

Rare Diseases Pipeline



<i>Proposed Indication</i>	<i>Product Candidate</i>	<i>Technology</i>	<i>Phase 1</i>	<i>Phase 2</i>	<i>Phase 3</i>
IOPD ¹	Avalglucosidase alfa*	Protein-based therapy			
Gaucher disease type 3 ²	Venglustat	Small molecule			
Fabry disease ³	Venglustat	Small molecule			
Achondroplasia ⁴	SAR442501	Anti-FGFR3 antibody			
Phenylketonuria ⁵	SAR444836	PAH replacement AAV-based gene therapy			
Alpha-1 antitrypsin deficiency ⁶	SAR447537	Protein-based therapy			
Primary Focal Segmental Glomerulosclerosis/Minimal Change Disease ⁷	Frexalimab	Anti-CD40L mAb			
	SAR442970	Anti-TNF- α /OX40L			
	Rilzabrutinib	BTK inhibitor			
Osteogenesis imperfecta ⁸	SAR439459	Anti-TGF- β mAb			

***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; BTK, bruton's tyrosine kinase; CD, cluster of differentiation; FGFR3, fibroblast growth factor receptor 3; IOPD, infantile-onset Pompe disease; mAb, monoclonal antibody; MAPK, mitogen-activated protein kinase; PAH, phenylalanine hydroxylase; RNAi, ribonucleic acid interference; TGF- β , transforming growth factor-beta; TNF- α , tumor necrosis factor-alpha.

Clinicaltrials.gov: 1. NCT04910776; 2. NCT05222906; 3. NCT05206773, NCT05280548; 4. NCT06067425; 5. NCT05972629; 6. NCT05856331; 7. NCT06500702; 8. NCT05231668.

IMPORTANT INFORMATION

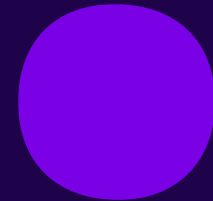
The agents and/or uses mentioned in this pipeline are investigational and have not been approved by the US Food and Drug Administration (FDA) or any other regulatory agency worldwide for the uses under investigation.

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



***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.

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Avalglucosidase alfa*

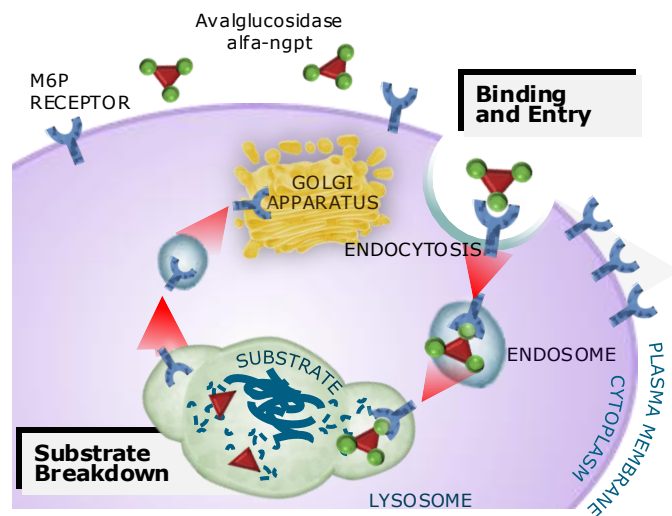
IOPD

Proposed mechanism of action

Baby-COMET (Phase 3 study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- 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.

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

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

References

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Avalglucosidase alfa*

IOPD

Proposed mechanism of action

Baby-COMET (Phase 3 study)

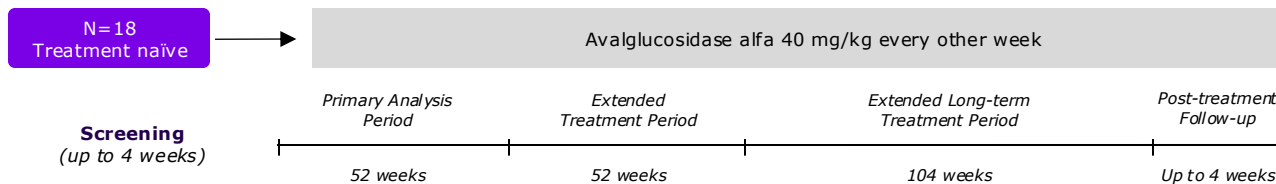
Study design

- Patient population
- Participating countries



Study design

Single group, multinational, multicenter, phase 3, open-label study to assess efficacy, safety, pharmacokinetics, and pharmacodynamics of avalglucosidase alfa in treatment-naïve patients with IOPD



Primary endpoint

- Proportion of patients who are alive and free of invasive ventilation at Week 52

Secondary endpoints

- Proportion of patients who are alive and free of invasive ventilation at Week 52, 12 months and 18 months of age
- Change from baseline to Week 52 in LVM Z-score, AIMS score, body length and weight, head circumference Z-scores, and urinary Hex4
- Pompe-PEDI, Motor Milestones checklist, Bayley Scale of Infant and Toddler Development

AIMS score, abnormal involuntary movement score; Hex4, hexose tetrasaccharide; IOPD, infantile-onset Pompe disease; LVM Z-score, left ventricular mass Z-score; Pompe-PEDI, Pompe pediatric evaluation of disability inventory

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Avalglucosidase alfa*

IOPD

Proposed mechanism of action

Baby-COMET (Phase 3 study)

- 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 IOPD diagnosis
- Presence of cardiomyopathy at time of diagnosis

Exclusion criteria

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

CRIM, cross-reactive immunological material; IOPD, infantile-onset Pompe disease.

A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT04910776).

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

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Avalglucosidase alfa*

IOPD

Proposed mechanism of action

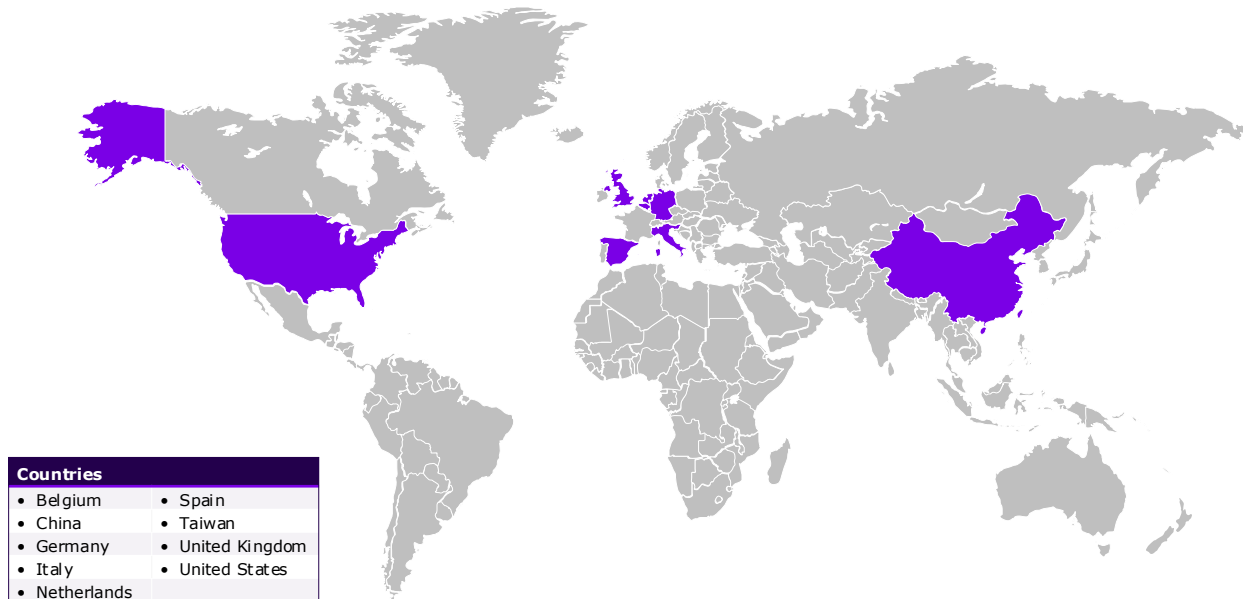
Baby-COMET (Phase 3 study)

- Study design
- Patient population

● Participating countries



Participating countries



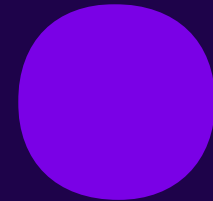
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Rare Diseases Pipeline

VENGLUSTAT* IN GAUCHER DISEASE TYPE 3



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Venglustat

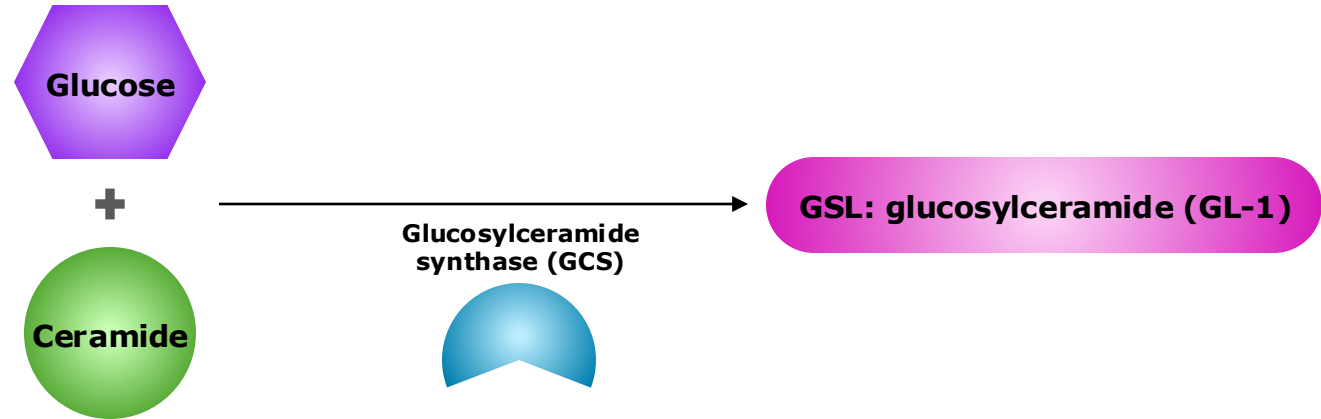
Gaucher disease type 3

Proposed mechanism of action

LEAP2MONO (Phase 3 study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- 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.

