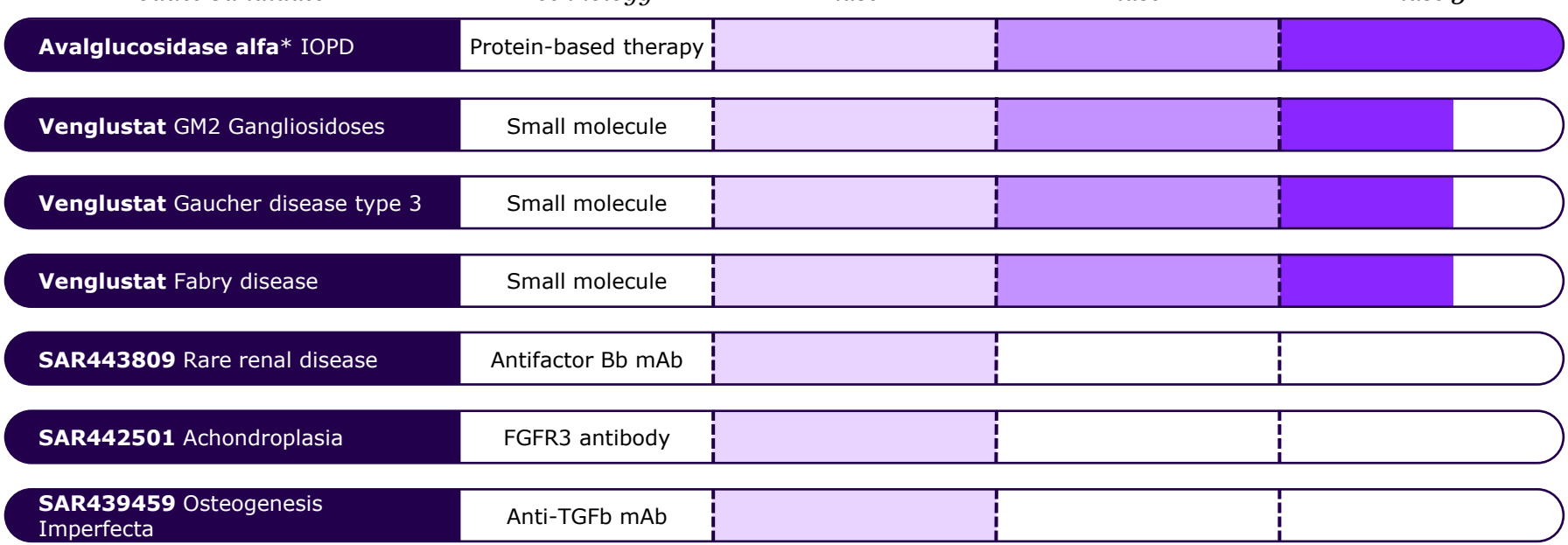
Rare Diseases Pipeline

Click on the topics for more information



***Avalglucosidase alfa has received marketing authorization in several countries for infantile-onset Pompe disease (IOPD) and/or late-onset Pompe disease (LOPD). In the United States, it was approved in August 2021 for patients with LOPD ≥1 year of age and, in the European Union (EU), it was approved in June 2022 for the treatment of patients with Pompe disease. The other agents mentioned here are investigational and have not been approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA) or any other regulatory agency worldwide for their uses under investigation.**

Bb, fragment on factor B; FGFR3, fibroblast growth factor receptor 3; IOPD, infantile-onset Pompe disease; mAb, monoclonal antibody; TGFb, transforming growth factor-β.

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Exp date: 4/10/2024

Rare Diseases Pipeline

AVALGLUCOSIDASE ALFA* IN IOPD

***Avalglucosidase alfa has received marketing authorization in several countries for infantile-onset Pompe disease (IOPD) and/or late-onset Pompe disease (LOPD). In the United States, it was approved in August 2021 for patients with LOPD ≥1 year of age and in the European Union (EU), it was approved in June 2022 for the treatment of patients with Pompe disease.**

IOPD, Infantile-onset Pompe disease.

MAT-US-2100084 v8.0 –P
Exp date: 4/10/2024

Avalglucosidase alfa*

IOPD

- Proposed mechanism of action

Proposed mechanism of action

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For illustrative purposes only. The clinical significance of this mechanism of action is under investigation.

IOPD, Infantile-onset Pompe disease.

