AMENDED CLINICAL TRIAL PROTOCOL 06

Protocol title:	A multicenter, multinational, randomized, double-blind, placebo-controlled study to assess the efficacy, pharmacodynamics, pharmacokinetics, safety, and tolerability of venglustat in late-onset GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease) together with a separate basket for juvenile/adolescent late-onset GM2 gangliosidosis and ultra-rare diseases within the same and similar glucosylceramide-based sphingolipid pathway
Protocol number:	**EFC15299**
Amendment number:	**06**
Compound number (INN/Trademark):	**GZ402671** **Venglustat**
Study phase:	**Phase 3**
Short title:	A multinational, randomized, double-blind, placebo-controlled study to assess the efficacy, pharmacodynamics, pharmacokinetics, and safety of venglustat in late-onset GM2 (AMETHIST)
Sponsor name:	**Genzyme Corporation** **450 Water Street** **Cambridge** **MA 02141** **USA**
Legal registered address:	
Monitoring Team's Representative Name and Contact Information	

Regulatory agency identifier number(s):

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WHO:	U1111-1197-7905
Other:	Not applicable

Approval Date: 16-Aug-2023 Total number of pages: 135

PROTOCOL AMENDMENT SUMMARY OF CHANGES

DOCUMENT HISTORY

Document	Country/countries impacted by amendment	Date, version
Amended Clinical Trial Protocol 06	All	16 August 2023, version 1 (electronic 8.0)
Amended Clinical Trial Protocol 05	All	11 November 2022, version 1 (electronic 6.0)
Amended Clinical Trial Protocol 04	All	20 April 2022, version 1 (electronic 5.0)
Amended Clinical Trial Protocol 03	All	08 March 2021, version 2 (electronic 4.0)
Amended Clinical Trial Protocol 02	All	09 March 2020, version 1 (electronic 2.0)
Amended Clinical Trial Protocol 01	All	05 November 2019, version 1 (electronic 1.0)
Original Protocol		06 August 2019, version 2 (electronic 2.0)

Amended protocol 06 (16 August 2023)

This amended protocol 06 (Amendment 06) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to update the statistical considerations section, mainly to account for potential outliers in the primary and secondary analyses, and add a secondary endpoint per FDA recommendation.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis, Objectives and endpoints	For the primary population, add a secondary endpoint of absolute change in CSF GM2 biomarker from baseline to Week 104	As per FDA recommendation related to the addition of this secondary endpoint in the primary population
Section 3, Table 3 Objectives and endpoints	For the secondary population, add a secondary endpoint to assess the acceptability and palatability of the venglustat tablet	The addition of this secondary endpoint for the secondary population is to align with the PIP commitment to document as an endpoint. The assessments have been included in this study.
Section 1.1 Synopsis, Statistical considerations	Primary analysis of 9-HPT with Bayesian analysis using noninformative prior is replaced by a Frequentist analysis	Bayesian analysis using non-informative prior is equivalent to a Frequentist analysis. Bayesian analysis with informative prior remains a secondary analysis of the 9-HPT.

Section # and Name	Description of Change	Brief Rationale
	For primary and secondary endpoints, use of robust ANCOVA in case of outliers.	Simulations showed that the power of the linear mixed effect model would be severely impacted if a small proportion of participants have extreme slope
	Include in the analysis of secondary endpoints the new secondary endpoint of absolute change in CSF GM2 biomarker	Inclusion of new secondary endpoint as per FDA recommendation
Section 1.3 Schedule of Activities, Visit at clinical site	Clarify that, for United States participants, Visits 3, 8, 10, and 12 can be provided remotely under a decentralized clinical trial (DCT) model	Clarification of remote visits option for United States participants
	Removed the specification that the IMP can be dispensed and sent to participants at the visits provided under DCT model via DTP shipment except if the local regulatory authority requires the IMP dispensed at site.	Editorial correction
Section 1.3 Schedule of Activities, Venglustat or placebo	Added note to clarify the first dose in the open-label extension phase	Clarification
Section 1.3 Schedule of Activities, Dispense IMP	Replaced: "In addition to the IMP dispensing at these site visits, the IMP will be dispensed and sent to participants at W39 and W65 via DTP shipment." With: “In addition to the IMP dispensing at these clinical site visits, IMP will be dispensed at remote site visits where appplicable via DTP shipment. At Visit 4.1 (W39) and Visit 5.1(W65), IMP will be dispensed and sent to participants via DTP shipment.”	Clarification of IMP dispensation via DTP
Section 1.3 Schedule of Activities, Dispense/check Participant Diary	Changed title to: “Dispense/Check/Retrieve Patient Diary”	Clarification to check diary at each visit
Section 1.3 Schedule of Activities, 12-lead ECG	Add in column Notes: “Please note that ECG is required in triplicate only at Visit 2”	Clarification of EGC at Visit 2
Section 1.3 Schedule of Activities, Urine biochemistry (including UPCR and UACR)	Reduced the number of urine samples collected for protein:creatinine and albumin:creatinine ratios from 3 samples collected on successive days (2 days preceding a visit, plus the day of the visit) to single samples collected on the day of a visit.	Venglustat study participants found the collection of second-void morning samples on 3 successive days to be burdensome. One first-void morning sample will therefore be collected which should also aid compliance.
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities, ophthalmological examination	A full ophthalmological examination will also be performed at Week 130, Week 156, and Week 182 for participants aged ≥2 and <18 years	Revised to include participants aged ≥2 and <18 years
Section 1.3 Schedule of Activities, PK Plasma samples	Clarify the PK sample ID for early withdrawal visit	Clarification
Section 2.3.1.1 Potential risks specific for pediatric population	Update potential risk for venglustat-mediated lenticular degeneration in pediatric population	Clarification
Section 2.3.1.1 Potential risks specific for pediatric population	Risk title updated: Potential male infertility due to exposure in childhood (<12 years of age)	For alignment and clarification
	Deleted the wording audited draft results for JUV0046 study	JUV0046 study results final report available
Table 2 Risk mitigation strategy	Potential risk of new or worsening lens opacity is updated to include children two to less than 18 years old	Per FDA feedback
	Risk title updated: Potential male infertility due to exposure in childhood (<12 years of age)	For alignment and clarification
Section 3, Table 3 Objectives and endpoints	Added in exploratory endpoints for primary population "Additional plasma and CSF biomarkers may include but are not limited to: lipidomics, glycoprotein nonmetastatic protein B (gpNMB), neurofilament"	To clarify the exploratory biomarkers endpoints of primary population and align with Section 8.6
Section 6.5.1.3, Medications with risk to cause cataract	Revised text to specify that listed medications are prohibited for participants age <18 (rather than for participants age <12).	Updated for consistency with safety information regarding cataract risks.
Section 8.2.5 Ophthalmological examination	A full ophthalmological examination will be performed at Week 26, Week 52, and Week 78 for all participants and also at Week 130, Week 156, and Week 182 for participants aged ≥2 and <18 ~~12~~ years	Revised to include participants aged ≥2 and <18 years
Section 8.7 acceptability and palatability	Add this section that clarifies the acceptability and palatability assessments	To align with the PIP commitment, which missed documenting acceptability and palatability of venglustat tablet as endpoints. The assessments have been included in this study
Section 9.4.1 Efficacy analyses	For primary and secondary endpoints in the primary population: primary analyses are updated to use a robust ANCOVA in case of outliers, with pre-specified criteria.	Simulations showed that the power of the linear mixed effect model would be severely impacted if a small proportion of participants have extreme slope.

Section # and Name	Description of Change	Brief Rationale
	Primary analysis of 9-HPT with Bayesian analysis using noninformative prior is replaced by a Frequentist analysis	Bayesian analysis using non-informative prior is equivalent to a Frequentist analysis. Bayesian analysis with informative prior remains a secondary analysis of the 9-HPT.
	Update of prior distribution of placebo slope, used as secondary analysis of the 9-HPT	Prior distribution in the initial protocol was based on data collected from 2015 to 2018 during the National Tay-Sachs and Allied Disease annual conference. Additional data were collected in 2019 and integrated in updated analysis.
	Addition of the analysis planned for the new secondary endpoint of absolute change in CSF GM2 biomarker from baseline to Week 104, similar to the analysis of the percent change in CSF GM2 biomarker	For consistency between analyses of the co-primary efficacy endpoint of percent change in CSF GM2 and secondary efficacy endpoint of absolute change in CSF GM2, similar methodology will be used
	The procedure for handling multiplicity of tests for secondary endpoints using a hierarchical approach was replaced by the Hochberg procedure	To account for the new secondary efficacy endpoint that was added

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1 PROTOCOL SUMMARY

1.1 SYNOPSIS

Protocol title:

A multicenter, multinational, randomized, double-blind, placebo-controlled study to assess the efficacy, pharmacodynamics, pharmacokinetics, safety, and tolerability of venglustat in late-onset GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease) together with a separate basket for juvenile/adolescent late-onset GM2 gangliosidosis and ultra-rare diseases within the same and similar glucosylceramide-based sphingolipid pathway

Short title:

A multinational, randomized, double-blind, placebo-controlled study to assess the efficacy, pharmacodynamics, pharmacokinetics, and safety of venglustat in late-onset GM2 (AMETHIST)

Rationale:

[redacted]

Objectives and endpoints

Objectives	Endpoints
Primary	
Primary population: • To assess the efficacy and pharmacodynamics (PD) of daily oral dosing of venglustat when administered over a 104-week period.	Co-primary endpoints: • Percent change in cerebrospinal fluid (CSF) GM2 biomarker from baseline to Week 104. • Annualized rate of change in the 9-hole peg test (9-HPT) from baseline to Week 104.
Secondary population: • To assess PD response (plasma and CSF GL-1 biomarker and disease specific biomarkers) of venglustat when administered once daily over a 104-week period.	• Plasma and CSF GL-1 biomarker and a pathway specific biomarker will be assessed as follows: **Disease** / **Biomarker** GM2 gangliosidosis / GL-1, GM2 GM1 gangliosidosis / GL-1, GM1 Sialidosis / GL-1, GM2, GM3 Galactosialidosis / GL-1, GM1, GM3 Saposin C Deficiency / GL-1 only • Additional plasma and CSF biomarkers may include but are not limited to: lipidomics, glycoprotein nonmetastatic protein B (gpNMB), neurofilament.
Secondary	
Primary population: • To assess the PD of daily oral dosing of venglustat and the effect of venglustat on selected performance test and scale over a 104-week period.	• Absolute change in CSF GM2 biomarker from baseline to Week 104. • Change in 25-foot walk test (25FWT) from baseline to Week 104 (in participants able to walk at baseline). • Change in the neurological examination of the Friedreich's Ataxia Rating Scale (FARS) from baseline to Week 104.
Primary population: • To determine the safety and tolerability of venglustat when administered orally once daily over a 104-week period.	• Changes from baseline to Week 104 in the following: - Assessment of adverse events (AEs) and concomitant medication - Neurological examination - Ophthalmological examination - Vital signs - Clinical laboratory evaluations including hematology, biochemistry, urinalysis, and serology - Electrocardiogram (ECG)