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Venglustat

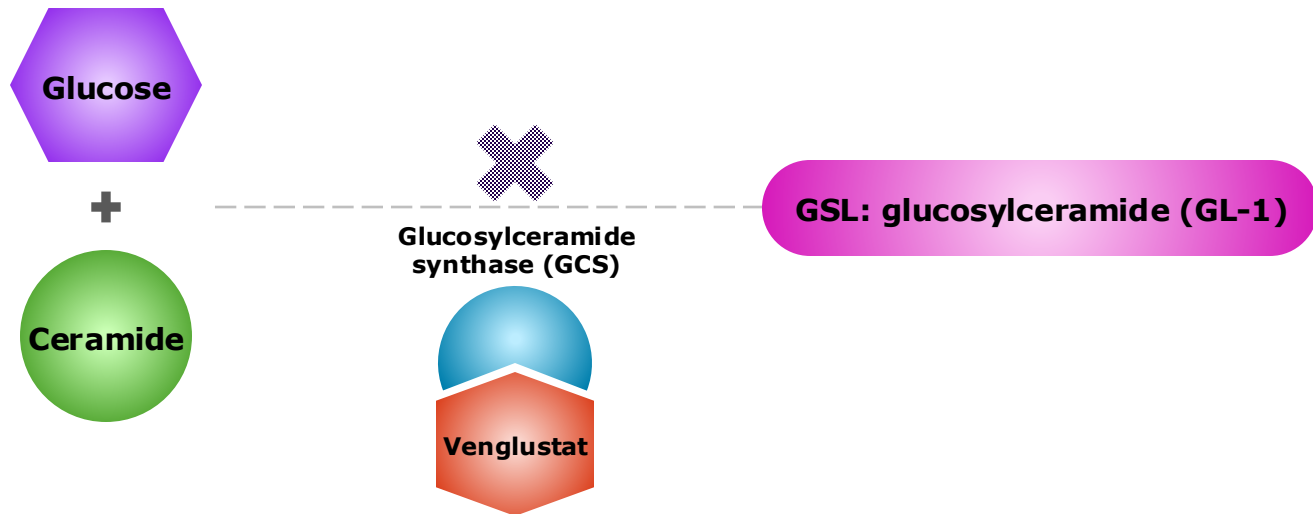
Gaucher disease type 3

Proposed mechanism of action

LEAP2MONO (Phase 3 study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



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

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

GCS, glucosylceramide synthase; GL-1, glucosylceramide; GSL, glycosphingolipids; LSD, lysosomal storage disorders.

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Venglustat

Gaucher disease type 3

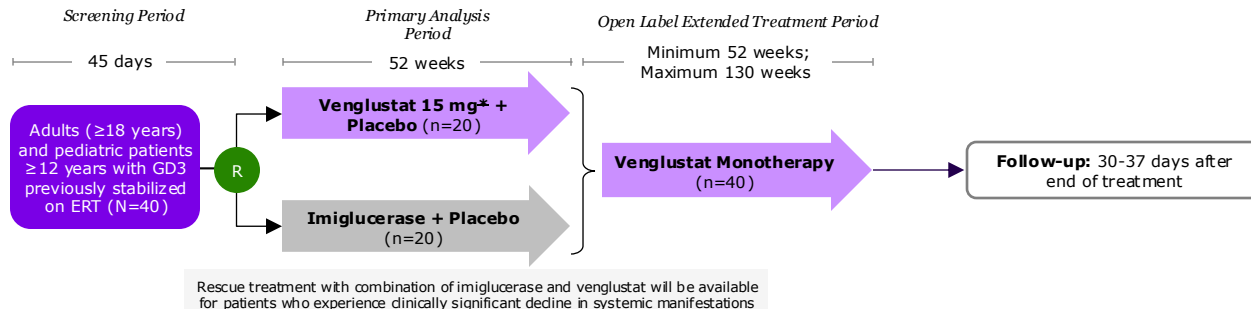
Proposed mechanism of action

LEAP2MONO (Phase 3 study)



Study design

Multicenter, multinational, randomized, parallel arm, phase 3, 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

- Percent changes from baseline to Week 52 in spleen volume (MN), liver volume (MN), platelet count, hemoglobin levels, and plasma and CSF GL-1 and lyso-GL-1 levels
- Change from baseline to Week 52 in score of Beck Depression Inventory II (BDI-II) and Patient Health Questionnaire 9 (PHQ-9) during the treatment-emergent period (for patients 12 years of age at baseline)
- Safety and tolerability

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

CSF, cerebrospinal fluid; ERT, enzyme replacement therapy; GD3, Gaucher disease type 3; GL-1, glucosylceramide; lyso-GL-1, glucosylsphingosine; MN, multiples of normal; R, randomization.

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Venglustat

Gaucher disease type 3

Proposed mechanism of action

LEAP2MONO (Phase 3 study)

• Study design

● Patient population

• Participating countries



Patient population

Inclusion criteria

- Adults: ≥ 18 years of age; pediatric patients: ≥ 12 years to < 18 years of age
- Clinical diagnosis of GD3 and documented deficiency of acid β -glucosidase activity
- Modified SARA score ≥ 1
- Presence of gaze palsy, predominantly horizontal, with slow or absent saccades
- ≥ 3 years of ERT prior to enrollment, on a stable dose for ≥ 6 months within therapeutic goals*
- Contraception for sexually active male patients or female patient; not pregnant or breastfeeding; no sperm donating for male patient
- Weight ≥ 30 kg

Exclusion criteria

- Progressive myoclonic epilepsy
- Invasive ventilatory support and non-invasive ventilatory support > 12 hours daily
- Blood transfusion-dependence
- Prior esophageal varices or liver infarction or current liver enzymes (ALT/AST) or total bilirubin $> 2X$ 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 $\geq 100,000/\text{mm}^3$; 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. A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT05222906).

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Venglustat

Gaucher disease type 3

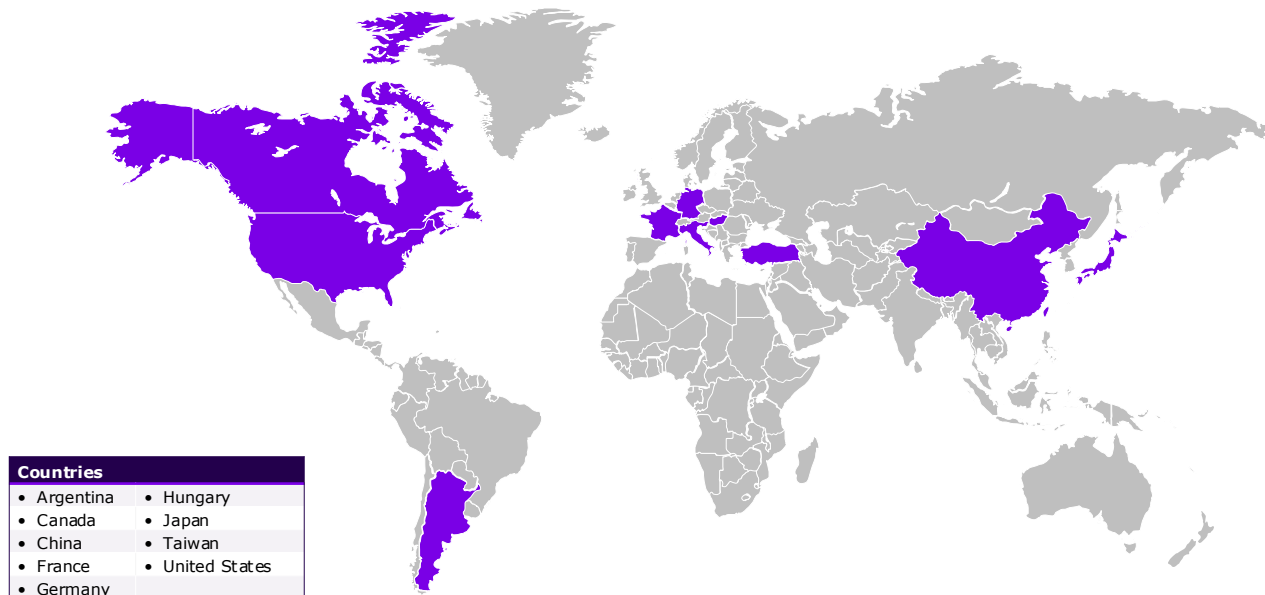
Proposed mechanism of action

LEAP2MONO (Phase 3 study)

- Study design
- Patient population
- Participating countries



Participating countries



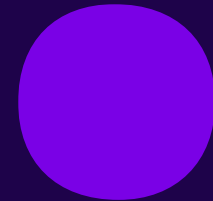
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Rare Diseases Pipeline

VENGLUSTAT* IN FABRY DISEASE



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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

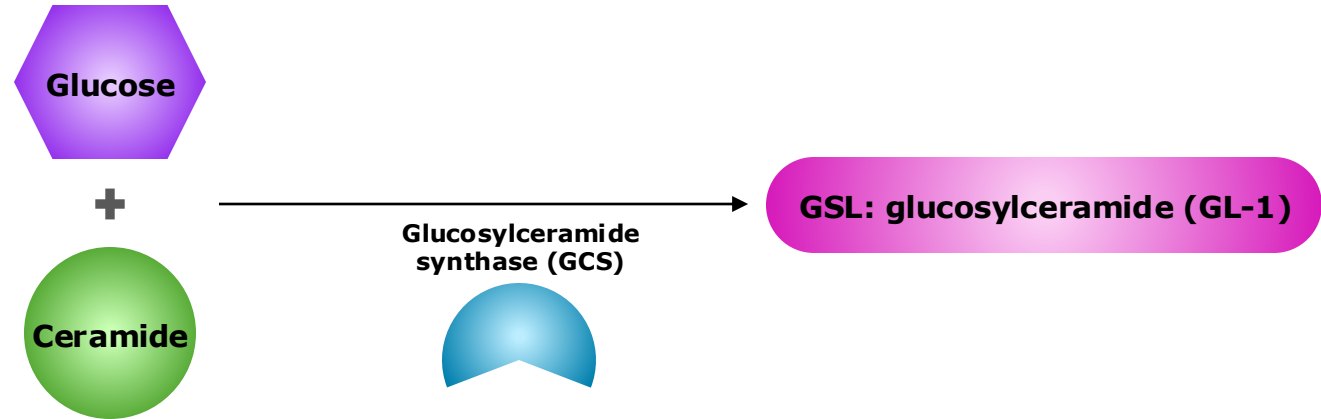
- Study design
- Patient population
- Participating countries

CARAT (Phase 3 study)

- Study design
- Patient population
- Participating countries

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Proposed mechanism of action under investigation



- 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.

