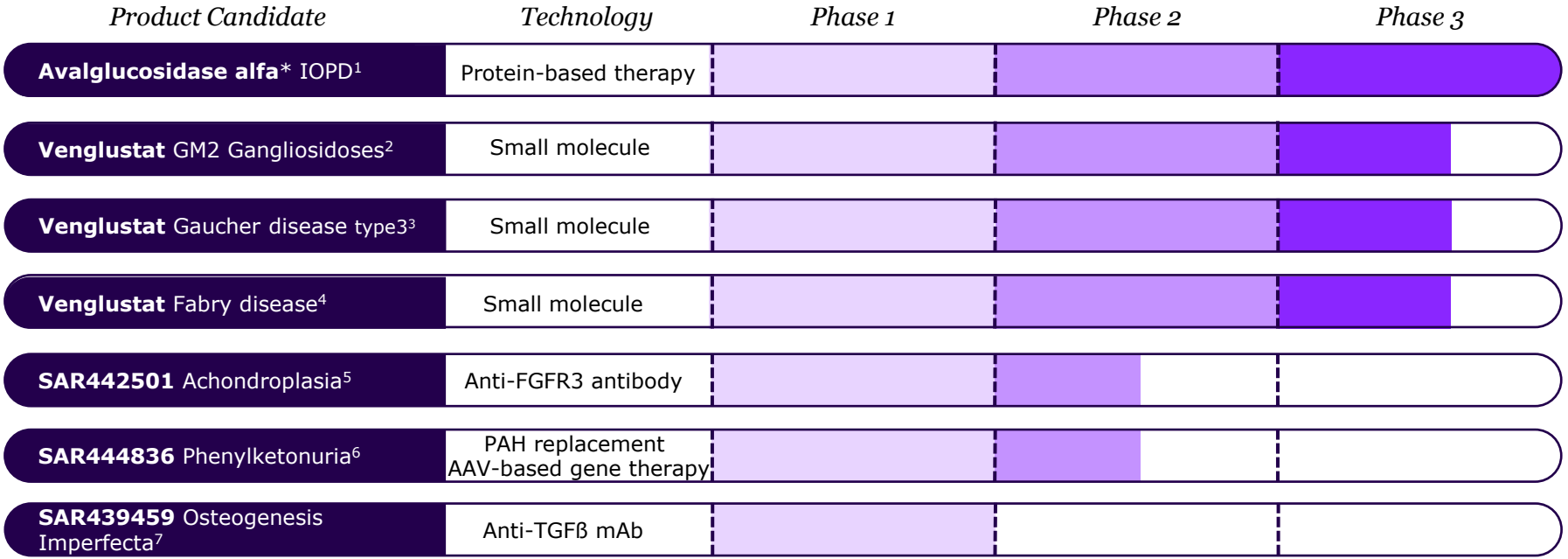
Rare Diseases Pipeline



***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.

AAV, adeno-associated virus; FGFR3, fibroblast growth factor receptor 3; IOPD, infantile-onset Pompe disease; mAb, monoclonal antibody; PAH, phenylalanine hydroxylase; TGFb, transforming growth factor-β.

Clinicaltrials.gov: 1. NCT04910776 2. NCT04221451 3. NCT05222906 4. NCT05206773, NCT05280548 5. NCT06067425 6. NCT05972629 7. NCT05231668

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IMPORTANT INFORMATION

The agents mentioned in this interactive pipeline are investigational and have not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency worldwide for the uses under investigation.
No conclusions regarding safety and efficacy should be drawn for such agents.

This information is being provided to healthcare professionals for purposes of scientific exchange and should not be considered promotional.

Rare Diseases Pipeline

AVALGLUCOSIDASE ALFA* IN IOPD

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IOPD, Infantile-onset Pompe disease.

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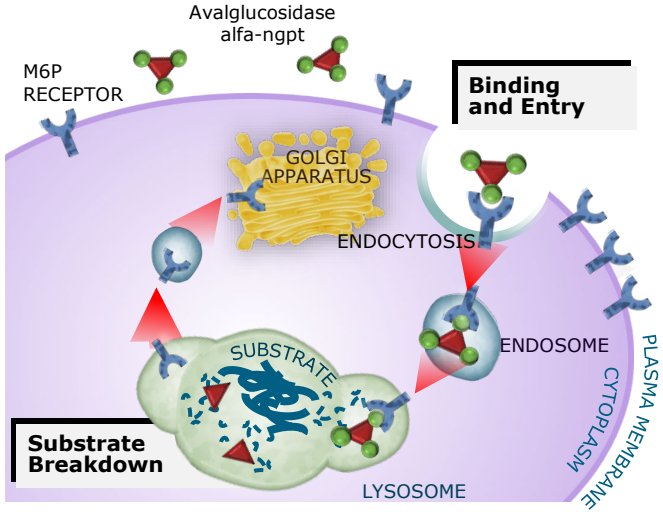
Avalglucosidase alfa*

IOPD

Baby-COMET *(Phase 3 study)*

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

Proposed mechanism of action



- Avalglucosidase alfa-ngpt is a recombinant human α-glucosidase enzyme. This was developed by increasing the mannose-6-phosphate (M6P) content through oxime chemistry to achieve greater affinity to M6P receptors.
- Endogenous lysosomal hydrolases (including GAA) are synthesized and glycosylated in the rough endoplasmic reticulum and then transferred to the Golgi apparatus.
- In the Golgi apparatus, these enzymes acquire mannose-6-phosphate (M6P) residues on their sugar chains, which are then bound by the cation-independent M6P receptor (CI-M6PR), transporting them to the lysosome.
- Avalglucosidase alfa-ngpt is internalized and transported into lysosomes upon binding to M6P receptors, resulting in increased GAA enzymatic activity.

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References

For illustrative purposes only. The clinical significance of this mechanism of action is under investigation.
IOPD, Infantile-onset Pompe disease; M6P, mannose-6-phosphate.

Avalglucosidase alfa*

IOPD

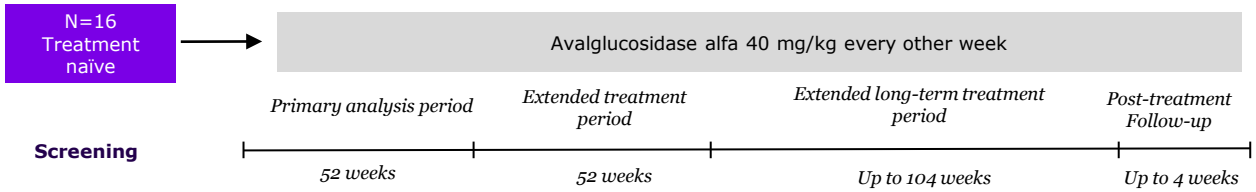
Baby-COMET *(Phase 3 study)*

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

baby COMET

Study design

Single group, multinational, multicenter, phase 3, open-label study to assess efficacy, safety, pharmacokinetic (PK), pharmacodynamics (PD) of avalglucosidase alfa in treatment-naïve patients with IOPD



Primary endpoint

- Efficacy on survival and ventilator-free survival after 52 weeks of treatment

Secondary endpoints

- Efficacy on survival and invasive ventilator-free survival at 12 and 18 months of age.
- Change in
  - LVM Z score
  - AIMS score
  - Body length and weight, head circumference Z scores
  - Urinary Hex4
- Pompe-PEDI, Motor Milestones checklist, Bayley Scale of Infant and Toddler development

AIMS-Score, abnormal involuntary movement score; IOPD, infantile-onset Pompe disease; LVM Z score, left ventricular mass Z-Scores; Pompe-PEDI, Pompe pediatric evaluation of disability inventory.

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References

Avalglucosidase alfa*

IOPD

Baby-COMET *(Phase 3 study)*

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

Patient population

Inclusion criteria

- Infants ≤ 12 months
- Established cross-reactive Immunological material (CRIM) status available
- Treatment-naïve patients with confirmed infantile-onset Pompe disease (IOPD) diagnosis
- Presence of cardiomyopathy at time of diagnosis

Exclusion criteria

- Ventilator use, major congenital abnormality
- Previous use of enzyme replacement therapy (ERT) or any other Pompe disease specific therapy

CRIM, cross-reactive immunological material; ERT, enzyme replacement; IOPD, Infantile-onset Pompe disease.

