Design of a Phase 1/2 Study to Evaluate the Safety and Efficacy of PR001, an AAV9-Based Gene Therapy in Infants with Type 2 Gaucher Disease (PROVIDE Trial)

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**Background**

Gaucher disease (GD) is an autosomal recessive lysosomal storage disorder diagnosed by the presence of biallelic pathogenic mutations in GBA1 or a finding of less than 15% of normal activity of the GBA1-encoded enzyme glucocerebrosidase (GC). GD is a classic loss-of-function disease: GBA1 mutations causing more profound enzyme deficiencies are associated with earlier onset of GD, faster progression of symptoms, and a higher likelihood of neurological manifestations, termed neuropathic Gaucher disease (nGD).

Infants with Type 2 GD (GD2), the acute neuropathic form, have the most severe reductions of GCase. By 6 months of age, in addition to the peripheral manifestations of GD, infants present with progressive and severe neurologic manifestations, such as supranuclear gaze palsy and convergent squint, severe stridor and apnea, spasticity, opisthotonos, and failure to achieve motor, behavior, and cognitive milestones. Most infants die by age 2.

Though the majority of peripheral GD manifestations can be attenuated by treatment with enzyme replacement therapies (ERTs), the neurological manifestations of GD do not respond as ERTs do not penetrate the central nervous system (CNS). Thus, there is a high unmet need for an effective treatment for the devastating neurological symptoms of Type 2 GD.

**PR001 Background**

- The AAV9 vector is particularly well suited to deliver the GBA1 gene to the CNS, given its ability to transduce multiple CNS cell types, the expression of transgene, and existing safety data
- PR001 is an investigational AAV9 vector-based gene therapy that transduces the human GBA1 gene to the cells of the CNS
- PR001 is intended to directly treat the underlying genetic cause of GD2, and to thereby modify the course of the disease
- Single injection into the cisterna magna is planned to achieve maximal brain distribution
- Intra-cisterna magna delivery has been shown in non-clinical studies and in clinical practice to be a minimally invasive and safe procedure

**Efficacy in Preclinical Models**

- PR001 efficacy was examined in 2 established mouse models of GCase deficiency that displays phenotypic characteristics consistent with nGD
- In the CBE model, intraventricular PR001 treatment resulted in increased GCase expression, elevation of GCase enzyme activity, reduction of the accumulation of glycopolipid substrates of GCase, correction of neuroinflammation, and behavioral improvements
- Broad vector genome biodistribution of PR001 was seen in the CNS and peripheral organs, including the liver, spleen and lung
- PR001 treatment resulted in sustained GCase expression and suppression of glycopolipid accumulation over 6 months

**Safety in Preclinical Models**

- PR001 treatment also resulted in a significant increase in GCase activity along with decreased glycopolipid accumulation and amelioration of behavioral deficits in a genetic mouse model of nGD (data not shown)

**PROVIDE Phase 1/2 Trial Design**

An Open-label, Phase 1/2 Study to Evaluate the Safety and Efficacy of Single-Dose PR001 in Infants with Type 2 Gaucher Disease

**Study Objectives**

**Primary**

Safety and tolerability of PR001 administered via suboccipital injection into the cisterna magna

**Secondary**

Effects of PR001 on:
- Time to death
- Clinical measures and events, cognition, adaptive behavior and functioning
- GCase levels in blood and CSF
- Glycolipid panel (e.g. GluCer, GluSph) in blood and CSF

**References**


**Disclosures**

All authors are currently employed by Preval Therapeutics.