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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

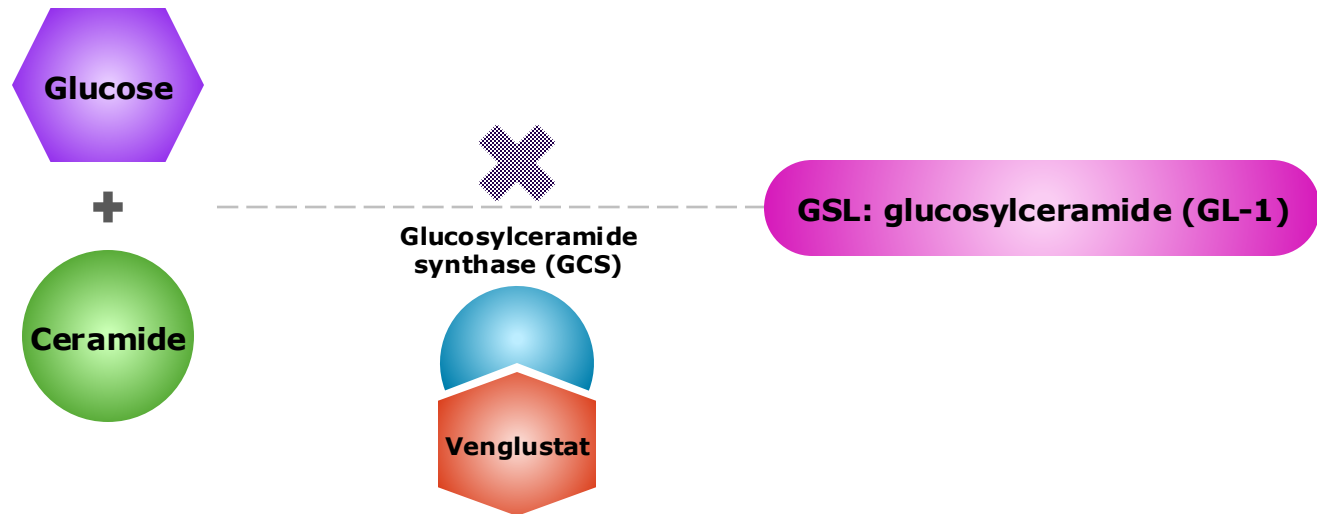
- Study design
- Patient population
- Participating countries

CARAT (Phase 3 study)

- Study design
- Patient population
- Participating countries

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Proposed mechanism of action under investigation



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

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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

Study design

- Patient population
- Participating countries

CARAT (Phase 3 study)

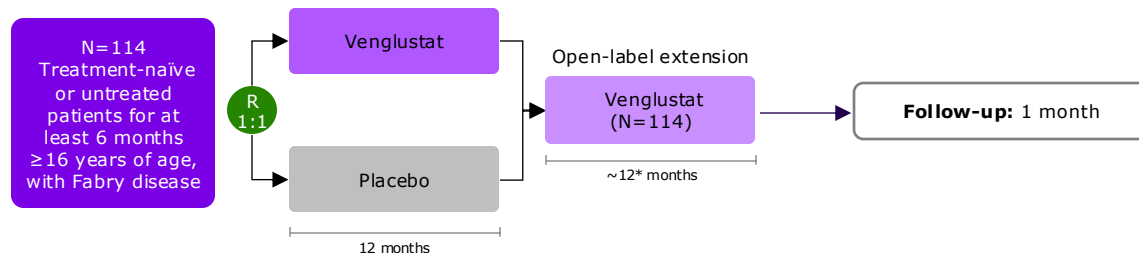
- Study design
- Patient population
- Participating countries

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Study design

Phase 3, randomized, double-blind, placebo-controlled study to evaluate 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 endpoints

- 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
 - BDI-II score
 - Lens clarity by ophthalmological examination
- Proportion of responders in neuropathic or abdominal pain, as assessed by FD-PRO
- Safety and tolerability
- Pharmacokinetics

*The total duration will be approximately of 31 months (12 month of OLE treatment, additional OLE treatment until a common study end of treatment date, and 1 month of follow-up period).

BD-II, Beck Depression Inventory-II; FD-PRO, Fabry Disease Patient-Reported Outcome; lyso-GL-3, globotriaosylsphingosine.

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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

- Study design

● Patient population

- Participating countries

CARAT (Phase 3 study)

- Study design
- Patient population
- Participating countries

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Patient population

Inclusion criteria

- Patients ≥ 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-naïve, 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 BDI-II score > 28
- Moderate to severe hepatic impairment, history of or active hepatobiliary disease
- Liver enzymes (ALT/AST) or total bilirubin $> 2X$ ULN

ALT, alanine transaminase; AST, aspartate transaminase; BD-II, Beck Depression Inventory-II; FD-PRO, Fabry Disease Patient-Reported Outcome; GL-3, globotriaosylceramide; lyso-GL-3, globotriaosylsphingosine; ULN, upper limit of normal.
A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT05206773).

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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

- Study design
- Patient population

● Participating countries

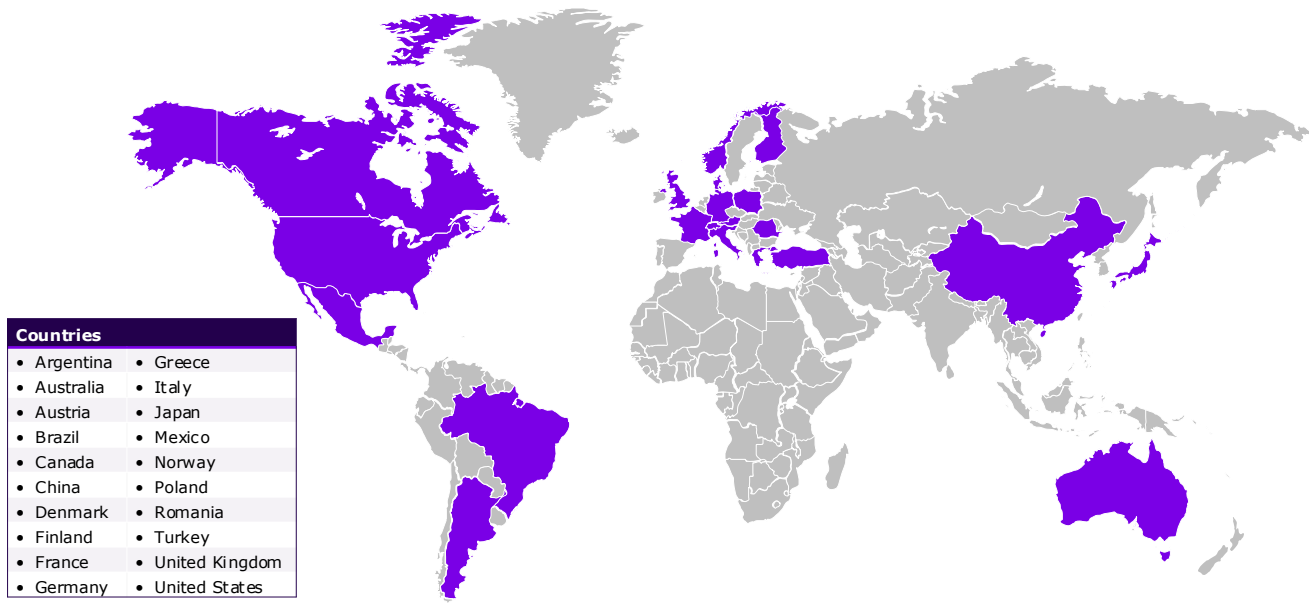
CARAT (Phase 3 study)

- Study design
- Patient population
- Participating countries

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Participating countries



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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

- Study design
- Patient population
- Participating countries

CARAT (Phase 3 study)

Study design

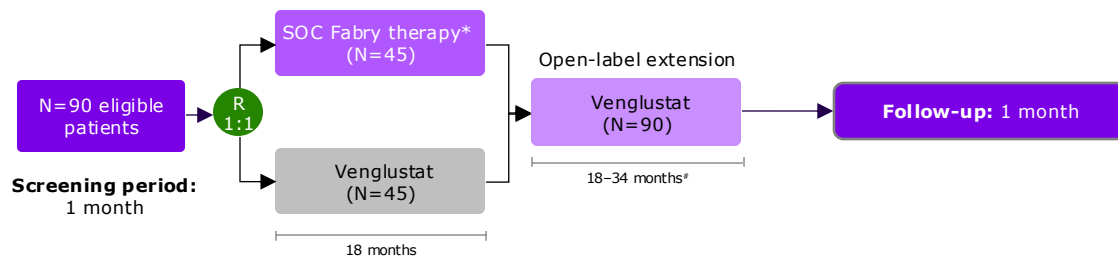
- Patient population
- Participating countries

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Study design

Multicenter, randomized, open-label, active-control, parallel-group, phase 3 study to evaluate the effect of venglustat compared with standard of care therapy on LVMI in patients with Fabry disease and left ventricular hypertrophy



Primary endpoints

- Change from baseline to 18 months in venglustat vs SOC 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 assessed by the chronic kidney disease epidemiology collaboration (CKD-EPI) creatinine equation, 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

*agalsidase alfa, agalsidase beta, or migalastat; 20-40% patients per therapy; *the total duration will be from minimum 19 months (18 months of treatment and 1 month of follow-up period) to maximum 35 months (34 months of treatment and 1 month of follow-up period). The maximum total study duration is approximately 4.4 years. eGFR, estimated glomerular filtration rate; FD-PRO, Fabry Disease Patient-Reported Outcome; LVMI, left ventricular mass index; MRI, magnetic resonance imaging; SOC: standard of care.