Objectives	Endpoints
Primary population: • To assess the pharmacokinetics (PK) of venglustat in plasma and CSF.	• Plasma and CSF venglustat concentrations at prespecified visits over the study duration and plasma PK parameters (when applicable) including maximum plasma concentration observed (C_{max}), t_{max}, and area under the plasma concentration versus time curve calculated using the trapezoidal method over a predefined time period (from time t=0 to 24 hours; AUC_{0-24}).
Secondary population: • To assess the effect of venglustat on selected performance tests and scale over a 104-week period.	• Annualized rate of change in the 9-HPT from baseline to Week 104. • Change in 25FWT from baseline to Week 104 (in participants able to walk at baseline). • Change in the neurological examination of the FARS from baseline to Week 104. •
Secondary population: • To determine the safety and tolerability of venglustat when administered once daily over a 104-week period.	• Changes from baseline to Week 104 in the following: - Assessment of AEs and concomitant medication - Neurological examination - Ophthalmological examination - Vital signs - Clinical laboratory evaluations including hematology, biochemistry, urinalysis, and serology - ECG
Secondary population: • To assess the PK of venglustat in plasma and CSF.	• Plasma and CSF venglustat concentrations over the study duration and plasma PK parameters (when applicable) including C_{max}, t_{max}, and AUC_{0-24} calculated using the trapezoidal method.
Secondary population: • To assess the acceptability and palatability of the venglustat tablet	• Acceptability and palatability assessments

Overall design:

This is a multicenter, multinational, randomized, double-blind, placebo-controlled, 2-arm, 104-week study (primary population only) to assess the efficacy and safety of venglustat as compared with placebo in adult participants with a diagnosis of late-onset GM2 gangliosidosis (referred to as primary population) and venglustat received in an open-label design in participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis,

GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis, if any of the sites have such participants meeting the inclusion and none of the exclusion criteria (referred to as secondary population). The secondary population is composed of participants with juvenile/adolescent late-onset GM2 gangliosidosis and ultra-rare conditions within the same biochemical pathway as the primary population. The 104-week treatment period (primary analysis period) will be followed by an open-label extension period with venglustat treatment for all patients. The study will be conducted at multiple multinational sites (approximately 30 sites).

The study will include 4 main periods:

1. Period 1 (screening period from Day -60 to Day -1): Participant and/or participant's parent(s)/legal guardian(s) will sign and date informed consent and the participant will undergo screening assessments to determine participant eligibility. If all eligibility criteria are met, the participant will start study treatment.
2. Period 2 (primary analysis period, 104-week treatment period): Participants in the primary population will be randomly assigned in a 2:1 ratio to receive venglustat or placebo once daily for 104 weeks in a double-blind design. Randomization will be stratified on the participant's ability to walk at the baseline visit (yes/no). Participants in the secondary population will receive venglustat for 104 weeks in an open-label design. Safety, tolerability, PK, PD, and efficacy of venglustat once daily administration will be determined during the 104-week treatment period.
3. Period 3 (104-week OLE period): Participants in both the primary and secondary populations will be automatically entered into the OLE period following completion of the primary analysis period (period 2). All participants will receive venglustat for 104 weeks in an open-label design. Long-term safety, tolerability, PD, and efficacy of venglustat once daily administration will be assessed during the 104-week OLE period. Participants who complete the primary analysis period but would not continue to the OLE period, and safety follow-up/end-of-study (EOS) visit will be conducted 6 weeks after the W104 visit. Participants who complete the primary analysis period within 3 months prior to the OLE (amended protocol 4) approval by local regulations, will have the option to enroll into the OLE when the OLE (amended protocol 4) is approved. Participants who prematurely discontinue the study treatment from the primary analysis period will not have the option to enroll into the OLE.
4. Period 4 (post-treatment safety observation period, 6-week follow-up period). The post-treatment safety observation period will be for 6 weeks after Period 3, and safety and tolerability will continue to be assessed.

Post-trial access to venglustat will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

Disclosure Statement: This is a Parallel, Treatment study with 2 arms that are blinded/masked for Investigator and participants in the primary population for the primary analysis at 104 weeks. For the secondary population, this is an open-label, single-arm treatment study.

Number of participants:

Approximately 57 participants with late-onset adult GM2 gangliosidosis will be treated in the study (primary population). After safety data from Week 1/Day 1 to Week 12 visits for the first 5 participants of the primary population are reviewed and considered satisfactory, enrollment of the secondary population will begin. In addition to the primary population, up to 20 participants in total are planned for the secondary population. An attempt will be made and first prioritized to enroll at least 1 participant (age 2 years or older) in each of the following disorders: juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, and juvenile/adult galactosialidosis.

Intervention groups and duration:

During the 104-week primary analysis treatment period, participants in the primary population will be randomly assigned in a 2:1 ratio to receive venglustat or placebo once daily in a double-blind manner. Randomization will be stratified on the participant's ability to walk at the baseline visit (yes/no). Participants in the secondary population will receive venglustat for 104 weeks in an open-label manner.

During the 104-week OLE treatment period, all participants in both primary and secondary populations will receive venglustat in an open-label manner.

Study intervention(s)

Investigational medicinal products: Venglustat or placebo

- Formulation: venglustat [redacted] and 15 mg and placebo (identical to venglustat 15 mg tablets in appearance) tablets. The placebo is only for 15 mg venglustat tablets. Strength refers to the free base corresponding to the active moiety.
- Route of administration: oral.
- Dose regimen:
  - The investigational medicinal product (IMP) can be swallowed whole or chewed and then swallowed. Administration of IMP by chewing and swallowing or swallowing whole should be as consistent as possible throughout study treatment, and the method should be documented in the electronic case report form.
  - Adult onset GM2 gangliosidosis participants will receive a venglustat 15 mg tablet or placebo once daily in the primary analysis period and will receive a venglustat 15 mg tablet once daily in the OLE treatment period.
  - Adult participants in the secondary population will receive a venglustat 15 mg tablet once daily in the primary analysis period and OLE treatment period.
  - Adolescents and juvenile participants in the secondary population (≥2 years of age) will receive venglustat [redacted]
    As adolescent and juvenile participants grow, venglustat doses [redacted]

[redacted]

Statistical considerations:

- **Sample size calculations**: In the primary population, approximately 57 participants will be randomly assigned with a 2:1 randomization ratio to venglustat (n=38) or placebo (n=19). This sample size will provide approximately 80% power to detect a difference between venglustat and placebo with regards to the primary efficacy endpoint of annualized rate of change in 9-HPT. It will also provide >99% power to detect a difference between venglustat and placebo with regards to the co-primary endpoint of percent change in CSF GM2 biomarker from baseline to Week 104. The sample size for the secondary population up to 20 is not based on statistical power calculation, but on empirical considerations. The Sponsor will attempt to enroll at least 1 participant, aged 2 years or older (or ages 2 to <18 years for juvenile/adolescent late-onset GM2 gangliosidosis), in each disorder. This is in addition to the 57 participants from the primary population.
- **Primary analysis**: Percent change in cerebrospinal fluid (CSF) GM2 biomarker from baseline to Week 104 will be analyzed using an analysis of covariance (ANCOVA) including the fixed effect of treatment (venglustat versus placebo) and the continuous fixed covariate of baseline value. If the results from the ANCOVA approach are severely impacted by the presence of outliers, a robust ANCOVA, using Huber's M estimation, will be used. Annualized rate of change in 9-HPT from baseline to Week 104 will be compared between venglustat and placebo using a linear mixed-effect model with random intercept and slopes, estimated in a frequentist framework. Actual time relative to randomization of all planned assessments at Week 12, Week 26, Week 52, Week 78, and Week 104 will be taken into account in the model. If the results from the linear mixed-effect model are severely impacted by the presence of outliers, a robust ANCOVA on individual slopes, using Huber's M estimation, will be used. A secondary analysis will use a Bayesian approach with an informative prior distribution for the slope in the placebo arm, based on natural history data.
- **Analysis of secondary endpoints**: Absolute change in CSF GM2 biomarker will be analyzed using an ANCOVA or a robust ANCOVA; similar to the model use for the percent change in CSF GM2.

  Change in 25FWT and neurological examination of the FARS will be compared between venglustat and placebo using a linear mixed-effect model with random intercept and slopes or using a robust ANCOVA on individual slopes, similar to the model used for 9-HPT.

- Plasma and CSF GL-1 biomarker and pathway specific biomarkers in the secondary population will be summarized descriptively. Percent change from baseline in plasma and CSF GL-1 biomarker will be described for the entire secondary population. The pathway specific biomarker will be described separately for each disease in the secondary population. When at least 5 participants have available data in the entire secondary population or within a specific disease, a 95% confidence interval for the percent change from baseline will be provided. In addition, biomarker data will be summarized descriptively with individual plots and listings. No formal comparison will be performed in the secondary population.

Data Monitoring Committee: Yes

1.2 SCHEMA

Figure 1 - Graphical study design

1.3 SCHEDULE OF ACTIVITIES (SOA)

Table 1 - Schedule of assessments

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW [b]**	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1[c]**	**5**	**5.1[c]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
Visit at clinical site	X	X	X	X		X		X	X	X	X	X	X	X	For participants in United States, Visit 3, 8, 10 and 12 can be provided remotely under a decentralized clinical trial (DCT) model (Optional). For Visits 8 (W130), 10 (W182) and 12 (W214), may be provided remotely under a DCT model (optional) where applicable, allowed by local regulations, and approved by the participant.
Informed consent	X														
Inclusion/exclusion criteria	X	X													
Demographics and baseline characteristics	X														
Medical/surgical/treatment history/alcohol use history	X														
Experience of participating in the Natural History Study (NIH/NTSAD)	X														For participants in the United States only.

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW[b]**	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1[c]**	**5**	**5.1[c]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
Hexosaminidase enzyme activity	X	X													Only for primary population. Samples will be collected for all participants during screening or at D1 (predose). Only 1 sample will be collected, during screening or at D1 after 4 hr fasting. For those with historical results, they may begin the study without
[redacted]															
Lumbar puncture	X[d]								X[e]						*d* LP will be performed once participant demonstrates eligibility based on screening criteria. The LP may be done during the screening period within 14 days prior to treatment initiation (D -14 to D -1). The LP should be done successfully before first dose and/or randomization. *e* The LP should be done after all other assessments if possible.

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW *b***	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1[c]**	**5**	**5.1[c]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
Study IMP administration															
Randomization		X													For the primary population only.
IRT contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	For Canadian participants enrolled in the US, see Section 10.8.
Dispense IMP		X	X	X	X	X	X	X	X	X	X	X			In addition to the IMP dispensing at these clinical site visits, IMP will be dispensed at remote site visits where applicable via DTP shipment. At Visit 4.1 (W39) and Visit 5.1(W65), IMP will be dispensed and sent to participants via DTP shipment. For Canadian participants enrolled in the US, see Section 10.8. .

