate Disability, Upper Moderate Disability, Lower Good Recovery, and Upper Good Recovery.

The null hypothesis that the global assessment of outcome, as measured by the GOS-E at 3 or 6 months, is the same in each treatment group will be tested using the 2-sided Wilcoxon Rank-Sum test, which can be obtained from the NPAR1WAY procedure in SAS®.

A two-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 global assessment of outcome between the 2 treatment groups, as measured by the GOS-E. The

magnitude of the summary statistics will be examined to determine the direction of the treatment difference.

8.4.4 Quality of Life using SF-36

Summary statistics for the 8 scales and the physical and mental composite summary scores of the SF-36 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. The ANCOVA model will include treatment group, age as a covariate and the stratification factors as outlined for the primary efficacy analysis, namely region (North America, Europe, Asia, and South America), GCS motor score, pupil response, and CT classification.

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.

8.4.5 Exploratory Clinical Parameters: ICP, CPP and TIL

Impact of study treatment on three clinical assessment parameters - ICP, CPP and TIL - will be analyzed. Please also refer to the Statistical Analysis Plan (SAP) for further details.

- ICP: If an ICP monitor is placed, the ICP will be recorded daily at designated timepoints, as well as whenever ICP management changes (see Section 7.3.4) up to six days post admission. These data will be summarized descriptively for each treatment group.
- CPP: CPP will be calculated from blood pressure and ICP readings. Data will be summarized descriptively for each treatment group. Summary statistics of the number of non-missing observations, absolute and relative frequency of CPP measurements in the following categories will be presented for each treatment group: less than 50 mmHg, 50-60 mmHg, 60-70 mmHg and greater than 70 mmHg.
- TIL: The therapies used for ICP management will be calculated based on the time that each therapy was received. The percentage of time each therapy is used will be calculated for each 24-hour period post dosing and for all time periods. The hours of use for each therapy will be summarized descriptively for each treatment.

8.4.6 Exploratory Parameter: CT Scan

Effect of study treatment on the progression of intracranial pathology will be assessed by a central reader from baseline (admission) and end-infusion Day 6 (+/- 1 Day) CT scans to assess the progression of lesion volume and brain edema. The findings will be classified in accordance with the Marshall classification.

No patient is expected to have CT classification I, as this indicates a normal CT scan.

The number of non-missing observations, absolute and relative frequency (n and percentages) will be tabulated by treatment group. The magnitude of the summary statistics will be examined to determine the direction of the treatment difference.

8.5 Adverse Event Safety Data

Data on adverse events will be presented descriptively, grouping events by body system. Results will be presented for all adverse events, including instances of neuorworsening and abnormal clinically significant laboratory findings deemed as AEs by the Investigator.

The occurrence of adverse events will be compared between treatment groups, including the proportion of subjects in each arm suffering at least one episode of the event as well as the comparison of the distribution of the number of occurrences of the event. Additional presentations of AE data may be requested by the Data and Safety Monitoring Board (DSMB) (see Section 10.4).

8.6 Interim Analysis

A formal interim analysis will be performed once 200 subjects in each treatment arm (400 total subjects) have completed the study, i.e. have been assessed for the 6-month GOS.

8.6.1 Interim Analysis for Efficacy

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, continuation of the trial will be evaluated. In order to stop the trial at the interim analysis, the significance level will need to be less than the critical p-value.

At the planned interim analysis, a two-sided test will be performed to detect either an increase or decrease in the common odds ratio. 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 (Table 2). The actual critical values and p-values will be computed using statistical methods for group sequential testing with the O'Brien Fleming method (O'Brien and Fleming, 1979; Lee and Quan, 1993).

Table 2
Critical Values and p-Values for Planned Interim Analysis

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

8.6.2 Futility Analysis

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.

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 (1984) and Lan, Simon and Halperin (1982) (Table 3).