References

Rare Diseases Pipeline

VENGLUSTAT IN GM2 GANGLIOSIDOSES

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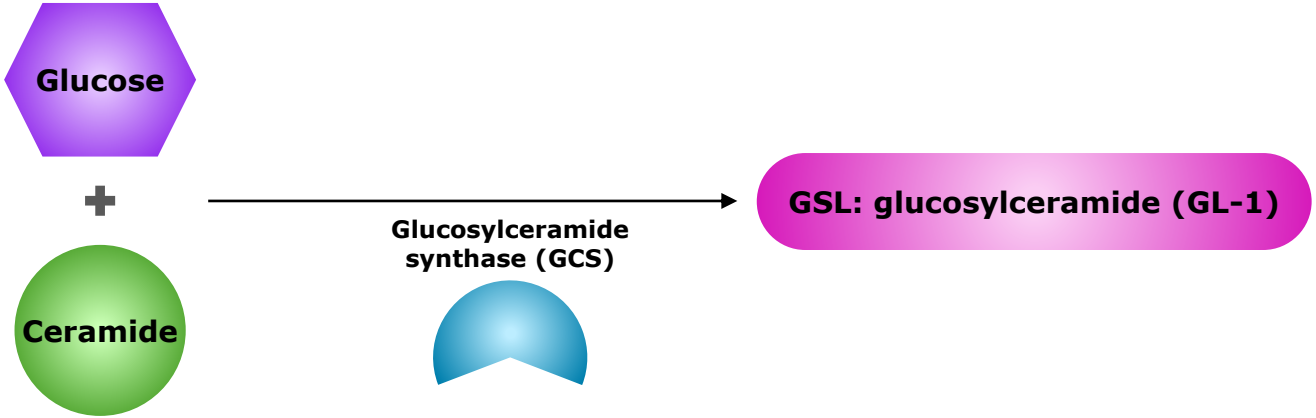
Exp date: 4/10/2024

Venglustat

GM2 gangliosidoses

- Proposed mechanism of action

Proposed mechanism of action



- One of the first steps in GSL production is catalyzed by an enzyme called glucosylceramide synthase (GCS)
- GCS converts glucose and ceramide into glucosylceramide (GL-1)
- GL-1 is a key substrate for the biosynthesis of other GSLs
- Each type of GSL is broken down by a specific lysosomal enzyme

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For illustrative purposes only. The clinical significance of this mechanism of action is under investigation.

GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

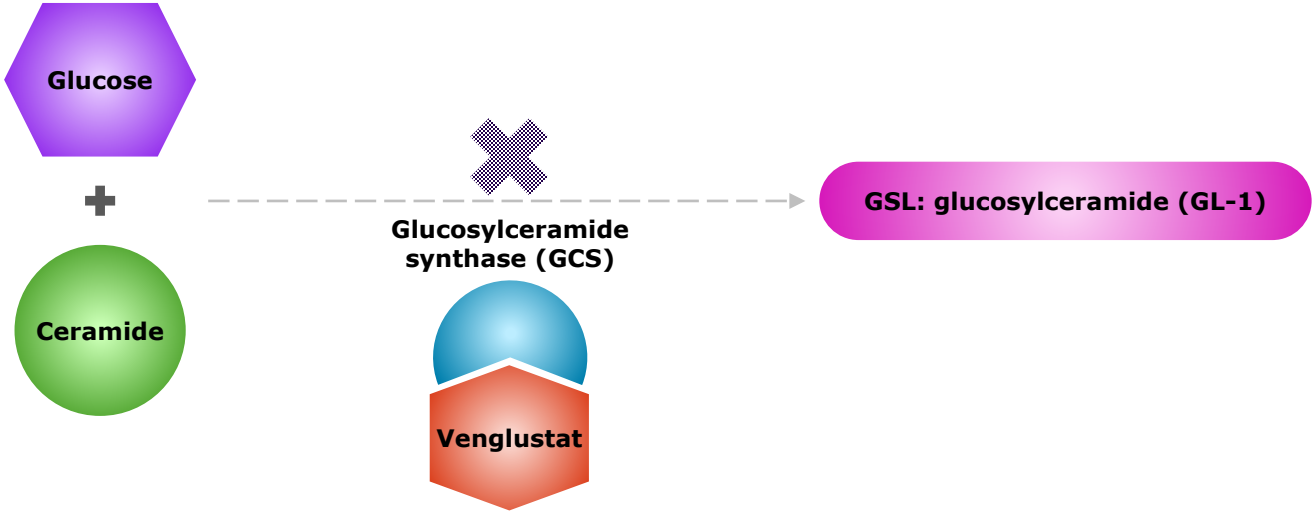
References

Venglustat

GM2 gangliosidoses

- Proposed mechanism of action

Proposed mechanism of action



- Venglustat blocks the active site of the GCS enzyme to reduce production of GL-1 and thus synthesis of GSLs implicated in LSD pathophysiology

