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Health Technology Briefing
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Venglustat for treating late onset GM2 gangliosidosis, GM1 gangliosidosis and other ultra-rare disease

Company/Developer	Sanofi

☒ New Active Substance ☐ Significant Licence Extension (SLE)

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Licensing and Market Availability Plans

Currently in phase III clinical development.

Summary

Venglustat is currently in clinical development for the treatment of adult and paediatric patients with GM2 gangliosidosis (which includes Tay-Sachs disease and its more severe form; Sandhoff disease) as well as other rare disorders including GM1 gangliosidosis, galactosialidosis and sialidosis. All these conditions are caused by genetic mutations involving a mechanism called the glucosylceramide-based sphingolipid pathway that results in an inability to properly break down large fatty molecules called lipids. The resulting abnormal build-up of lipids can cause damage in the cells and tissues in the brain and nervous system. Symptoms vary between the individual conditions but can include motor and muscle weakness, speech and swallowing problems, skeletal complications, seizures and loss of vision. There are currently no approved treatment options for GM2 and GM1 gangliosidosis, galactosialidosis and sialidosis.

Venglustat is an investigational therapy small-molecule drug that inhibits abnormal lipid build up, by preventing enzymes that lead to this build-up from working. It will be administered as an oral tablet. If licensed venglustat, will provide the first treatment option for patients with GM2 gangliosidosis, GM1 gangliosidosis, galactosidosis and siladosis.

Proposed Indication

Treatment of patients 2 years of age and older with GM2 gangliosidosis and other lysosomal storage disorders.[1]

Technology

Description

Venglustat (GZ402671) is a novel, oral investigational therapy that has the potential to slow the progression of certain diseases by inhibiting abnormal glycosphingolipid accumulation.[2] It is a small-molecule glucosylceramide synthase (GCS) inhibitor designed to reduce the production of glucosylceramide (GL-1) and thus is expected to substantially reduce formation of glucosylceramide-based glycosphingolipids. Because of its effect on glycosphingolipid formation, GCS inhibition has therapeutic potential across many disorders affecting glycosphingolipid metabolism. [1,3]

Venglustat is currently in phase III clinical development for the treatment of adult patients aged 18+ years with late onset GM2 gangliodosis, as a primary population and then patients aged 2+ years with GM1 gangliodosis and other ultra-rare diseases (sialidosis type 1 or juvenile adult galactosialidosis), as a secondary population. In the phase III trial (NCT04221451), patients are administered oral venglustat tablet once daily at various doses for 104 weeks.[1]

Key Innovation

Currently, there are no approved therapies for GM2 gangliosidosis.[4] There are also currently no effective therapies for GM1 gangliosidosis, siladosis or galactosialidosis.[5-7] If licensed, venglustat would be the first therapy approved for the treatment of GM2 gangliosidosis, as well as GM1 gangliosidosis, siladosis and galactosialidosis.[4] Venglustat is expected to improve the symptoms of GM2 gangliosidosis and help patients live longer.[8]

Regulatory & Development Status

Venglustat does not currently have marketing authorisation in the EU/UK for any indication.

Venglustat is also in phase II and III clinical development for:[9]

- Fabry disease
- Gaucher's disease type III

Venglustat has been awarded the following regulatory designations:

- An Orphan drug in the EU in 2020 for the treatment of GM2 gangliosidosis.[10]

Patient Group

Disease Area and Clinical Need

The gangliosidoses are a group of rare inherited metabolic diseases caused by a deficiency of the different enzymes needed to break down lipids.[11,12] Abnormal build-up of lipids can cause permanent damage in the cells and tissues in the brain and nervous systems, particularly in nerve cells, and elsewhere in the body (including the liver and spleen). There are two distinct groups of the gangliosidoses that can affect males and females equally: GM1 and GM2. The GM2 gangliosidoses include Tay-Sachs disease and its more severe form, Sandhoff disease, both of which result from a deficiency of the enzyme beta-hexosaminidase.[12] GM2 gangliosidosis is most often caused by a mutation in the HEXA or the GM2A gene.[13] Sandhoff disease is a progressive neurodegenerative disorder characterised by an accumulation of GM2 gangliosides, particularly in neurons, and is clinically indistinguishable from Tay-Sachs disease.[14] Tay-