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 subjects with 590 in each arm. This sample size is calculated based on the defined baseline outcome distribution (30% GR, 21% MD, 19% SD and 30% VS/D) to detect a common odds ratio of 1.5 of improvement in outcome with 90% power and 1% significance level (two-sided).

8.6.3 Outcomes of Interim Analysis

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 could be stopped for efficacy.

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.

9. ADVERSE EVENT COLLECTION AND REPORTING

9.1 Adverse Event Collection

All AEs will be recorded for the first 15 days after the start of administration of the study drug (5 days of drug infusion and 10 days post infusion). SAEs will be recorded for the entire 6-month period. The Adverse Events eCRF must be completed for all reported AEs and SAEs.

An adverse event is defined as: "Any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product that does not necessarily have a causal relationship with this treatment." An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. This includes any newly occurring event or previous condition that has increased in severity or frequency since the administration of study drug. Instances of neuroworsening are considered AEs.

Details of any adverse or unexpected events, signs, and symptoms will be collected including details of onset, resolution, frequency, severity (as defined below), seriousness, relationship to the drug, effect on the study drug, treatments administered, and outcome. Any AE will be followed, whenever possible, until it returns to the baseline condition or becomes stable with no further change expected.

9.2 Reporting of Adverse Events

Diagnoses vs. signs/symptoms:

Each AE should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values if not constituting AEs themselves or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded as an adverse event(s).

Laboratory values and ECG findings:

Changes in laboratory values or ECG parameters may be considered AEs if they are judged to be clinically significant (i.e., if some action or intervention is required or if the Investigator judges the change to be beyond the range of normal physiological fluctuation). Clinically significant abnormal lab values not considered AEs by the Investigator will be followed as indicated in Section 7.2.3. If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g., increased creatinine in renal failure), the diagnosis only should be reported as an AE.

Pre-existing conditions:

Pre-existing conditions (present before the start of the AE collection period) are considered concurrent medical conditions and should NOT be recorded as AEs. However, if the subject experiences a worsening or complication of such a concurrent condition, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g., "worsening of….").

Preplanned surgeries or procedures:

Preplanned procedures (surgeries or therapies) that were scheduled prior to the start of adverse event collection are not considered AEs. However, if a preplanned procedure is performed early (e.g., as an emergency) due to a worsening of the preexisting condition, the worsening of the condition should be captured as an AE.

Elective surgeries or procedures:

Elective procedures performed where there is no change in the subject's medical condition should not be recorded as AEs, but should be documented in the subject's source documents.

Insufficient clinical response (lack of efficacy):

Insufficient clinical response, efficacy, or pharmacological action, should NOT be recorded as an AE. The Principal Investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

Cases of drug overdose without manifested side effects are NOT considered AEs.

Relationship to Study Drug:

The AE/SAE relationship to the study treatment will be judged as not related, possibly related, probably related, or related. It should be noted that the half-life of progesterone in BHR-100 was found to be 5.30 hrs (SD 0.66) in BHR's Phase 1 trial of healthy male subjects, with progesterone largely cleared by 24 hours.

9.3 Assessment of Adverse Event Severity

The following guidelines for rating severity of adverse events should be used:

Mild:
Awareness of signs or symptoms, but easily tolerated; are of minor irritant type; no loss of time from normal activities; symptoms would not require medication or a medical evaluation; signs and symptoms may be transient, disappearing during continued treatment with study medication.

Moderate:
Discomfort enough to cause interference with usual activities; the study medication may have been interrupted.

Severe:
Incapacitating with inability to do work or do usual activities; signs and symptoms may be of systemic nature or require medical evaluation; the study drug may have been stopped, and treatment for the event may be required.

The term "severe" is often used to describe the intensity of a specific event, as in mild, moderate, or severe myocardial infarction; the event itself, however, may be of relatively minor medical significance, such as severe headache. This is not the same as serious, which is based on

subject/event outcome or action criteria usually associated with events that pose a threat to a subject's life or functioning. The Investigator must decide whether each AE meets the definition of an SAE.