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References

Rare Diseases Pipeline

VENGLUSTAT IN GAUCHER DISEASE TYPE 3

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MAT-US-2100084 v8.0 –P
Exp date: 4/10/2024

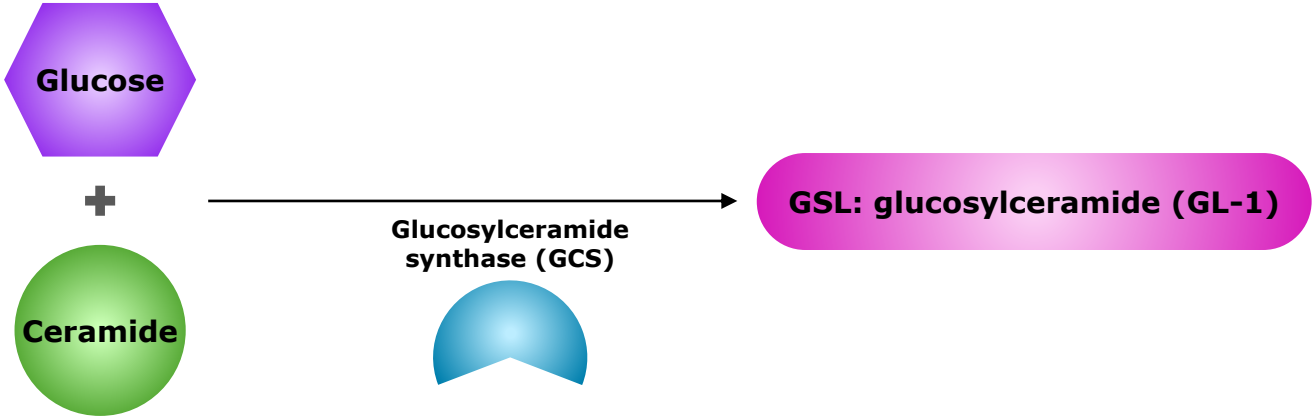
Venglustat

Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Patient population
- Enrolling countries

Proposed mechanism of action



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GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

References

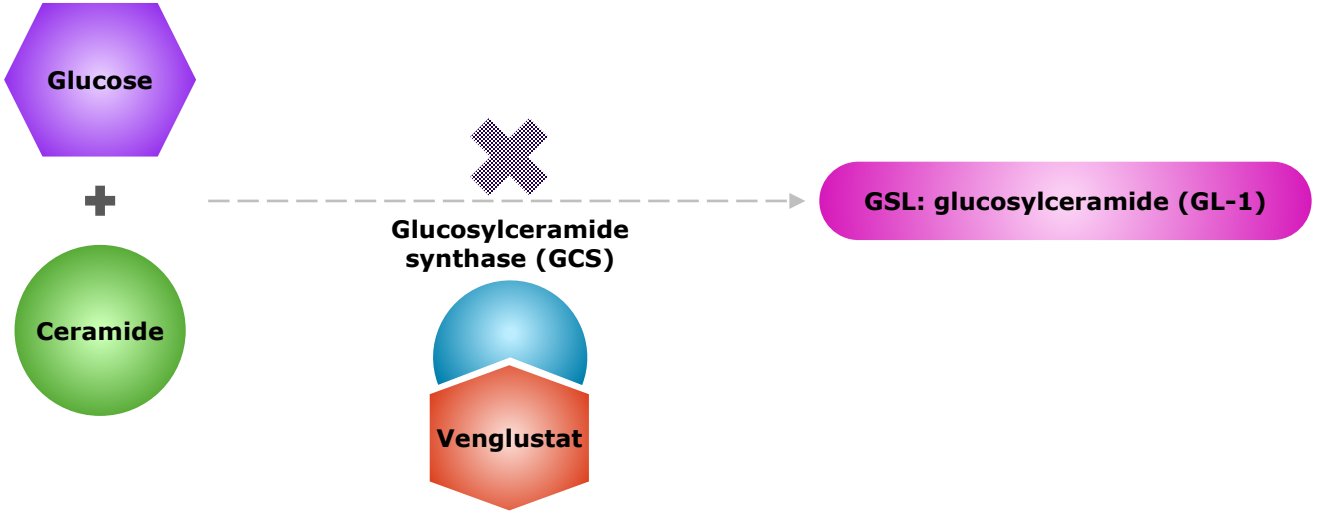
Venglustat

Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Patient population
- Enrolling countries

Proposed mechanism of action



- Venglustat blocks the active site of the GCS enzyme to reduce production of GL-1 and thus synthesis of GSLs implicated in LSD pathophysiology

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committees. 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.