[a] Information provided by Sanofi

Sachs disease is a rare inherited condition. It stops the nerves working properly and is usually fatal.[11] Symptoms of Tay-Sachs disease and Sandhoff's disease include motor weakness, being overly startled by noises and movement, loss of vision, progressive mental and motor deterioration.[11,14] GM1 gangliosidosis is a progressive, neurosomatic disorder caused by mutations in the GLB1 gene encoding β-galactosidase. Symptoms include progressive disability, speech disturbances, swallowing difficulty, neurological symptoms (seizures), skeletal abnormalities.[15] Sialidosis is a rare, inherited, autosomal recessive condition, caused by α-N-acetyl neuraminidase deficiency due to a mutation in the neuraminidase gene (NEU1). This leads to abnormal intracellular accumulation of sialyloligosaccharides. Symptoms may include gait abnormalities, visual problems, progressive disability and neurological symptoms (such as tremors).[16] Galactosialidosis is a glycoprotein storage disease caused by mutations in the cathepsin A gene resulting in deficiency of both β-galactosidase and α-neuraminidase enzymes. Symptoms include hepatosplenomegaly, spine abnormalities, cardiac involvement, seizures, visual and hearing impairment, progressive cognitive impairment.[17]

Tay–Sachs and Sandhoff disease are rare and between 2 and 6 children a year are born with the diseases in the UK. The incidence of Tay-Sachs is 1 in 320,000 and Sandhoff is 1 in 300,000.[18,19] However, 1 in 300 people are carriers of the genes which cause either Tay-Sachs or Sandhoff disease.[20] In England, 2021-22, there were 17 finished consultant episodes (FCE) and 12 admissions for GM2 gangliosidosis (ICD-10 code E75.0) which resulted in 33 FCE bed days and 7 day cases.[21]

GM1 gangliosidosis is estimated to occur in 1 in 100,000 to 200,000 new-borns. Type I is reported more frequently than the other forms of this disease. GM1 gangliosidosis is more common in those of Japanese descent than other ethnicities; Sialidoses incidence is estimated at 1-4 in 200,000 (general population – not UK/EU) and, due to the ultra-rare nature of galactosialdosis, prevalence is currently unknown.[6,17,22]

Recommended Treatment Options

There are currently no National Institute for Health and Care Excellence (NICE) recommended treatment options for GM2 gangliosidosis, GM1 gangliosidosis, Siladosis or Galactosilidosis.[4,23-26]

Clinical Trial Information

Trial	**AMETHIST; NCT04221451; EudraCT-2019-002375-34.** A Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Pharmacodynamics, Pharmacokinetics, Safety, and Tolerability of Venglustat in Late-onset GM2 Gangliosidosis (Tay-Sachs Disease and Sandhoff Disease) Together With a Separate Basket for Juvenile/Adolescent Late-onset GM2 Gangliosidosis and Ultra-rare Diseases Within the Same and Similar Glucosylceramide-based Sphingolipid Pathway **Phase III:** Active, not recruiting **Locations: 7 countries in EU,** UK, USA, South America and Asia **Primary completion date:** February 2024
Trial Design	Randomised, parallel assignment, quadruple masked
Population	N=74 (actual); Participants with a diagnosis of late onset GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease) caused by genetic β-hexosaminidase deficiency resulting from mutations in the HEXA or HEXB genes (primary population only); a secondary population will enroll patients with diagnosis of juvenile/adolescent GM2 gangliosidosis, GM1 gangliosidosis, saposin C deficiency, sialidosis type 1 or juvenile adult galactosialidosis;Primary population

