Health Technology Briefing
June 2024

Govorestat for treating galactosemia in people aged 2-65 years

Company/Developer	ADVANZ Pharma

☒ New Active Substance ☐ Significant Licence Extension (SLE)

NIHRIO ID: 28511	NICE ID: Not Available	UKPS ID: Not Available

Licensing and Market Availability Plans

In phase III clinical development.

Summary

Govorestat is in clinical development for treating classic galactosemia. Classic galactosemia is a rare disorder affecting the body's ability to break down (metabolise) the sugar present in milk (galactose) into another type of sugar called glucose. Glucose provides a source of energy for body cells. Classic galactosemia is caused by a faulty (mutated) gene, meaning that the body can't make an enzyme (protein) which normally breaks down galactose into glucose. When not broken down properly, galactose is converted to a toxic substance called galactitol, which builds up in cells. This causes damage to different tissues in the body, leading to complications such as juvenile cataracts and learning difficulties. Currently, classic galactosemia is treated by removing dairy products, the main source of galactose, from the diet. This can help to control symptoms in babies; however, it does not prevent long-term complications of the disease such as mental disabilities that develop later in life. There are currently no drug treatments available for patients with classic galactosemia.

Govorestat prevents the build-up of galactitol in cells to control symptoms of classic galactosemia and possibly prevent long-term complications associated with the condition. Govorestat can enter the central nervous system (brain/ spinal cord), preventing neurological complications of classic galactosemia. If licensed, govorestat will offer a treatment option for patients with classic galactosemia, who have few effective therapies available.

Proposed Indication

Treatment of classic galactosemia in people aged 2-65 years.[1,2]

Technology

Description

Govorestat (AT-007) is an aldose reductase inhibitor that is able to cross the blood-brain barrier into the central nervous system.[3] Aldose reductase is an enzyme that breaks down galactose into a toxic metabolite called galactitol, which is a biomarker associated with disease severity that is unable to diffuse out of cells due to its composition, leading to accumulation of galactitol in cells.[4] Govorestat inhibits the activity of aldose reductase, preventing build-up of galactitol in cells and limiting toxicity in patients with classic galactosemia. Since Govorestat is able to penetrate the central nervous system, it can also reduce levels of galactitol therein and potentially prevent neurological complications associated with classic galactosemia.[5]

Govorestat is in clinical development for people aged 2 to 65 years old with classic galactosemia.[1,2] In the phase III trial (NCT05418829), govorestat is given at 20mg/kg orally, once daily, to adults (18-65 years).[1] In another phase III trial (NCT04902781), govorestat is given at 5mg/kg to all paediatric age groups (2-17 years), to evaluate the optimum dose. [2]

Key Innovation

The current standard of care for patients with classic galactosemia is a galactose restricted diet, however this is only effective for treating neonatal complications, and does not prevent chronic complications from developing.[4] Govorestat directly targets formation of galactitol, with evidence suggesting it can significantly reduce levels of galactitol in children.[5] Govorestat was also reported to be considered well tolerated and safe.[5] If licensed, govorestat will offer a treatment option to patients who have few effective therapies available.

Regulatory & Development Status

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

Govorestat is in phase II/III clinical development for sorbitol dehydrogenase deficiency.[6]

Govorestat has the following regulatory designations/awards:[7,8]

- An orphan drug in the EU in 2022 for the treatment of galactosaemia.
- An orphan drug in the EU in 2023 for the treatment of Charcot-Marie-Tooth disease.

Patient Group

Disease Area and Clinical Need

Classic galactosemia is a rare, hereditary disorder of carbohydrate metabolism that affects the body's ability to convert galactose to glucose.[9] The disorder is caused by a deficiency of the enzyme galactose-1-phosphate uridylyl transferase, which results in the accumulation of the toxic metabolite galactitol when galactose is metabolised by the enzyme aldose reductase.[3,9] Early diagnosis and treatment with a lactose-restricted (dairy-free) diet is essential to avoid profound intellectual disability, liver failure and death in the newborn period.[9] Galactosemia is inherited as an autosomal recessive genetic condition. Classic

galactosemia results in life-threatening health problems unless lactose is removed from the diet shortly after birth.[9] Early symptoms of classic galactosemia in infants can include jaundice, hepatomegaly, diarrhoea and lethargy.[9] In children who have not received early treatment, symptoms can include arrested mental and physical development, and susceptibility to cataracts.[9]

