Venglustat, a Novel Brain-Penetrant Glucosylceramide Synthase Inhibitor, for GM2 Gangliosidosis and Related Diseases: Phase 3 AMETHIST Trial Design

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GM2 Gangliosidoses

The GM2 gangliosidoses, including Tay-Sachs and Sandhoff diseases, are autosomal recessive disorders caused by pathogenic variants of hexosaminidase genes A or B, resulting in insufficient hexosaminidase activity. Consequent lysosomal GM2 accumulation leads to progressive neuromotor disability and premature death.¹ No approved treatment exists.

Venglustat Treatment

Venglustat is a novel, small-molecule, brain-penetrant glucosylceramide synthase inhibitor designed to reduce production of the sphingolipid precursor glucosylceramide (GL-1), and is being studied as a disease-modifying therapy for multiple diseases associated with pathogenic glycosphingolipid accumulation.

AMETHIST Study

AMETHIST (NCT04221451) is a phase 3, multinational, randomized, double-blind, placebo-controlled trial of venglustat in patients with GM2 gangliosidosis and related diseases.

Study Objectives

► **Primary objectives**: to assess efficacy and pharmacodynamics (PD) of venglustat over a 104-week period

► **Secondary objectives**: to assess the effect of venglustat on selected performance tests and scale, determine safety and tolerability of venglustat, and assess the pharmacokinetics (PK) of venglustat in plasma and cerebrospinal fluid (CSF) over 104 weeks

Main Eligibility Criteria

► **Primary population**: adults with late-onset GM2 gangliosidosis

► **Secondary population**: 2- to 18-year-old patients with juvenile-/adolescent-onset GM2 gangliosidosis, and ≥2-year-old patients with GM1 gangliosidosis, saposin C deficiency, sialidosis type I, or juvenile/ adult galactosialidosis; body weight ≥10 kg

Study Design

► The primary population (57 planned) will be randomized 2:1 to once-daily oral venglustat or placebo for 104 weeks; the secondary population (up to 20) will receive the same venglustat regimen open label (dosed by weight in <18-year-olds)
Key Outcome Measures

► **Primary endpoints** are annualized rate of change in 9-Hole Peg Test and percentage change from baseline to Week 104 in CSF level of GM2 biomarker (primary population) and changes in plasma and CSF levels of GL-1 and disease-specific biomarkers (secondary population)

► **Secondary endpoints** (primary population only) are safety, tolerability, PK, and neurologic tests (change in Timed 25-Foot Walk and Friedreich Ataxia Rating Scale); safety, tolerability, and PK will be followed for 6 weeks after last dose

Figure: AMETHIST Study Design
As of October 18, 2021, patients are still being recruited into the AMETHIST trial at 24 sites in 14 countries.

More information is available: https://clinicaltrials.gov/ct2/show/NCT04221451

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