9.4 Serious Adverse Events and Expedited Reporting

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

- Results in death.
- Is life-threatening. Life-threatening, in the definition of serious, refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is considered medically significant by the Investigator or requires intervention to prevent any one of the outcomes above. Medically significant are those events considered important in the Investigator's opinion that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the other outcomes listed in the definition above. These will also usually be considered serious.

All SAEs will be recorded from the time of the start of the study infusion through the subject's participation in the study (6 months). The Medical Monitor must be notified within 24 hours. All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Cause of death is required whenever known. If an autopsy was performed, an autopsy report should be provided. Death should usually be reported as the outcome of a specific SAE.

Reports for hospitalization of elective procedures do not need to be reported as SAEs if there are no precipitating signs/symptoms or worsening of a pre-existing condition that necessitated the procedure. However, SAEs must be reported for any complications resulting from a procedure that prolonged the hospitalization.

The following is a list of events that are anticipated to occur in the targeted severe TBI population, in the absence of study drug.

- hypoxemia
- hypotension
- dyspnoea
- increased ICP
- pneumonia
- sepsis
- cerebral infarction

- death
- posttraumatic seizures
- behavioral disorders

In general, these SAEs will not be reported to regulatory authorities in an expedited safety report, however country-specific reporting requirements will be followed. All AEs and SAEs will be closely monitored by the DSMB. During the course of the trial, if aggregate analyses indicate that the events are occurring more frequently in the BHR-100 treatment group, the sponsor will notify regulatory authorities expeditiously as appropriate.

Delayed post-craniotomy/craniectomy closure of the skull and/or re-implantation of the bone flap should not be reported as an SAE.

9.5 Notification of Sponsor

The Investigator must notify the Medical Monitor of any SAEs. These must be reported by telephone or written report within 24 hours of knowledge of the occurrence. This includes all SAEs that occur during the study period through Month 6. Additionally, if an Investigator learns of any SAEs that occurred after the follow-up period for which there is a reasonable possibility of study drug relationship, that event will be reported to the Medical Monitor within 24 hours.

The SAE Reporting Form will be completed as much as possible with the information below, and faxed to the Sponsor's designee.

Required SAE information:

- Name of reporter/investigator
- Subject identification number
- Description of the SAE
- Date of onset
- Date of resolution, if known
- Criteria of seriousness
- Study drug relationship

Serious Adverse Event Reporting:

[redacted]

Medical Monitoring:

For each SAE, the Investigator and Sponsor will independently assess whether there is a reasonable possibility that the event may have been caused by the study drug ("drug-related"). The Sponsor will evaluate each drug-related SAE to determine if the event was unexpected. If the SAE is assessed to be both drug-related and unexpected, the Sponsor or designee will report it to the appropriate regulatory authorities and notify Investigators as required by applicable local regulations. The Sponsor or designee will report SAEs, including narratives, to the U.S. FDA and local regulatory authorities as required by 21 CFR 312.32 and ICH Guideline for Good Clinical Practice. The Investigator is responsible for notifying his/her respective IRB/IEC.

9.6 Procedures for Reporting Pregnancy Exposure and Birth Events

Should a female subject become pregnant or be suspected of being pregnant while participating in this study, the event must be reported to the Sponsor upon receipt of information by the study staff. While the pregnancy itself is not considered to be an AE or SAE, any pregnancy complications should be recorded as AEs or SAEs (if applicable). Any pregnancy will be followed through delivery for the observation of any SAEs. Fatalities and spontaneous abortions must be reported as SAEs.

10. REGULATORY AND PROCEDURAL REQUIREMENTS

10.1 Ethical Conduct of the Study

Good Clinical Practice (GCP) is an international ethical and scientific quality standard for designing, conducting, recording, and reporting studies that involve the participation of human subjects. This study will be conducted in compliance with GCP and the applicable national regulations so as to assure that the rights, safety, and wellbeing of the participating study subjects are protected consistent with the ethical principles that have their origin in the Declaration of Helsinki.