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW*a***	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW *b***	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1*c***	**5**	**5.1*c***	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
Venglustat or placebo		<---------- Once daily ---------->													Participants in the primary population will receive venglustat or placebo once daily for 104 weeks in a double-blind manner in the primary analysis period and receive venglustat once daily for 104 weeks in an open-label manner in the open-label extension period. Participants in the secondary population will receive venglustat for 208 weeks in an open-label manner. Participants will take the first IMP dose of open-label extension period dispensed at Visit 7 on the day after completion all Visit 7assessments.
Dispense /Check/Retrieve Patient Diary	X*f*	X	X	X		X		X	X	X	X	X	X	X*g*	*f* dispense only *g* retrieve only
Telephone call to participants		<----------													Telephone call follow-ups to occur every 60 ±3 days after D 1, except for scheduled follow up phone calls which would fall within a few days (up to 10 days) from a site visit. Assessments include participant status, AEs, participant diary, IMP compliance, and concomitant medications. For participants who withdraw early from the treatment, follow-up telephone call should occur up to 6 weeks after last dose of study IMP. An unscheduled

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW [b]**	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1[c]**	**5**	**5.1[c]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
															phone visit or a remote monitoring may be required due to regional or national emergency as declared by a governmental agency.
Physical examination	X[h]	X[h]	X[h]	X[h]		X[h]		X[h]	X[h]	X[h]	X[h]	X[h]	X[h]	X[i]	*h* complete/full physical examination including visual acuity. *i* abbreviated/brief physical examination.
Neurological examination	X								X		X		X		When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed before the ophthalmological examination.
Body weight	X	X	X	X		X		X	X	X	X	X	X	X	
Height	X	X[j]	X[j]	X[j]		X[j]		X[j]	X[j]	X[j]	X[j]	X[j]	X[j]		*j* For juvenile and adolescent participants only.
Archival blood sample		X													This sample will be collected and stored for use if any unexpected safety issue occurs to ensure that a predose baseline value is available for previously nonassessed parameters.
Vital signs	X	X	X	X		X		X	X	X	X	X	X	X	Includes heart rate, systolic and diastolic blood pressure, respiratory rate, and body temperature.
Serum β-hCG	X														

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW** *b*	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1**[c]	**5**	**5.1**[c]	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
pregnancy test (for WOCBP)															
Urine pregnancy test (for WOCBP)		<----------*Every 4 weeks*---------->													Female patients of childbearing potential only. Results will be captured in patient diary when test is not taken at the clinic. At V2, it must be negative before the first IMP administration.
Serology tests for hepatitis B, C, and other infectious disease, if locally required	X														
Hematology, biochemistry, urinalysis	X	X	X	X		X		X	X	X	X	X	X	X	Urinalysis by dipstick will be performed at the site. If abnormal, a complete urinalysis will be performed by the central laboratory
Urine biochemistry (including UPCR and UACR) [k]		X	X	X		X		X	X	X	X	X	X		

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	Up to 60 d before D1	W1/D1	W12 (±7d)	W26 (±7d)	W39 (±7d)	W52 (±7d)	W65 (±7d)	W78 (±7d)	W104 (±7d)/ EW[a]	W130 (±14d)	W156 (±14d)	W182 (±14d)	W208 (±14d)/ EOT/EW [b]	W214 (±7d) SFU after EOT	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	1	2	3	4	4.1[c]	5	5.1[c]	6	7	8	9	10	11	12	For further details, see footnote "c" at the end of the table.
															k First morning void urine sample to be collected on the day of the site visit or home visit (where allowed per local regulations). Second morning void urine sample can be collected if first morning void urine sample was not collected. Courier transportation can be arranged as required and if allowed per local regulations. Urine sample should be sent to the central laboratory for quantitative measurement of creatinine, total protein and albumin which will be used to calculate the urine albumin/creatinine ratio and urine protein/creatinine ratio.
12-lead ECG	X	X[l]		X		X		X	X		X		X		*l* ECG in triplicate will be performed prior to IMP administration. Please note that ECG is required in triplicate only at Visit 2.
Ophthalmological examination	X[m]			X[n]		X[n]		X[n]	X[m]	X[o]	X[o]	X[o]	X[m]		*m* Full ophthalmological examination (including slit lamp fundoscopy with dilation), photography, and ARLNS for all participants.

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	Up to 60 d before D1	W1/D1	W12 (±7d)	W26 (±7d)	W39 (±7d)	W52 (±7d)	W65 (±7d)	W78 (±7d)	W104 (±7d)/ EW[a]	W130 (±14d)	W156 (±14d)	W182 (±14d)	W208 (±14d)/ EOT/EW [b]	W214 (±7d) SFU after EOT	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	1	2	3	4	4.1[c]	5	5.1[c]	6	7	8	9	10	11	12	For further details, see footnote "c" at the end of the table.
															n Full ophthalmological examination (including slit lamp fundoscopy with dilation) for all participants. *o* Full ophthalmological examination (including slit lamp fundoscopy with dilation), for participants ≥2 and <18 years of age only. Full ophthalmological examination, photography, and ARLNS can be performed at any time if deemed medically necessary. When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed before the ophthalmological examination.
AE collection	X	X	X	X		X		X	X	X	X	X	X	X	AEs will be captured from the time the participant provides signed informed consent through the safety follow-up period up to 6 weeks after the W208 EOT visit.
Prior and concomitant medications	X	X	X	X		X		X	X	X	X	X	X	X	

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW** *b*	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1**[c]	**5**	**5.1**[c]	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote
[redacted]															
Pharmacokinetics															
Plasma samples		X[r]	X[s]	X[t]		X[t]			X[u]						*r* For primary population, sampling will be performed predose and 0.5, 3, 8, 12, and 24 hours postdose in 15 participants (Plasma sample ID P00, P01, P02, P03, P04, P05, respectively). This PK profile sub study will stop when required numbers of samplings are collected. For all other participants, sampling will be performed only at 3 hours postdose (P02). Participants will receive IMP at clinical site on this day.

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW [b]**	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1[c]**	**5**	**5.1[c]**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
															s Sampling will be performed predose and 0.5, 3, 8, 12, and 24 hours postdose (Plasma sample ID P06, P07, P08, P09, P10, P11 respectively). *t* Sampling will be performed predose and 3 hours postdose. (Plasma sample ID P12, P13 at Visit 4/Week 26 and P14 and P15 at Visit 5/Week 52, respectively). Participants will receive IMP at the clinical site on these days. *u* Sampling will be performed predose (plasma sample ID P16 for participants who complete the V7/W104 visit; plasma sample ID P18 for participants who complete the EW visit.)
CSF samples									X[v]						*v* Sampling will be performed predose (CSF sample ID C00).
Assessments															
9-HPT	X	X	X	X		X		X	X		X		X		
Timed 25-FWT	X	X	X	X		X		X	X		X		X		
FARS Part I, functional staging of ataxia	X	X	X	X		X		X	X		X		X		
FARS Part II, Activities of Daily	X	X	X	X		X		X	X		X		X		

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	**Up to 60 d before D1**	**W1/D1**	**W12 (±7d)**	**W26 (±7d)**	**W39 (±7d)**	**W52 (±7d)**	**W65 (±7d)**	**W78 (±7d)**	**W104 (±7d)/ EW[a]**	**W130 (±14d)**	**W156 (±14d)**	**W182 (±14d)**	**W208 (±14d)/ EOT/EW** *b*	**W214 (±7d) SFU after EOT**	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	**1**	**2**	**3**	**4**	**4.1**[c]	**5**	**5.1**[c]	**6**	**7**	**8**	**9**	**10**	**11**	**12**	For further details, see footnote "c" at the end of the table.
Living															
FARS Part III, neurological examination	X	X	X	X		X		X	X		X		X		
Muscle weakness of triceps and quadriceps		X	X	X		X		X	X		X		X		
FARS functional test, PATA	X	X	X	X		X		X	X		X		X		
[redacted]															

Study Period/ Procedure	Screening	Primary analysis treatment period								Open-label extension treatment period				FU Period	Notes
Day or Week	Up to 60 d before D1	W1/D1	W12 (±7d)	W26 (±7d)	W39 (±7d)	W52 (±7d)	W65 (±7d)	W78 (±7d)	W104 (±7d)/ EW[a]	W130 (±14d)	W156 (±14d)	W182 (±14d)	W208 (±14d)/ EOT/EW *b*	W214 (±7d) SFU after EOT	W1/D1 visit will be Baseline visit. For further details, see footnotes "a" and "b" at end of the table.
Visit number	1	2	3	4	4.1[c]	5	5.1[c]	6	7	8	9	10	11	12	For further details, see footnote "c" at the end of the table.
[redacted]															

Abbreviations: 9-HPT, 9-hole peg test; ADL, activities of daily living, a PRO from the FARS; ADME, absorption, distribution, metabolism, excretion; [redacted]; AE, adverse event; ARLNS, Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System; β-hCG, beta human chorionic gonadotropin; [redacted]; CSF, cerebrospinal fluid; d, days; D, day; DTP, direct to patient; ECG, electrocardiogram; EOT, end of treatment; EW, early withdrawal; FARS, Friedreich's Ataxia Rating Scale; FU, follow-up; HBV, hepatitis B; HCV, hepatitis C; HIV, human immunodeficiency virus; IMP, investigational medicinal product; IRT, interactive response technology; LP, lumbar puncture; [redacted] NIH, National Institutes of Health; NTSAD, National Tay-Sachs & Allied Diseases Associations; [redacted] PATA, a speech test using the phrase "pata"; [redacted] PK, pharmacokinetic; [redacted]; W, week; WOCBP, woman of childbearing potential.

Note: All screening assessments are not required to be repeated for participant rescreening. Cognitive, behavioral, and ataxia assessments are not required to be repeated if performed within 3 months.

Note: [redacted] questionnaires should be completed by the participants before the consultation and/or clinical tests.

a In case of early treatment withdrawal before W104, and if participant does not wish to stay in the study, assessments mentioned in the W104 visit will be performed, followed by safety follow-up visit 6 weeks after the W104/EW visit.

b In case of early treatment withdrawal after W104, and if participant does not wish to stay in the study after W104, assessments mentioned in the W208 will be performed, followed by safety follow-up visit 6 weeks after the W208/EOT/EW visit.

c The IMP can be dispensed and sent to participants at Visits 4.1 (W39) and 5.1 (W65) via DTP shipment except if the local regulatory authority requires the IMP dispensed at site. No other study assessments are planned during these 2 visits.

2 INTRODUCTION

Sanofi Genzyme is investigating venglustat (GZ/SAR402671) as a possible oral SRT for the treatment of lysosomal storage disorders characterized by deficits in the GL-1 catabolism pathway. In this trial, venglustat will be investigated in adult late-onset GM2 gangliosidosis (late-onset Tay-Sachs disease and Sandhoff disease) together with a separate basket for juvenile/adolescent late-onset GM2 gangliosidosis and ultra-rare diseases within the same and similar GL-1-based sphingolipid pathway.

2.1 STUDY RATIONALE

[redacted].

2.2 BACKGROUND

2.2.1 GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease)

Tay-Sachs disease and Sandhoff disease are known as GM2 gangliosidosis due to excessive accumulation of GM2 and related glycolipids in the lysosomes and neurons. Degradation of GM2 requires it to be complexed with a substrate-specific cofactor known as GM2 activator and presented to the catabolic enzyme beta-hexosaminidase comprised of alpha and beta subunits encoded by the HEXA and HEXB genes, respectively. Beta-hexosaminidase exists as 2 distinct isozymes; beta-hexosaminidase A (an alpha/beta heterodimer that associates with the GM2 activator protein) and beta-hexosaminidase B (a beta/beta homodimer). Patients with Tay-Sachs disease have mutations in the HEXA gene, lack of beta-hexosaminidase A activity, and accumulation of GM2 in the brain and spinal cord leading to progressive neurodegeneration. Defects in the HEXB gene result in the loss of both beta-hexosaminidase A and B and cause the more severe Sandhoff disease associated with the accumulation of GM2, GM2's asialo derivative (GA2), and a number of oligosaccharides and glycoproteins that contain hexosaminidase substrates. The clinical phenotypes associated with Tay-Sachs disease and Sandhoff disease vary depending upon the age at which symptoms first appear. Infantile-onset disease is a rapidly progressive neurodegenerative disease culminating in death before age of 4 years (classical Tay-Sachs disease and Sandhoff disease, as well as GM2 activator deficiency). Late-onset, subacute or chronic, and progressive neurologic conditions are compatible with survival into childhood or teens (subacute form) or long survival (chronic form). Chronic forms include several different clinical phenotypes in which symptoms referable to one or another part of the CNS dominate, including progressive dystonia, spinocerebellar degeneration, motor neuron disease, or psychosis. Specific therapy for GM2 gangliosidosis is not available to date (4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15).

