

BHR Pharma, LLC (www.bhr-pharma.com) (BHR) is a wholly owned subsidiary of Besins Healthcare SA (www.besins-healthcare.com).

In June 2010, BHR initiated a global, Phase 3, multi-center pivotal trial (www.synapse-trial.com) of BHR-100 (intravenous progesterone infusion) in treating severe Traumatic Brain Injury (TBI) patients.

- More than 100 sites worldwide – United States, Western Europe, Israel and other regions
- Approximately 1,200 patients
- Patients will be followed for six months post-injury

The study will evaluate the safety and effectiveness of BHR-100 (one of BHR's lead products) as a neuroprotective agent for treating severe, closed-head TBI patients (Glasgow Coma Scale scores of 4-8).

Patients will receive a five-day (120-hour) continuous intravenous infusion of progesterone, beginning within eight hours of injury.

- BHR-100 is a ready-to-use infusion designed to meet all U.S. Food and Drug Administration approval requirements, unlike other intravenous progesterone infusions found in the medical literature.

BHR is conducting the study in collaboration with the American Brain Injury Consortium (ABIC) and the European Brain Injury Consortium (EBIC) to identify the trial sites and design the clinical study.

PRA International is the Contract Research Organization for the trial.

BHR has exclusively licensed the rights to a patent family claiming the use of progesterone to treat TBI, along with preclinical and clinical data from a Phase 2 study that showed a mortality benefit in TBI patients.¹

Traumatic Brain Injury (TBI)

TBI is a non-degenerative, non-congenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairments of cognitive, physical, and psychosocial functions with an associated diminished or altered state of consciousness.²

Approximately 1.7 million Americans suffer a traumatic brain injury per year, resulting in 52,000 deaths, 275,000 hospitalizations and 80,000 cases of long-term disability.³ Incidence of TBI in all industrialized countries is comparable to the US, with estimates ranging from 150 to more than 300 per 100,000.⁴ There are approximately 66,000 deaths annually attributed to TBI in Europe.⁵

¹ See Wright *et al.*, (2007) *supra*.

² Dawodu *et al.*, Traumatic Brain Injury: Definition, Epidemiology, Pathophysiology <http://www.emedicine.com/pmr/TOPI212.HTM> (2007).

³ Traumatic Brain Injury in the United States: A Report to Congress (1999)

⁴ Traumatic Brain Injury: Methods for Clinical and Forensic Neuropsychiatric Assessment, p.2, Granacher, ed. (CRC Press 2003).

The leading cause of TBI in the world is road traffic accidents, accounting for 40-50 percent of the hospitalizations for TBI⁶ and approximately 3,000 people die and 30,000 people are injured daily in traffic accidents.⁷ As safety precautions increase in the industrialized world, mortality from road traffic accidents has declined, but the problem is increasing in developing countries.⁸ This epidemic of traffic accidents in developing countries is accentuated by high mortality rates:

Country/Region ⁹	TBI Mortality Rate/ 100,000 population
Europe	15
Scandinavia	10
India	20
United States	30
China, Province of Taiwan	38
South Africa	81
Colombia	120

Progesterone as a Neuroprotective Agent in TBI

Progesterone, though widely considered to be primarily a sex hormone important in pregnancy and female reproductive functions, in fact, exerts a variety of activities on the central nervous system of both men and women.¹⁰ In animal models, progesterone has been shown to improve outcomes in an experimental model¹¹ and enhances survival and functional outcomes in human TBI patients.¹² Progesterone exerts a variety of effects that may be responsible for these observations:

- Reducing both vasogenic and cytotoxic edema;
- Reducing lipid peroxidation by a variety of mechanisms;
- Controlling inflammation by reducing cytokine release and inhibiting immune cell activation and migration;
- Reducing neuronal apoptosis;
- Upregulating GABA-A, which decreases release of glutamate and other excitatory neurotransmitters; and
- Inducing remyelination.¹³

To date there are no approved medications or interventional treatments to improve outcomes following TBI.¹⁴

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⁵ Socin *et al.* *JAMA* 273:22 (1995)

⁶ *Id.* at 168.

⁷ *Id.*

⁸ *Id.*

⁹ *Id.* at 166.

¹⁰ Stein, *Brain Res. Rev.* 57:386-97 (2007).

¹¹ *Id.*

¹² Wright *et al.*, (2007) *supra.*; Xiao *et al.*, *Critical Care* 12:R61 (2008).

¹³ Stein, (2007) *supra.*

¹⁴ Wright *et al.*, *Annals of Emer. Med.* 49: 391-402 (2007).`