Statistical Analysis Plan

CONIVAPTAN FOR THE REDUCTION OF CEREBRAL EDEMA IN INTRACEREBRAL HEMORRHAGE – A Safety and Tolerability Study

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1. List of Abbreviations

AE – adverse event
ALT – alanine transaminase
AQP4 – aquaporin-4
AST – aspartate transaminase
AVP – arginine-vasopressin
BSI – blood stream infection
BWC – brain water content
CBF – cerebral blood flow
CE - cerebral edema
CPP – cerebral perfusion pressure
CSF – cerebral spinal fluid
CT - computed tomography
EEG – electroencephalogram
EMR – electronic medical record
EVD – external ventricular drain
FWD – free-water deficits
GCS – Glasgow coma scale
GFR – glomerular filtration rate
HC – hyperchloremia
HS – hypertonic saline
ICH – Intracerebral hemorrhage
ICP - intracerebral pressure
ICU – intensive care unit
IV – intravenous
LAR – legally authorized representative
LOS – length-of-stay
mRS – modified Rankin scale
Na+ - sodium
PEG – percutaneous endoscopic gastrostomy
PICC – peripherally inserted central catheter
RRT – renal replacement therapy
SAE – serious adverse event
TBI – traumatic brain injury
UTI – urinary tract infection

2. Introduction

Intracerebral hemorrhage (ICH) represents ~10-15% of all strokes in the United States, numbering 50-70,000 cases per year. Mortality and morbidity are high in ICH, with a 30-day mortality of ~40%, and only 20% of ICH patients classified as independent at 6 months. Only admission to a neuro-intensive care unit (ICU), and the use of a computed tomography (CT) scanner, have been shown to improve outcome from ICH. With respect to cost, ICH represents 34% of years of potential life lost to stroke.

Complicating ICH is the development of cerebral edema (CE). Worsening CE has been implicated in delayed neurological deterioration, and worse patient outcomes, largely due to the elevation of intracerebral pressure (ICP). Elevations in ICP reduce the ability of blood to reach the brain, exacerbating the injury and producing ischemia. Reduction of this edema may reduce the degree of neuronal death, decreasing hospital length-of-stay (LOS), and improving short-term outcomes.

Wide variability exists in the treatment of ICP and CE among intensivists. The use of mannitol, which elevates the osmolarity within the cerebral vasculature, promoting water movement across the blood-brain barrier and into the capillary system, is common, but is limited by its deleterious effects on renal function, fluctuations in intravascular volume, and pH. Most concerning is the slow elimination of mannitol from the cerebrospinal fluid (CSF), which may potentially require progressively higher doses, over time to control ICP, and may result in rebound CE. Increasingly, hypertonic saline (HS), which acts similar to mannitol, is being used to abate CE. However, this therapy has not demonstrated any survival or outcome benefit despite reductions in ICP. A retrospective review of available data at Henry Ford Health System preliminarily demonstrates adverse effects on renal function with the use of HS. Further, anecdotal observations have noted changes in renal function and difficulty replacing free-water deficits (FWD) following aggressive antecedent use of HS. A known side-effect of HS therapy is hyperchloremia (HC). Chlorine is a potent renal vasoconstrictor, thus potentially reducing blood flow, precipitating renal ischemia, and reducing glomerular filtration rate. Finally, the use of HS may be associated with increased risk of blood-stream infections (BSI), and trends to increased risk of nosocomial and urinary tract infections (UTI).

In sum, neurocritical care needs a safer alternative therapy that can reduce the development of CE, potentially decreasing ICU LOS and possibly improving outcomes. Conivaptan, a non-selective Arginine-Vasopressin (AVP) V_{1A}/V_2 antagonist, reduces the production of aquaporin-4 (AQP4) production, the predominant class of water channel in the brain, thus promoting aqueresis. Conivaptan is approved for the treatment of euvolemic and hypervolemic hyponatremia. This mechanism of action suggests that conivaptan could potentially be used clinically to reduce CE. Current clinical data in traumatic brain injury (TBI) patients demonstrate conivaptan is safe and well tolerated using a single dose to increase sodium (Na^+) in a controlled fashion to reduce ICP. Further, additional work has demonstrated the safety and tolerability of conivaptan in doses ranging from 10-80 mg/day in the neurocritical care population. Recently, bolusing of conivaptan (20 mg) has been shown to lower ICP in hyponatremia following TBI and cerebral ischemia. The authors reported improvements in cerebral perfusion pressure (CPP) and stable blood pressure, and a prolonged reduction in ICP. They theorize that the antagonism of V_2 by conivaptan promotes free water loss to reduce brain water content (BWC), while the antagonism of V_1 antagonism may improve

cerebral blood flow (CBF) and reduce blood brain barrier permeability.

