PERIDOT

Patient **E**xpe**RI**ence in Fabry **D**isease **O**n Venglusta**T**

Venglustat Phase 3 Fabry Disease Clinical Trial Program

SANOFI GENZYME

Sanofi Genzyme Commitment

Sanofi Genzyme has pioneered the development and delivery of therapies for patients affected by rare and debilitating diseases for over 30 years. With a focus on rare disease, multiple sclerosis, immunology, oncology and rare blood disorders, we are dedicated to making a positive impact on the lives of patients and families we serve. This goal guides and inspires us every day.

Fabry Disease

Fabry disease is a potentially life-threatening, inherited, multi-systemic disorder affecting both males and females and is caused by reduced or absent alpha-galactosidase A (α-Gal A) activity due to mutations in the GLA gene. Deficient α-GAL A activity results in accumulation of glycosphingolipid (particularly globotriasylceramide, also known as GL-3) in lysosomes, leading to cellular and organ damage that affect the renal, cardiovascular and cerebrovascular systems as well as reduced life expectancy and quality of life.[1,2]

Neuropathic pain, abdominal pain and other gastrointestinal symptoms are amongst the first clinical manifestations of Fabry disease[3] and can substantially impact activities of day-to-day living.[4,5] These symptoms impact the health, quality of life and function of affected individuals and add to the burden of Fabry disease.

Venglustat is an investigational oral glucosylceramide synthase (GCS) inhibitor that is designed to reduce the accumulation of GL-3 in Fabry disease and is also currently being investigated as a potential treatment for several rare diseases.[7] GL-3 accumulation in dorsal root ganglia and endothelial cells of the vasa nervorum have been proposed as possible causes of the length-dependent small fiber neuropathy which may induce a variety of peripheral and central symptoms, including chronic peripheral pain and acute pain crises.[6] In a completed Phase 2 study (ACT13739/LTS14116), previously untreated male participants with classic Fabry disease who received venglustat for up to 3 years showed reduction in skin capillary endothelial cell GL-3, plasma GL-3, and its derivative plasma lyso-GL-3. Improvements in the severity and duration of abdominal pain (among those with pain at baseline) and bodily pain component of the SF-36 (36-Item Short Form Health Survey) were also observed in the majority of patients during the study. Albuminuria and estimated glomerular filtration rate (eGFR) were stable throughout the study, and there was overall no significant clinical progression of Fabry disease (NCT02228460).

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EFC17045 (PRO study)

This Phase 3 trial is an international, multicenter, randomized, double-blind, placebo-controlled study to characterize the efficacy and safety of venglustat on neuropathic and abdominal pain in patients with Fabry disease.

The primary endpoint is the percent change from baseline in venglustat vs placebo on the patient-defined most bothersome symptom (of neuropathic pain in upper extremities, neuropathic pain in lower extremities, or abdominal pain), as assessed by the Fabry Disease Patient-Reported Outcome (FD-PRO) instrument, a newly developed disease-specific tool that measures symptoms and impacts of Fabry disease.[8]

Secondary endpoints include percent change from baseline in lyso-GL-3, frequency of rescue pain medication use, change from baseline in the percentage of days with diarrhea, percent change from baseline in tiredness component of FD-PRO, safety and tolerability, and pharmacokinetics.

Patients will be randomized in a 1:1 ratio to venglustat or placebo for 12 months.

Key inclusion criteria:

- Adults ≥ 18 years of age
- Treatment-naive, or no Fabry disease-related treatment within last 6 months
- Classic or late onset Fabry disease
- Plasma lyso-GL-3 level ≥5 ng/mL at screening, or a previous biopsy of any organ that shows deposition of GL-3
- Neuropathic upper extremity pain, lower extremity pain, and/or abdominal pain at baseline of > 3 severity (0=no symptoms, 10=symptoms as bad as you can imagine) as assessed by FD-PRO

Key exclusion criteria

- Advanced kidney, cardiovascular or cerebrovascular disease
- Any manifestations of Fabry disease that preclude placebo administration
- Neuropathic or abdominal pain that is attributable to causes other than Fabry disease

A complete list of eligibility requirements can be round at www.clinicaltrials.gov (Identifier: NCT05206773)

References:

1. Germain DP, et al. Fabry disease. *Orphanet J Rare Dis.* 2010 Nov 22;5:30.
2. Morand O, et al. Symptoms and Quality of Life in Patients with Fabry Disease: Results from an International Patient Survey. *Adv Ther.* 2019;36(10):2866-80.
3. Hopkin RJ, et al. Characterization of Fabry disease in 352 pediatric patients in the Fabry Registry. *Pediatr Res.* 2008;64(5):550-55.
4. Arends M, et al. Phenotype, disease severity and pain are major determinants of quality of life in Fabry disease: results from a large multicenter cohort study. *J Inherit Metab Dis.* 2018;41(1):141-49.
5. Hilz MJ, et al. Non-specific gastrointestinal features: Could it be Fabry disease? *Dig Liver Dis.* 2018;50(5):429-37.
6. Burlina AP, et al. Early diagnosis of peripheral nervous system involvement in Fabry disease and treatment of neuropathic pain: the report of an expert panel. *BMC Neurol*. 2011;11:61.
7. Peterschmitt MJ, Crawford NPS, Gaemers SJM, Ji AJ, Sharma J, Pham TT. Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of Oral Venglustat in Healthy Volunteers. *Clin Pharmacol Drug Dev.* 2021 Jan;10(1):86-98. doi: 10.1002/cpdd.865.
8. Hamed A, et al. Development of the Fabry Disease Patient-Reported Outcome (FD-PRO): a new instrument to measure the symptoms and impacts of Fabry Disease. *Orphanet J Rare Dis.* 2021;16(1):285.

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