A Novel Intranasal Pharmaceutical for Treatment of mild Traumatic Brain Injury in the Field

About Concussion

A milder type of traumatic brain injury, caused by a blow to the head or upper body causing the brain to stretch and twist inside of the skull. Yearly occurrence of approximately 70M worldwide

Symptoms and Outcome

A change in mental status such as amnesia, disorientation, mental fogginess and confusion. Can include nausea or vomiting, blurred vision, headache or loss of consciousness

- at least 21 distinct symptoms
- due to variability of severity, long-term effects and recovery time are difficult to determine. Continued symptoms beyond 90-days leads to a diagnosis of Post-Concussion Syndrome (PCS)

About ONP-002

New chemical entity: Proprietary neurosteroid enantiomer and spray-dried formulation

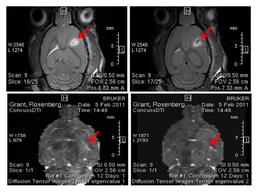
Administration using a proprietary intranasal device allows for fast and efficient drug delivery to the brain with less systemic organ exposure

In-vivo efficacy in animal concussion models through molecular induction of anti-inflammatories, anti-oxidants, efflux fluid channels and cell debris transporters as well as behavioral improvements in memory, emotion and sensory-motor performance

A large safety margin seen in toxicology testing (rat, dog, monkey)

Phase I Single and Multiple Ascending Dose safety trials complete and well tolerated in healthy human volunteers

Diffusion Weighted Imaging (DWI)



Diffusion Tensor Imaging (dTI)

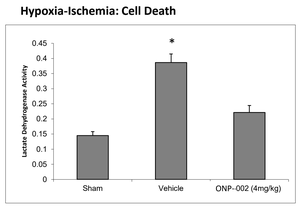
ONP-002 Mechanism of Action

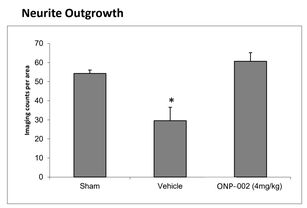
ONP-002 induces the Pregnane X Receptor (PXR). The PXR is an intracellular receptor found in brain cells and endothelial cells of the Blood Brain-Barrier (BBB)

Engagement of ONP-002 with the PXR activates multiple gene response elements resulting in cell debris clean-up, concomitant with reduced inflammation, oxidative stress and cerebral edema

ONP-002 is not a GABAergic compound, avoiding drug-induced sedation and learning deficits

ONP-002 effects on Brain Cell Damage and Death – Cell Culture



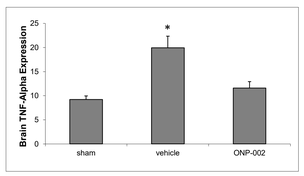


Hypoxia-ischemia induced lactate dehydrogenase release indicates neuronal cell membrane damage and cell death. ONP-002 reduces hypoxia-ischemia induced neuronal cell damage and death

Neurite outgrowth indicates cellular health and connectivity. ONP-002 enhances neurite outgrowth in an SH-SY5Y hypoxia-ischemia model representing neuronal cell recovery and reduced cell death

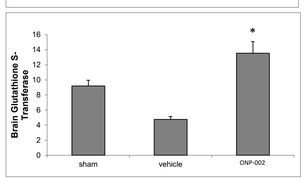
ONP-002 effects on Brain Inflammation and Oxidative Stress - Animal

- Neuroinflammation begins in the acute phase of trauma
- TNF-α is a neuroinflammatory cytokine that leads to neuronal damage
- Activation of the PXR can reduce inflammation by preventing NFκβ mediated pathology mediated by TNF-α
- Intranasal ONP-002 given acutely reduces protein expression of TNF- α



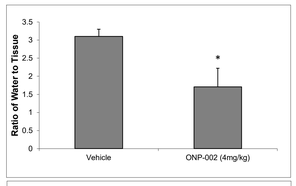
- Oxidative stress can damage and destroy brain cells. It occurs acutely following trama due to altered blood flow and energy metabolism
- Acute intranasal ONP-002 increases the protein expression of Glutathione s-transferase an anti-oxidant that protects against oxidative damage.