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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

- Study design
- Patient population
- Participating countries

CARAT (Phase 3 study)

- Study design
- Patient population
- Participating countries

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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
- History of transient ischemic attack, stroke, myocardial infarction, heart failure, clinically significant cardiac arrhythmia, major cardiovascular surgery or kidney transplantation
- Estimated glomerular filtration rate <45 mL/min/1.73m²
- History of seizures currently requiring treatment
- Severe depression measured by BDI-II >28
- Moderate to severe hepatic impairment, history of or active hepatobiliary disease
- Liver enzymes (ALT/AST) or total bilirubin $>2X$ ULN

*agalsidase alfa, agalsidase beta, or migalastat.

ALT, alanine transaminase; AST, aspartate transaminase; BDI-II, Beck Depression Inventory-II; MRI, magnetic resonance imaging; ULN, upper limit of normal.

A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov. (NCT05280548).

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. 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 or efficacy should be drawn.



References

MAT-US-2100084 v11.0 – P
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Venglustat

Fabry Disease

Proposed mechanism of action

PERIDOT (Phase 3 study)

- Study design
- Patient population
- Participating countries

CARAT (Phase 3 study)

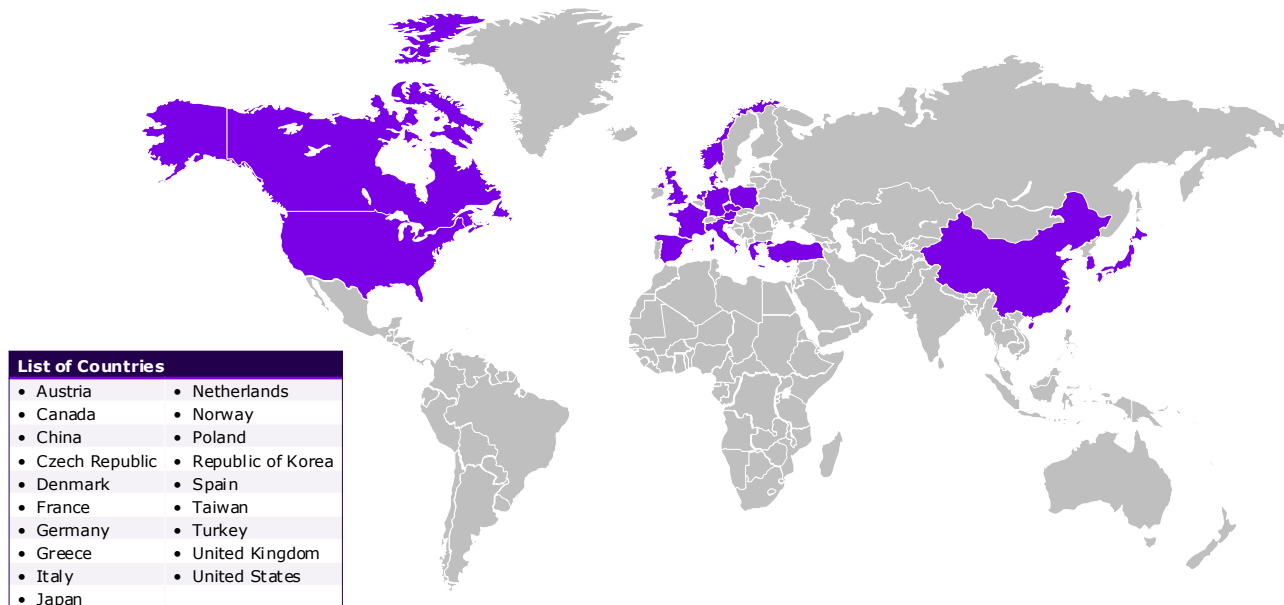
- Study design
- Patient population

• Participating countries

sanofi



Participating countries



This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. 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 or efficacy should be drawn.

References

MAT-US-2100084 v11.0 - P
Expiration date: 09/25/2026

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.

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SAR442501

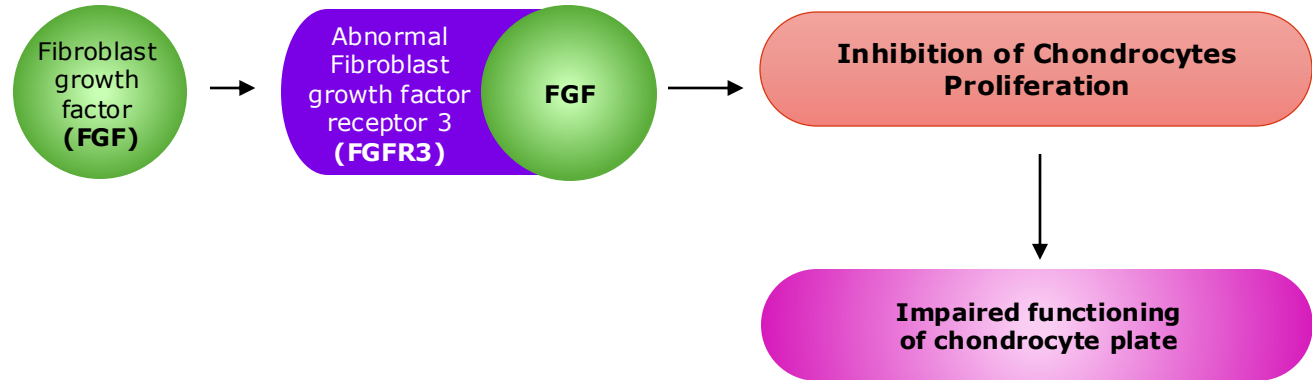
Achondroplasia

Proposed mechanism of action

upreACH-2 (Phase 2 study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- 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.

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

References

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SAR442501

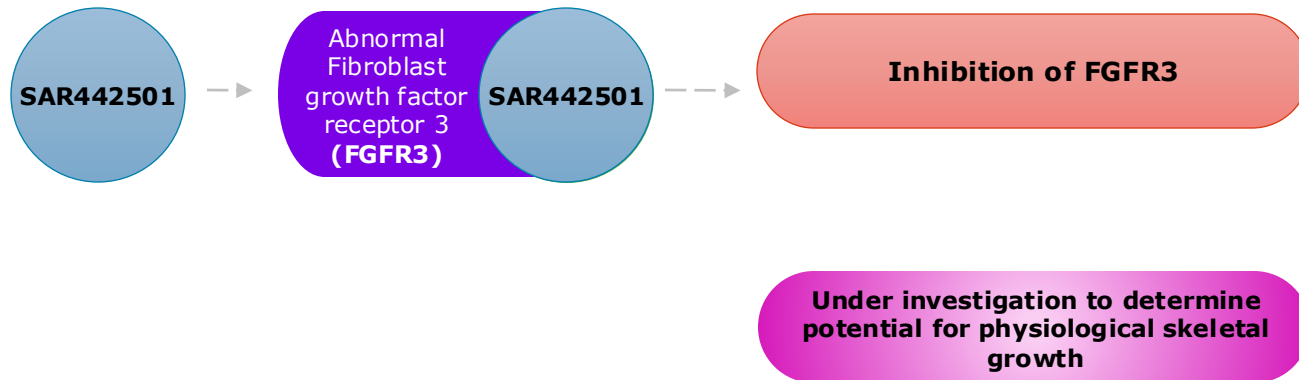
Achondroplasia

Proposed mechanism of action

upreACH-2 (Phase 2 study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- SAR442501 is a monoclonal antibody derivative that binds only to the FGFR3 receptor, limiting its activity
- Under investigation for its potential 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.

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

References

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Expiration date: 09/25/2026

SAR442501

Achondroplasia

Proposed mechanism of action

upreACH-2 (Phase 2 study)

Study design

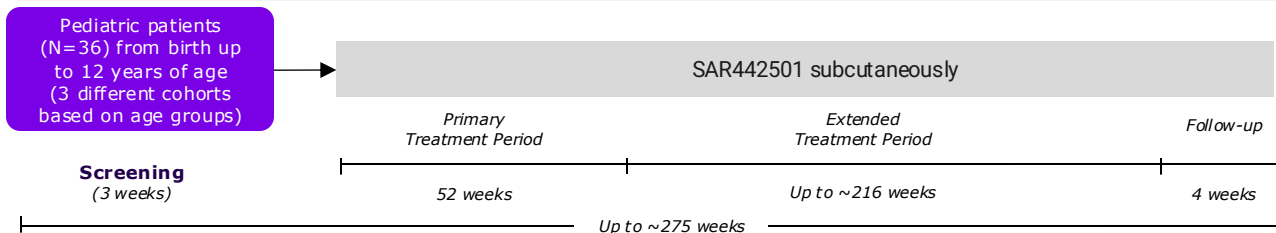
- Patient population
- Participating countries

sanofi



Study design

Phase 2, global, open-label, multicenter, 2-stage sequential cohort, dose escalation study to evaluate safety, tolerability, pharmacokinetics, pharmacodynamics, and efficacy of SAR442501 in pediatric patients with achondroplasia



Primary endpoint

Number of patients 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 from baseline to Week 26 and Week 52 in:
 - Annualized growth velocity (AGV) Z-score
 - Body proportions
 - Overall health-related quality of life score in the PedsQL Inventory Generic Core Scale, fatigue score in the PedsQL Multidimensional Fatigue Scale, present pain and worst pain rating (PPQ) score, mobility and symptom rating (STEMS) score
 - Neurological examination
- Change from baseline to Week 52 in brainstem parameter, skull parameter, spine morphometric parameter, volumetric parameter, developmental score in the Achondroplasia Developmental Recording Form
 - Immunogenicity, pharmacokinetics, and pharmacodynamics

QoL, quality of life; SC, subcutaneous.