[a] Information provided by Sanofi

	and adult secondary population: age ≥ 18 years;Juvenile/adolescent secondary population: 2 ≥ age < 18 years with weight ≥ 10 kg
Intervention(s)	Venglustat (oral tablet)
Comparator(s)	Matched placebo (oral tablet) (Primary population only)[a]
Outcome(s)	Primary outcome measures: • Change in cerebrospinal fluid (CSF) GM2 biomarker [Time frame: from baseline to week 104] • Change in the 9-hole pegboard test (9-HPT) [Time frame: from baseline to week 104] • Assessment of pharmacodynamics (PD) response in plasma: GL-1, GM1 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in plasma: GL-1, GM2 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in plasma: GL-1, GM2, GM3 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in plasma: GL-1 biomarker [Time frame: from baseline to week 104] • Assessment of PD in CSF: GL-1, GM1 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in CSF: GL-1, GM2 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in CSF: GL-1, GM2, GM3 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in CSF: GL-1, GM1, GM3 biomarkers [Time frame: from baseline to week 104] • Assessment of PD response in CSF: GL-1 biomarker [Time frame: from baseline to week 104] See trial record for full list of other outcomes.
Results (efficacy)	-
Results (safety)	-

Estimated Cost

The cost of venglustat is not yet known.

Relevant Guidance

NICE Guidance

There is no NICE guidance currently available for this indication.

NHS England (Policy/Commissioning) Guidance

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

[a] Information provided by Sanofi

Other Guidance

- Dr D Lumsden. Clinical Guideline: Paediatric Neurology: Management and Investigation of Dystonia in Childhood. 2016.[27]

Additional Information

References

NB: This briefing presents independent research funded by the National Institute for Health and Care Research (NIHR). The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health.

1 Clinicaltrials.gov. *A Multicenter, Multinational, Randomized, Double-blind, Placebo-controlled Study to Assess the Efficacy, Pharmacodynamics, Pharmacokinetics, Safety, and Tolerability of Venglustat in Late-onset GM2 Gangliosidosis (Tay-Sachs Disease and Sandhoff Disease) Together With a Separate Basket for Juvenile/Adolescent Late-onset GM2 Gangliosidosis and Ultra-rare Diseases Within the Same and Similar Glucosylceramide-based Sphingolipid Pathway*. *Trial ID: NCT04221451*. 2020. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/ct2/show/record/NCT04221451 [Accessed 04 April 2023].

2 Sanofi. *Sanofi provides update on venglustat clinical program*. Press release. Available from: https://www.sanofi.com/en/media-room/press-releases/2021/2021-06-01-05-00-00-2239122 [Accessed 04 April 2023].

3 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;10(1):86-98. Available from: https://doi.org/10.1002/cpdd.865.

4 Leal AF, Benincore-Flórez E, Solano-Galarza D, Garzón Jaramillo RG, Echeverri-Peña OY, Suarez DA, et al. GM2 Gangliosidoses: Clinical Features, Pathophysiological Aspects, and Current Therapies. *Int J Mol Sci*. 2020;21(17). Available from: https://doi.org/10.3390/ijms21176213.

5 Hayward C, Patel HC, Manohar SG, Lyon AR. Gene therapy for GM1 gangliosidosis: challenges of translational medicine. *Ann Transl Med*. 2015;3(Suppl 1):S28. Available from: https://doi.org/10.3978/j.issn.2305-5839.2015.02.28.

6 Rarediseases.org. *Sialidosis*. 2016. Available from: https://rarediseases.org/rare-diseases/sialidosis/ [Accessed 25 May 2023].

7 International Society for Mannosidosis and Related Diseases. *Galactosialidosis*. 2023. Available from: https://www.ismrd.org/glycoprotein-diseases/galactosialidosis/ [Accessed 12 June 2023].

8 European Medicines Agency (EMA). *Public summary of opinion on orphan designation - Venglustat for the treatment of GM2 gangliosidosis*. 2020. Available from: https://www.ema.europa.eu/en/documents/orphan-designation/eu/3/20/2325-public-summary-opinion-orphan-designation-venglustat-treatment-gm2-gangliosidosis_en.pdf.

9 Clinicaltrials.gov. *Venglustat*. Available from: https://clinicaltrials.gov/ct2/results?term=Venglustat&recrs=b&recrs=a&recrs=f&recrs=d&age_v=&gndr=&type=&rslt=&phase=1&phase=2&Search=Apply [Accessed 06 April 2023].