10.2 Independent Ethics Committee or Institutional Review Board

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) is responsible for following the regional law where the study is to be conducted to obtain written approval for the clinical study protocol (including all substantial protocol amendments), the subject informed consent (including written assent, when applicable), informed consent updates, subject recruitment procedures (e.g., advertisements) and any other information to be provided to subjects from an IEC/IRB that complies with the local regulatory requirements.

Written approval of the study must be obtained from the IEC/IRB prior to the study being implemented (i.e., shipment of clinical supplies to the Investigator or screening of subjects). Copies of the approval documentation will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the designated study documentation files.

The Sponsor (or an authorized representative) or the Investigator (according to national provisions) will submit written reports of the clinical study status to the IEC/IRB annually, or more frequently if requested by the IEC/IRB. A final study notification should be forwarded to the IEC/IRB within 90 days after the study has completed, or in the event of premature termination of the study within 15 days, with the rationale for study termination clearly explained. Copies of all clinical study status reports (including termination) will be maintained by both the Investigator and the Sponsor (or an authorized representative) in the study documentation files.

In accordance with national provisions and the rules of the Food and Drug Administration (FDA), European Parliaments Clinical Trial Directive, or applicable national or state laws, the Sponsor (or an authorized representative) will inform all participating IECs/IRBs and national authorities of all SAEs or other safety-related information, which occur during the clinical study as appropriate.

10.3 Subject Information and Consent

As patients in this study will not be able to provide informed consent at baseline due to clinical status, informed consent will be obtained following the regional law where the study is being conducted, under the guidance of the IRB/IEC while remaining fully compliant with ICH guidelines.

The Investigator is responsible for assuring the appropriate content of the informed consent form and that informed consent is obtained for each subject in accordance with the applicable local

regulations and guidelines. The original signed informed consent is to be retained in the study documentation files.

The Investigator shall maintain a log of all subjects for whom informed consent is obtained and indicate if the subject received study drug or, if not, the reason why. The subject's medical records should also document that the informed consent was obtained, including date and time, and that the appropriate local legal requirements regarding informed consent were followed.

The Investigator will give the subject's LAR information about the trial in a form that the LAR can read and understand. If the LAR is unable to read, oral information on the trial will need to be provided to the LAR using the Patient Information Sheet in the presence of a witness, if applicable, according to regional law.

Informed consent will be obtained for this trial in two phases: First, where applicable by local law, a LAR or other authorized representative may provide consent and second, subjects may provide consent later if and when they become capable of self-consent. The subject (and/or the subject's LAR) will be informed that he/she could withdraw from the trial at any time for any reason.

The subject will be informed about the trial if and whenever he/she becomes competent to give an opinion on continuation in the trial, and the subject will be given the opportunity to withdraw from the trial. If the subject consents to continue in the trial, the subject will be requested to record consent by signing the Subject Informed Consent Form. If consent is denied by the subject, the subject will be immediately withdrawn from the trial. If a subject dies before becoming able to consent, then the above rights to trial data will remain with the LAR.

10.4 Data Safety Monitoring Board

An independent DSMB will be appointed to have responsibility for safeguarding the interests of trial subjects, and assessing the safety and efficacy of the study treatments during the trial. The DSMB's assessments will be based on safety and efficacy data periodically sent to the DSMB statistician at approximately 100-subject intervals, with precise intervals to be determined in consultation with the DSMB. The DSMB will have the authority to recommend stopping the trial at any point based upon stopping rules agreed upon with the Sponsor.

Based on its review, the DSMB might also provide the Sponsor with recommendations regarding study modification. The DSMB will consist of independent clinicians and biostatisticians that, collectively, have experience in the management of patients with TBI and in the conduct and monitoring of randomized clinical trials. The DSMB will function in accordance with a dedicated charter and the study protocol.