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Avalglucosidase alfa*

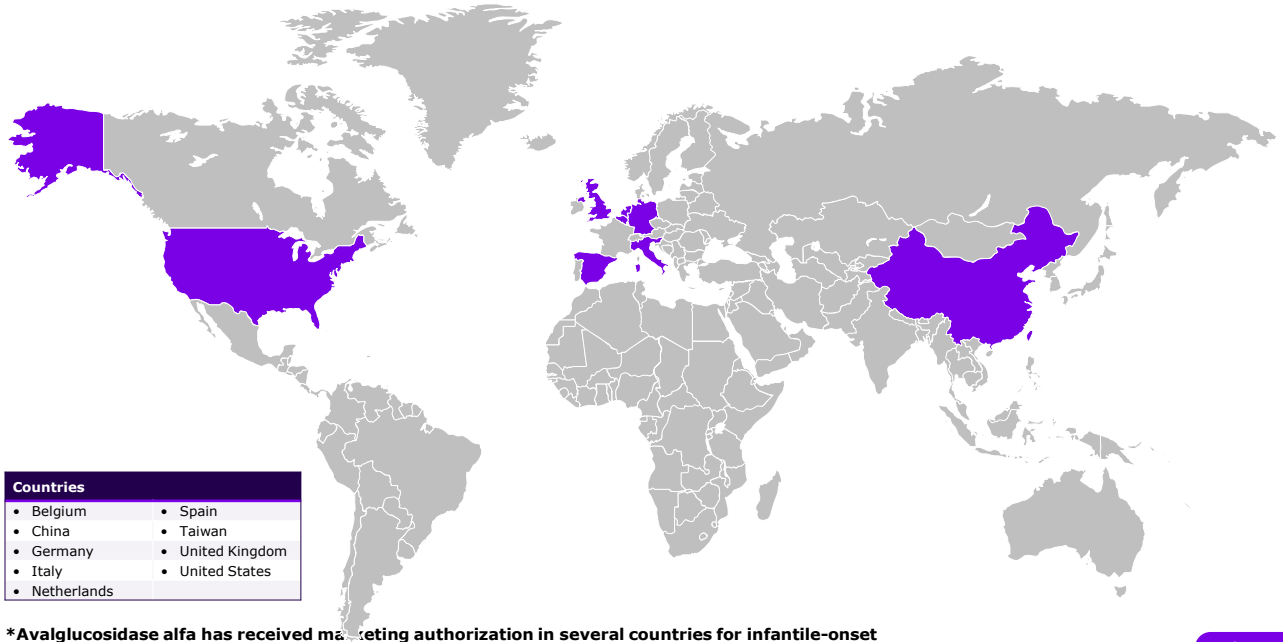
IOPD

Baby-COMET *(Phase 3 study)*

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

baby COMET

Participating countries



Countries	
• Belgium	• Spain
• China	• Taiwan
• Germany	• United Kingdom
• Italy	• United States
• Netherlands	

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References

Rare Diseases Pipeline

VENGLUSTAT IN GM2 GANGLIOSIDOSES

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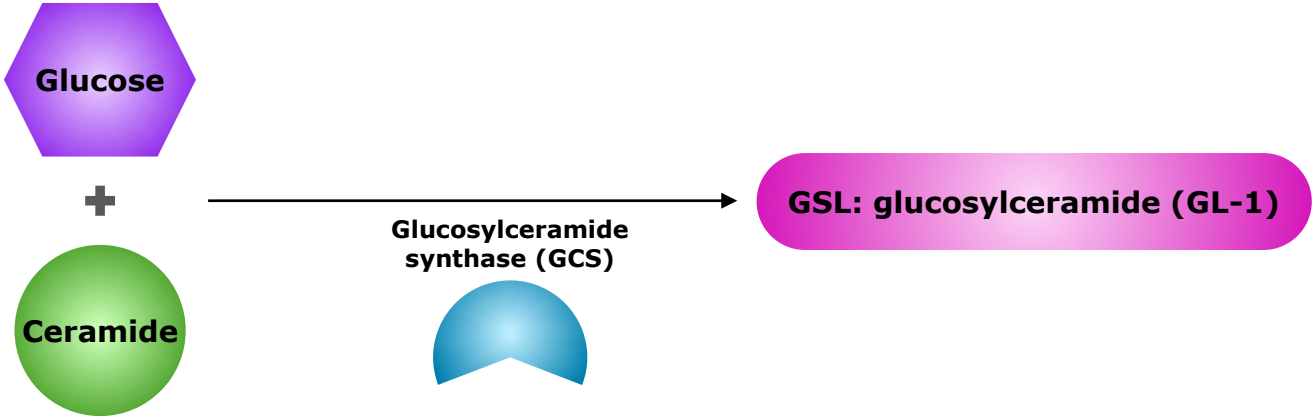
Venglustat

GM2 gangliosidoses

AMETHIST *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Study endpoints
- Patient population
- Participating countries

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

For illustrative purposes only. The clinical significance of this mechanism of action is under investigation.
GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

References

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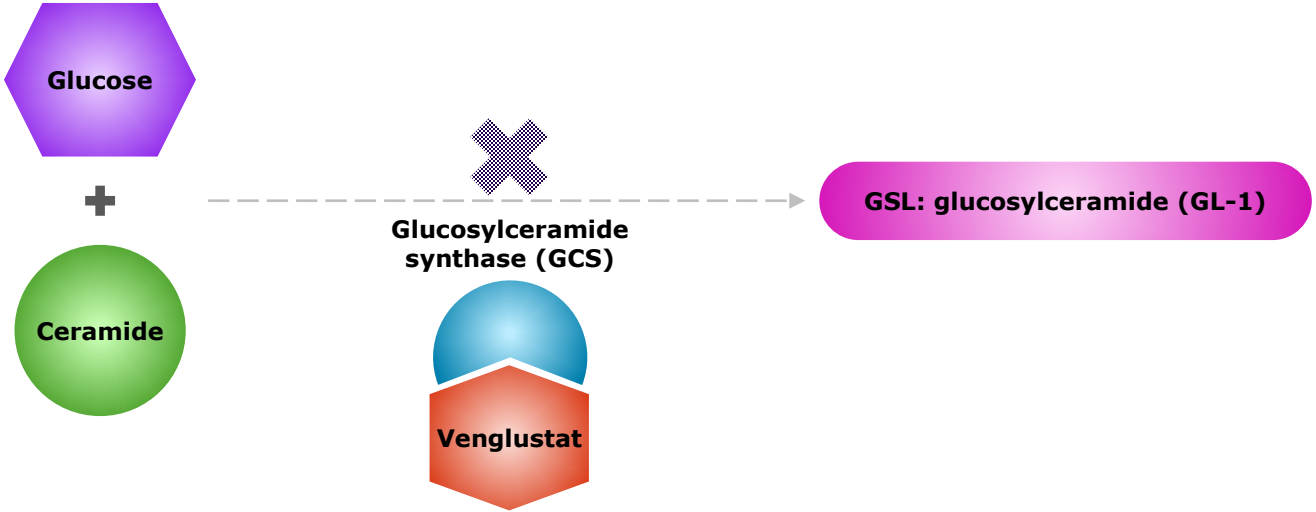
Venglustat

GM2 gangliosidoses

AMETHIST *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Study endpoints
- Patient population
- Participating 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

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Venglustat

GM2 gangliosidoses

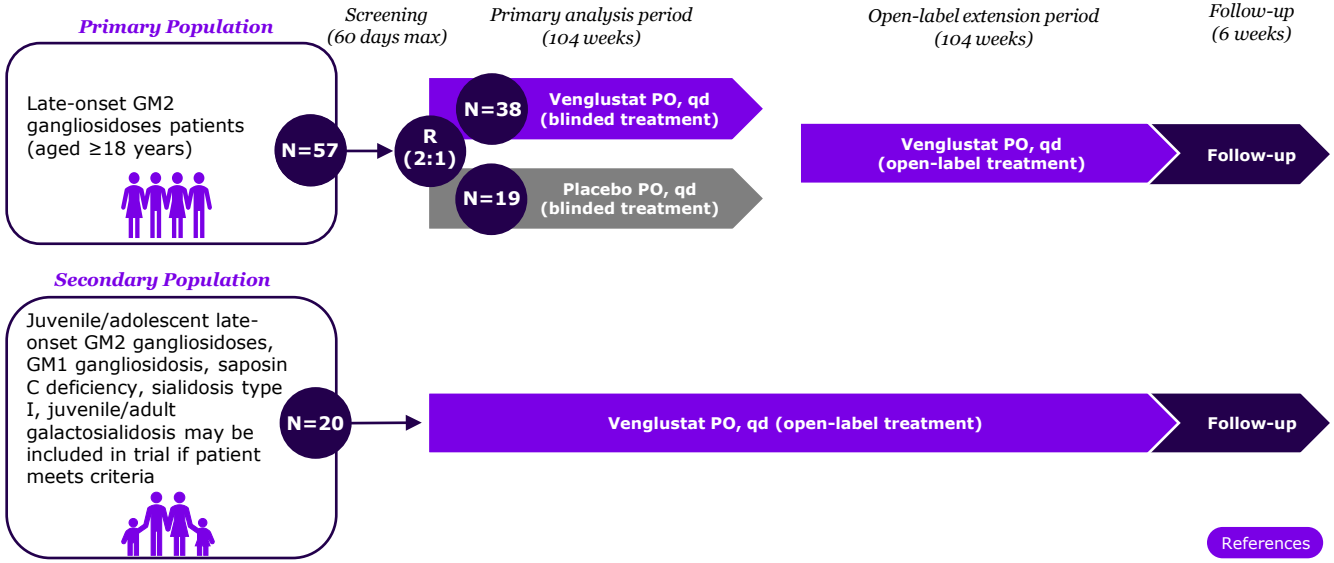
AMETHIST *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Study endpoints
- Patient population
- Participating countries

AMETHIST

Study design

A multicenter, multinational, randomized, double-blind, placebo-controlled trial to assess the efficacy, pharmacodynamics, pharmacokinetics, safety, and tolerability of venglustat in patients with late-onset GM2 gangliosidoses (late-onset Tay-Sachs disease, late-onset Sandhoff disease; referred to as the primary population) combined with an open-label arm in juvenile/adolescent late-onset GM2 gangliosidoses and other related rare diseases* (referred to as the secondary population).



