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

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON38198

Source
ToetsingOnline

Brief title
Progesterone efficacy and safety study in TBI

Condition

- Other condition

Synonym
brain injury, TBI

Health condition

traumatisch hersenletsel

Research involving
Human

Sponsors and support

Primary sponsor: BHR Pharma, LLC
Source(s) of monetary or material Support: BHR Pharma;LLC

Intervention

Keyword: Efficacy, Progesterone, Safety, Traumatic Brain Injury

Outcome measures

Primary outcome

GOS evaluated at 6 months post injury.

Secondary outcome

* 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 day 6 (+/-1 Day) end-infusion CT scans

Study description

Background 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).

Study objective

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 design

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.

Intervention

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.

A total of 5 days (120 hours) of continuous infusion treatment.

Study burden and risks

Progesterone for the treatment of traumatic brain injury has been tested in three human studies.

In these trials, the only side effect attributed to progesterone was inflammation of the vein at the site of infusion in one patient, and this did not require medical treatment.
These three studies used various mixtures of progesterone. The mixture of progesterone in BHR-100 has not yet been studied in patients with severe traumatic brain injury.

The following potential risks were previously identified as associated with prolonged (greater than 3 months) administration of progesterone (in women):

Common Side Effects (> 5% of subjects):
* Chest pain
* Viral infection
* Migraine (severe headache)

Rare Side Effects (< 1% of subjects):
* Heart attack
* Blood clots
* Stroke
* Liver function abnormalities
* Pneumonia
* Meningitis
* Allergic reaction
* Abnormal vision
* Fluid retention

There may be other side effects that are not known at this time.

Blood Collection
There may be pain, swelling, or bruising around the vein where your blood was collected. Subject may get an infection at the place on your body from which the blood was collected.

Risks to Unborn Children
Women who are pregnant or nursing a child may not take part in this study. There may be risks to the embryo or fetus should you become pregnant which are currently unknown.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Male or female patients, age between 18 and 70 years, inclusive (or lower 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

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. 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)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-03-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	/
Generic name:	progesterone

Ethics review

Approved WMO Date:	22-07-2010
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-01-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	17-01-2011
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2011
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	27-02-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-08-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Approved WMO Date:	05-09-2012
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	12-06-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2010-018283-16-NL
ClinicalTrials.gov	NCT01143064
CCMO	NL32418.029.10