10.5 Steering Committee

A TBI Steering Committee, composed of members of American Brain Injury Consortium (ABIC) and European Brain Injury Consortium (EBIC), and other experts in the fields of TBI clinical research, provides scientific and academic leadership for this study in consultation with the Sponsor. The goals and study design have been endorsed by ABIC and EBIC.

10.6 ABIC (American Brain Injury Consortium)

ABIC is a group of distinguished neurosurgeons and clinicians dedicated to improving the outcome of brain injury patients, and whose mission is to increase the scientific merit of TBI clinical trials.

ABIC Quality Review:

For quality assurance purposes, ABIC will review clinical data in the eCRF of selected trial subjects to ensure that all medications and procedures required to treat the subject's TBI were administered according to the study protocol.

Based on its Quality Review, ABIC will provide the Sponsor or its designee with Quality Review Reports regarding clinical sites' compliance with the study protocol.

10.7 Investigator Obligations

The Principal Investigator agrees to conduct the clinical study in compliance with this protocol which was approved by the IEC/IRB in compliance with local regulatory requirements. The Investigator and the Sponsor will sign the protocol (Page 2) to confirm this agreement.

10.8 Electronic Case Report Forms (eCRFs)

Data collection for this protocol will be accomplished using an Electronic Data Capture system (EDC). Therefore, the term eCRF will be utilized.

eCRFs are required and must be completed for each randomized subject. It is the Investigator's responsibility to ensure the accuracy, completeness, , and timeliness of the data reported on the subject's eCRF. eCRFs should be completed in a timely fashion to support the study timelines. Source documentation supporting the eCRF data should indicate the subject's participation in the study and should document the dates and details of informed consent, study procedures, adverse events, and status. The Investigator or designee should complete and the Investigator should verify the source documents as the information is collected. Completed case report forms must be submitted for each randomized subject. The Investigator will retain a copy of all completed source documents.

10.9 Monitoring the Study

Site visits and inspections will be conducted by the Sponsor or designee at regular intervals in accordance with FDA and International Conference on Harmonization (ICH) guidelines. The Investigator will permit representatives of the sponsor's monitoring team, FDA or local health authority auditors to inspect facilities and records relevant to this study.

10.10 Protocol Deviations

The Investigator will make every attempt to avoid deviations from the protocol, except in medical emergencies. In the event of a medical emergency, the Medical Monitor must be notified as soon as possible. The governing IRB/IEC will be informed of all protocol changes issued by the Sponsor by the investigator in accordance with the IRB/IEC's established procedure.

11. DATA HANDLING AND RECORDKEEPING

11.1 Disclosure of Data

Individual subjects' medical information obtained as a result of this study is considered confidential and disclosure to third parties other than those noted below is prohibited. Subject confidentiality will be further assured by utilizing subject identification code numbers. If results of this study are reported in medical journals or at meetings, the subject's identity will remain confidential. Medical information may be provided to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare.

Data generated as a result of this study are to be available for inspection on request by FDA/local health authority auditors, the sponsor's monitors, and by the IRBs/IECs. If the FDA or other regulatory agency should schedule an inspection, the Medical Monitor should be advised immediately.

11.2 Publication

By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor.

Publications or presentations based on the study may not be made until the study is completed, unless so decided by the Sponsor. Once the Sponsor or designee publishes the final report and main study manuscript, or if publication has not occurred within 18 months after completion of the study (final database lock), an Investigator may individually publish or present information on this study, preferably providing the manuscript to the Sponsor for review prior to publication. The Clinical Trial Agreement between the Investigator and the Sponsor may provide additional terms regarding publication or presentation based on the study.