In the UK, classic galactosemia is estimated to occur in 1 in every 45,000 births.[10] In England, between 2022-2023 there were 20 finished consult episodes (FCEs) and 15 admissions for disorders of galactose metabolism (ICD10 code E742), resulting in 5 day cases and 76 FCE bed days.[11]

Recommended Treatment Options

There is no treatment option recommended by NICE for classic galactosemia. There are currently no approved pharmacological treatment options available for patients with classic galactosemia.

Guidance from the galactosemia foundation includes the following treatments:[12]

- Dietary management
- Hormone replacement therapy (for girls with classic galactosemia)
- Psychological support

Clinical Trial Information

Trial	NCT04902781; A sequential, two-part study to evaluate the clinical benefit, safety, pharmacokinetics, and pharmacodynamic of govorestat in pediatric subjects with classic galactosemia **Phase II/III –** Active, not recruiting **Location:** United States **Primary completion date:** September 2023
Trial Design	Randomised, parallel assignment, quadruple blinded
Population	N = 47 (actual); Subjects with classic galactosemia; aged 2 to 17 years old.
Intervention(s)	Govorestat given orally. In part A (dose escalation) of the study a dose of 5mg/kg for all age groups will be used. Part B (optimum dose) of the study will not start until the optimum dose evaluated in part A has been identified.
Comparator(s)	Placebo given orally.
Outcome(s)	Primary outcomes: • National institute of health toolbox cognition battery score [Time Frame: Every 6 months in Part B] • National institute of health toolbox motor battery score [Time Frame: Every 6 months in Part B] • Vineland adaptive behaviour scales score [Time Frame: Every 6 months in Part B] • Oral and written language scales score [Time Frame: Every 6 months in Part B] See trial record for full list of all outcomes
Results (efficacy)	-

Results (safety)	-

Trial	NCT04117711; A phase 1-2, dose-escalating, 4-part study to evaluate the safety and pharmacokinetics of single and multiple doses of govorestat in healthy adult subjects and adult subjects with classic galactosemia **Phase I/II –** Completed **Location:** United States **Actual study completion date:** December 2021	NCT05418829; An open-label study to evaluate the long-term safety and pharmacodynamic efficacy of govorestat in adult subjects with classic galactosemia **Phase III –** Active, not recruiting **Location:** United States **Primary completion date:** December 2022
Trial Design	Randomised, parallel assignment, triple blinded.	Single group assignment, open label.
Population	N = 100 (actual). Adults, 18 to 55 years old with classic galactosemia diagnosis.	N = 7 (actual). Adults and older adults, 18 to 65 years old with classic galactosemia diagnosis, who participated in study govorestat-1001 part D and/or part D extension.
Intervention(s)	Govorestat taken orally once daily, prior to breakfast.	Govorestat 20 mg/kg once daily delivered orally.
Comparator(s)	Matching placebo administered once daily prior to breakfast.	-
Outcome(s)	Primary outcome: Number of participants with treatment-emergent adverse events. See trial record for full list of all outcomes.	Primary outcomes: • Long term safety of govorestat assessed by adverse events • Long term safety of govorestat assessed by clinical laboratory test results • Long term safety of govorestat assessed by physical examination See trial record for full list of all outcomes.
Results (efficacy)	See trial record.	-
Results (safety)	See trial record.	-

Estimated Cost

The cost of govorestat is not yet known.

Relevant Guidance

NICE Guidance

No relevant NICE guidance identified.