References

PO, orally; qd, once daily; R, randomization; W, week.

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Venglustat

GM2 gangliosidoses

AMETHIST *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Study endpoints
- Patient population
- Participating countries

AMETHIST

Study endpoints

Primary endpoints

Primary Population (co-primary endpoints):

- Percent change in CSF GM2 biomarker from baseline to Week 104.
- Annualized rate of change in the 9-HPT from baseline to Week 104.

Secondary population:

- Plasma and CSF GL-1 biomarker and a pathway specific biomarker will be assessed as follows:
  - Disease
    - GM2 gangliosidosis
    - GM1 gangliosidosis
    - Sialidosis Type 1
    - Galactosialidosis
    - Saposin C Deficiency
  - Biomarker
    - GL-1, GM2
    - GL-1, GM1
    - GL-1, GM2, GM3
    - GL-1, GM1, GM3
    - GL-1 only
- Additional plasma and CSF biomarkers may include but are not limited to: lipidomics, glycoprotein nonmetastatic protein B, neurofilament.

Secondary endpoints

Primary Population:

Change from baseline to Week 104:

- In 25FWT (in participants able to walk at baseline).
- The neurological examination of the FARS.

Absolute change in CSF GM2 biomarker from baseline to week 104

Secondary population:

Change from baseline to Week 104:

- Annualized rate of change in the 9-HPT.
- In 25FWT (in participants able to walk at baseline).
- In the neurological examination of the FARS.

Primary and Secondary Populations:

- Safety and tolerability in overall population, changes from baseline to Week 104:
  - Assessment of AEs and concomitant medication
  - Neurological and ophthalmological examinations
  - Vital signs
  - Clinical laboratory evaluations including hematology, biochemistry, urinalysis, and serology
  - ECG
- Plasma and CSF venglustat concentrations over the study duration and plasma PK parameters (when applicable)

25FWT, 25-foot walk test, 9-HPT, 9-hole peg test; AE, adverse events; ECG, electrocardiogram; FARS, Friedreich Ataxia Rating Scale.

References

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Venglustat

GM2 gangliosidoses

AMETHIST *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Study endpoints
- Patient population
- Participating countries

AMETHIST

Patient population

Inclusion criteria

Primary population

- Adult participants
- Diagnosis of late-onset GM2 gangliosidoses (Tay-Sachs disease and Sandhoff disease caused by genetic β-hexosaminidase deficiency resulting from pathogenic variants in the *HEXA* or *HEXB* genes)
- Ability to perform the 9-HPT at the screening visit in ≤240 seconds for the 2 consecutive trials of the dominant hand and the 2 consecutive trials of the nondominant hand

Secondary population

- For the juvenile and adolescent, weight ≥10 kg
- Age ≥2 to <18 years with diagnosis of late-onset GM2 gangliosidoses or age ≥2 years with diagnosis of GM1 gangliosidosis, saposin C deficiency, sialidosis type 1 or juvenile/adult galactosialidosis

Exclusion criteria

- Features of Tay-Sachs or Sandhoff disease not caused by β-hexosaminidase deficiency resulting from pathogenic variants in *HEXA* or *HEXB* and/or without clinical features
- World Health Organization (WHO) grade ≥2 cortical cataract or a grade ≥2 posterior subcapsular cataract; patients with nuclear cataracts will be accepted
- Previous treatment with substrate reduction therapy within 3 months or strong or moderate inducers or inhibitors of CYP3A4 within 14 days or 5 half-lives prior to enrollment.
- Use of investigational medicinal product within 3 months or 5 half-lives, whichever is longer, before study enrollment

A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT04221451).
9-HPT, 9-hole peg test.

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Venglustat

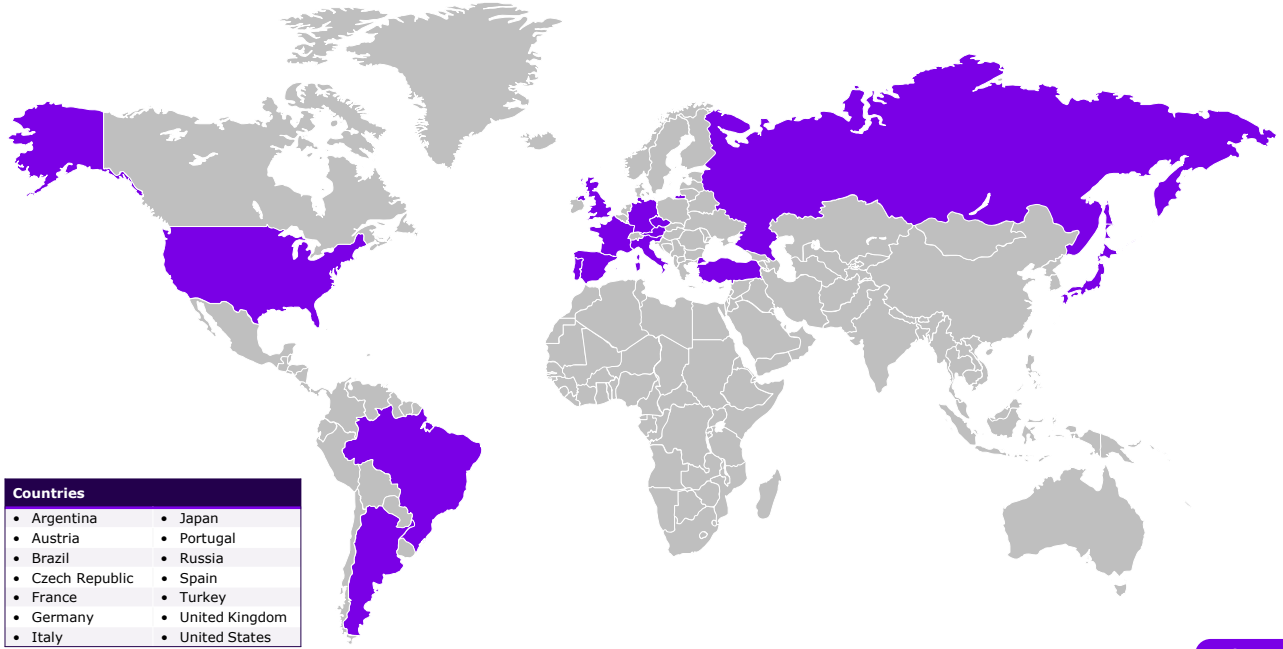
GM2 gangliosidoses

AMETHIST *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Study endpoints
- Patient population
- Participating countries

AMETHIST

Participating countries



Countries	
• Argentina	• Japan
• Austria	• Portugal
• Brazil	• Russia
• Czech Republic	• Spain
• France	• Turkey
• Germany	• United Kingdom
• Italy	• United States

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Rare Diseases Pipeline

VENGLUSTAT IN GAUCHER DISEASE TYPE 3

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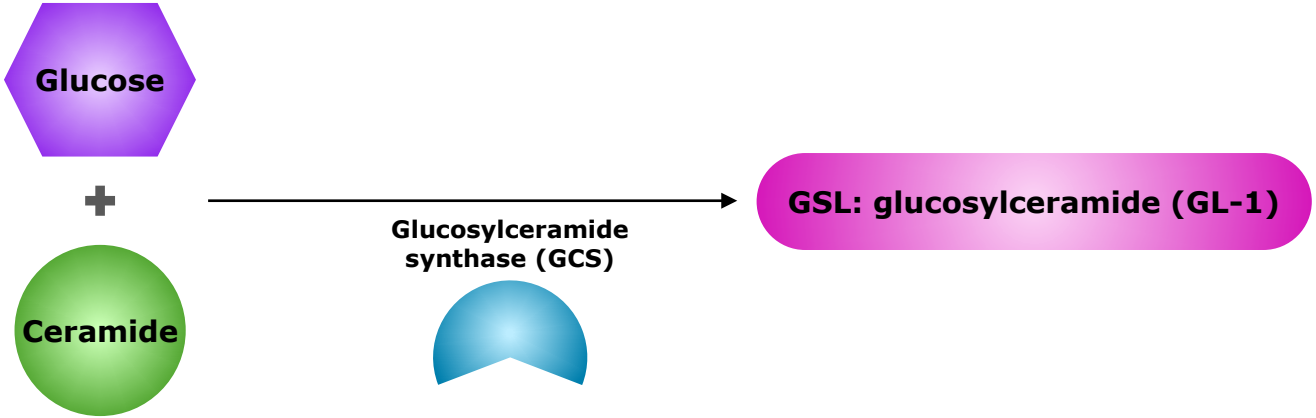
Venglustat

Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

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

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)
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- Each type of GSL is broken down by a specific lysosomal enzyme

For illustrative purposes only. The clinical significance of this mechanism of action is under investigation.
GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids.