11.3 Record keeping and Retention

The Investigator must maintain adequate records for the study including completed case report forms, medical records, laboratory reports, signed informed consent documents, drug disposition records, adverse experience reports, information regarding subjects who discontinued, all correspondence with the IRB/IEC and the sponsor, and other pertinent data.

All records are to be retained by the Investigator for a minimum period of 2 years after the United States Food and Drug Administration/local health authority approves the New Drug Application (NDA); or a minimum period of 2 years following the termination or withdrawal of the health regulatory agency exemption (e.g., Investigational New Drug (IND) or clinical trial application) under which the study was conducted. To avoid any possible errors, the Investigator must contact the Sponsor prior to the destruction of any study records. The Investigator will also notify the Sponsor in the event of accidental loss or destruction of any study records.

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APPENDIX A
SCHEDULE OF EVENTS

Study Procedure	Screening (Within 8 hrs of injury)	Day 1-5 (infusion period: 120 hours)	Day 6 (post-infusion)	Days 7-15	Day 30 (1 month)	Day 90 (3 months)	Day 180 (6 months)
Inclusion/exclusion criteria	X						
Informed consent	X						
Demographics	X						
Medical history	X						
Concomitant medications/procedures[1]	X	X	X	X			
Physical exam	X		X				
Body Weight	X		X				
Serum/urine pregnancy test[2]	X						
Study treatment		X					
ECG	X		X				
Vital Signs, pupil response[3]	X	X	X				
ICP[3] and TIL[4]	X	X	X				
CT scan	X		X				
Local labs/urinalysis	X		X	Day 15			
Arterial blood gases[5]	X	X	X				
Daily fluid balance		X	X				
GCS[6]	X	X	X	Day 15			
Pre-Injury Narrative for GOS Assessment[7]		X					
GOS (in-person assessment)						X	X
GOS-E (in-person assessment)						X	X
Adverse Events		X	X	X			
Neuroworsening (if applicable)		X	X	X			
Serious Adverse Events		X	X	X	X	X	X
SF-36 (in-person assessment)						X	X
Progesterone sampling[8]		X					
ICU/hospital discharge dates				X	X	X	X
Mortality					X		X

[1] To be recorded starting after informed consent has been obtained; [2] Only for females of childbearing potential

[3] Vital Signs [heart rate (bpm), respiration rate (per min), systolic and diastolic blood pressure (mm Hg), temperature (Cº), and pupil response] and ICP recorded for a period of up to 6 days; duration of ICP monitoring at discretion of the Investigator; ICP at 4 times per day, and ICP and vital signs whenever TIL changes

[4] TIL recorded for up to 6 days while ICP being monitored; [5] ABGs daily while subject is intubated; [6] GCS best score daily if possible to obtain

[7] Must complete within 14 days of Randomization; [8] To be analyzed by the Central Lab; 1 blood draw on Day 2 (48+/- 6 hrs after initiation of the study drug infusion); additional PK sampling only at selected sites.

APPENDIX B
LABORATORY ASSESSMENTS
(SCREENING, DAY 6, DAY 15)

Serum Chemistry:

- Aspartate aminotransferase (AST)
- Alanine aminotransferase (ALT)
- Alkaline phosphatase
- Gamma glutamyl transferase (GGT)
- Sodium
- Potassium
- Chloride
- Glucose
- Total protein
- Total Cholesterol
- Triglycerides

Hematology:

- White blood cell count (WBC)
- Red blood cell count (RBC)
- Hemoglobin
- Hematocrit
- Platelet count
- Differential WBC
- Reticulocyte count

Urinalysis:

- Microscopic examination
- Specific gravity
- pH
- Protein
- Glucose
- Blood

Arterial Blood Gases:
(if the subject is intubated or has an arterial line placed; not required at Day 15):

- pH
- PaO_2
- HCO_3
- $PaCO_2$
- SaO_2
- FiO_2

Other:

- International Normalized Ratio (INR)
- Serum or urine pregnancy test (females of child bearing potential)– Screening Only