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GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

References

Venglustat

Gaucher disease type 3

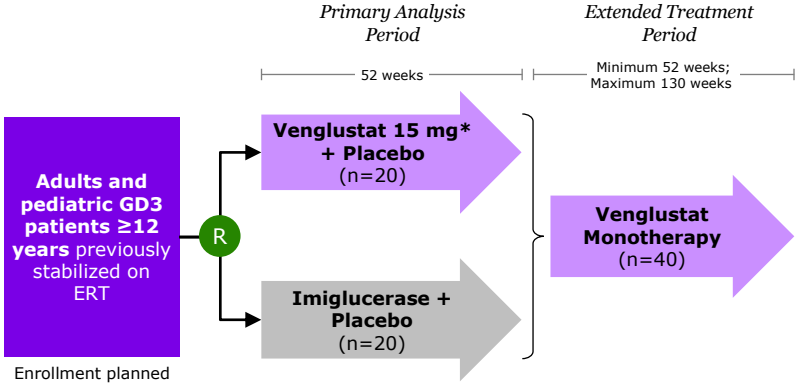
LEAP2MONO *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Patient population
- Enrolling countries

LEAP 2 MONO

Study design

Multicenter, multinational, randomized, double-blind, double-dummy, active-comparator 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)



Enrollment planned for 40 participants, stratified by age group (<18 years old vs ≥18 years old).

Rescue treatment with combination of imiglucerase and venglustat will be available for patients who experience clinically significant decline in systemic manifestations

Co-primary endpoints

Change from baseline to Week 52 in:

- Scale for Assessment and Rating of Ataxia (SARA) modified total score
- Repeatable Battery for the Assessment of Neuropsychological Status (RBANS) total scale index score

Secondary endpoints

- Changes from baseline to Week 52 in:
  - Spleen volume (MN)
  - Liver volume (MN)
  - Platelets
  - Hemoglobin
  - Score of Beck Depression Inventory II (BDI-II)
  - Lens clarity by ophthalmological examination
- Safety and tolerability

*Venglustat patients who meet prespecified criteria for decline in GD status can receive ERT rescue therapy.

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ERT, enzyme replacement therapy; GD, Gaucher disease; GL-1, glucosylceramide; lyso-GL-1, glucosylsphingosine.

References

Venglustat

Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Patient population
- Enrolling countries

LEAP 2 MONO

Patient population

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
- ≥ 3years of ERT prior to enrollment, on a stable dose for at least 6 months within therapeutic goals*
- Contraception for sexually active male participants or female patient; not pregnant or breastfeeding; no sperm donating for male participant
- Weight ≥30 kg

Exclusion criteria

- Myoclonic seizures
- Grade cortical cataract-2 or Grade posterior subcapsular cataract-2
- Invasive ventilatory support and noninvasive ventilatory support >12 hours daily
- Blood transfusion-dependence
- Esophageal varices or liver infarction or current liver enzymes or total bilirubin >2 times ULN (exception: Gilbert Syndrome diagnosis)
- Clinically significant disease, other than GD, renal insufficiency, cancer history (except basal cell carcinoma)
- Chaperone therapy within 6 months, substrate reduction therapy other than venglustat within 6 months or venglustat substrate reduction therapy prior to enrolment
- Exposure to investigational drug, including venglustat, strong or moderate inducers of CYP3A within the last 30 days or 5 half-lives from screening

*Therapeutic goals: Hemoglobin level ≥11.0 g/dL (females) and ≥12.0 g/dL (males); platelet count ≥100 000/mm^3; spleen volume <10 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.

ALT, alanine transaminase; AST, aspartate aminotransferase; ERT, enzyme replacement therapy; GD3, Gaucher disease type 3; MN, multiples of normal; SARA, Scale for Assessment and Rating of Ataxia; ULN, upper limit of normal.