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References

SAR442501

Achondroplasia

Proposed mechanism of action

upreACH-2 (Phase 2 study)

- Study design

- Patient population

- Participating countries

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Patient population

Inclusion criteria

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

Exclusion criteria

- Hypochondroplasia or short stature condition other than ACH
- Received any dose of medications or investigational product until enrollment (Week 0/Day 1/Visit 2), including human growth hormone, intended to affect stature or body proportions of patients
- History of growth plate closure
- Long bone fracture within 3 months of enrollment (Week 0/Day 1/Visit 2)
- Current evidence of corneal or retinal disorder/keratopathy
- Previous surgical intervention involving the foramen magnum (Stage 2 only)
- Hyperphosphatemia

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

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

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. 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 v11.0 – P
Expiration date: 09/25/2026

References

SAR442501

Achondroplasia

Proposed mechanism of action

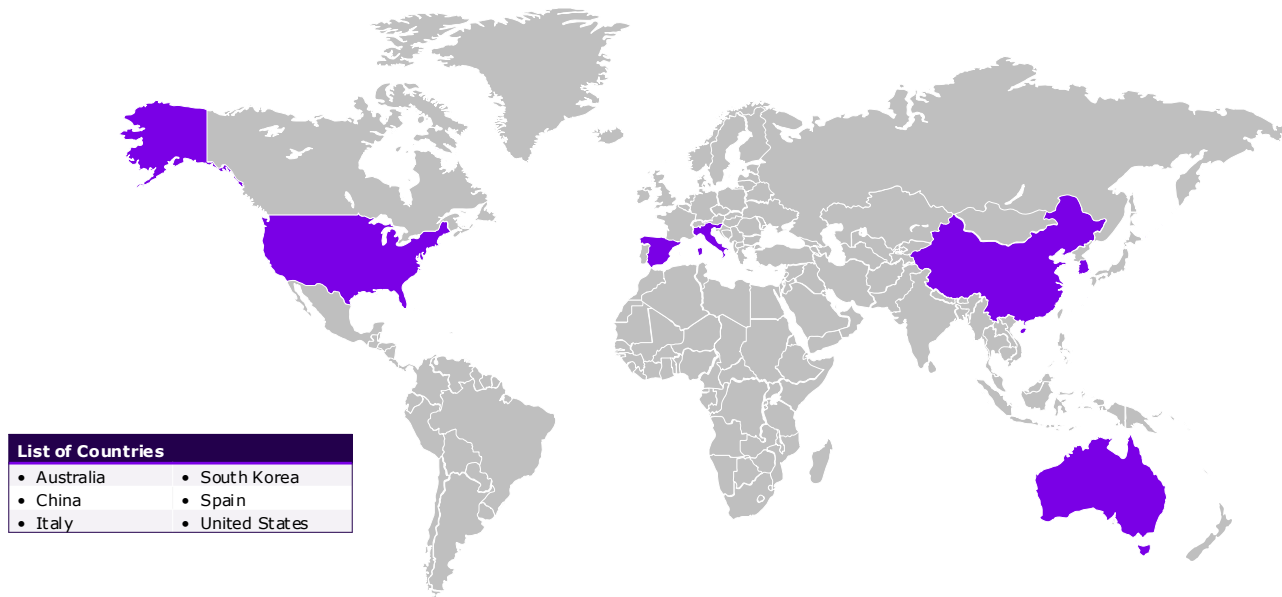
upreACH-2 (Phase 2 study)

- Study design
- Patient population

● Participating countries



Participating countries



List of Countries

- | | |
|-------------|-----------------|
| • Australia | • South Korea |
| • China | • Spain |
| • Italy | • United States |

Rare Diseases Pipeline

SAR444836* IN 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 v11.0 – P
Expiration date: 09/25/2026



SAR444836

Phenylketonuria

Proposed mechanism of action

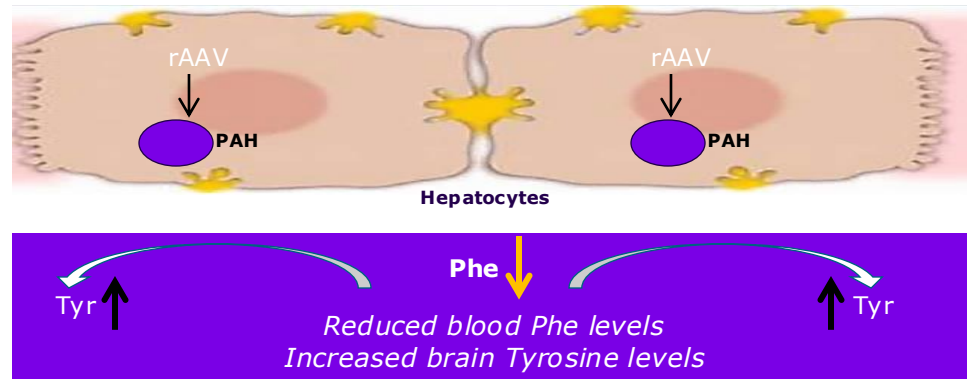
pheby (Phase 1/Phase 2)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation

- 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.

Single administration of rAAVSNY001-hPAH may restore PAH activity



AAV, adeno-associated virus; PAH, phenylalanine hydroxylase; Phe, phenylalanine; Tyr, tyrosine.

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. 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 v11.0 - P
Expiration date: 09/25/2026

References

SAR444836

Phenylketonuria

Proposed mechanism of action

pheby (Phase 1/Phase 2)

Study design

- Patient population
- Participating countries

sanofi



Study design

Phase 1/ Phase 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

N= 32 eligible patients

Screening period:
Up to ~6 weeks

Dose escalation phase

Safe and
effective dose
level identified

Dose expansion phase

Follow-up:
96 weeks

~ 102 weeks

Primary endpoint

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

Secondary endpoints

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

- Proportion of patients with sustained plasma level of Phe without dietary Phe restriction (Phe <360 $\mu\text{mol/L}$ for ≥ 4 weeks, Phe <120 $\mu\text{mol/L}$ for ≥ 4 weeks, Phe <600 $\mu\text{mol/L}$ for ≥ 4 weeks)
- Plasma level of Phe, dietary protein intake, plasma Phe: Tyr ratio
- Number of patients 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

AAV, adeno-associated virus; PAH, phenylalanine hydroxylase; Phe, phenylalanine; Tyr, tyrosine.

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References

MAT-US-2100084 v11.0 - P
Expiration date: 09/25/2026

SAR444836

Phenylketonuria

Proposed mechanism of action

pheby (Phase 1/Phase 2)

- Study design

- Patient population

- Participating countries



Patient population

Inclusion criteria

- Adult males, and females (non-childbearing potential), 18–65 years of age at the time of informed consent
- Diagnosis of uncontrolled classical PKU due to PAH deficiency
- Two historical plasma Phe values ≥ 600 $\mu\text{mol/L}$ in the preceding 12 months while on Phe restricted diet therapy
- Two plasma Phe values ≥ 600 $\mu\text{mol/L}$ 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

Exclusion criteria

- Presence of neutralizing antibodies against the AAV SNY001 capsid
- Abnormal liver function evidenced by ALT $> 1.5\text{X}$ ULN, AST $> 1.5\text{X}$ ULN, alkaline phosphatase $> 1.5\text{X}$ ULN, total and direct bilirubin $> 1.5\text{X}$ ULN (except documented history or laboratory evidence of 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 $> 1.5\text{X}$ 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; Phe, phenylalanine; PKU, Phenylketonuria, ULN, upper limit normal.
A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT05972629).

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References

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Expiration date: 09/25/2026

SAR444836

Phenylketonuria

Proposed mechanism of action

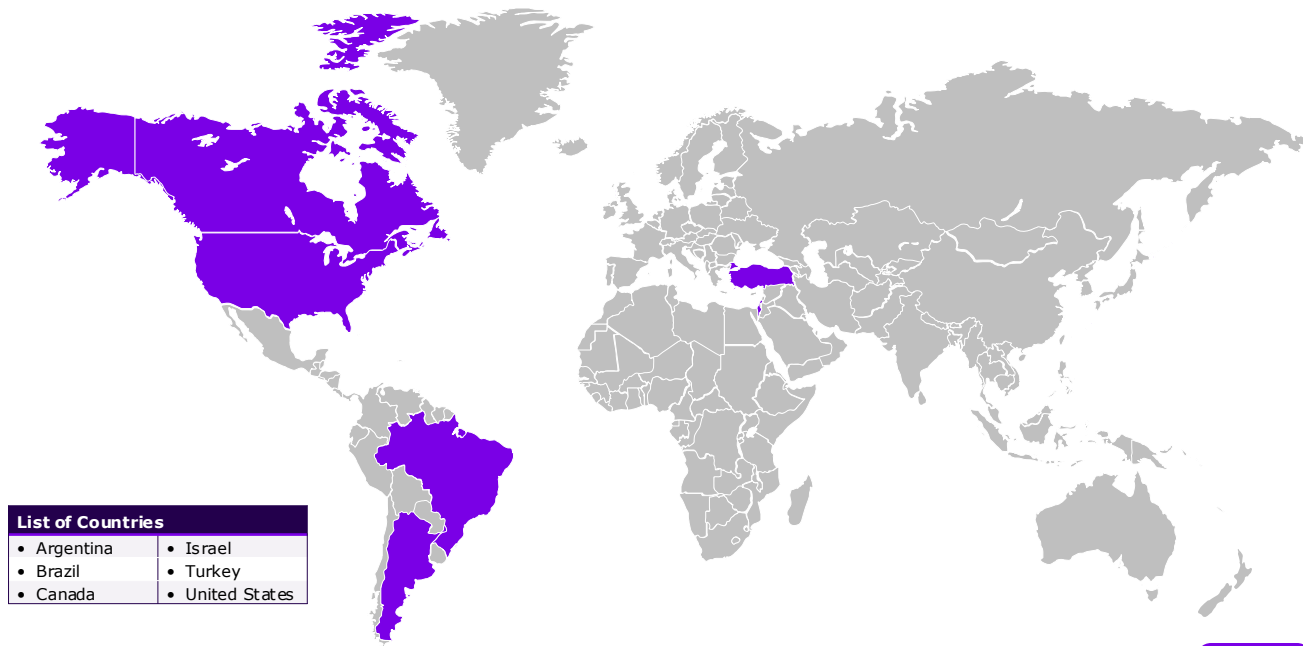
pheby (Phase 1/Phase 2)

