Health Technology Briefing
March 2023

Venglustat for treating type 3 Gaucher disease after 1 therapy

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 11067	NICE TSID: 10612	UKPS ID: 661602

Licensing and Market Availability Plans

Currently in phase III clinical trials.

Summary

Venglustat is in clinical development for the treatment of patients with Gaucher disease type 3 (GD3) who have been effectively treated with Enzyme Replacement Therapy (ERT) for at least 3 years. Gaucher Disease (GD) is a genetic disorder caused by an enzyme deficiency where fatty substances build up in areas such as the spleen, liver, and bone marrow. This builds up to cause organ enlargement and can affect their function. GD3 is the chronic neuropathic form of the disease. GD3 affects the central nervous system and causes neurological symptoms including eye movement disorders, seizures, and other cognitive difficulties. There are currently no approved therapies to treat the neurological manifestations of GD3. Patients with GD3 can currently receive ERT or substrate replacement therapy to address symptoms not involving the brain, like organ enlargement and bone issues.

Venglustat is an orally administrated tablet. As a small-molecule drug, it is being investigated for its ability to pass through the brain barrier to improve neurological manifestations associated with GD3 (as well as to stabilise the non-neurological manifestations). Venglustat is anticipated to work by stopping the fat laden Gaucher cells building up in areas like the spleen, liver, and bone marrow. If licensed, venglustat will provide a new oral treatment to improve/stabilise the symptoms of GD3.

Proposed Indication

Treatment of adult and paediatric patients with type 3 Gaucher disease. [1]

Technology

Description

Venglustat (ibiglustat) for GD3 is an oral inhibitor of an enzyme called glucosylceramide synthase (GCS).[2] GCS modify specific molecules called substrates. GCS turns its substrate, ceramide, into glucosylceramide (GL-1) during lipid metabolism, a series of biochemical reactions that degrade and generate lipids. GL-1 acts as a substrate to other enzymes and is turned into globosides, a subclass of lipids where globotriaosylceramide (Gb3) belongs. When venglustat inhibits GCS, it prevents the synthesis of GL-1, thereby reducing the substrate of the following reactions that lead to the formation of Gb3 and its accumulation in the absence of α-galactosidase.[2]

Venglustat is in clinical development for treatment of patients with GD3 who have been treated with Enzyme Replacement Therapy (ERT) for at least 3 years. In the phase III clinical trial (LEAP2MONO; NCT05222906), venglustat will be administered as an oral tablet.[1,3]

Key Innovation

While ERT has demonstrated efficacy in treating the systemic non-neurological manifestations of GD, ERT has had negligible effects GD3 patients.[4] Occasionally people have an allergic or hypersensitivity reaction to enzyme treatment.[5] ERT is an IV medication, which can be an inconvenience for patients. IV medications are also more invasive than oral medication.[6] Currently, there are no approved therapies for the treatment of the neurological manifestations of GD3.[4]

If licensed, venglustat will provide an oral treatment option for patients with Gaucher disease type 3 who currently have few effective therapies available.

Regulatory & Development Status

Venglustat does not currently have Marketing Authorisation in the EU/UK for any indication.

Venglustat is also in phase II/III clinical development for other indications, including:[7]

- Fabry's disease.
- Late-onset GM2 gangliosidosis (including Sandhoff's disease and Tay-Sachs disease), as well as ultra-rare diseases within the same and similar glucosylceramide-based sphingolipid pathway (such as GM1 gangliosidosis, saposin C deficiency, sialidosis type 1 or juvenile adult galactosialidosis).