References

Venglustat

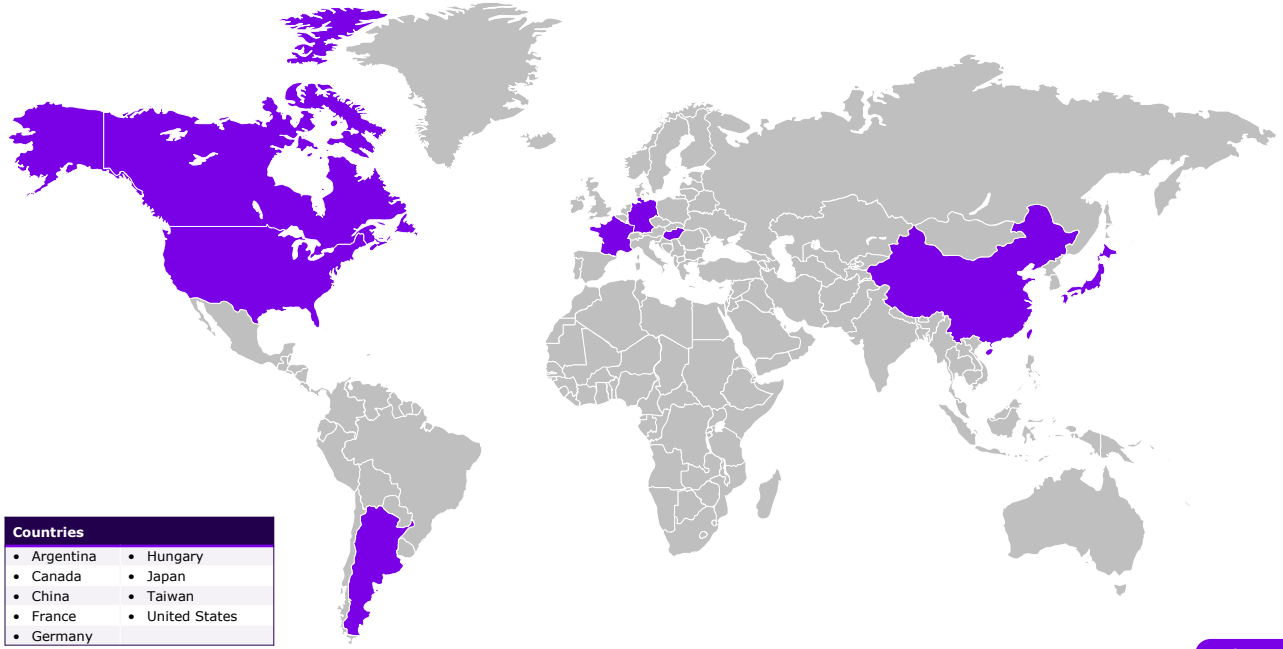
Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Patient population
- Enrolling countries

LEAP 2 MONO

Enrolling countries



Countries	
• Argentina	• Hungary
• Canada	• Japan
• China	• Taiwan
• France	• United States
• Germany	

References

MAT-US-2100084 v8.0 –P
Exp date: 4/10/2024

Rare Diseases Pipeline

VENGLUSTAT IN FABRY DISEASE

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MAT-US-2100084 v8.0 –P
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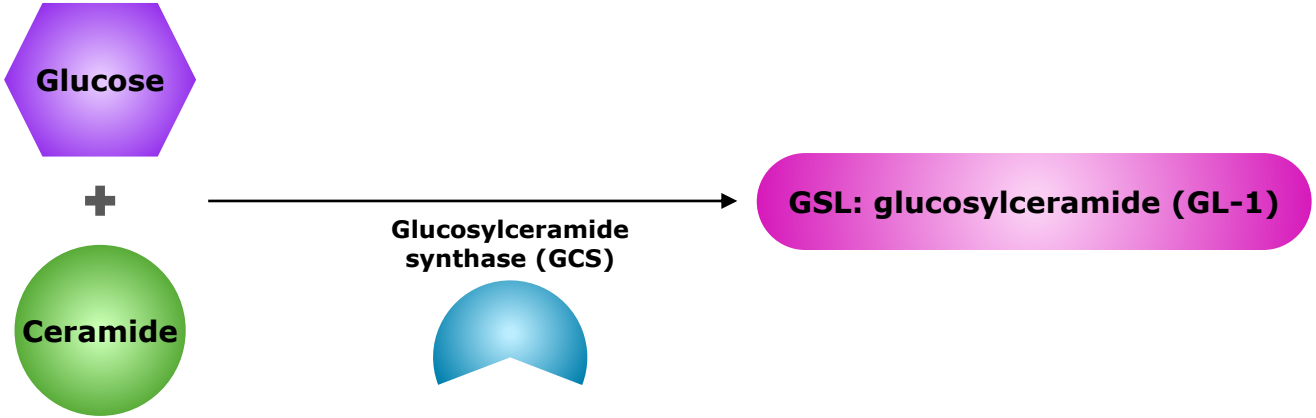
Venglustat

Fabry Disease

Proposed mechanism of action



- One of the first steps in GSL production is catalyzed by an enzyme called glucosylceramide synthase (GCS)
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- GL-1 is a key substrate for the biosynthesis of other GSLs
- Each type of GSL is broken down by a specific lysosomal enzyme