References

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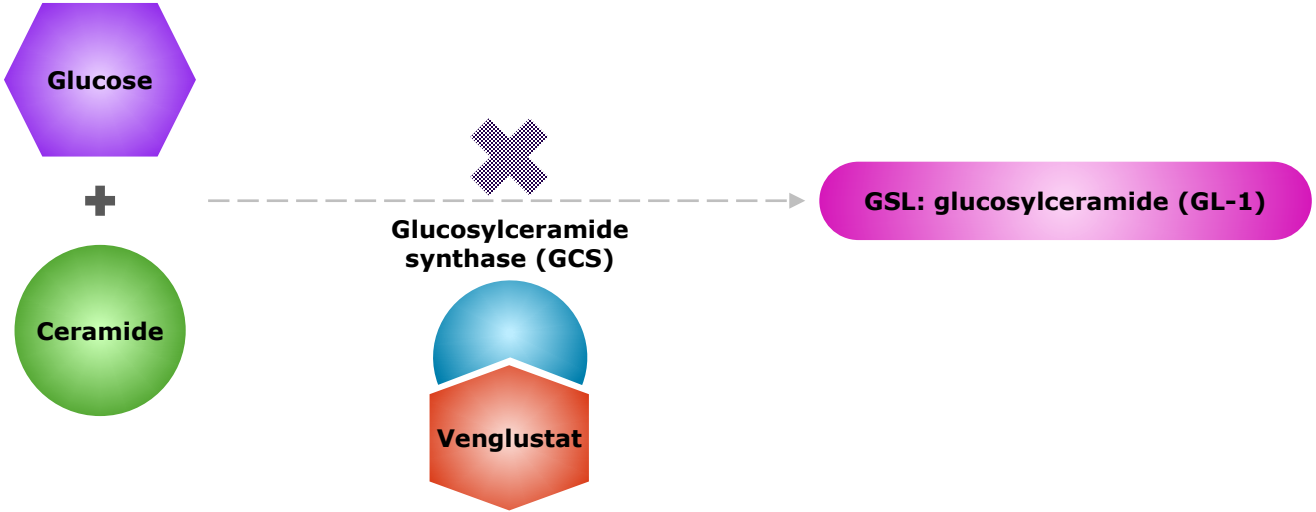
Venglustat

Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

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

Proposed mechanism of action



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References

Venglustat

Gaucher disease type 3

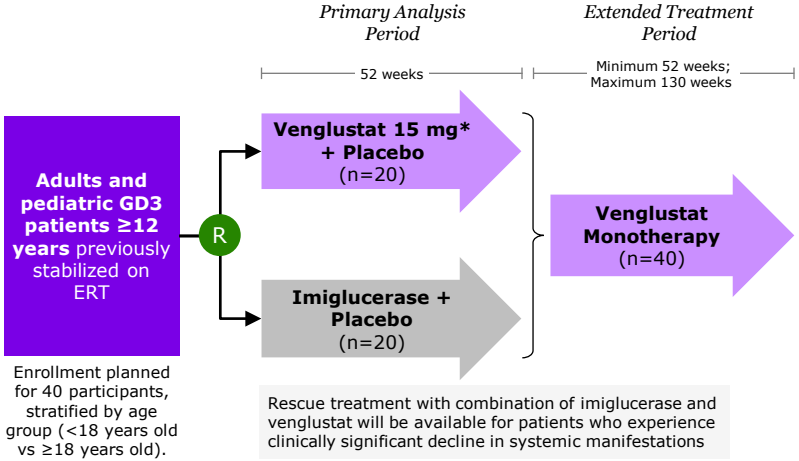
LEAP2MONO *(Phase 3 study)*

- Proposed mechanism of action
- Study design
- Patient population
- Participating 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)



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

References

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Venglustat

Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

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

LEAP 2 MONO

Patient population

Inclusion criteria

- 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

- Progressive myoclonic epiliepsy
- Invasive ventilatory support and noninvasive ventilatory support >12 hours daily
- Blood transfusion-dependence
- Esophageal varices or liver infarction or current liver enzymes (ALT/AST) 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 enrollment
- Exposure to investigational drug, including venglustat within the last 30 days, strong or moderate inducers or inhibitors of CYP3A within the last 14 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

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Venglustat

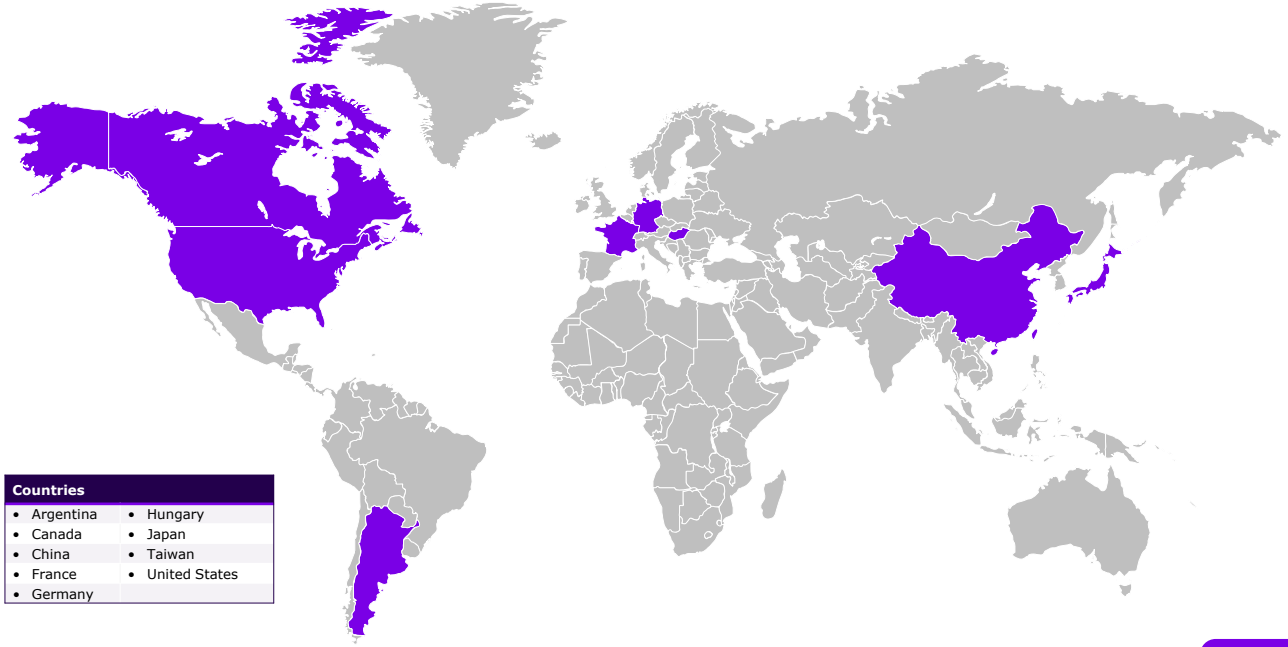
Gaucher disease type 3

LEAP2MONO *(Phase 3 study)*

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

LEAP 2 MONO

Participating countries



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

References

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Rare Diseases Pipeline

VENGLUSTAT IN FABRY DISEASE

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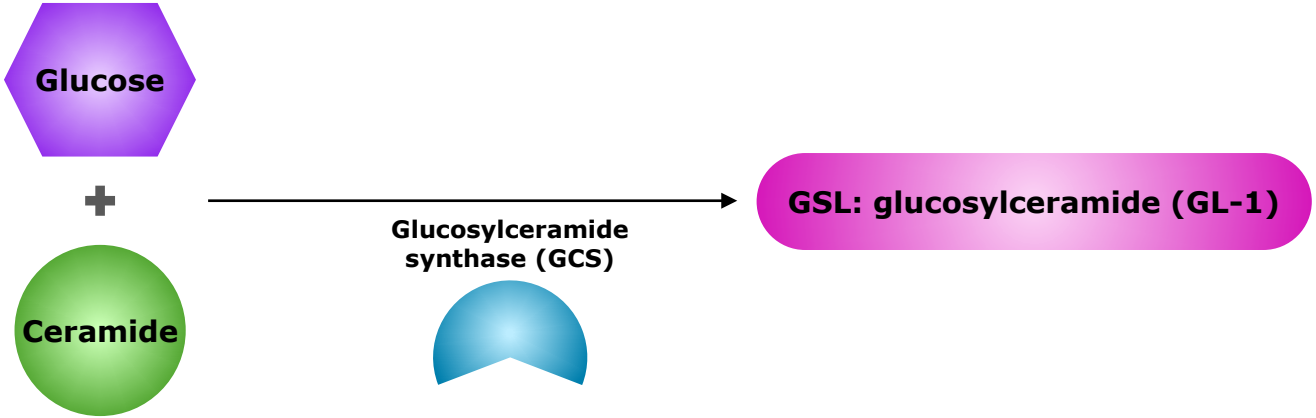
Venglustat