NHS England (Policy/Commissioning) Guidance

- NHS England. 2013/14 NHS Standard contract for paediatric neurorehabilitation. E09/S/d
- NHS England. 2013/14 NHS Standard contract for paediatric neuroscience – neurodisability. E09/S/c
- NHS England. 2013/14 NHS Standard contract for paediatric high dependency care. E07/S/B
- NHS England. 2013/14 NHS Standard contract for specialised ophthalmology (paediatric). D12/S/b

Other Guidance

- Welling L, Bernstein LE, Berry GT, Burlina AB, Eyskens F *et al.* International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. 2016.[12]
- Adam MP, Feldman J, Mirzaa GM *et al*. Classic Galactosemia and Clinical Variant Galactosemia. 2021.[13]

Additional Information

ADVANZ Pharma did not enter information about this technology onto the UK PharmaScan database; the primary source of information for UK horizon scanning organisations on new medicines in development. As a result, the NIHR Innovation Observatory has had to obtain data from other sources. UK PharmaScan is an essential tool to support effective NHS forward planning; allowing more effective decision making and faster uptake of innovative new medicines for patients who could benefit. We urge pharmaceutical companies to use UK PharmaScan so that we can be assured of up-to-date, accurate and comprehensive information on new medicines

References

1 ClinicalTrials.gov. *An Open-Label Study to Evaluate the Long-Term Safety and Pharmacodynamic Efficacy of AT-007 in Adult Subjects With Classic Galactosemia (CG). Trial ID: NCT05418829*. 2021. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/study/NCT05418829#study-overview [Accessed 15 April 2024].

2 ClinicalTrials.gov *A Sequential, Two-Part Study to Evaluate the Clinical Benefit, Safety, Pharmacokinetics, and Pharmacodynamic of AT-007 in Pediatric Subjects With Classic Galactosemia (CG). Trial ID: NCT04902781*. 2021. Status: Active, not recruiting. Available from: https://clinicaltrials.gov/study/NCT04902781#study-overview [Accessed 15 April 2024].

3 Applied Therapeutics. *Govorestat*. No publication date available. . Available from: https://www.appliedtherapeutics.com/pipeline/govorestat/ [Accessed 15 April 2024].

4 Delnoy B, Coelho AI, Rubio-Gozalbo ME. Current and Future Treatments for Classic Galactosemia. *J Pers Med*. 2021;11(2). Available from: https://doi.org/10.3390/jpm11020075.

5 Bailey E, Wang S, Saltonstall L, Perfetti R, Shendelman S. OP005: AT-007 significantly reduces toxic galactitol in ACTION-galactosemia kids - the 1st therapeutic interventional clinical trial

in children with classic galactosemia. *Genetics in Medicine*. 2022;24(3, Supplement):S336. Available from: https://www.sciencedirect.com/science/article/pii/S1098360022005731

6 ClinicalTrials.gov. *ClinicalTrials.gov: Search*. 2019. Available from: https://clinicaltrials.gov/search?intr=AT-007 [Accessed 29 April 2024].

7 European Medicines Agency. *EU/3/22/2642 - orphan designation for treatment of galactosaemia*. 2022. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-22-2642 [Accessed 29 April 2024].

8 European Medicines Agency *EU/3/23/2783 - orphan designation for treatment of Charcot-Marie-Tooth disease*. 2023. Available from: https://www.ema.europa.eu/en/medicines/human/orphan-designations/eu-3-23-2783 [Accessed 29 April 2024].

9 National Organisation for Rare Disorders. *Galactosemia*. 2016. Available from: https://rarediseases.org/rare-diseases/galactosemia/ [Accessed 16 April 2024].

10 Metabolic Support UK. *Galactosemia*. No publication date available. . Available from: https://metabolicsupportuk.org/condition/galactosaemia/#:~:text=In%20the%20UK%2C%20Galactosaemia%20is%20estimated%20to,occur%20in%201%20in%20every%2045%2C000%20births. [Accessed 16 April 2024].

11 Office for National Statistics *Hospital Admitted Patient Care Activity, 2022-23*. 2023. Available from: https://digital.nhs.uk/data-and-information/publications/statistical/hospital-admitted-patient-care-activity/2022-23 [Accessed 26 Janaury 2024].

12 Welling L, Bernstein LE, Berry GT, Burlina AB, Eyskens F, Gautschi M, et al. International clinical guideline for the management of classical galactosemia: diagnosis, treatment, and follow-up. *J Inherit Metab Dis*. 2017;40(2):171-6. Available from: https://doi.org/10.1007/s10545-016-9990-5.

13 MP A, J F, GM M. *Classic Galactosemia and Clinical Variant Galactosemia*. GeneReviews. 2000. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1518/ [Accessed 16 April 2024].

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