2.2.2 Venglustat

Venglustat is a novel GCS inhibitor that partially inhibits the synthesis of GL-1. Venglustat has been shown to have CNS activity and/or exposure in nonclinical studies performed in rats and dogs respectively and in ongoing clinical studies in patients with GD3 and GBA-PD.

As GL-1 serves as the central building block for more complex glycosphingolipids such as globotriaosylceramide, GM3, and GM2 ganglioside, SRT with GCS inhibitors is expected to have broad therapeutic applicability across a number of lysosomal storage diseases.

In vitro studies demonstrate that venglustat is a potent and selective inhibitor of murine and human GCS in biochemical and cell-based assays. In vivo pharmacology studies utilized plasma GL-1 lowering as a PD marker of GCS inhibition. In vivo activity was established in rodents and dogs with reductions in plasma (rodent and dog) and tissue (rodents only) GL-1 following oral

administration of venglustat. In both species, the effects of venglustat on plasma GL-1 were dose-dependent and correlated with plasma exposure of the compound. In rodents, venglustat has been shown to cross the BBB and reduce the synthesis of the major isoform of GL-1 in the CNS (ie, C18 GL-1). The CNS exposure has also been confirmed in dogs where the CSF concentrations of venglustat following repeat oral dosing were approximately 2-fold greater than the unbound plasma concentration of drug.

In Phase 1 healthy volunteer studies, once daily oral administration of venglustat at free base doses ranging from 3.72 mg to 14.9 mg was shown to be safe and reduce plasma levels of GL-1 in a time and dose-dependent manner. In these studies, venglustat was absorbed with a median t_{max} of 2 to 3 hours and eliminated with a pooled geometric mean terminal elimination half-life of 31.3 hours on Day 14.

The therapeutic effect of SRT for the treatment of systemic disease in GD1 has been established clinically with eliglustat (Cerdelga®), a specific, but structurally unrelated GCS inhibitor and negligible exposure in the brain, in both previously untreated, and ERT-controlled patients (1, 2). By reducing substrate influx, eliglustat significantly improved disease manifestations in untreated GD1 patients with existing visceral and hematologic involvement. In this cohort with GD1 and substantial disease manifestations, the slight decrease in clinical status of patients in the placebo group over 9 months underscored the progressive nature of GD. The magnitude of the improvements observed suggests that SRT alone has the potential to effectively restore balance in the production and degradation of GL-1 without prior reconstitution of the macrophage system with exogenous acid β-glucosidase. In GD1 patients already receiving ERT, and having reached therapeutic goals, oral eliglustat as monotherapy maintained hematological and organ volume stability (2).

Given the positive impact on visceral disease with SRT, it is anticipated that GCS inhibitors with appropriate CNS exposure and activity could address other lysosomal storage diseases where gangliosides and globosides accumulate. This hypothesis has been tested in HEXb-/- mice, a model of Sandhoff disease where the lipids that accumulate, GM2 and GA2, are downstream of GL1. Substrate accumulation in the Sandhoff mice is apparent throughout the CNS as well as in visceral tissues with CNS manifestations of disease apparent by approximately 90 days resulting in a median lifespan of approximately 130 days. In this aggressive model (complete deficiency), treatment with GZ466161, a GCS inhibitor from the same chemical series as venglustat, starting at 4 weeks of age was shown to delay the onset of clinical symptoms, reduce lipid accumulation in the CNS/liver and significantly increase the median survival of the mice (3). Analysis of lipids in the feline Sandhoff model via a gene therapy study further support the GCS inhibition hypothesis (16). Central nervous system, CSF, and serum samples from control and Sandhoff cats with or without AAV hexosaminidase gene therapy were analyzed for GM2 and lyso-GM2 levels. Preliminary data demonstrated a marked increase in GM2/lyso-GM2 in CNS tissue and CSF of Sandhoff cats relative to controls, and a reduction of lipids in both compartments following enzyme replacement (internal data, not published). Treatment of Sandhoff cats with the AAV same therapy results in improved clinical conditions scores and prolonged survival (16, 17).

More information on the safety of venglustat and on the clinical program can be found in the Investigator's Brochure.

2.3 BENEFIT/RISK ASSESSMENT

Venglustat has not been studied in patients with GM2 gangliosidosis. The information provided below mainly concern venglustat. More detailed information about the known and expected benefits and risks and reasonably expected Adverse Events (AEs) of venglustat may be found in the Investigator's Brochure (IB).

In the completed Phase 1 clinical trials in healthy volunteers, oral administration of venglustat was safe and well tolerated.

Ongoing studies are being conducted in patients with GD3 and Fabry disease (FD). One study in patients with GBA-PD and 2 studies in patients with autosomal dominant polycystic kidney disease were terminated due to lack of efficacy. The studies' termination was not due to safety reasons. The majority of reported AEs were assessed as mild to moderate; most of which resolved spontaneously. Serious adverse events (SAEs) and discontinuations due to AEs have been limited in Phase 2 studies. Based on an evaluation of the cumulative safety data from the clinical program, venglustat is generally safe and well tolerated.

2.3.1 Risk assessment

There is no important identified risk in humans at this time. Potential risks identified based on available non-clinical and clinical data are described below:

2.3.1.1 Potential risks specific for pediatric population

New or worsening lens opacity in children two to less than 18 years old

An important potential risk of new or worsening lens opacity was initially identified from juvenile toxicity study, where reversible lens degeneration was observed in both male and female rats administered 45 and ≥ 15 mg/kg/day venglustat, respectively. It was also reported from a 26-week study in adult female rats given a high dose of 20 mg/kg/day; incidence and severity decreased after the treatment-free period.

The potential risk of new or worsening lens opacities/cataracts in humans was evaluated in two large, placebo-controlled studies of venglustat. Studies EFC15392 and ACT14820 were randomized, double-blind, placebo-controlled trials in adult participants with autosomal dominant polycystic kidney disease (ADPKD) and adult participants with Parkinson's disease associated with *GBA* mutations (GBA-PD), respectively. Further details of these studies are provided in Section 6.2 of the Investigator's Brochure.

Both studies included comprehensive ophthalmological examinations, and the incidence of new or worsening cataracts was evaluated as an adverse event of special interest. Pooled data from both trials comparing placebo to venglustat 15 mg (placebo n=321, venglustat n=322) showed that the overall incidence of any treatment-emergent cataract was balanced between the treatment arms (7.5% in venglustat 15 mg vs 8.1% in placebo, respectively). The incidence of cataract subtypes (nuclear, cortical, subcapsular) was also balanced between placebo and venglustat 15 mg. Furthermore, Kaplan-Meier analyses did not demonstrate differences in the time to onset of new

cataracts or worsening of pre-existing cataracts. In EFC15392, decrease in distance best corrected visual acuity (BCVA) by one or more lines was comparable in placebo vs venglustat 15 mg (placebo 13.0%, venglustat 11.6%).

Based on these data, new or worsening lens opacity is no longer considered an important potential risk of venglustat in adults, and therefore the frequency of ophthalmological examinations is reduced in OLE phase in this study for adult participants.

During the time of the review of this risk on 15th August 2022, there were 13 participants aged 2 to <18 years enrolled in the AMETHIST study, 8 of whom were aged 2 to <12, and no lens opacity or cataracts have been observed in these participants. However, there is the potential for venglustat-related lenticular degeneration based on results from the juvenile rat toxicity study. Due to limited pediatric data in children from 2 to <18 years old, there still is a potential for venglustat-mediated lenticular degeneration and therefore children are potentially at greater risk than adults (EM = 3.7), given that juvenile female rat NOAEL exposure is less than therapeutic (ie, EM = 0.6). Importantly, a cataract that develops during childhood before the age of 8 to 10 year can lead to irreversible severe sequelae including blindness. The outcome of cataract surgery for younger participants is not as successful as for adults. Therefore, the potential risk of new or worsening lens opacity cannot be excluded in children 2 to less than 18 years old. Close ophthalmology monitoring of this population, if included in venglustat studies, will therefore be maintained. Children <2 years of age are excluded in the venglustat development program.

If a participant develops signs or symptoms concerning for cataract development or other visual problems at any time during the study, the Investigator may refer the participant to a specialist for a comprehensive ophthalmological examination as a part of participant's medical care.

Potential male infertility due to exposure in childhood (<12 years of age)

Potential effects on male fertility is an important potential risk derived from preclinical findings. In the 10-week oral juvenile toxicity study in the rat, degeneration of the germinal epithelium of the testes was observed at 45 mg/kg/day given from postnatal days 22 to 92 (age of the animals at the beginning of the dosing corresponds to 2-year-old humans). This finding was generally reversible at the end of the 12-week recovery period. In a male juvenile toxicity study with an 18-week recovery period (JUV0046), non-reversing microscopic changes in the testes (degeneration/atrophy) and epididymides (cellular debris, decreased sperm) were observed in rats administered 45 mg/kg/day during PND 22-90 and PND 22-50. In addition, non-reversing microscopic changes in the coagulating glands (mixed cell inflammation) were noted for males administered 45 mg/kg/day during PND 22-90 and PND 35-63. No venglustat-related effect on reproductive performance (male mating, fertility, and pregnancy indices) was observed. Slightly lower mean epididymal sperm concentrations that were not statistically significant were noted in the 45 mg/kg/day PND 22-90 and PND 22-50 groups compared to the control group. There were no other venglustat-related effects on sperm parameters (concentration, motility, and morphology) across all test article-treated groups during the dosing and recovery periods. No venglustat-related effects were noted for any parameter tested at 15 mg/kg/day. There were no similar findings in the 13-week-repeat-dose toxicity study in the adult rat in which there was a comparable level and duration of drug exposure. Also, no similar findings were observed in the 4-week and 26-week studies in the rat (age of the rats in the 26-week-repeat-dose study corresponds to 12-year-old humans), and in the 4-, 13-, and 39-week-repeat-dose studies in the adult dog.

The finding of degeneration of testicular germinal epithelium, which was restricted to juvenile rats, could be related to the development stage of the animals, and is currently considered to be a potential risk only for male participants exposed to venglustat below the age of 12 years. Exposure under 12 years of age has a potential to negatively impact male fertility, an effect which would manifest at the time of sexual maturity. Monitoring the effects of venglustat on germinal testicular epithelium in pediatric patients would be invasive, requiring the use of tissue biopsies. Given that there are currently no available therapies indicated or used in these pediatric patients and the burden of disease includes significant neurological deficits and reduced life expectancy, the expected benefit of venglustat in preventing or slowing disease progression appears to outweigh the potential risk of future male fertility issues. Although the secondary population will include patients aged ≤12 years, the Sponsor does not consider clinical monitoring of effects on germinal testicular epithelium in this study.