[a] Information provided by Sanofi

10 European Medicines Agency (EMA). *EU/3/20/2325: Orphan designation for the treatment of GM2 gangliosidosis* 2020. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu3202325 [Accessed 10 May 2023].
11 National Health Service (NHS). *Tay-Sachs disease*. 2021. Available from: https://www.nhs.uk/conditions/tay-sachs-disease/ [Accessed 12 April 2023].
12 National Institute of Neurological Disorders and Stroke. *Gangliosidoses*. Available from: https://www.ninds.nih.gov/health-information/disorders/gangliosidoses?search-term=GM2%20gangliosidosis [Accessed 12 April 2023].
13 Boston Children's Hospital. *GM2 Gangliosidosis*. 2023. Available from: https://www.childrenshospital.org/conditions/gm2-gangliosidosis [Accessed 10 May 2023].
14 National Health Service - The Leeds Teaching Hospitals. *Sandhoff Disease*. 2023. Available from: https://www.leedsth.nhs.uk/a-z-of-services/the-leeds-genetics-laboratory/constitutional-genetics/molecular-genetics/by-disorder/sandhoff-disease/ [Accessed 10 May 2023].
15 Nicoli ER, Annunziata I, d'Azzo A, Platt FM, Tifft CJ, Stepien KM. GM1 Gangliosidosis-A Mini-Review. *Front Genet*. 2021;12:734878. Available from: https://doi.org/10.3389/fgene.2021.734878.
16 Pattison S, Pankarican M, Rupar CA, Graham FL, Igdoura SA. Five novel mutations in the lysosomal sialidase gene (NEU1) in type II sialidosis patients and assessment of their impact on enzyme activity and intracellular targeting using adenovirus-mediated expression. *Human Mutation*. 2004;23(1):32-9. https://doi.org/10.1002/humu.10278.
17 Annunziata I, d'Azzo A. Galactosialidosis: historic aspects and overview of investigated and emerging treatment options. *Expert Opin Orphan Drugs*. 2017;5(2):131-41. Available from: https://doi.org/10.1080/21678707.2016.1266933.
18 Cure and Action for Tay-Sachs Foundation (CATS). *WHAT IS TAY-SACHS?* 2023. Available from: https://cats-foundation.org/what-is-tay-sachs/ [Accessed 12 June 2023].
19 Cure and Action for Tay-Sachs Foundation (CATS). *KEY FACTS OF SANDHOFF*. 2023. Available from: https://cats-foundation.org//what-is-sandhoff/ [Accessed 14 June 2023].
20 Cure and Action for Tay-Sachs Foundation (CATS). *What is Sandhoff?* Available from: https://cats-foundation.org/tay-sachs-sandhoff-disease/ [Accessed 12 April 2023].
21 National Health Service Digital (NHS). *Hospital Admitted Patient Care Activity, 2021-22*. 2022. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2021-22.
22 MPS Society. *GM1 Gangliosidosis*. 2023. Available from: https://www.mpssociety.org.uk/gm1gangliosidosis [Accessed 14 June 2023].
23 National Institute for Health and Care Excellence (NICE). *No results found*. 2023. Available from: https://www.nice.org.uk/search?q=GM2+gangliosidoses [Accessed 13 April 2023].
24 National Institute for Health and Care Excellence. *GM1 gangliosidosis*. 2023. Available from: https://www.nice.org.uk/search?q=GM1+gangliosidosis [Accessed 12 June 2023].
25 National Institute for Health and Care Excellence. *Sialidosis* 2023. Available from: https://www.nice.org.uk/search?q=sialidosis.
26 National Institute for Health and Care Excellence (NICE). *Galactosilidosis*. 2023. Available from: https://www.nice.org.uk/search?q=Galactosilidosis [Accessed 12 June 2023].
27 Lumsden D. *Clinical guideline: Paediatric Neurology: Management and Investigation of Dystonia in Childhood*. Available from: https://paediatricguidelineexchange.files.wordpress.com/2018/03/dystonia.pdf [Accessed 13 April 2023].

[a] Information provided by Sanofi