NH001: A Treatment for Cognition Recovery in Brain Injury Patients

Summary: NeuroHealing is a private company in the Boston, USA area developing neuro-rehabilitation products based on repositioning small molecule CNS active compounds. NH001 is a potent and broad acting dopamine agonist to help regain consciousness, accelerate recovery and improve the functional outcome of patients who remain in a vegetative state (VS) or minimally conscious state (MCS) **weeks to months after** brain injury. Currently, there are no approved drugs for this severe, life-threatening indication. In a pilot clinical trial, NH001 demonstrated excellent responses in VS and MCS patients. In addition, NH001 was recently observed to help rehabilitation in a stroke patient (Sanz 2019).

Some salient considerations:
- = strategic entry to untapped neuro rehabilitation market
- = lower risk clinical program, based on drug with well-known safety profile
- = favorable regulatory path: FDA IND filed under subpart E; orphan designations; FDA clinical grant
- = US$ billion range product, marketable by a small sale force, no approved product for indication
- = for **use 1-4 months post brain injury** (and distinct by mechanism, pathobiology, clinical trials & marketing from acute tbi indication).

Active Ingredient and Mechanism of Action

Apomorphine HCl

Apomorphine is a broad dopamine agonist active on both D_1 and D_2 class receptors. It is used with syringe injectors for the treatment of hypomobility in advanced Parkinson's disease as a rescue treatment once other less potent drugs have lost efficacy. In patients remaining in a vegetative state or minimally conscious state after a TBI, areas of the brain remain viable, but the connections between functional sections are impaired due to the diffuse axonal injury. Advanced brain imaging techniques have elucidated defects in dopamine neural networks of action (Jenkins 2018; Fridman 2019). Apomorphine stimulates the dopaminergic pathways and promotes integration between distant functional regions of the brain, which results in the regaining of consciousness. Once consciousness is restored, the patient can engage in active rehabilitation. Accelerating the recovery of consciousness helps patients to achieve their best possible functional outcome.

Delivery System

NH001 is delivered subcutaneously, 12 hours per day, through a continuous infusion pump in pre-filled reservoir cartridges. Subcutaneous NH001 is rapidly absorbed and readily crosses the blood–brain barrier, reaching brain concentrations six times higher than in plasma. NH001 is the only dopaminergic agent that can be delivered parenterally, and rapidly achieve and maintain a steady and high brain concentration. **NH001 treatment is administered daily for a period of 2-6 months**.

Market

Each year in the U.S., it is estimated that 25,000 to 50,000 patients sustain a traumatic brain injury (TBI) with loss of consciousness for more than 2 weeks. Currently there are no drugs approved for this patient population. The cost of care for severe TBI patients is very high, with the lifetime cost estimated at over $1 million per patient. Most patients are in rehab facilities such that NH001 can be marketed with a small specialty sales force.

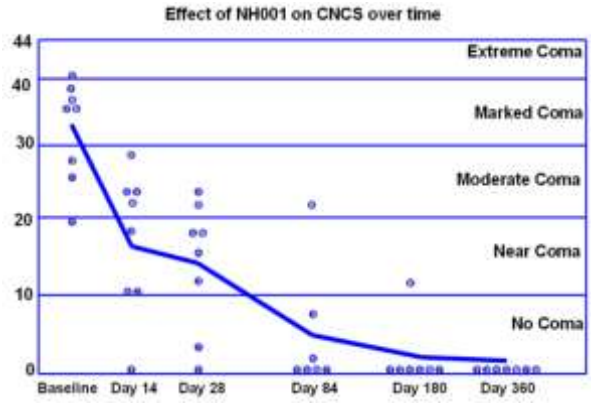
Intellectual Property

NeuroHealing filed and fully owns patents on methods of using NH001 to treat subjects in an altered consciousness state. A patent entitled "*High Potency Dopaminergic Treatment of Neurological Impairment Associated with Brain Injury*" includes claims for formulations containing dopaminergic agents optimized for continuous infusion and as a kit attached to an infusion pump. Patents have issued in the United States (No 7,943,632), Europe, Canada and Australia.

NH001 has been granted orphan drug status from the FDA Office of Orphan Products Development. The orphan drug designation covers the use of NH001 for the treatment of patients in a vegetative state or minimally conscious state for up to twelve months following brain injury (TBI or stroke). NH001 has also been designated as an Orphan Drug in Europe by the EMA.

Clinical Data

An open-label clinical trial demonstrated that shortly after NH001 administration patients improved their consciousness levels and were able to start active rehabilitation (Fridman, et al, *Brain Injury*). Patients in the study fared much better than the expected incident of recovery based on published historical data (see below). These data suggest that NH001 may accelerate the recovery of post-TBI patients and patients may achieve a better long-term functional outcome.



	Incidence of Recovery *	Responses with NH001
	n=434	n=7
Death	33%	14%
Vegetative State	15%	0%
Severe Disability	28%	29%
Moderate Disability	24%	57%
Good Recovery		

* New England J Medicine 330:1572

Clinical Development Status

NeuroHealing began a phase II double-blind placebo-controlled study in unconscious patients at the Spaulding Rehab Hospital, Harvard Medical School. The PI Ross Zafonte is Chair of the Dept of PM&R at Harvard, VP of Medical Affairs for Spaulding, and a recognized leader in the field of drug treatments for patients with low neurological functioning. The IND was filed under 21CFR601 subpart E: Accelerated Approval of Biological Products for Serious or Life-Threatening Illnesses, also referred to as 'fast track.' The study was initiated under an FDA Orphan Drug clinical grant.

A study in Europe is underway to confirm previously observed clinical responses of unconscious patients to apo drug treatment and to correlate behavioral improvements with advanced multimodal brain imaging (fMRI, PET) and neurophysiological measures (EEG, actigraphy, et al). Clinical protocol details: www.frontiersin.org/articles/10.3389/fneur.2019.00248/full.

To test responses of drug treatment in patients with non-tbi cause of unconsciousness, one stroke patient (carotid aneurysm rupture) was recently treated and a positive response observed (Sanz 2019, "Apomorphine treatment in a patient with chronic disorder of consciousness following brain hemorrhage").