Fabry Disease

Proposed mechanism of action



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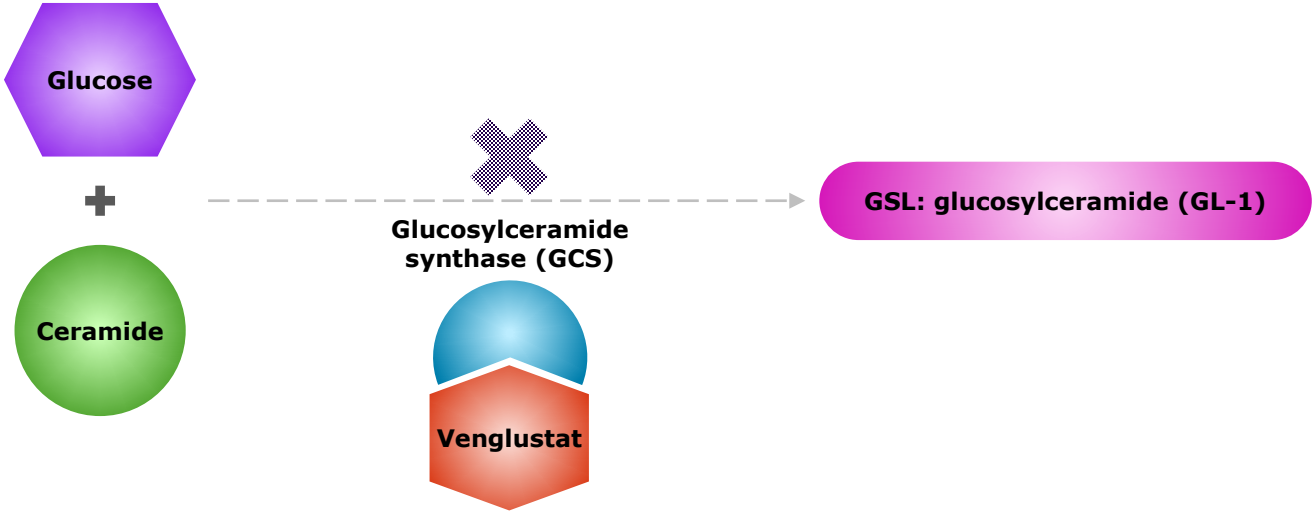
References

Venglustat

Fabry Disease

Proposed mechanism of action



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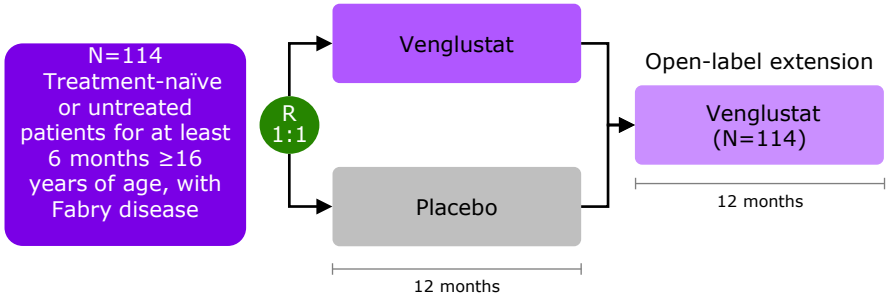
References

MAT-US-2100084 v10.0 – P
Expiration date: 01/29/2025

PERIDOT
Patient ExpeRIence in Fabry Disease On VenglustaT

Study design

Randomized, double-blind, placebo-controlled study to characterize the efficacy and safety of venglustat on neuropathic and abdominal pain in adult patients with Fabry disease who are treatment-naïve or untreated for at least 6 months



Primary endpoint

- Percentage change from baseline to 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 from baseline to 6 and 12 months in:
- Plasma lyso-GL-3
- Frequency of rescue pain medication use
- Percentage of days with diarrhea
- 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

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

References

PERIDOT
Patient ExpeRIence in Fabry Disease On VenglustaT

Patient population

Inclusion criteria

- Participants ≥16 years with a confirmed diagnosis of 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 at screening
- Treatment-naive, or no Fabry disease-related treatment within last 6 months

Exclusion criteria

- 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

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

Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT *(Phase 3 study)*

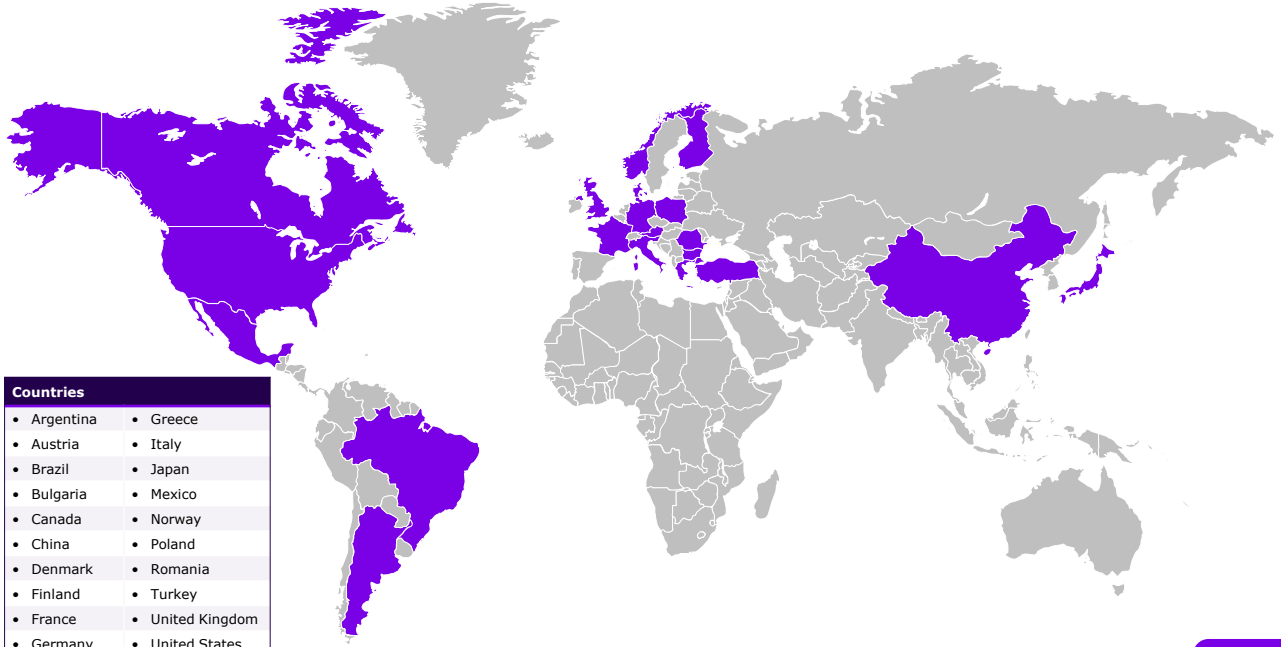
- Study design
- Patient population
- Enrolling countries

CARAT *(Phase 3 study)*

- Study design
- Patient population
- Participating countries

PERIDOT
Patient ExpeRIence in Fabry Disease On VenglustaT

Participating 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

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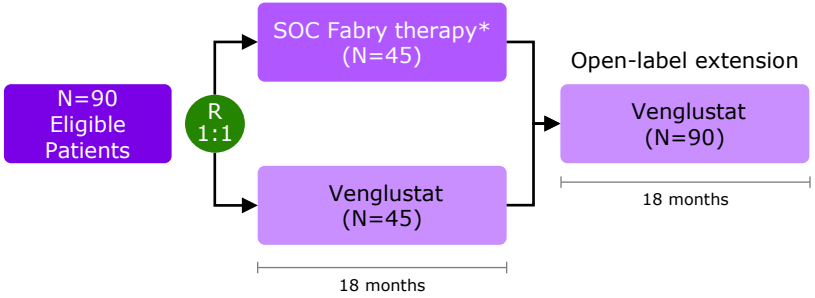
Expiration date: 01/29/2025

CARAT
CARdiac AssessmenT in Fabry Patients on Venglustat

Study design

Randomized, open-label, parallel-group study to evaluate the effect of venglustat compared with standard of care on LVMI in patients with Fabry disease and left ventricular hypertrophy



*agalsidase alfa, agalsidase beta, or migalastat; 20-40% patients per therapy.
eGFR, estimated glomerular filtration rate; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; SOC: standard of care.