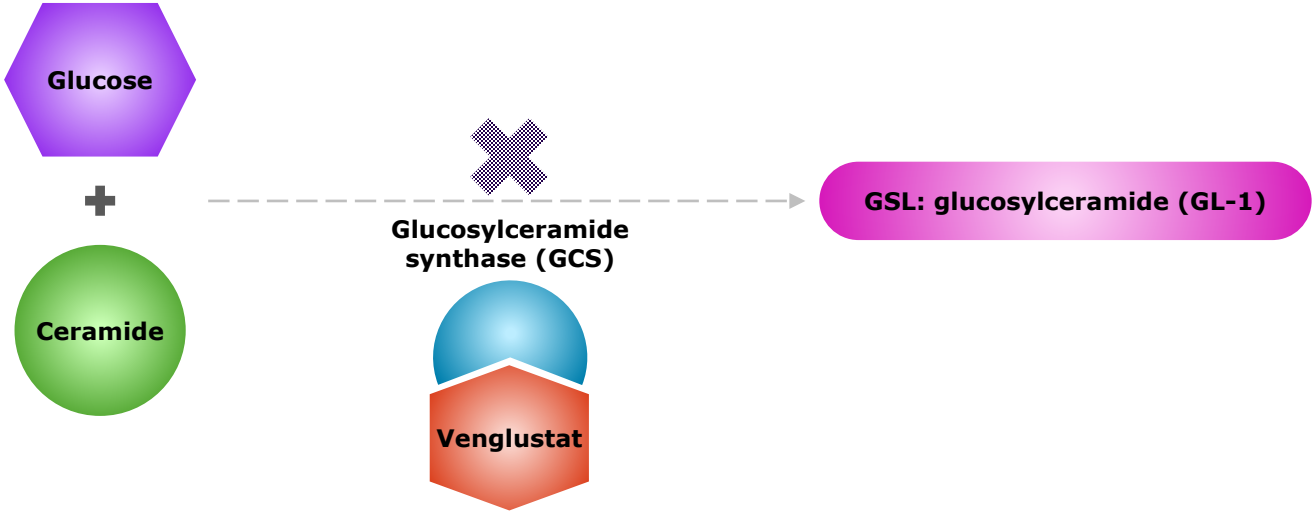
GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

References

Venglustat

Fabry Disease

Proposed mechanism of action



- Venglustat blocks the active site of the GCS enzyme to reduce production of GL-1 and thus synthesis of GSLs implicated in LSD pathophysiology

GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

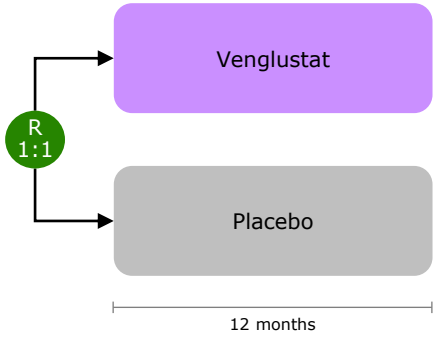
References

PERIDOT
Patient ExpeRIence in Fabry Disease On VenglustaT

Study design

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

N = 114
Treatment-naïve or untreated patients for at least 6 months ≥ 18 years of age, with Classic or late onset Fabry disease



Primary endpoint

- Percentage change from baseline at 6 and 12 months in venglustat vs placebo on the patient-defined most bothersome symptom of 3 FD-PRO items (neuropathic pain in upper extremities, neuropathic pain in lower extremities, and abdominal pain)

Secondary endpoints

- Percentage change in lyso-GL-3 from baseline to 6 and 12 months
- 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
- Proportion of responders in neuropathic or abdominal pain, as assessed by FD-PRO
- Change in the lens clarity by ophthalmological examination
- Change in Beck Depression Inventory-II (BDI-II) score
- Safety and tolerability
- Pharmacokinetics

References

FD-PRO, Fabry Disease Patient-Reported Outcome; lyso-GL-3, globotriaosylsphingosine.

PERIDOT
Patient ExpeRIence in Fabry Disease On VenglustaT

Patient population

Inclusion criteria

- Adults ≥ 18 years
- Classic or late-onset Fabry disease
- 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
- Treatment-naive, or no Fabry disease-related treatment within last 6 months

*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
- History of seizures currently requiring treatment
- Severe depression measured by Beck Depression Inventory (BDI)-II >28
- Moderate to severe hepatic impairment, history of or active hepatobiliary disease

*This list is not complete. Refer to clinicaltrials.gov for a complete list of exclusion criteria.

FD-PRO, Fabry Disease Patient-Reported Outcome; GL-3, globotriaosylceramide; lyso-GL-3, globotriaosylsphingosine.

