Venglustat for Gaucher Disease type 3 (GD3):

LEAP 2 MONO | *Clinical Trial*

GAUCHER DISEASE TYPE 3 (GD3)

Gaucher disease (GD) is an autosomal recessively inherited lysosomal storage disease that results from a deficiency of acid β-glucosidase (glucocerebrosidase [GCase]). Deficient GCase activity leads to the accumulation of glycosphingolipids, primarily glucosylceramide (GL-1) and glucosylsphingosine (otherwise known as lyso-GL-1), particularly in macrophages of the spleen, liver, bone marrow, and lung.[1-4] Clinically, three major forms of GD continue to be distinguished at age of disease onset based upon the presence or absence and rate of progression of the classically described constellation of neurological manifestations. The most common form, Gaucher disease type 1 (GD1), is characterized by the lack of (or late) central nervous system (CNS) involvement. Gaucher disease type 2 (GD2), or the acute neuronopathic form, has an early onset of CNS involvement before age 2 and early death. GD3, or the chronic neuronopathic form, typically has later onset of CNS involvement with slower progression.[5]

In GD3, accumulation of glucosylceramide and glucosylsphingosine in the CNS results in neuronopathic manifestations including the hallmark sign gaze palsy, predominantly horizontal with slow or absent saccades, in addition to the systemic manifestations seen in GD1.[6-13] Cognitive and behavioral defects such as squint, gait ataxia, intention tremor, dysarthria, dysphagia, spasticity, abnormal tone and posturing, delayed gross and fne motor skills, seizures (including progressive and myoclonic epilepsy), and dementia may also be present in GD3.[13-17]

Venglustat is an investigational small-molecule oral glucosylceramide synthase (GCS) inhibitor which crosses the blood brain barrier and is under investigation for treatment of neurologic manifestations of GD3. In the LEAP trial (NCT02843035), therapeutic potential of venglustat in combination with imiglucerase in treating the neurologic manifestations of GD3 was demonstrated.

Venglustat is investigational and has not been approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA), or any other regulatory agency worldwide for its uses under investigation. No conclusions regarding safety and efficacy should be drawn. Patient enrollment is dependent on approval by local ethics committees. This material is for scientific purposes only and is intended only for healthcare practitioners.

LEAP2MONO (EFC17215)

The LEAP2MONO study is a phase 3, multicenter, multinational, randomized, double-blind, double-dummy, active-comparator, superiority study to evaluate the efficacy and safety of venglustat in adult and pediatric patients with GD3 who have reached therapeutic goals with Enzyme Replacement Therapy (ERT).

The co-primary endpoints for the study include change in Scale for Assessment and Rating of Ataxia (SARA) modifed total score ⓘ and change in Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score ⓘ from baseline to week 52.

Secondary endpoints include percent change from baseline in spleen volume (MN); liver volume (MN); platelet count; and change from baseline in hemoglobin levels at week 52.

Secondary endpoints will also include safety and tolerability as well as change in score of Beck Depression Inventory II (BD-II) during the treatment-emergent period.

Patients will be randomized to receive either oral venglustat once daily and placebo or imiglucerase infusion every two weeks and placebo for 52 weeks.

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Key Inclusion Criteria

- Adult and pediatric participants:
  - ➔ Adults: ≥ 18 years of age
  - ➔ Pediatric participants: ≥ 12 years to <18 years of age
- Diagnosis of GD3 and documented deficiency of acid β-glucosidase activity
- Participants must have a modified SARA score of 1 or above
- Presence of gaze palsy, predominantly horizontal, with slow or absent saccades
- The participant has received ERT (imiglucerase or other ERT; as deemed appropriate by local regulations) for at least 3 years prior to enrollment, on a stable dose for at least 6 months and is within the therapeutic goals: hemoglobin level of ≥11.0 g/dL for females and ≥12.0 g/dL for males, platelet count ≥100 000/mm3, spleen volume <10 multiples of normal (MN), liver volume <1.5 MN, no bone crisis and free of symptomatic bone disease such as bone pain attributable to osteonecrosis and/or pathological fractures within 3 months prior to screening, and is deemed clinically stable for at least 1 year by the Investigator.

Key Exclusion Criteria

- Prior esophageal varices, liver infarction, current liver enzymes (ALT/AST), or total bilirubin >2 times the upper limit of normal, unless the participant has a diagnosis of Gilbert Syndrome.
- Progressive myoclonic epilepsy
- Received chaperone therapy, substrate reduction therapy other then venglustat, or venglustat within 6 months prior to enrollment.

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