Given the enormous costs of ICH, problems with current therapies, and variability in treatment, there is an urgent need to identify a therapy that has a better safety and effectiveness profile than the the currently used agents. Our central hypothesis is that through reductions in AQP4 expression, the early use of conivaptan will reduce CE while also being safe in the ICH population. Our long term goal is to show that early use of conivaptan in ICH will reduce CE, thus improving outcomes and reducing the need for rescue therapies, ICU LOS, and overall treatment cost. The objective of this proposal is to first establish whether conivaptan use, at a dose currently determined as safe (40 mg/day), can reduce CE. This is an essential first step in understanding the role of conivaptan in CE management. If this proof-of-concept study demonstrates the desired effect, work can take place identifying the optimal dosing and frequency needed for maximal effect.

3. Study Objectives and Endpoints

Study Objectives

The study population consists of patients with ICH at risk for developing CE.

a. Primary Objective – Safety and Tolerability

An evaluation of the safety assessment parameters of each of the seven (7) subjects will be done by the PI and Co-I during the patient's care. Should events occur regarding the administration of conivaptan that raise safety concerns, the PI has the authority to withdraw the subject and/or halt the study pending further investigation.

b. Secondary Objectives

Several secondary hypotheses can be tested for data generated by this investigation:

1. Reduction in CE as measured on CT. Goal is a 5-10% reduction in CE over time.

2. Patient outcomes: the modified Rankin Scale (mRS) will be used to assess patient outcomes at hospital discharge. This scale assess functional deficits on a scale from 0 (no deficit) to 6 (death).

3. Cost of care: Several proximal measures will be used to assess cost, including length of stay in the ICU, the need for EVD/bolt or surgical procedures to reduce or manage CE, the need for lines (central venous, arterial, PICC) or tracheostomy/PEGs, and the number of patients that required ventilation.

Study Endpoints

1. Laboratory values: assessment will end at the completion of conivaptan administration (Day 3).

2. Long-term Outcome: Patients will be observed for three months, beginning at enrollment, to determine long-term outcomes of conivaptan treatment.

4. Investigation Plan

This a single-center, open-label prospective study which aims to evaluate the safety and tolerability of conivaptan in patients with ICH that are at risk for developing CE. The study will include 7 patients with a diagnosis of ICH that is ≥ 20 cc in volume, aged between 18 – 80 years. All patients will receive 20mg IV of conivaptan every 12 hours equaling 40mg/day over 2 days (4 doses total), in addition to the standardized ICH management.

All observations and assessments will be conducted as displayed in Table 1 of the Protocol. Patients will have CT scans at baseline and ~24, 72, and 168 hours (7 days) from enrollment to check for bleeding, lasting edema, or rebound edema. An 8 hour variance is permitted. It is preferable that the CT scans be done at 3mm increments as this is helpful for volume analysis, but 5mm is acceptable. Further imaging is left to the discretion of the treating/primary service physician. Electrolytes (standard-of-care, basic metabolic panel) for all subjects/patients will be measured every 12 hours for the first 72 hours of the study, and then daily after 72 hours. This is considered a regular schedule based on clinical need. However, during the ~48 hour period when the subjects are receiving conivaptan, a comprehensive metabolic panel, Mg, and PO_4 will be drawn and analyzed 6 hours after each conivaptan dose. These labs may be done sooner based on the patient's progress/need and/or the attending physician's direction. Neurological exams (e.g., EEGs), vital signs, and urine output measurements will be conducted as per Neuro-ICU protocol. The need for ancillary monitoring tools (i.e. EVDs, bolts, microdialysis, EEG, near-infrared spectroscopy) will be at the discretion of the treating physicians. Subjects will return for a 3 month follow-up assessment to assess neurological function and a final CT scan.