2.3.1.2 Depression

Adverse neurological and psychiatric events are being monitored in all venglustat studies given the compound's access to the central nervous system.

This is based on the fact that venglustat crosses the blood brain barrier and venglustat-related central nervous system (CNS) AEs were observed at 100 mg/kg/day in a non-Good Laboratory Practice (GLP) 7-day functional observational battery (FOB) study in rats. In this study, venglustat-related CNS AEs were reported, such as abnormal gait, abnormal breathing, hunched posture, ptyalism, piloerection, hypoactivity, and abnormal responses to auditory and tactile to stimuli and to a sudden noise. Given the poor clinical condition of the animals at this high dose/exposure, a direct effect on the CNS is unclear. In the 28-day-repeat-dose study, slight piloerection, hypoactivity, abnormal gait, or posture along with marked lower motor activity was noted for 45 mg/kg/day females, the highest dose evaluated. No venglustat-related CNS microscopic findings were observed at the highest dose of 45 mg/kg/day. A study to assess seizure threshold did not reveal any effect of venglustat in rats. Venglustat was detected in dog cerebrospinal fluid following a single and repeated oral administration at 10 mg/kg/day. Exposure of venglustat in cerebrospinal fluid was approximately 2-fold greater than the unbound plasma exposure in dogs.

An analysis of the clinical data from all venglustat study participants (FD, ADPKD, GBA-PD, GD3, GM2) concluded that depression is a potential risk in GBA-PD. Available data in the other populations receiving venglustat (ie, FD, GD3, GM2) was not sufficient to draw any conclusion. Periodic assessment of depression symptoms will continue as a monitored event in all ongoing and upcoming venglustat clinical programs.

2.3.1.3 Syncope

In the completed placebo-controlled phase 2 study ACT14820 for GBA-PD indication, the events of syncope were more frequently observed in venglustat arm compared to placebo arm.
An analysis of this information concluded that syncope is a potential risk specific for GBA-PD participants. Data were not sufficient to draw any conclusions in the other populations receiving venglustat (ie, FD, GD3, GM2).

2.3.1.4 [redacted]

[redacted]

2.3.1.5 Transient increase in blood pressure

In the completed or unblinded phase 2/3 studies in ADPKD, and GBA-PD indications, a transient increase in systolic (SBP) and diastolic blood pressure (DBP) was observed in the venglustat arm compared to the placebo arm. This difference peaked at Month 1 by approximately 5 mm Hg from the mean value of placebo-treated participants, and no notable difference compared to placebo was observed after 6 months. In the Phase 2 FD (Study ACT13739/LTS14116) and GD3 (PDY13949/LEAP), the SBP and DBP returned to baseline by Month 6. It should be noted that although the renal and cardiovascular systems are affected during the course of Fabry disease, based on the 3 year follow up data from the completed ACT13739/LTS14116 study, there is no evidence of disease progression and consequently no impact of the transient increase in BP on the course of disease.

In non-clinical studies, the cardiovascular system was not considered to be a target based on macroscopic and microscopic evaluation of the heart, electrocardiographic evaluations, and measurement of BP in repeat-dose studies up to 39 weeks in duration in dogs or in an in vivo cardiovascular safety pharmacology study in dogs.

Based on the above information, it was concluded that transient increase of blood pressure is a potential risk in all indications.

Blood pressure monitoring is part of the safety monitoring plan in all venglustat trials and is detailed in the SoA for this study. The management of hypertension should be in accordance with the protocol and at the discretion of the Investigator.

2.3.1.6 Embryo-fetal toxicity

The important potential risk of embryo-fetal toxicity is based on the non-clinical findings in rats and rabbits such as increased implantation loss (in rats) and reduced fetal weight (in both rats and rabbits). In the pre-/postnatal development toxicity study in rats, increased unaccounted-for sites (implantation sites without a corresponding pup), decreased mean numbers of pups born and decreased mean pup weight were observed. There have been no studies of venglustat in pregnant women.

Pregnant women should not receive venglustat, thus contraception measures are part of the protocol (Section 5.1 and Section 10.4).

Table 2 - Risk mitigation strategy

Description	Summary of data/rationale	Mitigation strategy
Potential risks (venglustat)		
New or worsening lens opacity in children two to less than 18 years old (important potential risk)	Based on the review of the available clinical data, and the development of human eye, this is no longer considered as potential risk in adult populations. In the absence of clinical pediatric data in children two-years to <18 years of age, children are potentially at risk for venglustat. Importantly, cataract that develops during childhood before the age of eight to 10 year can lead to irreversible severe sequelae including blindness.	For pediatric population: comprehensive ophthalmological examination and periodic monitoring. If a participant develops signs or symptoms concerning for cataract development or other visual problems at any time during the study, comprehensive ophthalmological examination will be performed.
Potential male infertility due to exposure in childhood (<12 years of age) (important potential risk)	Preclinical findings (rat). See IB Section 7.1.	Individual benefit-risk assessment by the Investigator and patients/parents/guardians.
Depression Adverse neurological and psychiatric events are being monitored in all venglustat studies given the compound's access to the central nervous system. Based on the available clinical data the risk of depression was assessed as a potential risk for GBA-PD population. The limited available data doesn't allow	Ability of venglustat to cross the blood-brain barrier. See IB Section 7.1.	Neurological examinations Depression is considered as a treatment monitored event in all ongoing and upcoming venglustat clinical programs. [redacted]

Description	Summary of data/rationale	Mitigation strategy
to confirm this risk for other venglustat indications.		
Syncope Based on the available clinical data the risk of syncope was assessed as a potential risk for GBA-PD population. The limited available data doesn't allow to confirm this risk for other venglustat indications	Clinical findings specific for GBA-PD population suggesting more frequent events of syncope in venglustat arm compared to placebo arm.	Neurological examinations and adverse events monitoring.
[redacted]		
Transient increase in BP at the beginning of venglustat treatment	Transient BP increase in venglustat-treated participants of approximately 5 mmHg, within the first 6 months of treatment. See IB Section 7.1.	BP monitoring at site visits and at home. See SOA (Section 1.3) and Section 8.3 of the protocol.
Embryo-fetal toxicity (important potential risk)	In the embryo-fetal toxicology studies in rats and rabbits, increased implantation loss (in rats) and reduced fetal weight (in both rats and rabbits) were observed. See IB, Section 7.2.1.3.	Men and women of childbearing potential (premenopausal and not surgically sterile) are required to either practice true abstinence consistent with their preferred and usual lifestyle, or use double contraceptive methods, including a highly effective method (see Section 5.1 and Section 10.4 for details) for the entire duration of the study and for at least 6 weeks for females and at least 90 days for males following their last dose of IMP.
Drug interactions		
[redacted]	[redacted]	[redacted]

Abbreviations: [redacted] IB=Investigator's Brochure; IMP=Investigational Medicinal Product.

2.3.2 Benefit assessment

[redacted]

2.3.3 Overall benefit: risk conclusion

[redacted]

[redacted]

3 OBJECTIVES AND ENDPOINTS

Table 3 - Objectives and endpoints

Objectives	Endpoints
Primary	
Primary population: • To assess the efficacy and pharmacodynamics (PD) of daily oral dosing of venglustat when administered over a 104-week period.	Co-primary endpoints: • Percent change in cerebrospinal fluid (CSF) GM2 biomarker from baseline to Week 104. • Annualized rate of change in the 9-hole peg test (9-HPT) from baseline to Week 104.
Secondary population: • To assess PD response (plasma and CSF GL-1 biomarker and disease specific biomarkers) of venglustat when administered once daily over a 104-week period.	• Plasma and CSF GL-1 biomarker and a pathway specific biomarker will be assessed as follows: **Disease** / **Biomarker** GM2 gangliosidosis / GL-1, GM2 GM1 gangliosidosis / GL-1, GM1 Sialidosis / GL-1, GM2, GM3 Galactosialidosis / GL-1, GM1, GM3 Saposin C Deficiency / GL-1 only • Additional plasma and CSF biomarkers may include but are not limited to: lipidomics, glycoprotein nonmetastatic protein B (gpNMB), neurofilament.
Secondary	
Primary population: • To assess the PD of daily oral dosing of venglustat and the effect of venglustat on selected performance test and scale over a 104-week period.	• Absolute change in CSF GM2 biomarker from baseline to Week 104. • Change in 25-foot walk test (25FWT) from baseline to Week 104 (in participants able to walk at baseline). • Change in the neurological examination of the Friedreich's Ataxia Rating Scale (FARS) from baseline to Week 104.
Primary population: • To determine the safety and tolerability of venglustat when administered orally once daily over a 104-week period.	• Changes from baseline to Week 104 in the following: - Assessment of adverse events (AEs) and concomitant medication - Neurological examination - Ophthalmological examination - Vital signs - Clinical laboratory evaluations including hematology, biochemistry, urinalysis, and serology - Electrocardiogram (ECG)

Objectives	Endpoints
Primary population: • To assess the pharmacokinetics (PK) of venglustat in plasma and CSF.	• Plasma and CSF venglustat concentrations at prespecified visits over the study duration and plasma PK parameters (when applicable) including maximum plasma concentration observed (C_{max}), t_{max}, and area under the plasma concentration versus time curve calculated using the trapezoidal method over a predefined time period (from time t=0 to 24 hours; AUC_{0-24}).
Secondary population: • To assess the effect of venglustat on selected performance tests and scale over a 104-week period.	• Annualized rate of change in the 9-HPT from baseline to Week 104. • Change in 25FWT from baseline to Week 104 (in participants able to walk at baseline). • Change in the neurological examination of the FARS from baseline to Week 104.
Secondary population: • To determine the safety and tolerability of venglustat when administered once daily over a 104-week period.	• Changes from baseline to Week 104 in the following: - Assessment of AEs and concomitant medication - Neurological examination - Ophthalmological examination - Vital signs - Clinical laboratory evaluations including hematology, biochemistry, urinalysis, and serology - ECG
Secondary population: • To assess the PK of venglustat in plasma and CSF.	• Plasma and CSF venglustat concentrations over the study duration and plasma PK parameters (when applicable) including C_{max}, t_{max}, and AUC_{0-24} calculated using the trapezoidal method.
Secondary population: • To assess the acceptability and palatability of the venglustat tablet	• Acceptability and palatability assessments
Tertiary/exploratory	
[redacted]	

Objectives	Endpoints
[redacted]	

Objectives	Endpoints
[redacted]	

Objectives	Endpoints
[redacted]	

3.1 APPROPRIATENESS OF MEASUREMENTS

One of the co-primary endpoints is the percent change from baseline in CSF GM2 biomarker levels. The pathology of GM2 gangliosidosis and the related secondary indications result from an accumulation of GM2 or other glycosphingolipids in the CNS. Demonstration of a reduction of these accumulation products with venglustat would demonstrate CNS exposure and is expected to predict clinical efficacy.

The 9-HPT is to be used as another co-primary efficacy endpoint for this group of participants. This assessment was chosen based on natural history data collected from the National Tay-Sachs & Allied Diseases Associations (NTSAD) which showed 9-HPT progression over time. It assesses the function of upper extremity mobility, one of the most bothersome aspects of the disease for the patients. This can be assessed in all patients including many of whom may be nonambulatory during the study. This clinical endpoint selection makes it a consistent and homogeneous measure for consideration in the full trial population. This assessment has demonstrated a decline in the natural history data. Therefore, without active treatment this assessment would be expected to decline in this target population. This assessment would also support the use of the GM2 biomarker as a mechanistic and confirmatory endpoint supporting the assumption that venglustat crosses the BBB and results in an expected lowering of the GM2 biomarker with resultant improvement or stabilization of the 9-HPT result over time versus a placebo population.