References

Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT *(Phase 3 study)*

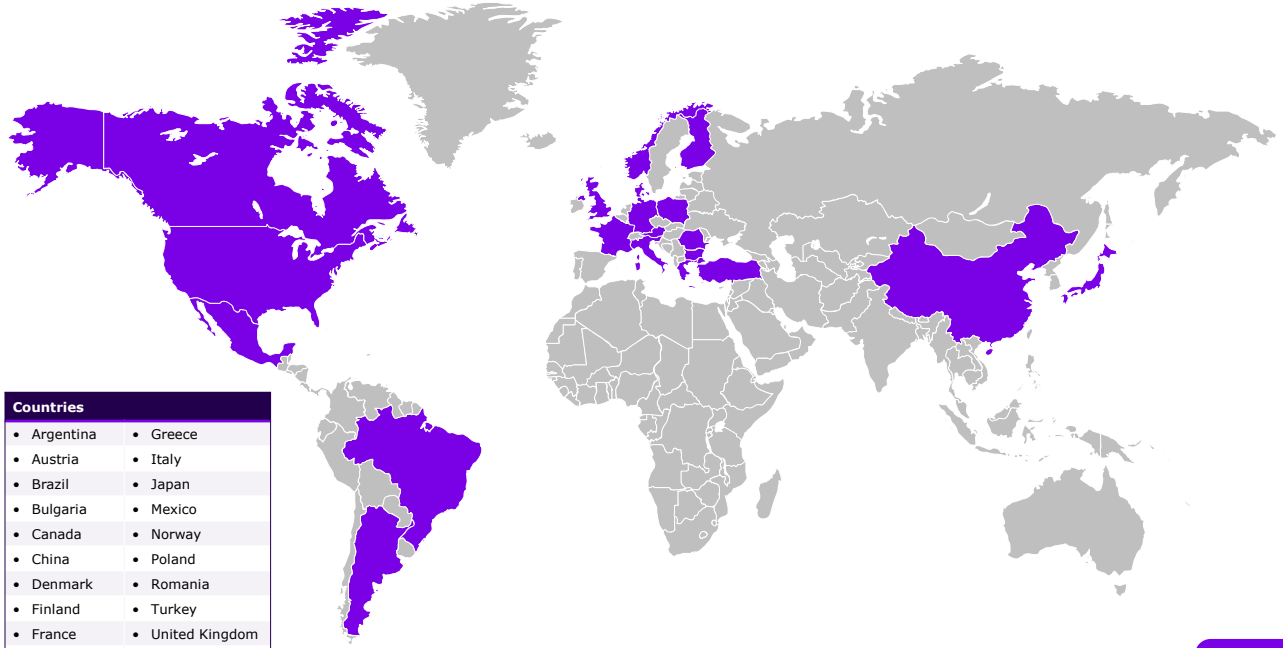
- Study design
- Patient population
- Enrolling countries

CARAT *(Phase 3 study)*

- Study design
- Patient population
- Enrolling countries

PERIDOT
Patient ExpeRIence in Fabry Disease On VenglustaT

Enrolling countries



Countries	
• Argentina	• Greece
• Austria	• Italy
• Brazil	• Japan
• Bulgaria	• Mexico
• Canada	• Norway
• China	• Poland
• Denmark	• Romania
• Finland	• Turkey
• France	• United Kingdom
• Germany	• United States

References

MAT-US-2100084 v8.0 –P
Exp date: 4/10/2024

Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT *(Phase 3 study)*

- Study design
- Patient population
- Enrolling countries

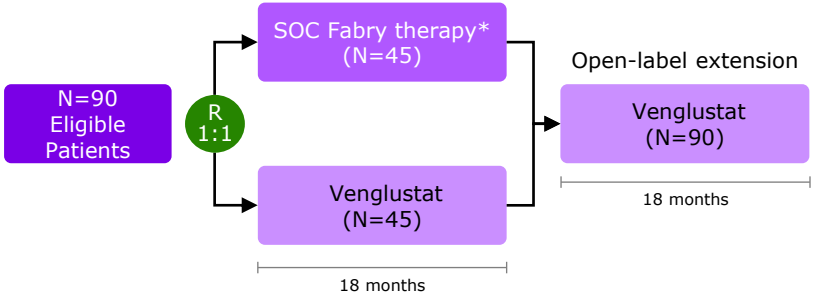
CARAT *(Phase 3 study)*

- Study design
- Patient population
- Enrolling countries

CARAT
CARdiac AssessmenT in Fabry Patients on Venglustat

Study design

International, multicenter, randomized, open label, parallel-group study to evaluate the effect of venglustat on LVMI in patients with Fabry disease and left ventricular hypertrophy



Primary endpoint

- Change from baseline to 18 months in venglustat vs standard of care on the slope of LVMI measured by cardiac MRI

Secondary endpoints

- Change from baseline to 18 months in:
  - Kidney function measured by slope of eGFR and changes in other measures of cardiac storage and function (T1 relaxation time by MRI and global longitudinal strain by echocardiogram)
  - Percent change in components of FD-PRO: tiredness and swelling in lower extremities
  - Score of Beck Depression Inventory II (BDI-II)
  - Lens clarity by ophthalmological examination
- Safety and tolerability
- Pharmacokinetics

References

*agalsidase alfa, agalsidase beta, or migalastat; 20-40% patients per therapy.