Study Duration: Each subject is expected to participate in the study for 7 days (including medication administration and wash-out) and the 3-month follow up.

Inclusion Criteria

- Age ≥18 years old and < 80 years.
- Diagnosis of primary ICH ≥ 20 cc in volume.
- Enrollment within 48 hours from initial symptoms.
- Signed informed consent from the patient or obtained via their legally authorized representative (if the patient is not able to sign the informed consent themselves). The patient's decisional capacity to either provide or refuse consent will be determined using the Glasgow Coma Scale (GCS), which is being assessed at baseline and at 24 hours (+/- 6hrs) after enrollment. A potential study participant with a GCS > 14 will be asked to provide their own initial study consent. A GCS ≤ 14 would indicate the need to pursue consent via legally authorized representative. Patient and/or LAR must be English speaking.

Exclusion Criteria

- Current need for renal replacement therapy (RRT).
- GFR of <30 mL/minute at time of admission.
- Participation in another study for ICH or intraventricular hemorrhage.
- ICH related to infection, thrombolysis, subarachnoid hemorrhage, trauma or tumor.
- Presence of HIV or active fungal infection that is known based on information in the EMR.

- Continued use of digoxin or amlodipine (as recommended by the manufacturer due to CYP3A inhibition).
- Active hepatic failure as defined by AST >160 units/L and/or ALT >180 units/L, or total bilirubin levels greater than four times normal levels (>4.8mg/dL).
- Serum $Na^+ \geq$ 145 mmol/L (admission labs or any time prior to recruitment/enrollment).
- Unable to receive conivaptan based on contraindications indicated by the manufacturer.
- Pregnant or lactating females.
- Not expected to survive within 48 hours of admission, or a presumed diagnosis of brain death.

5. Statistical Methods

5.1: Study Subjects and Analysis Sets

All enrolled patients will be included in a single analysis set and data will be summarized using frequencies and percentages.

5.2: General Methodology

This study is looking to preliminarily evaluate the safety, tolerability, and efficacy of conivaptan treatment. Unfortunately, it is not powered to provide robust statistical evaluation of safety and tolerability, nor to detect differences in efficacy between subjects. As such, all analysis will be descriptive in nature. Categorical variables will be summarized using counts and percentages. Continuous variables will be summarized using descriptive statistics: number of patients, mean, median, and full range, as appropriate.

Statistical analysis will consist of:

- Descriptive analysis of patient characteristics
- Frequency of relevant complications and medical interventions
- Changes in CE volume

5.3 Evaluation of Objectives

Safety and tolerability will be assessed via the number of patients that experience abnormal seizure activity, show abnormal laboratory values, have increased infection rates, or exhibit an adverse events directly related to treatment with conivaptan. The change in CE volume will be reported as a measure of potential efficacy, and potential impacts on cost of care will be assessed by the length of stay in the ICU and the use of medical interventions to reduce CE volumes. Patient outcomes will be assessed using the mRS at discharge. Due to the small number of patients in this trial and absence of a control group, all evaluation will be descriptive only.

5.4 Safety Evaluation

Subjects will be monitored throughout their hospital stay. Adverse events (AE) will be assessed in terms of their seriousness, duration, intensity, and relationship to the study drug. All

anticipated and unanticipated AE will be collected. Subjects will be able to contact the investigator at any time during the study. The outcome of each event, including any interventions used, will be observed and documented.

a. Adverse Event Definitions and Reporting Requirements

An AE is any complaint or untoward medical occurrence that is an unintended disease or injury or untoward clinical sign (including abnormal laboratory findings) in a subject, whether or not it is related to the investigational drug.

A Serious Adverse Event (SAE) is an untoward medical occurrence in a subject that may or may not be related to the investigational drug, but that meets the criteria of “serious” by resulting in one of the following outcomes:

- Death
- Requires initial or prolonged inpatient hospitalization
- Is life-threatening (that is, immediate risk of dying).
- Is a persistent or significant disability/incapacity.
- Other significant medical hazard.

All adverse events will be collected and documented throughout the study. The PI will asses each AE to determine severity, relatedness to the study drug, and if it was anticipated or unanticipated.