The 25FWT is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The patient is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the patient has reached the 25-foot mark. The task is immediately administered again by having the patient walk back the same distance. Patients may use assistive devices when doing this task. Administration time will vary depending upon the ability of the patient. Total administration time should be approximately 1 to 5 minutes. The score for the 25FWT is the average of the 2 completed trials. The 25FWT will be administered in patients able to walk at baseline. Patients who cannot walk even with assistance will not be assessed. Since approximately 21% of patients who participated in the NTSAD study were wheelchair bound, it is expected that 25FWT will not be ascertained in a substantial fraction of the study population. For this reason, the 25FWT will not be considered as the primary endpoint in this study but will be included as a supportive secondary endpoint.

The FARS includes a neurological examination that specifically reflects neural substrates affected in Friedreich ataxia. The FARS-neuro is a performance outcome (PerfO), composed of 4 sections that assess different neurological faculties: bulbar activity (4 items), upper limb coordination (5 items), lower limb coordination (2 items), peripheral nervous system (5 items) and upright stability (7 items). The total score ranges from 0 to 117. The neurological examination domain of FARS is conducted by the clinician and has shown sensitivity to change overtime in a Sanofi natural history study. Based on the study findings, FARS neuro could be used to assess the different neurological signs in patients with GM2 gangliosidosis. To avoid dilution of this small effect in this slowly progressive disease, the Sponsor proposes studying the change in the neurological component of the FARS as an individual secondary endpoint.

Further, a functional staging of ataxia and activities of daily living (ADL) assessment are incorporated. Depending on the progression of the GM2 disease, these patients have varying abilities to utilize their upper and lower limbs. This limited mobility impairs the ability to conduct ADL. This clinical study allows the inclusion of patients provided that they have the use of their upper limbs. Therefore, the FARS will allow for monitoring and comparison of additional aspects of upper body function over the treatment period.

4 STUDY DESIGN

4.1 OVERALL DESIGN

This is a multicenter, multinational, randomized, double-blind, placebo-controlled, 2-arm, 104-week study (primary population only) to assess the efficacy and safety of venglustat as compared with placebo in adult participants with a diagnosis of late-onset GM2 gangliosidosis (referred to as the primary population) and venglustat received in an open-label design in participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis if any of the sites have such participants meeting the inclusion and none of the exclusion criteria (referred to as secondary population). The secondary population is composed of participants with juvenile/adolescent late-onset GM2 gangliosidosis and ultra-rare conditions within the same biochemical pathway as the primary population. The 104-week treatment period (primary analysis period) will be followed by an OLE period with venglustat treatment for all patients. The study will be conducted at multiple, multinational sites (approximately 30 sites).

The study will include 4 main periods:

1. Period 1 (screening period from Day -60 to Day -1): Participant and/or participant's parent(s)/legal guardian(s) will sign and date the informed consent and the participant will undergo screening assessments to determine participant eligibility. If all eligibility criteria are met, the participant will start study treatment.
2. Period 2 (primary analysis period, 104-week treatment period): Participants in the primary population will be randomly assigned in a 2:1 ratio to receive venglustat or placebo once daily for 104 weeks in a double-blind manner. Randomization will be stratified on the participant's ability to walk at the baseline visit (yes/no). Participants in the secondary population will receive venglustat for 104 weeks in an open-label manner. Safety, tolerability, PK, PD, and efficacy of venglustat once-daily administration will be determined during the 104-week treatment period.
3. Period 3 (104-week OLE period): Participants in both the primary and secondary population will be automatically entered into the OLE period following completion of primary analysis period (period 2). All participants will receive venglustat for 104 weeks in an open-label design. Long-term safety, tolerability, PD, and efficacy of venglustat once daily administration will be assessed during the 104-week treatment period. Participants who complete the primary analysis period but would not continue to OLE period, and safety follow up /end of study (EOS) visit will be conducted 6 weeks after the W104 visit. Participants who complete the primary analysis period within 3 months prior to the OLE (amended protocol 4) approval by local regulations, will have the option to enroll into the OLE when the OLE (amended protocol 4) is approved. Participants who prematurely discontinue the study treatment from the primary analysis period will not have the option to enroll into the OLE.
4. Period 4 (post-treatment safety observation period, 6-week follow-up period). The post-treatment safety observation period will be for 6 weeks after Period 3, and safety and tolerability will continue to be assessed.

Post-trial access to venglustat will be in compliance with all applicable national and local laws and regulations, including safety reporting obligations.

After safety data from Week 1/Day 1 to Week 12 visits of the first 5 participants of the primary population are reviewed and considered satisfactory by the DMC, enrollment of the secondary population will begin. In addition to the primary population, up to 20 participants in total are planned for the secondary population. An attempt will be made and first prioritized to enroll at least 1 participant (aged 2 years or older) in each of the following disorders: juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, and juvenile/adult galactosialidosis (secondary population).

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

This is a multicenter, multinational, randomized, double-blind, placebo-controlled study in the primary population (adult participants with late-onset GM2 gangliosidosis). Safety/tolerability, PK, PD, and efficacy assessment will be conducted. The primary objective is evaluation of CSF GM2 biomarker changes and clinical efficacy of venglustat using the 9-HPT. After safety data from Week 1/Day 1 to Week 12 visits of the first 5 participants of the primary population are reviewed and considered satisfactory by the DMC, enrollment of the secondary population will begin. The trial will include 104 weeks of IMP dosing, during which venglustat or placebo will be administered orally once daily in a double-blind manner. Of note, to date, no large-scale studies have been successful in specifically addressing the relative benefits and risks of a treatment for participants with late-onset GM2 gangliosidosis. Thus, there is a high medical need to address motor, coordination and speech, and neuropsychiatric manifestations in in these patients.

The study may also enroll a secondary population of participants (≥2 years of age) with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis and an ultra-rare bundle consisting of GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, and juvenile/adult galactosialidosis, if any of the sites have such participants meeting the inclusion criteria and none of the exclusion criteria. Such participants will be enrolled only after a 12-week safety data review of the first 5 treated adult late-onset GM2 gangliosidosis participants has been considered satisfactory. The secondary population will have the same assessments and evaluations as the primary population.

4.3 JUSTIFICATION FOR DOSE

[redacted]

[redacted]

[redacted]

[redacted]

4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if he/she has completed all phases of the study including the last visit.

The end of the study is defined as the date of the last visit of the last participant in the study.

5 STUDY POPULATION

Prospective approval of protocol deviations to recruitment and enrollment criteria, also known as protocol waivers or exemptions, is not permitted.

5.1 INCLUSION CRITERIA

Participants are eligible to be included in the study only if all of the following criteria apply:

Age

I 01. Participant must be at least 18 years of age at the time of signing the informed consent for the primary population and adult secondary population. Participant must be ≥2 to <18 years of age at the time of signing the informed consents [by parent(s)/guardian(s)] for the juvenile and adolescent secondary population.

Type of participant and disease characteristics

I 02. The participant has a clinical diagnosis of late-onset GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease) and documented respective enzyme deficiency (for the primary population only). The documented enzyme deficiency should support a genetically confirmed diagnosis of GM2-gangliosidosis caused by β-hexosaminidase deficiency resulting from mutations in the [redacted]

Note: The study may also enroll participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis if any of the sites have such participants meeting the other inclusion and none of the exclusion criteria (secondary population). The secondary population is composed of participants with ultra-rare conditions within the same biochemical pathway as the primary population.

I 03. For primary population, the participant has the ability to perform the 9-HPT at the screening visit in ≤240 seconds for the 2 consecutive trials of the dominant hands and the 2 consecutive trials of the nondominant hand.

I 04. If the participant has a history of seizures, they are well controlled under appropriate medication not identified as a [redacted].

I 05. The participant is cooperative, able to ingest oral medication, willing to travel to a study site (if applicable), and able to comply with all aspects of the study, including all assessments, according to the Investigator's judgment.

Weight

I 06. For the juvenile and adolescent secondary population, participant must have body weight ≥10 kg at the time of signing the informed consent.

Sex

I 07. Male or Female

Female patients of childbearing potential and sexually active male patients must be willing to practice true abstinence in line with their preferred and usual lifestyle, or use 2 acceptable effective methods of contraception for the duration of the study and for at least 6 weeks for females and 90 days for males following their last dose of IMP. In addition, male participants must refrain from donating sperm for the duration of the study and for 90 days after the last dose of IMP.

a) Sexually active male participants

A male participant must agree to use contraception as detailed in Appendix 4 (Section 10.4) of this protocol for the duration of the study and 90 days following their last dose of IMP.

b) Female participants

A female participant is eligible to participate if she is not pregnant (see Appendix 4 [Section 10.4]), not breastfeeding, and at least one of the following conditions applies:

- Not a woman of childbearing potential (WOCBP) as defined in Appendix 4 (Section 10.4)

OR

- A WOCBP who agrees to follow the contraceptive guidance in Appendix 4 (Section 10.4) for the duration of the study and for at least 6 weeks after the last dose of IMP.

Informed Consent

I 08. The participant or, if appropriate, parent(s) or legal guardian(s) must provide written informed assent/consent prior to any study-related procedures being performed as described in Appendix 1 (Section 10.1). Note: For criteria specific to participants enrolled in Japan and France, see Appendix 8 (Section 10.8).

5.2 EXCLUSION CRITERIA

Participants are excluded from the study if any of the following criteria apply:

Medical conditions

E 01. Participant has clinical features of Tay-Sachs or Sandhoff disease, but a completely negative result on a genetic test for GM2 gangliosidosis caused by β-hexosaminidase deficiency resulting from mutations in the [redacted] and/or is without clinical features.

E 02. For primary population and participants with juvenile/adolescent late onset GM2 gangliosidosis and GM1 gangliosidosis, the participant cannot understand and perform all age-appropriate study assessments, with the exception of 25FWT and PROs.

E 03. Any clinically relevant medical disorders other than late-onset GM2 gangliosidosis (primary population) or the diseases specified for the secondary population, clinically relevant findings in the physical examination, medical history, or laboratory assessments which would compromise the safety of the participant. This includes condition(s) that precludes the safe performance of routine lumbar puncture (eg, prohibitive lumbar spinal disease), as well as cardiovascular, renal, hepatic, gastrointestinal, pulmonary, neurologic, endocrine, metabolic (eg, hypokalemia, hypomagnesemia), or psychiatric disease, other medical conditions, or serious intercurrent illnesses.

E 04. The participant has a documented diagnosis of any of the following infections: hepatitis B, hepatitis C, human immunodeficiency virus 1 or 2.

E 05. A history of drug and/or alcohol abuse within the past year prior to the first screening visit.

E 06. The participant is scheduled for in-patient hospitalization including elective surgery during the study.

E 07. The participant has, according to World Health Organization (WHO) grading, a cortical cataract ≥ one-quarter of the lens circumference (Grade cortical cataract-2) or a posterior subcapsular cataract ≥2 mm (Grade posterior subcapsular cataract-2). Participants with nuclear cataracts will not be excluded.