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 cardiac 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

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Patient population

Inclusion criteria

- Adults 18 – 65 years of age with a 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
- Estimated glomerular filtration rate <45 mL/min/1.73m2
- 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

MRI, magnetic resonance imaging

Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT *(Phase 3 study)*

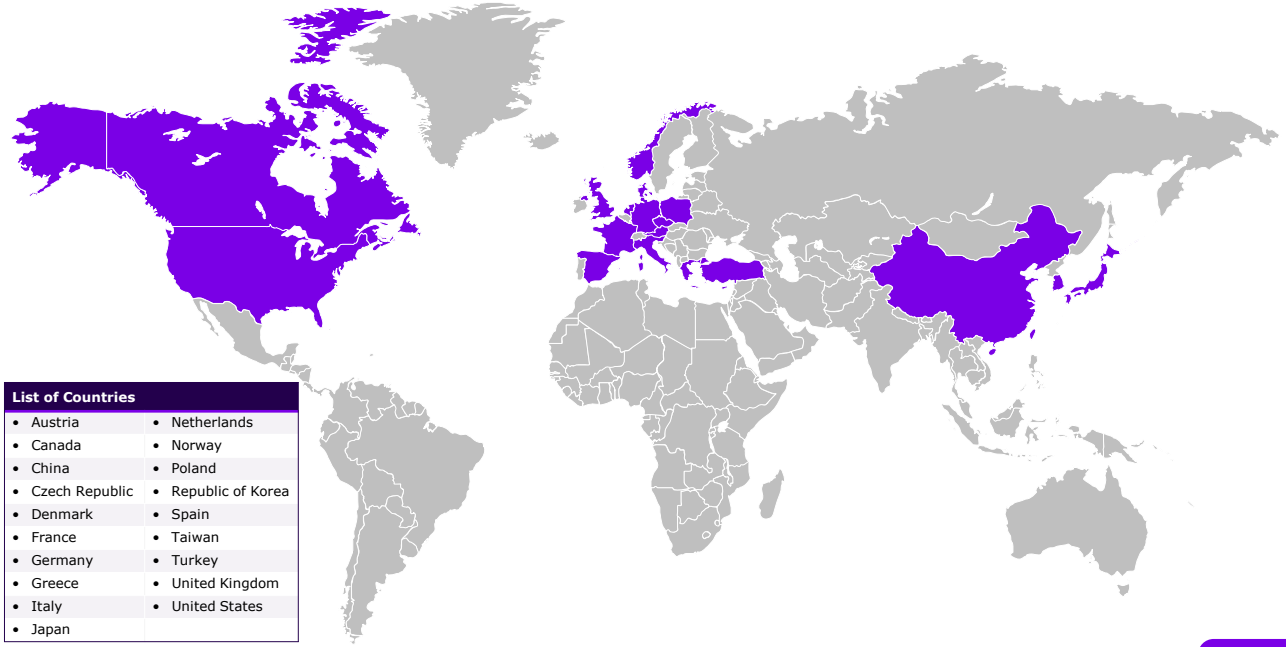
- Study design
- Patient population
- Enrolling countries

CARAT *(Phase 3 study)*

- Study design
- Patient population
- Participating countries

CARAT
CARdiac AssessmenT in Fabry Patients on Venglustat

Participating countries



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

References

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Rare Diseases Pipeline

SAR442501 IN ACHONDROPLASIA

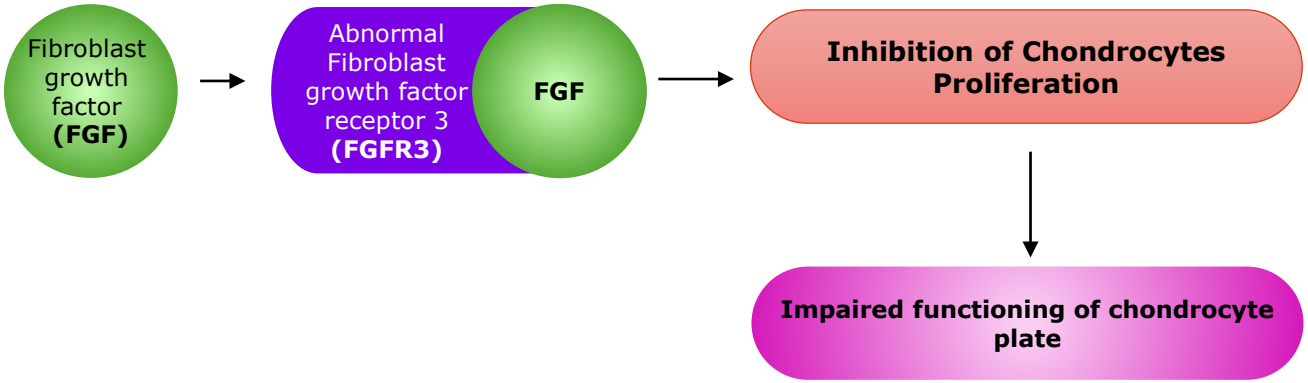
*SAR442501 is investigational and has not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency worldwide for the uses under investigation. No conclusions regarding safety and efficacy should be drawn for such agents.

MAT-US-2100084 v10.0 – P
Expiration date: 01/29/2025

SAR442501

Achondroplasia

Proposed mechanism of action



- Fibroblast growth factor receptor 3 (FGFR3) is a key negative regulator of endochondral ossification
- Pathogenic variants of the *FGFR3* gene lead to overactivation of the FGFR3 receptor and result in abnormal growth and development of the skeleton
- Pathogenic variants in *FGFR3* stop the proliferation of chondrocytes and impair the functioning of growth plate chondrocytes

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

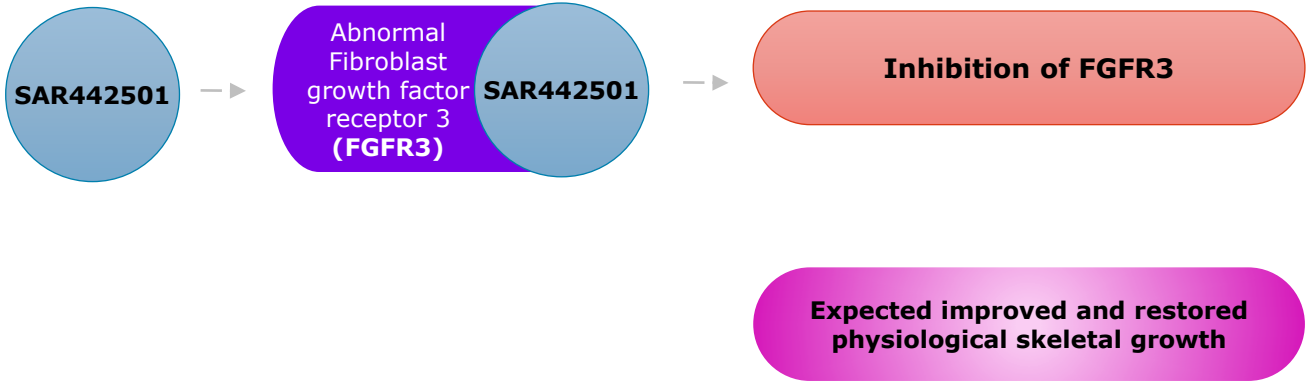
FGF, fibroblast growth factor; FGFR3, fibroblast growth factor receptor 3.

References

SAR442501

Achondroplasia

Proposed mechanism of action



- SAR442501 is a monoclonal antibody derivative that binds only to the FGFR3 receptor, limiting its activity
- May help to improve and restore physiological skeletal growth

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

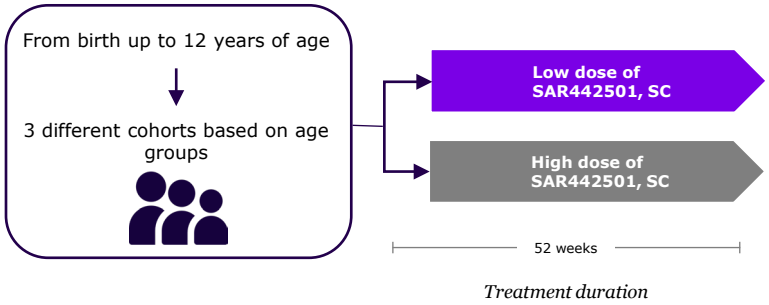
FGFR3, fibroblast growth factor receptor 3.