- Study design
- Patient population

Participating countries



Participating countries



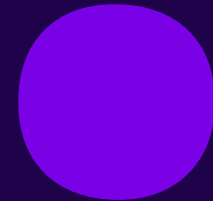
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MAT-US-2100084 v11.0 – P
Expiration date: 09/25/2026

References

Rare Diseases Pipeline

SAR447537* IN ALPHA-1 ANTITRYPSIN DEFICIENCY



*SAR447537 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 v11.0 – P
Expiration date: 09/25/2026



SAR447537

Alpha-1 Antitrypsin Deficiency

Proposed mechanism of action

elevAATe (Phase 2 study)

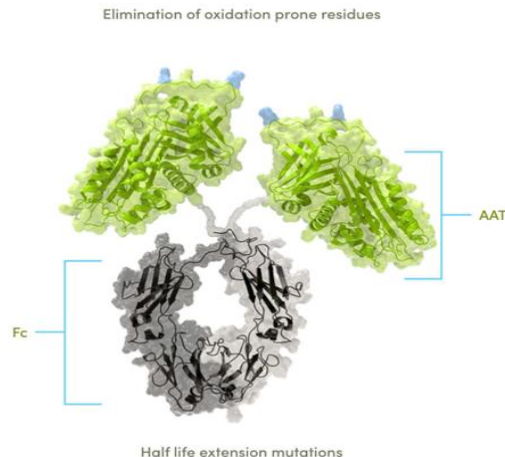
- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation

- SAR447537 is a rhAAT-Fc fusion protein under investigation for its potential to extend the dosing interval of augmentation therapy from weekly doses to once monthly.

4 mutations to reduce Ab-mediated cytotoxicity/ complement activation and increase the half-life

- S228P stabilizing mutation to prevent strand exchange with endogenous IgG4
- L235E to further silence IgG4 effector function
- M252Y and M428L to increase binding to FcRN and increase half-life



Two AAT molecules fused with an Fc* portion of IgG4, selected for its minimal effector function

*Fc is the tail region of an antibody that interacts with cell surface receptors.

AAT, alpha-1 antitrypsin; FcRN, neonatal Fc receptor; IgG4, immunoglobulin G4; rh-AAT, recombinant human AAT.

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. SAR447537 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.

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Expiration date: 09/25/2026



SAR447537

Alpha-1 Antitrypsin Deficiency

Proposed mechanism of action

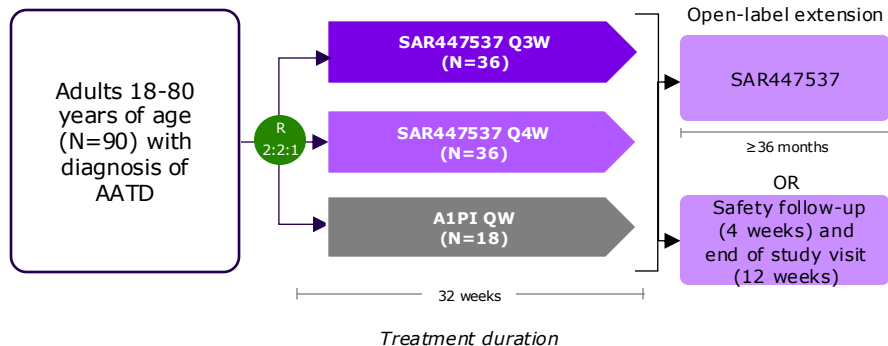
elevAATe (Phase 2 study)

Study design

- Patient population
- Participating countries

Study design

Phase 2, double-blind, randomized, active-control, parallel group to evaluate the pharmacokinetics, pharmacodynamics, immunogenicity, and safety of SAR447537* in adults with alpha-1 antitrypsin deficiency (AATD) emphysema



Primary endpoint

Steady state serum functional AAT (fAAT) levels at 32 weeks

Secondary endpoints

- Change from baseline to Week 32 in the following parameters:
 - fAAT concentration
 - Percentage of days with fAAT >LLN
- Safety, pharmacokinetics
- Frequency of anti-drug antibodies at 32 weeks

*versus plasma-derived alpha1-proteinase inhibitor (A1PI) augmentation therapy
A1PI, alpha1-proteinase inhibitor; AATD, alpha-1 antitrypsin deficiency; fAAT, functional alpha-1 antitrypsin; LLN, lower limit of normal; QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. SAR447537 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.

References

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SAR447537

Alpha-1 Antitrypsin Deficiency

Proposed mechanism of action

elevAATe (Phase 2 study)

- Study design

● Patient population

- Participating countries

Patient population

Inclusion criteria

- Males or females 18–80 years of age, inclusive, at the time of screening
- Diagnosis of AATD
- Evidence of emphysema secondary to AATD
- FEV₁ of $\geq 30\%$ and $\leq 80\%$ predicted at screening
- Current non-smoking status

Exclusion criteria

- Receipt of A1PI augmentation therapy within 5 weeks prior to the first dose of study drug
- Known or suspected allergy to components of SAR447537, A1PI or human IgG
- Known selective or severe Immunoglobulin A (IgA) deficiency
- Known or suspected diagnosis of type 1 diabetes or diagnosed with uncontrolled type 2 diabetes
- Received IV immunoglobulins, monoclonal antibodies and/or other biologic therapies within 30 days
- Acute respiratory tract infection or COPD exacerbation within 4 weeks prior to or during screening
- Active cancers or a history of malignancy within 5 years prior to screening
- On waiting list for lung or liver transplant
- Evidence of decompensated cirrhosis
- History of unstable cor pulmonale
- Clinically significant congestive heart failure

*versus plasma-derived alpha1-proteinase inhibitor (A1PI)
A1PI, alpha1-proteinase inhibitor; AATD, alpha-1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease;
fAAT, functional alpha-1 antitrypsin; FEV₁, forced expiratory volume in one second; IgG, immunoglobulin G; LLN, lower limit of normal;
QW, every week; Q3W, every 3 weeks; Q4W, every 4 weeks.
A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT05856331).

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. SAR447537 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.

References

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Expiration date: 09/25/2026



SAR447537

Alpha-1 Antitrypsin Deficiency

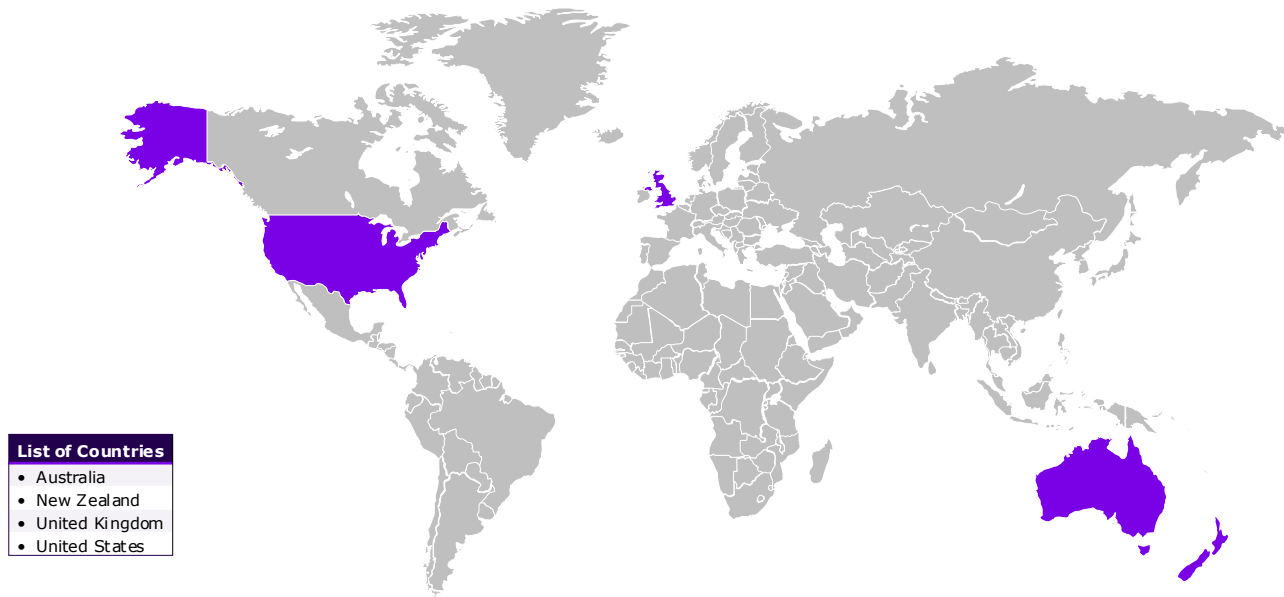
Proposed mechanism of action

elevAATe (Phase 2 study)

- Study design
- Patient population

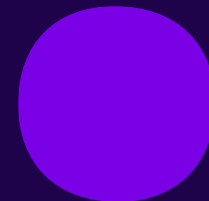
☒ Participating countries

Participating countries



Rare Diseases Pipeline

FREXALIMAB, SAR442970, AND RILZABRUTINIB* IN
PRIMARY FOCAL SEGMENTAL GLOMERULOSCLEROSIS
OR MINIMAL CHANGE DISEASE



*Frexalimab, SAR442970, and rilzabrutinib 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