Venglustat has the following regulatory designations:

- An Orphan drug designation in the EU in 2014 for GD.[8]

Patient Group

Disease Area and Clinical Need

Gaucher disease (GD) is one of the most common lysosomal storage disorders.[9] GD is an autosomal recessive disorder caused by mutations in the gene that encodes glucocerebrosidase, *GBA1*. Having two copies of the L444P mutation causes neurological symptoms associated with GD3.[10] GD is divided into three types. Type 1 – the most common form of GD accounts for 95% of patients in western countries. Type 2 GD is rare and involves severe neurological abnormalities. Patients with type 2 GD typically don't

survive past 2 years of age and is presently untreatable.[11] Type 3 GD (GD3) is most commonly associated with neurological manifestations. Symptoms usually develop in childhood. The initial problems are enlargement of the liver and spleen, poor feeding and failure to gain weight adequately.[12] In all forms of GD, there is a build-up of glucocerebrosidase in the liver and spleen. In type 3 patients in particular, there is accumulation of glucocerebrosidase within the nervous system.[13] Neurological symptoms of GD3 vary in severity from person to person and may include: cognitive problems, developmental delays, eye movement disorders, poor coordination and seizures.[14] Some patients with relatively mild neurological involvement live into their fifties. [15]

The global prevalence of GD varies by geography, but generally ranges from 0.70 to 1.75 per 100,000 individuals and is substantially higher among the Ashkenazi Jewish population.[16] In France, 2012, there was a reported 0.74 cases per 100,000.[17]According to the hospital episodes statistics for England in 2021-22 there were 73 finished consultant episodes (FCE), 65 admissions, and 231 FCE bed days (ICD-10 E75.22).[18]

Recommended Treatment Options

The National Institute for Health and Care Excellence (NICE) does not have any recommendations for GD3.

Imiglucerase is approved for long-term ERT in GD3 who exhibit significant non-neurological manifestations.[19]

Clinical Trial Information		
Trial	**LEAP2MONO;** NCT05222906; EudraCT: 2021-005402-10. A Phase 3, Multicenter, Multinational, Randomized, Double-blind, Double-dummy, Active-comparator Study to Evaluate the Efficacy and Safety of Venglustat in Adult and Pediatric Patients With Gaucher Disease Type 3 (GD3) Who Have Reached Therapeutic Goals With Enzyme Replacement Therapy (ERT) **Phase III** – Recruiting **Location(s)**: Three EU countries, USA, Canada, Argentina, Japan, and China. **Primary completion date**: August 2024.	**LEAP;** NCT02843035; EudraCT: 2014-002550-39. A 4-part, Open-label, Multicenter, Multinational Study of the Safety, Tolerability, Pharmacokinetics, Pharmacodynamic, and Exploratory Efficacy of Venglustat in Combination With Cerezyme in Adult Patients With Gaucher Disease Type 3 With Venglustat Monotherapy Extension. **Phase II –** Active, not recruiting. **Location(s):** Germany, United Kingdom, USA, Japan. **Primary completion date:** September 2025.
Trial Design	Randomised, parallel assignment, quadruple masking	Parallel assignment, open label.
Population	N= 40; aged 12 years and older; subjects with GD3 who have been treated with ERT for at least 3 years	N=13; ages 18 years and older; subjects with GD3 who have been treated with ERT for at least 3 years.

Intervention(s)	Venglustat will be administered orally as a tablet.[1]	Venglustat will be administered orally as a tablet.[3]
Comparator(s)	Imiglucerase via intravenous infusion.	-
Outcome(s)	Primary outcome measure: • Change in scale for assessment and rating of ataxia (SARA) modified total score [Time frame: from baseline to week 52]. • Change in repeatable battery for the assessment of neuropsychological status (RBANS) total scale index score [Time frame: from baseline to week 52].	Primary outcome measure: • Number of patients with Treatment Emergent Adverse Events (TEAEs) [Time Frame: From screening up to end of study, up to approximately 8.7 years]. • Assessment of pharmacodynamic (PD) parameter: Lyso-glucosylceramide (lyso-GL1) and glucosylceramide (GL-1) in cerebrospinal fluid (CSF) [Time Frame: From screening through Week 52]
Results (efficacy)	-	-
Results (safety)	-	-

Estimated Cost

The cost of venglustat is not yet known.

Relevant Guidance

NICE Guidance

No relevant guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard Contract for metabolic disorders (adult) E06/S/a.
- NHS England. 2013/14 NHS Standard Contract for lysosomal storage disorders service (children) E06/S(HSS)/c.

Other Guidance

No relevant guidance identified.

Additional Information

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