References

upreACH

Study design

Global, open-label, multicenter study to evaluate safety, tolerability and efficacy of SAR442501 in children with achondroplasia



Treatment duration

Primary endpoint

Number of participants reporting with adverse events, serious adverse events, and adverse events of special interest during the treatment-emergent period from baseline to week 52

Secondary endpoints

Change in:

- Annualized growth velocity (AGV)
- Body proportions
- Foramen magnum surface area in participants younger than age 3
- Effect on pain, fatigue and health-related QoL measures
- Immunogenicity, pharmacokinetics, and pharmacodynamics

QoL, quality of life; SC, subcutaneous.

References

sanofi

upreACH

Patient population

Inclusion criteria

- Confirmed pathogenic variant in the *FGFR3* gene
- Pediatric participants: from birth up to age 12 years

Exclusion criteria

- Hypochondroplasia or short stature condition other than ACH
- Received any dose of medications or investigational product within 6 months of enrollment, including human growth hormone, intended to affect stature or body proportions of participants
- History of growth plate closure

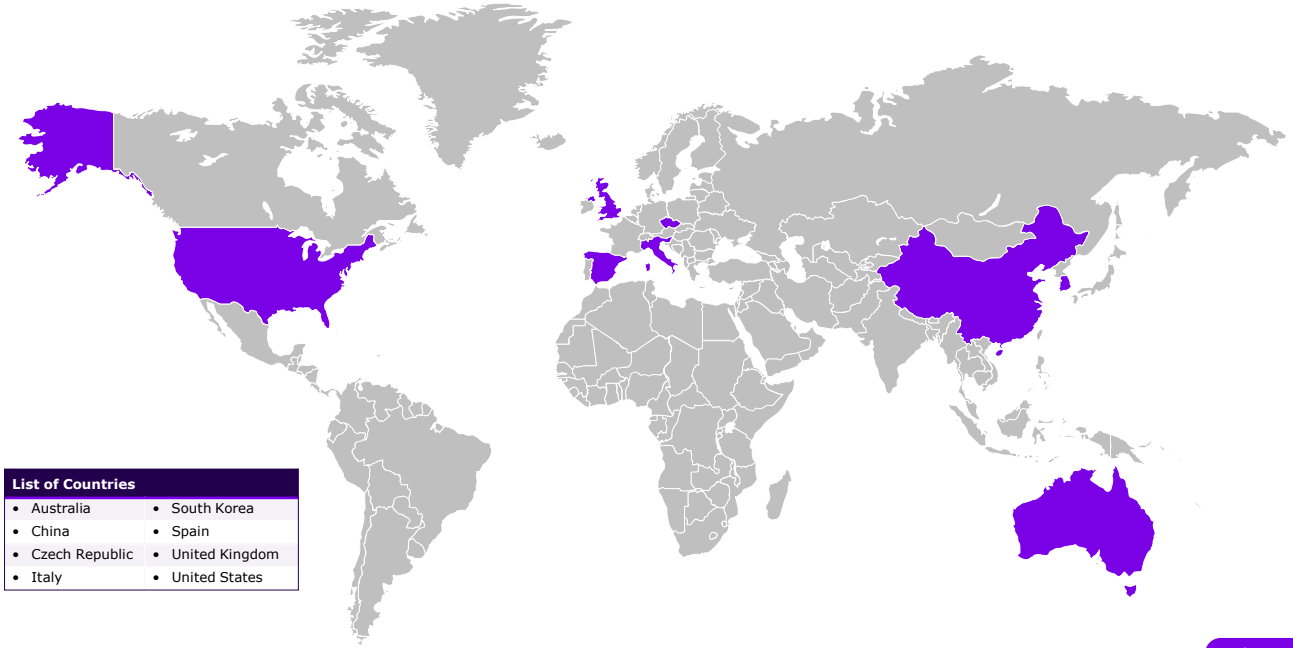
A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT06067425).

ACH, achondroplasia; FGFR3, fibroblast growth factor receptor 3.

References

upreACH

Participating countries



List of Countries	
• Australia	• South Korea
• China	• Spain
• Czech Republic	• United Kingdom
• Italy	• United States

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References

Rare Diseases Pipeline

SAR444836 PHENYLKETONURIA

*SAR444836 is investigational and has not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency worldwide for the uses under investigation. No conclusions regarding safety and efficacy should be drawn for such agents.

MAT-US-2100084 v10.0 – P
Expiration date: 01/29/2025

SAR444836

Phenylketonuria

- Proposed mechanism of action
- *(Phase 1/Phase 2)*
- Study design
- Patient population
- Participating countries

Proposed mechanism of action

SAR444836 is an adeno-associated virus (AAV) vector-mediated gene transfer of human *PAH* designed to target the liver and introduce a functional copy of the human *PAH* gene into hepatocytes.

PAH – phenylalanine hydroxylase.

References

SAR444836

Phenylketonuria

(Phase 2 study)

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

Study design

A Phase 1/ 2 single-arm, open-label study to evaluate the safety, tolerability, and efficacy of SAR444836, an adeno-associated virus vector-mediated gene transfer of human phenylalanine hydroxylase in adult patients with phenylketonuria

Participants will receive a one-time intravenous (IV) administration of SAR444836, an adeno-associated virus (AAV) vector-mediated **gene transfer** of human phenylalanine hydroxylase (PAH).

The study is constituted of 2 separate parts: a dose escalation part, and a dose expansion part where subsequent participants will be administered a safe and effective dose level identified during the dose escalation part.

The study duration will be approximately 102 weeks (approximately 2 years) for each participant and includes a 6-week screening phase and 96-week follow-up period after SAR444836 administration.

Primary endpoint

Incidence of treatment-emergent adverse events from baseline to Week 96

Secondary endpoint

Change from baseline to Week 96 and measured at Week 24 and Week 96 or End of Study following SAR444836 administration:

- Proportion of participants with sustained plasma level of Phe without dietary Phe restriction:
  - Phe <360 µmol/L for ≥4 weeks
  - Phe <120 µmol/L for ≥4 weeks
  - Phe <600 µmol/L for ≥4 weeks
- Plasma level of Phe
- Dietary protein intake
- Plasma Phe: Tyr ratio
- Number of participants with abnormal laboratory chemistry values
- Assessment of the duration of viral vector shedding of SAR444836 in sampling of urine, saliva, and semen at 4-week intervals

Phe, phenylalanine; Tyr, tyrosine

References

SAR444836

Phenylketonuria

Proposed mechanism of action

(Phase 1/Phase 2)

- Study design
- Patient population
- Participating countries

Patient population

Inclusion criteria

- Adult males, and females (non-child bearing potential), 18-65 years of age at the time of informed consent.
- Diagnosis of PKU due to PAH deficiency
- At least one plasma Phe value ≥ 600 µmol/L in the 24 months while on Phe restricted diet therapy. Two plasma Phe values ≥ 600 µmol/L drawn at least 72 hours apart during the screening period while on Phe restricted diet in the absence of an acute illness.
- Ability and willingness to maintain their present diet for the duration of the trial, unless otherwise directed as per protocol
- Body mass index ≤ 35 kg/m^2
- Willingness to use effective methods of contraception.

Exclusion criteria

- Presence of neutralizing antibodies against the AAV SNY001 capsid
- Abnormal liver function evidenced by ALT > 1.5 times ULN, AST > 1.5 times ULN, alkaline phosphatase >1.5 times ULN, total and direct bilirubin > 1.5 times ULN (except documented history or laboratory evidence or Gilbert's Disease)
- Any significant underlying liver disease or documented diagnoses, indicative of portal hypertension, splenomegaly or hepatic encephalopathy
- Serum albumin measurement below the lower limit of normal of the laboratory or AST-to-Platelet Ratio Index > 1.0
- Serum creatinine > 1.5 times ULN
- Hemoglobin A1c > 6.5% or fasting glucose > 126 mg/dL
- HIV; or active or prior hepatitis B virus (HBV) infection or active hepatitis C virus (HCV) infection

ALT, alanine aminotransferase; AST, aspartate transaminase ;HBV, hepatitis B virus; HCV, hepatitis C virus; HBsAg, hepatitis B surface antigen; HIV; human immunodeficiency viruses; PKU, Phenylketonuria, ULN, upper limit normal.