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Expiration date: 09/25/2026



Frexalimab, or SAR442970, or Rilzabrutinib

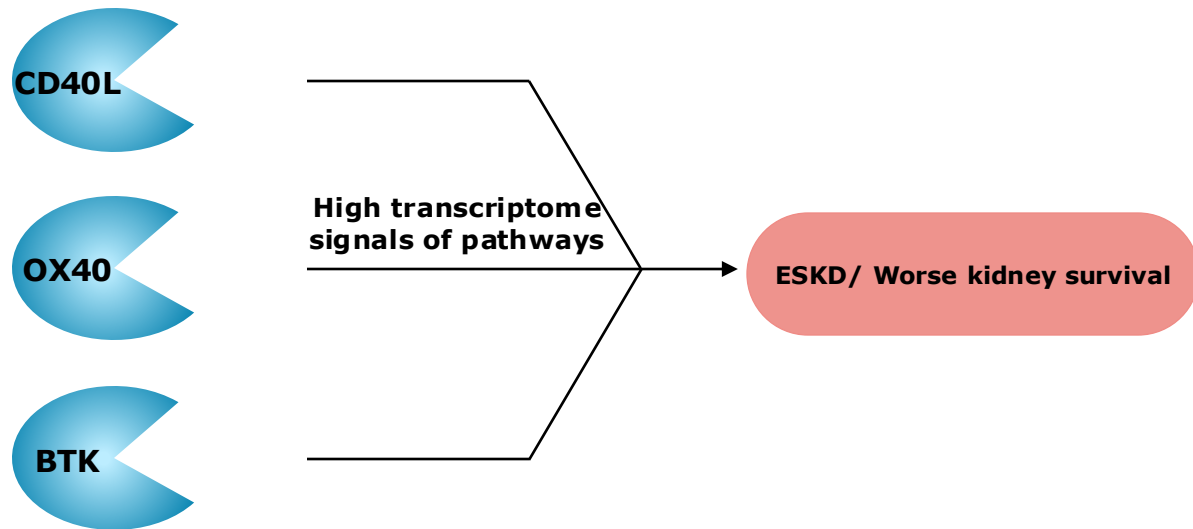
Focal Segmental Glomerulosclerosis or Minimal Change Disease

Proposed mechanism of action

RESULT (Phase 2a study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- High transcriptome signals of CD40L, OX40, and BTK pathways are associated with worse kidney survival.
- Transcriptomic genetic data analysis support CD40L, OX40, and BTK as potential therapeutic targets for primary FSGS and MCD.

BTK, bruton's tyrosine kinase; ESKD, end stage kidney disease; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease.

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. Frexalimab, SAR442970, and rilzabrutinib are 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.

References

MAT-US-2100084 v11.0 – P
Expiration date: 09/25/2026



Frexalimab, or SAR442970, or Rilzabrutinib

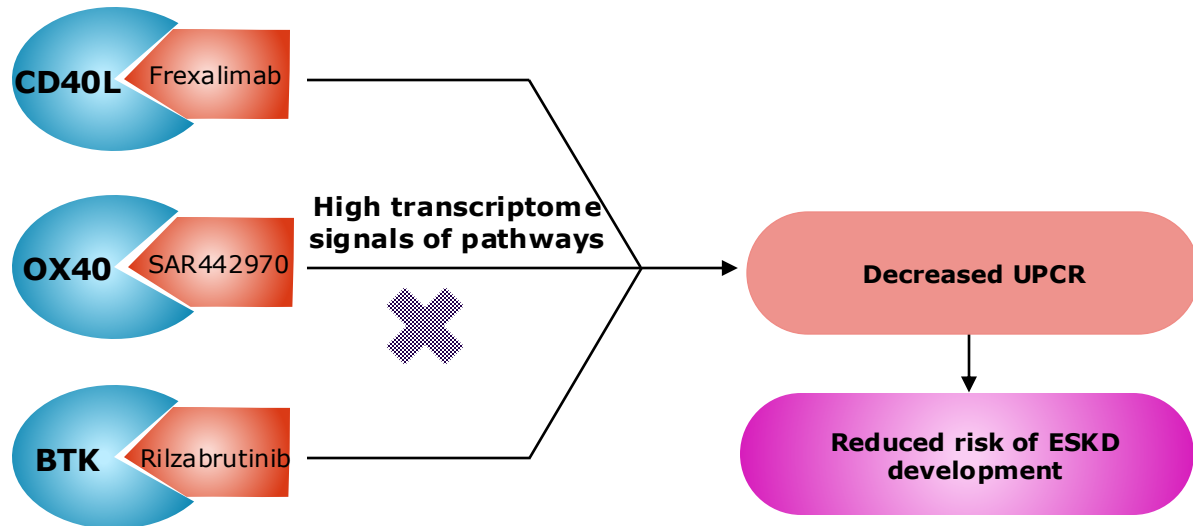
Focal Segmental Glomerulosclerosis or Minimal Change Disease

Proposed mechanism of action

RESULT (Phase 2a study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- Frexalimab, SAR442970, and rilzabrutinib target specific aspects of the adaptive immune response that drive the underlying pathogenesis of FSGS/MCD. Thereby, these drugs are under investigation for their potential to decrease the UPCR, thus reducing the risk of ESKD development.

BTK, bruton's tyrosine kinase; ESKD, end stage kidney disease; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; UPCR, urine protein to creatinine ratio.

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. Frexalimab, SAR442970, and rilzabrutinib are 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.

References

MAT-US-2100084 v11.0 - P
Expiration date: 09/25/2026

Frexalimab, or SAR442970, or Rilzabrutinib

Focal Segmental Glomerulosclerosis or Minimal Change Disease

Proposed mechanism of action

RESULT (Phase 2a study)

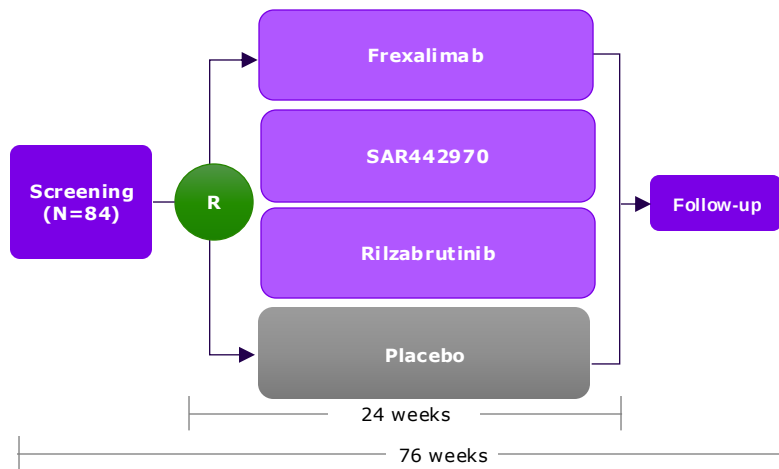
Study design

- Patient population
- Participating countries



Study design

Phase 2a, parallel, double-blind, multicenter, randomized, placebo-controlled, 6-arm, umbrella study to evaluate the efficacy and safety of frexalimab, SAR442970, or rilzabrutinib compared with placebo in patients with primary focal segmental glomerulosclerosis (FSGS) or primary minimal change disease (MCD)



Primary endpoint

- Percent reduction in urine protein to creatinine ratio (UPCR) from baseline to Week 12

Secondary endpoints

- Percentage of participants achieving FSGS partial remission* endpoint and achieving CR# at Week 12
- Incidence of TEAEs, treatment-emergent SAEs, treatment-emergent AESIs and IMP discontinuation due to TEAEs during the study up to Week 48
- Plasma concentrations of frexalimab and rilzabrutinib, and serum concentrations of SAR442970 up to Week 48
- Occurrence of ADAs against frexalimab and SAR442970 up to Week 48

*Defined as UPCR ≤ 1.5 g/g and $>40\%$ reduction of UPCR from baseline; #Defined as UPCR ≤ 0.3 g/g. ADA, anti-drug antibodies; AESIs, adverse events of special interest; CR, complete remission; FSGS, focal segmental glomerulosclerosis; IMP, investigational medicinal product; MCD, minimal change disease; SAEs, serious adverse events; UPCR, urine protein creatinine ratio; TEAEs, treatment-emergent adverse events.

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. Frexalimab, SAR442970, and rilzabrutinib are 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.





Frexalimab, or SAR442970, or Rilzabrutinib

Focal Segmental Glomerulosclerosis Or Minimal Change Disease

Proposed mechanism of action

RESULT (Phase 2a study)

- Study design

● Patient population

- Participating countries



Patient population

Inclusion criteria

- Patients aged 16 to 75 years
- Biopsy-proven primary FSGS or primary MCD
- UPCR ≥ 3 g/g at screening
- eGFR ≥ 45 mL/min/1.73 m² at screening
- Documented history of UPCR reduction by $\geq 40\%$ in response to corticosteroid or other immunosuppressive therapy when pre-treatment UPCR was ≥ 3.5 g/g
- ≤ 10 mg/day prednisone or equivalent and stable starting at least 1 week prior to randomization
- On stable dose of RAAS inhibitors for ≥ 4 weeks prior to screening (if applicable); starting RAAS inhibitors treatment will not be allowed during the double-blind or OLE treatment period
- On stable dose of SGLT2 inhibitor for ≥ 4 weeks prior to screening (if applicable); starting SGLT2 inhibitor treatment will not be allowed during the double-blind or OLE treatment periods
- Body weight within 45 to 120 kg (inclusive) at screening

Exclusion criteria

- Genetic or secondary FSGS or MCD; however, patients with *APOL1* risk alleles are eligible
- Collapsing variant of FSGS
- ESKD requiring dialysis or transplantation

eGFR, estimated glomerular filtration rate; ESKD, end stage kidney disease; FSGS, focal segmental glomerulosclerosis; MCD, minimal change disease; OLE, open label extension; RAAS, renin-angiotensin-aldosterone system; SGLT2, sodium-glucose transport protein 2; UPCR, urine protein to creatinine ratio.

A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT06500702).

This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. Frexalimab, SAR442970, and rilzabrutinib are 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.