* denotes p< 0.05 at 24-hrs post-injury



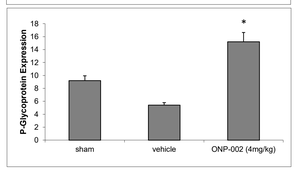
ONP-002 effects on Brain Edema aka Swelling and Autophagy - Animal

- Edema or swelling can occur after brain injury and result in increased intracranial pressure (ICP)
- Elevated ICP is associated with poor outcomes including increased mortality after brain injury
- Acute intranasal ONP-002 treatment reduces brain-injury related edema aka swelling. Sham was set to zero



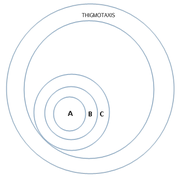
- Brain injury causes cell damage leading to intra and extracellular compartments filling with debris that impairs function
- P-glycoprotein (PGP) is a intracellular and blood brain-barrier transporter of debris through the process of autophagy
- PGP expression is controlled by the PXR and increased following acute intranasal brain injury treatment with ONP

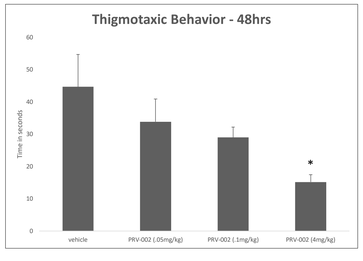
* denotes p< 0.05 at 24-hrs post-injury



ONP-002 effects on Depressive/Anxiety-Like Behavior- Animal

- Morris Water Maze (MWM)-Thigmotaxia a.k.a. wall-hugging represents fear-like **anxiety** in animals with brain injury
- Acute intranasal ONP-002 (4mg/kg) reduces brain-injury induced thigmotaxic behavior in a dose-dependent manner by 48hrs post-injury





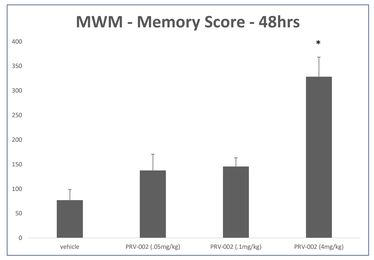
ONP-002 fka PRV-002. *denotes significance at p<0.05 in depressive/anxiety-like behavior improvement, n=8

ONP-002 improves Short-Term Memory - Animal

Brain injury can lead to neurocognitive impairment which includes memory loss, and impaired processing speed

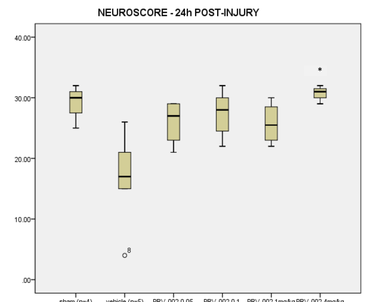
Morris Water Maze – Memory Score

- Animals were trained in a Morris Water Maze then subjected to brain trauma
- Post injury, animals were treated with either vehicle or ONP-002 (fka PRV-002) intranasally at 3 increasing concentrations
- Treatments were given at 1, 6 and 24hr post-injury
- Acute intranasal treatment with ONP-002 improves memory deficits associated with brain injury in a dose dependent manner by 48hrs



*denotes significance (4mg/kg) at p<0.05, in shorter-term memory performance, n=8

ONP-002 Improves Sensory-Motor Function - Animal



Sensory-motor impairment is representative of vestibular damage that can lead to anxiety, brain fog and imbalance following brain injury

Sensory-motor function was scored using the Neuroscore behavioral battery

- 4 separate movement behaviors were analyzed
- Movements were scored from -1 (non-functional) to +4 (highly functional) and a composite was created

ONP-002 (fka PRV-002) intranasal treatment improves sensorimotor performance by 24hrs in a dose dependent manner following brain injury

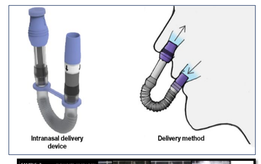
*denotes significance (4mg/kg) at p<0.05 in sensory-motor performance, n=8

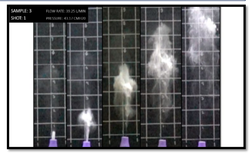
Patient Administration – Mouth to Nose

Intranasal (IN) administration allows rapid and direct accessibility to the brain

The Device – Intranasal Dispenser

- Allows patients to blow into device which closes the soft palate eliminating the flow of drug to the lungs or esophagus
- Minimizes systemic exposure and side effects
- Enhances dispersion to the superior nasal roof for direct olfactory nerve brain delivery via a novel double tube airflow system
- Compact, 1X use lightweight-field deliverable
- Exclusive US license to Odyssey NeuroPharma
- IP covering device and method of delivery for treatment of brain injury
- Spray-dried formulation is stable at high temperatures and not inhaled





The powder begins to expand at 1" from the end of the nozzle and becomes fully aerated at 5"

Toxicology and Phase I Study Findings

- ONP-002 was shown to have a 90+ safety margin in rat and dog toxicology studies
- ONP-002 was well-tolerated with no SAEs reported throughout the Phase I human SAD /MAD (5-day) trial
- Pharmacokinetic (PK) drug levels were dose responsive
- No drug accumulation was seen through 10-day follow-up
- Odyssey Health is in thE process of identifying clinical trial sites for a Phase II study