Prior/concomitant therapy

E 08. The participant requires use of invasive ventilatory support.

E 09. The participant is receiving current treatment with anticoagulants (eg, coumadin, heparin) that might preclude safe completion of the LP.

E 10. The participant has received SRT within 3 months prior to study enrollment.

[redacted]

E 12. The participant is currently receiving potentially cataractogenic medications as listed in Section 6.5.1.3 or any medication that may worsen the vision of participant with cataract (eg, alpha-adrenergic glaucoma medications) according to the prescribing information.

Prior/concurrent clinical study experience

E 13. Currently participating in another investigational interventional study.

E 14. Use of IMP, within 3 months or 5 half-lives, whichever is longer, before study enrollment. Note: For participants using N-acetyl-leucine as IMP, within 5 half-lives before study enrollment.

Diagnostic assessments

E 15. Liver enzymes (alanine aminotransferase [ALT]/aspartate aminotransferase [AST]) or total bilirubin >2 × the upper limit of normal (ULN) at the time of screening unless the participant has the diagnosis of Gilbert syndrome and maintains a level of total bilirubin <5 mg/dL and direct bilirubin <1 mg/dL (20%) of total bilirubin level.

[redacted]

Other exclusions

E 17. Individuals accommodated in an institution because of regulatory or legal order; prisoners or participants who are legally institutionalized.

E 18. Any country-related specific regulation that would prevent the participant from entering the study - see Appendix 8 (Section 10.8) (country-specific requirements).

E 19. Participant not suitable for participation, whatever the reason, including medical or clinical conditions, or participants potentially at risk of noncompliance to study procedures.

E 20. Participants are dependent on the Sponsor or Investigator (in conjunction with Section 1.61 of the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) Ordinance E6)

E 21. Participants are employees of the clinical study site or other individuals directly involved in the conduct of the study, or immediate family members of such individuals.

E 22. Any specific situation during study implementation/course that may raise ethics considerations.

E 23. Sensitivity to any of the study interventions, or components thereof, or drug or other allergy, that contraindicates participation in the study

Note: For exclusion criteria specific to participants enrolled in France, see Appendix 8 (Section 10.8).

5.3 LIFESTYLE CONSIDERATIONS

5.3.1 Meals and dietary restrictions

[redacted]

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in the clinical study but are not subsequently entered in the study. A minimal set of screen failure information is required to ensure transparent reporting of screen failure participants to meet the Consolidated Standards of Reporting Trials (CONSORT) publishing requirements and to respond to queries from regulatory authorities. Minimal information includes demography, screen failure reasons, eligibility criteria, and any SAE.

A participant cannot be randomized more than once in the study. Participants who fail screening may be rescreened once during the recruitment period in cases where the original screening failure was due to reasons expected to change at rescreening and based upon the Investigator's clinical judgment. Different participant identification will be issued for such participants.

There is no requirement for a waiting period between the screen-failure date and the rescreening date. The interactive response technology (IRT) report will flag rescreened participants. Participants that are rescreened must sign a new consent form. Not all screening assessments are required to be repeated for participants rescreening. Coordination and speech, behavioral, and ataxia assessments are not required to be repeated if performed within the past 3 months. For participants rescreened within 2 weeks of the initial screening visit, the Investigator may use the initial screening visit results for biomarkers, chemistry, hematology, and urinalysis.

6 STUDY INTERVENTION

Study intervention is defined as any investigational intervention(s), marketed product(s), placebo, or medical device(s) intended to be administered to a study participant according to the study protocol.

6.1 STUDY INTERVENTION(S) ADMINISTERED

Table 4 - Overview of study interventions administered

ARM name[a]	**Venglustat**	**Placebo**
Intervention name	Venglustat	Placebo
Type	Drug	Drug
Dose formulation	Tablet	Tablet
Unit dose strength(s)[b]	[redacted] and 15 mg	NA
Dosage level(s)	Adult onset GM2 gangliosidosis participants will receive venglustat a 15 mg tablet or placebo once daily. Adult participants in the secondary population will receive a venglustat 15 mg tablet once daily. Adolescents and juvenile participants in the secondary population (≥2 years) will receive venglustat [redacted]	
Route of administration	Oral: The IMP can be swallowed whole or chewed and then swallowed. Administration of IMP by chewing and swallowing or swallowing whole should be as consistent as possible throughout study treatment, and the method should be documented in the electronic case report form.	
IMP and NIMP	IMP	IMP
Packaging and labeling	During the primary analysis period, study Intervention will be provided in a double-blind wallet for the primary population and in an open-label wallet for the secondary population. Each wallet will be labeled as required per country requirements. During the OLE, study intervention will be provided in an open-label wallet for both primary and secondary populations.	During the primary analysis period, study Intervention will be provided in a double-blind wallet for the primary population. Each wallet will be labeled as required per country requirements. Not applicable during the OLE.
Current/Former name(s) or alias(es)	GZ/SAR402671	

Abbreviations: eCRF, electronic case report form; IMP, investigational medicinal product; NIMP, noninvestigational medicinal product.

a The placebo is only for the 15 mg venglustat tablets.

b Strength refers to the free base corresponding to the active moiety.

Between the protocol-scheduled on-site visits, interim visits may be required for IMP dispensing. As an alternative to these visits, venglustat or placebo may be supplied from the site to the participant via a Sponsor-approved courier company where allowed by local regulations and approved by the participant.

Venglustat or matching placebo is to be taken daily, around the same time each day throughout the study.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.11 (Appendix 11).

6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

1. The Investigator or designee must confirm appropriate temperature conditions have been maintained during transit for all study intervention received and any discrepancies are reported and resolved before use of the study intervention.
2. Only participants enrolled in the study may receive study intervention and only authorized site staff may supply or administer study intervention. All study intervention must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the Investigator and authorized site staff (Refer to Pharmacy manual for additional details).
3. The Investigator, institution, or the head of the medical institution (where applicable) is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).

Any quality issue noticed with the receipt or use of an IMP (deficiency in condition, appearance, pertaining documentation, labeling, expiration date, etc) must be promptly notified to the Sponsor. Some deficiencies may be recorded through a complaint procedure (see Section 8.3.6).

A potential defect in the quality of IMP may be subject to initiation of a recall procedure by the Sponsor. In this case, the Investigator will be responsible for promptly addressing any request made by the Sponsor, in order to recall the IMP and eliminate potential hazards.

Under no circumstances will the Investigator supply IMP to a third party (except for direct-to-patient (DTP) shipment, for which a courier company has been approved by the Sponsor), allow the IMP to be used other than as directed by this clinical trial protocol, or dispose of IMP in any other manner.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The randomized intervention kit number list will be generated centrally by the Sponsor. The IMPs will be packaged in accordance with this list. Participants in the primary population will be centrally assigned to randomized study IMP using IRT as summarized in the SOA (Section 1.3). The IRT will allocate the intervention kit numbers corresponding to the visit and the arm at each dispensation for each participant in the primary and secondary population. Before the study is initiated, instructions on how to access IRT will be provided to each site.

A randomized participant is a participant who has been randomly allocated to a study IMP, regardless whether the IMP kit was used or not. A participant cannot be randomly assigned more than once in the study.

Returned study IMP should not be redispensed to the participants.

Methods of blinding

For the primary population, Investigators and participants will be blinded to the allocation of active or placebo treatment arms. Venglustat and matching placebo for venglustat tablets will be indistinguishable from one another and be provided in identically matched packaging which includes labeling to protect the blind.

In accordance with the double-blind study design, Investigators will remain blinded to IMP and will not have access to the randomization (treatment) codes except under exceptional medical circumstances.

[redacted]

Randomization code breaking

The code may be broken only in the case of a serious, unexpected, related AE. If possible, contact should be initiated with the Monitoring Team before breaking the code. In case of an emergency, the Interactive Web Response System (IWRS) in the first instance/Interactive Voice Response System (IVRS) can be contacted by the Investigator or Sub-Investigator to reveal the IMP assignment of a particular patient. In case of a Suspected Unexpected Serious Adverse Reaction (SUSAR), the Global Pharmacovigilance department of the Sponsor will contact IWRS/IVRS to reveal IMP assignment for regulatory reporting requirements for the particular case. The IWRS/IVRS unblinding procedures should be followed as outlined in the IVRS manual.

Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the investigator should make every effort to contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant.

If the blind is broken by the Investigator he/she will document the date, time of day and reason for code breaking. The IWRS/IVRS will send a confirmation of unblinding report. The patient must discontinue study medication, but should be encouraged to continue in the study, completing all assessments at the scheduled time points. At a minimum, the patient may withdraw from the clinical trial and complete an end of treatment assessment visit (similar to Visit 7) followed by a safety follow-up visit (similar to Visit 12) 6 weeks after their last scheduled received dose or until resolution of the related SAE.

Patient withdrawal will only occur when the code break call is made at the site level and/or at the study level. This means that if the Emergency Unblinding transaction is performed by the Investigator (ie, at the site level), then the patient will be withdrawn from treatment. However, if the Emergency Unblinding transaction is performed by the Sponsor (ie, at the study level), then the patient may or may not be withdrawn from treatment.

Participants hold an ESMS (24 hours- Emergency Scientific and Medical Services) card, with ESMS phone number and back-up number to be called if the investigator (first contact person) cannot be reached. The 24-hour emergency system number is to be used in medical urgency situation by competent medical personnel after first study treatment administration.

6.4 STUDY INTERVENTION COMPLIANCE

Participant compliance with study intervention will be assessed at each visit. Compliance will be assessed by reviewing participant diary and counting returned tablets. Deviation(s) from the prescribed dosage regimen should be recorded in the eCRF.

The Investigator or designee will keep an accurate record of all IMP that is received, dispensed, and returned on a per participant basis using an IMP accountability log. Measures taken to ensure and document treatment compliance and IMP accountability include:

- Accurate recording of treatment kit number as required on appropriate eCRF page for accounting purposes.
- All medication treatment kits (whether empty or unused) are returned by the participant at each visit. In case of DTP process, the intervention units can be returned by the carrier (if defined in the contract).
- The Investigator or designee tracks treatment accountability/compliance, either by diary, or by counting the number of used treatment kits and fills in the appropriate page of the participant treatment log.
- The monitor in charge of the study then checks the data entered on the IMP administration page by comparing them with the IMP that has been retrieved and the participant treatment log form.

A participant diary will be issued to the participant at the screening visit with instructions to record any safety issue. For eligible participants, the same diary will be used to record missing doses after randomization. A brief explanation should be provided if a dose is missed. The participant should bring the diary and any remaining IMP to each clinic visit.

The site staff will review the participant diary during each clinic visit and record excursions from treatment into the eCRF. The participant diary will be retrieved when the participant finishes their participation in the study.

At the completion of the study, all IMPs will be accounted for and retained or destroyed according to regulatory requirements regarding drug accountability. Investigational medicinal products will not be destroyed unless the Sponsor provides written authorization. Authorization for destruction will be given by the Sponsor once reconciliation has been completed. Whenever possible, this destruction will occur on-site, depending on local regulations and site-specific capabilities; alternatively, IMP may be returned to the Sponsor or designee for destruction. Additional details will be provided in the pharmacy manual.