References

MAT-US-2100084 v11.0 – P
Expiration date: 09/25/2026



Frexalimab, or SAR442970, or Rilzabrutinib

Focal Segmental Glomerulosclerosis Or Minimal Change Disease

Proposed mechanism of action

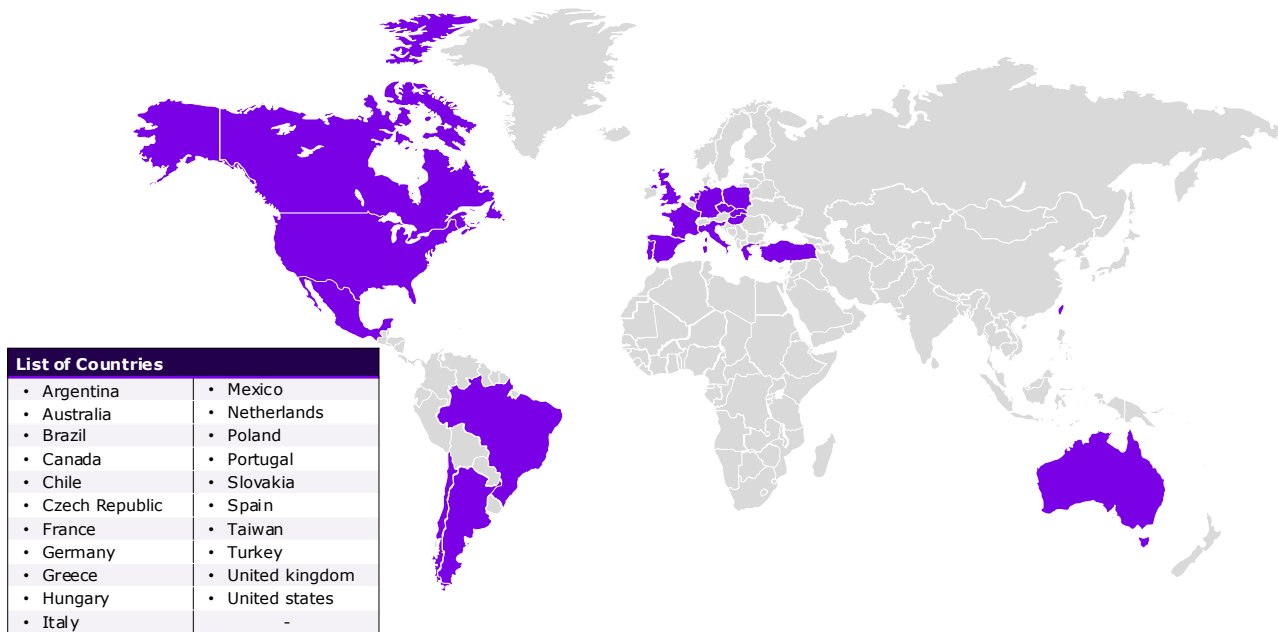
RESULT (Phase 2a study)

- Study design
- Patient population

☒ Participating countries



Participating countries



This material is for scientific purposes only and is intended only for healthcare practitioners. Patient enrollment is dependent on approval by local ethics committee. Frexalimab, SAR442970, and rilzabrutinib are 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.

References

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Rare Diseases Pipeline

SAR439459* IN OSTEogenesis IMPERFECTA



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SAR439459

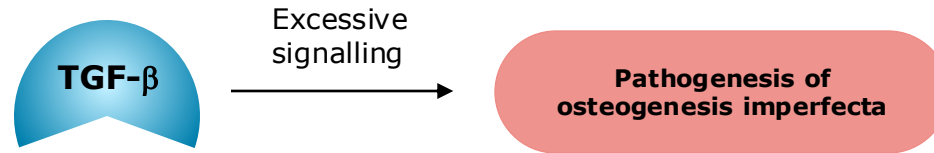
Osteogenesis Imperfecta

Proposed mechanism of action

POISE (Phase 1b study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- TGF- β is a protein that regulates collagen synthesis and is vital for coupling of bone resorption and bone formation.
- Excessive signalling of TGF- β is a driving pathogenic mechanism in osteogenesis imperfecta.

OI, osteogenesis imperfecta; TGF- β , transforming growth factor-beta.

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SAR439459

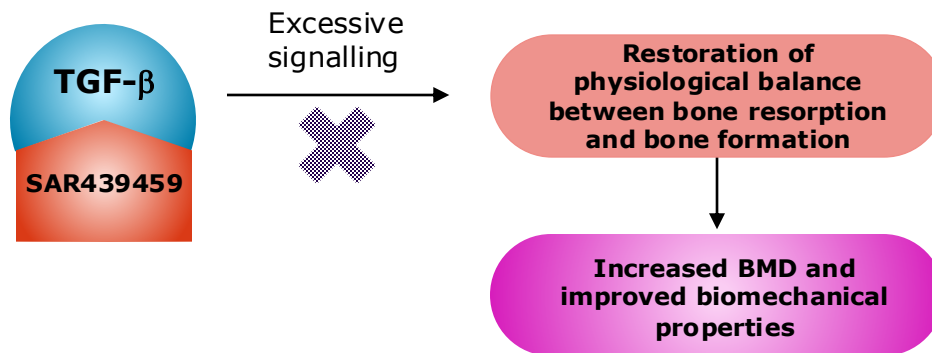
Osteogenesis Imperfecta

Proposed mechanism of action

POISE (Phase 1b study)

- Study design
- Patient population
- Participating countries

Proposed mechanism of action under investigation



- SAR439459, a pan-TGF- β inhibitor, is under investigation for its potential to improve biomechanical properties by inhibiting excessive TGF- β signalling and potentially restoring the physiological balance between bone resorption and bone formation.

BMD, bone mineral density; OI, osteogenesis imperfecta; TGF- β , transforming growth factor-beta.

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SAR439459

Osteogenesis Imperfecta

Proposed mechanism of action

POISE (Phase 1b study)

Study design

- Patient population
- Participating countries

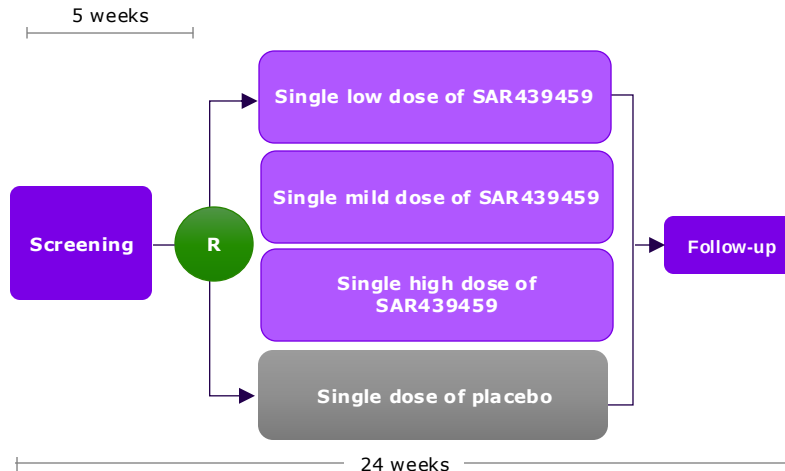
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POISE 1

Study design

Phase 1b, single ascending dose, randomized, double-blind study, to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics, and activity of a single dose of SAR439459, a human anti-transforming growth factor β (TGF β) monoclonal antibody, in adult patients with osteogenesis imperfecta



Primary endpoint

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

Secondary endpoints

- 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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SAR439459

Osteogenesis Imperfecta

Proposed mechanism of action

POISE (Phase 1b study)

- Study design

- Patient population

- Participating countries

POISE 1

Patient population

Inclusion criteria

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

Exclusion criteria

- Installed rods or metal hardware that could impact bone mineral density evaluation of the lumbar spine
- History of 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.

A full list of inclusion and exclusion criteria are available on www.clinicaltrials.gov (NCT05222906).

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SAR439459

Osteogenesis Imperfecta

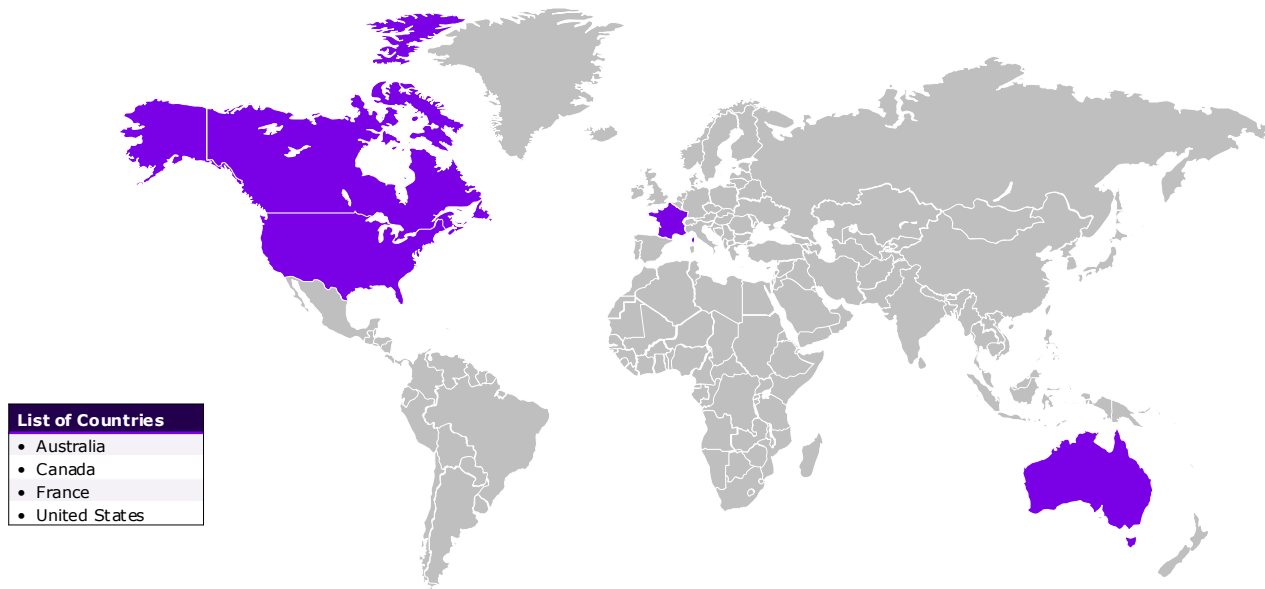
Proposed mechanism of action

POISE (Phase 1b study)

- Study design
- Patient population
- Participating countries

POISE 1

Participating countries



List of Countries

- Australia
- Canada
- France
- United States

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