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eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; SOC: standard of care.

CARAT
CARdiac AssessmenT in Fabry Patients on Venglustat

Patient population

Inclusion criteria

- Adults 18 – 65 years of age
- Confirmed diagnosis of Fabry disease
- Treatment-naïve, or previously/currently treated with approved Fabry therapy
- Left ventricular hypertrophy

Exclusion criteria

- Advanced cardiac fibrosis by cardiac MRI
- Asymmetric hypertrophy by cardiac MRI if considered not related to Fabry disease
- Underlying medical condition that may cause or contribute to left ventricular hypertrophy
- Advanced kidney or cerebrovascular disease
- History of seizures currently requiring treatment
- Severe depression measured by Beck Depression Inventory (BDI)-II >28
- Moderate to severe hepatic impairment, history of or active hepatobiliary disease

*This list is not complete. Refer to clinicaltrials.gov for a complete list of exclusion criteria.

MRI, magnetic resonance imaging.

References

Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT *(Phase 3 study)*

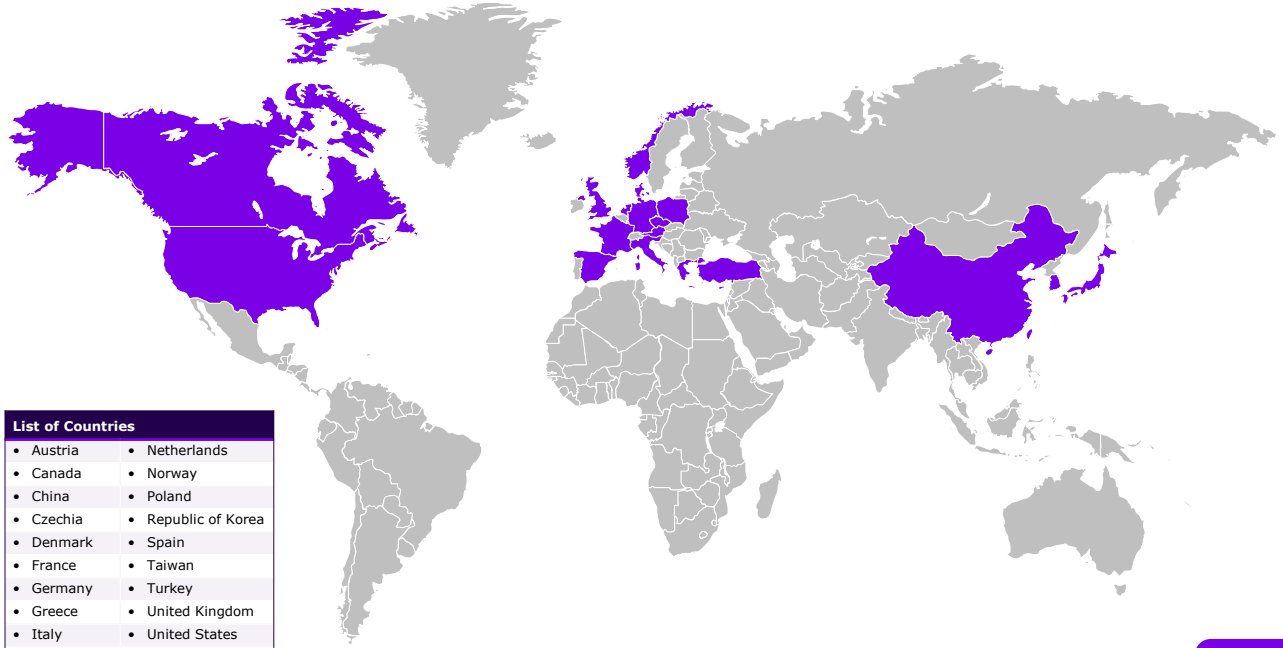
- Study design
- Patient population
- Enrolling countries

CARAT *(Phase 3 study)*

- Study design
- Patient population
- Enrolling countries

CARAT
CARdiac Assessment T in Fabry Patients on Venglustat

Enrolling countries



List of Countries	
• Austria	• Netherlands
• Canada	• Norway
• China	• Poland
• Czechia	• Republic of Korea
• Denmark	• Spain
• France	• Taiwan
• Germany	• Turkey
• Greece	• United Kingdom
• Italy	• United States
• Japan	

References

MAT-US-2100084 v8.0 –P
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