References

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Expiration date: 01/29/2025

SAR444836

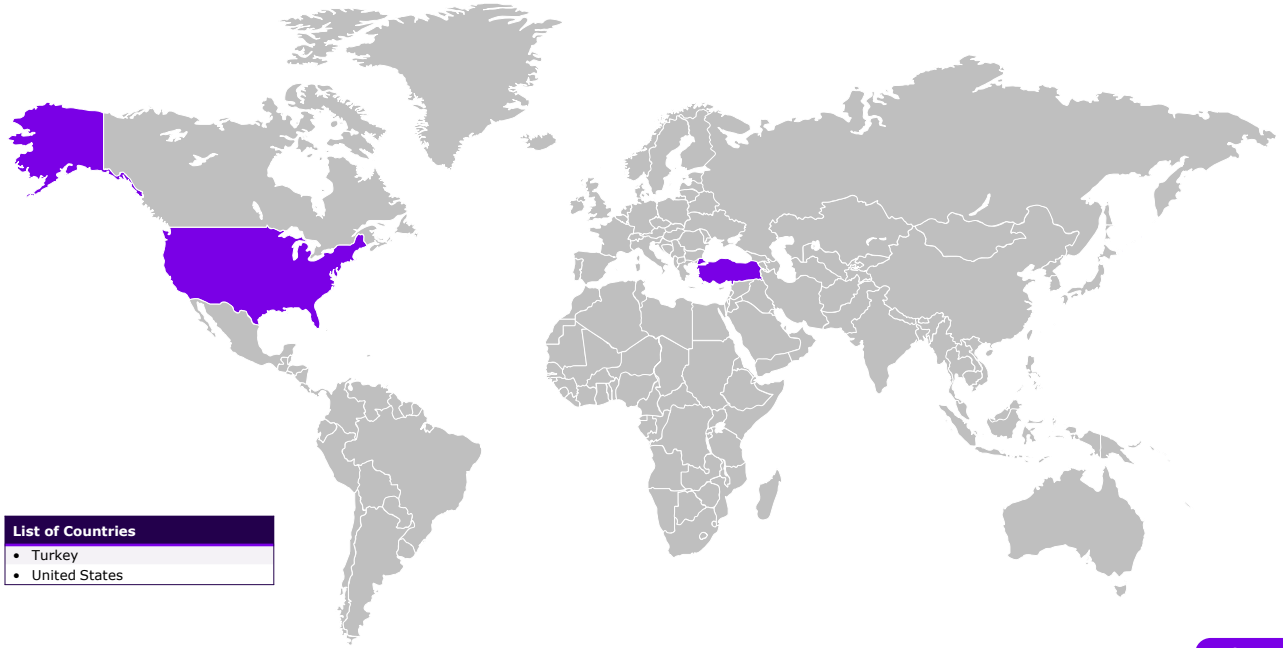
Phenylketonuria

Proposed mechanism of action

(Phase 1/Phase 2)

- Study design
- Patient population
- Participating countries

Participating countries



List of Countries
• Turkey
• United States

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References

Rare Diseases Pipeline

SAR439459 OSTEOGENESIS IMPERFECTA

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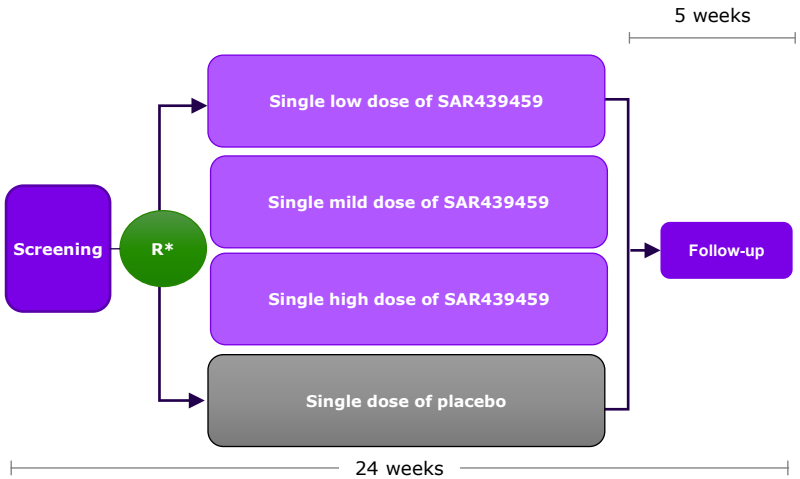
MAT-US-2100084 v10.0 – P
Expiration date: 01/29/2025

POISE 1

Study design

Global, randomized, double-blind, placebo-controlled phase 1 trial evaluating the safety of a single dose of SAR439459 in patients with osteogenesis imperfecta



Primary endpoint

Number of participants with adverse events or treatment-emergent adverse events from baseline to Week 24

Secondary endpoint

- Percent change from baseline to Week 24 in bone mineral density
- Change from baseline to Week 24 in:
  - PK parameters (AUC, C_{max}, t_{max})
  - Titer of anti-SAR439459 antibodies (if detected)

AUC, area under the curve; PK, pharmacokinetics; QoL, quality of life.

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References

POISE 1

Patient population

Inclusion criteria

- Adult patients aged 18 to 65 years
- Confirmed diagnosis of osteogenesis imperfecta Types I or IV with a previously documented pathogenic variant in the *COL1A1* or *COL1A2* genes.
- Experienced ≥ 2 bone fractures since the age of 18 or at least 1 bone fraction in the last 10 years.

Exclusion criteria

- Installed rods or metal hardware that could impact bone mineral density evaluation of the lumbar spine.
- Moderate to severe scoliosis assessed by Cobb angle.
- Postmenopausal women.
- Treatment with any therapy for osteogenesis imperfecta within 6 months prior to study baseline assessment.
- Any known bleeding disorder, any major surgery within the last 28 days prior to receiving SAR439459, or elective surgery or invasive procedure anticipated within 6 months after receiving SAR439459.
- History of skin cancer.
- Clinically significant cardiac valvular disorder or symptomatic heart failure.

COL1A1, collagen type 1 alpha 1 gene; COL1A2, collagen type 1 alpha 2 gene.

References

SAR439459

Osteogenesis Imperfecta

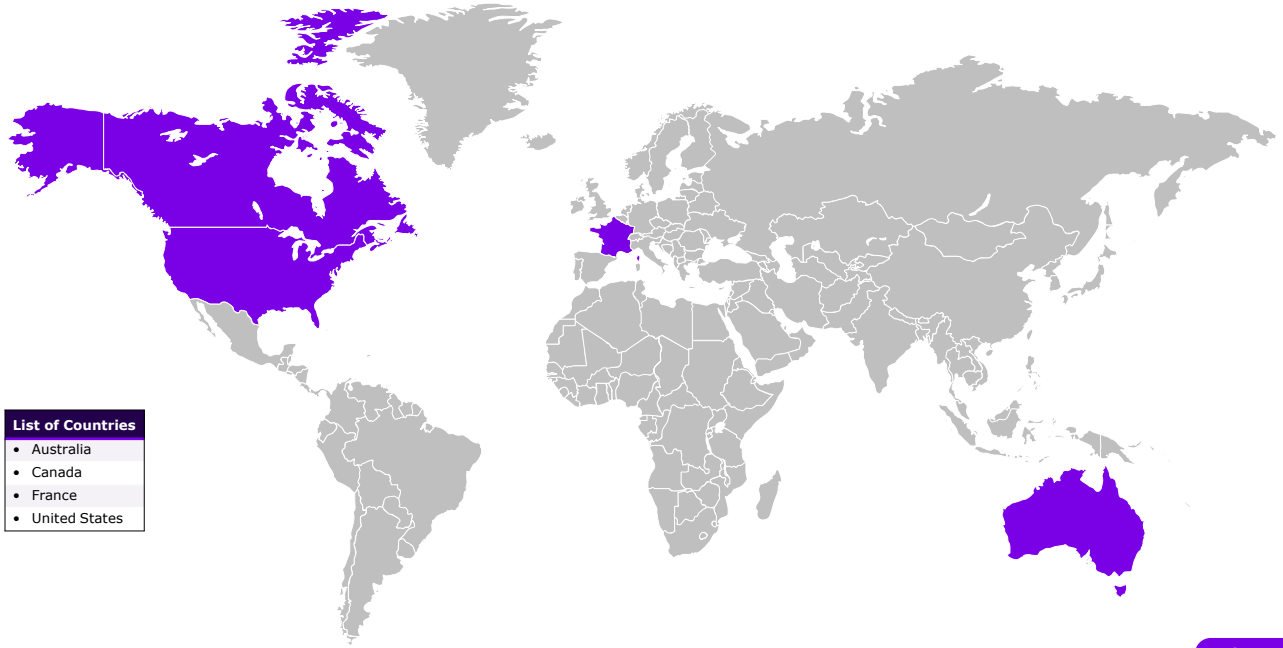
Proposed mechanism of action

POISE *(Phase 2 study)*

- Study design
- Patient population
- Participating countries

POISE 1

Participating countries



List of Countries
• Australia
• Canada
• France
• United States

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References

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