6.5 CONCOMITANT THERAPY

A concomitant medication is any treatment received by the participant during the study aside from the IMP. Any medication or vaccine (including over-the-counter or prescription medicines, vitamins, and/or herbal supplements) that the participant is receiving at the time of enrollment or receives during the study must be recorded along with:

- Reason for use
- Dates of administration including start and end dates
- Dosage information including dose and frequency

Concomitant medications should be kept to a minimum during the study. Furthermore, changes in concomitant medications should be kept to a minimum and only be administered if considered absolutely necessary in the medical judgement of the Investigator. If excluded prescription or nonprescription medicines are considered necessary for the patient's welfare and no alternative treatment is available, such treatment may be provided as long as it is unlikely to significantly interfere with the IMP. Participants may be given such therapy as rescue medication at the discretion of the Investigator and this must be recorded in the eCRF. The participants must abstain from taking pyrimethamine and/or acetyl-leucine throughout this clinical study.

6.5.1 Prohibited concomitant medicine

6.5.1.1 [redacted]

[redacted]

6.5.1.2 [redacted]

[redacted]

6.5.1.3 Medications with risk to cause cataract

Given nonclinical lens findings (see the latest Investigator's Brochure), a chronic regimen (ie, more frequent than once every 2 weeks) of the following medications is forbidden during the clinical trial for participants age <18:

- Corticosteroids:
  - May be used on a restricted basis in participants who require temporary use (≤1 week) for the treatment of any acute condition for which no appropriate substitute is found. Such medications must not be used on more than a total of 4 occasions (ie, up to 1 week per occasion) each 52 weeks, for an overall maximum of 8 occasions during the 104 weeks of treatment in Period 2.
  - A special provision is made to allow enrollment of GM2 gangliosidosis participants who require inhaled corticosteroids for the management of a stable medical condition (eg, allergies, asthma etc), in which corticosteroid withdrawal would be detrimental. In this case the Investigator would administer the lowest efficacious dose. The potential benefits expected by the administration of venglustat outweigh the potential drawbacks that can be observed by the initiation/worsening of cataracts.
- Psoralens used in dermatology with ultraviolet light therapy.
- Typical antipsychotics.

The Investigator should consider substituting medications listed in the previous paragraphs for noncataractogenic treatments, as appropriate.

In addition, alpha-adrenergic glaucoma medications are excluded from the current trial since they can worsen the vision of participants with cataracts.

Atypical antipsychotics are allowed.

6.5.1.4 Other medications

Other medications which are unlikely to interfere with the PK or PD of the IMP or confound interpretation of the study endpoints are allowed as needed and discussed with the Investigator. However, doses of chronically administered medicines should be kept fixed during the trial if at all possible.

6.5.2 COVID-19 vaccination

Immunotoxicology-related parameters (eg, immunophenotyping, total immunoglobulin levels) were not evaluated in the repeat-dose toxicology studies. Based on the available preclinical data (venglustat-related hematological and histopathological changes to immune system tissues/organs) and data from clinical studies, it is unlikely that venglustat has immunomodulatory properties and would have an impact on the immune system.

The coronavirus disease-2019 (COVID-19) vaccines that have been authorized for use are considered as a concomitant medication with no interaction that requires advice on timing or other aspects of the vaccination.

If the COVID-19 vaccine is authorized, available, and recommended by the local regulatory authority and/or health authority for patients like those in this study, the vaccine can be administered during the study and should be administered according to the label or recommendations of the local regulatory authority and/or health authority.

COVID-19 vaccination during study period should be reported in the 'concomitant medications' eCRF page.

Each injection will be reported into different loglines.

The vaccine name (brand or generic), dose and date of injection will be captured.

Adverse events related to COVID-19 vaccination will be collected and reported similarly to any other AEs in study.

6.6 DOSE MODIFICATION

[redacted]and criteria for study intervention discontinuation described in Section 7.1, study intervention dose reduction or modification is not allowed during the study.

6.7 INTERVENTION AFTER THE END OF THE STUDY

Not applicable.

7 DISCONTINUATION OF STUDY INTERVENTION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION

7.1.1 Definitive discontinuation

The IMP should be continued whenever possible.

In case the IMP is stopped, it should be determined whether the stop can be made temporarily. In rare instances, it may be necessary for a participant to permanently discontinue study intervention before the end of treatment visit. If study intervention is permanently discontinued, the participant will remain in the study to be evaluated for safety and efficacy. See the SoA (Section 1.3) for data to be collected at the time of discontinuation of study intervention.

Definitive intervention discontinuation is any intervention discontinuation associated with the definitive decision from the Investigator not to re-expose the participant to the IMP at any time during the study, or from the participant not to be re-exposed to the IMP due to whatever the reason.

The following may be justifiable reasons for the Investigator or Sponsor to discontinue a participant from treatment:

Participant specific:

- The participant experiences 2 similar SAEs or 1 life-threatening SAE (assessed as related by the Investigator and/or the Sponsor).
- The participant meets criteria for Hy's law (confirmed ALT >5 × ULN range or confirmed ALT >3 × ULN and bilirubin >2 × ULN).
- The participant is no longer deriving a therapeutic/clinical benefit in the opinion of the Investigator.
- The participant develops grade 3 cataract or higher.
- The participant becomes pregnant.

Study specific:

- Any AEs, per Investigator judgment, that may jeopardize the participant's safety.
- Any use of prohibited concomitant treatment (see Section 6.5.1).
- At participant's request, ie, withdrawal of the consent for treatment.

Discontinuation of study intervention for abnormal liver function should be considered by the Investigator when a participant meets one of the conditions outlined in Appendix 6 (Section 10.6) or if the Investigator believes that it is in best interest of the participant.

See the SoA for data to be collected at the time of intervention discontinuation and follow-up and for any further evaluations that need to be completed.

Any clinically significant abnormal laboratory value or ECG parameter will be immediately rechecked for confirmation before making a decision of definitive discontinuation of the IMP for the concerned participant.

The DMC will also review data if applicable to assist in determining if AEs should preclude continued treatment with study intervention and if stopping rules apply.

Handling of participants after definitive intervention discontinuation

Participants will be followed-up according to the study procedures specified in this protocol up to the scheduled date of study completion, or up to recovery or stabilization of any AE to be followed-up as specified in this protocol, whichever comes last.

If possible, and after the definitive discontinuation of intervention, the participants will be assessed using the procedure normally planned for the last dosing day with the IMP including a PK sample, if appropriate.

All cases of definitive intervention discontinuation must be recorded by the Investigator in the appropriate pages of the eCRF when considered as confirmed.

7.1.2 Discontinuation criteria

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs. In case of an SAE or ≥ Grade 3 AE (NCI, CTCAE v5) that is considered by the Investigator to be related to IMP and not to underlying disease or concomitant medication, the dose may be temporarily discontinued. For all temporary intervention discontinuations, duration should be recorded by the Investigator in the appropriate pages of the eCRF.

In the event that an SAE or ≥ Grade 3 AE (NCI CTCAE Version 5) is observed that is considered by the Investigator to be related to IMP and not to underlying disease or concomitant medication, the case will be communicated to the DMC and a decision reached regarding continued dosing. If ≥2 patients receiving IMP develop the same SAE or AE (≥ Grade 3) that is considered related to IMP dosing, the study may be halted. The DMC will review the data and provide recommendations on how to proceed. Additionally, the DMC can recommend stopping or modifying the study based on a single event or on aggregate analysis of multiple events. Should any major safety issues arise, final decisions regarding the study will be made by the Sponsor's Medical Lead and Global Safety Officer, taking into consideration the DMC opinion (as applicable).

Temporary intervention discontinuation may be considered by the Investigator because of suspected AEs, life emergencies for the patient, or disruption of the clinical trial due to a regional or national emergency declared by a governmental agency (Section 10.11 (Appendix 11): Contingency Measures for a regional or national emergency that is declared by a governmental agency). For all temporary intervention discontinuations, duration of the discontinuation should be recorded by the Investigator in the appropriate pages of the CRF or eCRF.

7.1.2.1 Rechallenge

Reinitiation of intervention with the IMP will be done under close and appropriate clinical/and or laboratory monitoring once the Investigator will have considered according to his/her best medical judgment that the responsibility of the IMP(s) in the occurrence of the concerned event was unlikely and if the selection criteria for the study are still met (refer Section 5.1 and Section 5.2).

During a regional or national emergency declared by a governmental agency, reinitiation of IMP can only occur once the Investigator has determined, according to his/her best judgement, that the contribution of the IMP(s) to the occurrence of the epidemic event (eg, COVID-19) was unlikely. For a regional or national emergency declared by a governmental agency, contingency measures are included in Section 10.11 (Appendix 11).

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

- A participant may withdraw from the study at any time at his/her own request, or may be withdrawn at any time at the discretion of the Investigator for safety, behavioral, compliance, or administrative reasons. This is expected to be uncommon.
- At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted, as shown in the SoA. See SoA for data to be collected at the time of study discontinuation and follow-up and for any further evaluations that need to be completed. Lumbar puncture will not be repeated if it has been performed recently and will be decided on case by case basis.
- The participant will be permanently discontinued both from the study intervention and from the study at that time.
- If the participant withdraws consent for disclosure of future information, the Sponsor may retain and continue to use any data collected before such a withdrawal of consent.
- If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the Investigator must document this in the site study records.

If participants no longer wish to take the IMP, they will be encouraged to remain in the study.

The Investigators should discuss with them key visits to attend. The value of all their study data collected during their continued involvement will be emphasized as important to the public health value of the study.

Participants who withdraw from the study intervention should be explicitly asked about the contribution of possible AEs to their decision, and any AE information elicited must be documented.

All study withdrawals should be recorded by the Investigator in the appropriate screens of the eCRF and in the participant's medical records. In the medical record, at least the date of the withdrawal and the reason should be documented.

In addition, a participant may withdraw his/her consent to stop participating in the study. Withdrawal of consent for intervention should be distinguished from withdrawal of consent for follow-up visits and from withdrawal of consent for nonparticipant contact follow-up, eg, medical record checks. The site should document any case of withdrawal of consent.

Participants who have withdrawn from the study cannot be re-enrolled in the study. Their inclusion and intervention numbers must not be reused.

7.3 LOST TO FOLLOW UP

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fails to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the Investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Discontinuation of specific sites or of the study as a whole are handled as part of Appendix 1 (Section 10.1.9).

8 STUDY ASSESSMENTS AND PROCEDURES

- Study procedures and their timing are summarized in the SoA. Protocol waivers or exemptions are not allowed.
- Adherence to the study design requirements, including those specified in the SoA, is essential and required for study conduct.
- All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The Investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable.
- Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the informed consent form (ICF) may be utilized for screening or baseline purposes provided the procedures met the protocol-specified criteria and were performed within the time frame defined in the SoA.
- The maximum amount of blood collected from each adult participant over the duration of the study, will be approximately 208 mL for participants of the main study and 216 mL for participants of the W1/D1 PK profile evaluation substudy. Additional repeat or unscheduled samples may be taken for safety reasons or for technical issues with the samples.

  For pediatric participants blood samples will be obtained as blood volume permits and will not exceed the blood volume collection limit of 5-7 mL/kg over an 8 week period. Sampling is prioritized for biomarker, PK hematology and biochemistry labs and then archival, ADME and pharmacogenetics tests.

8.1 EFFICACY ASSESSMENTS

8.1.1 9-hole peg test

The 9-HPT was originally introduced in 1971 as a measure of dexterity, in an official publication of the American Society for Occupational Therapy (19). The report provided approximate dimensions of the material and general procedures of administration. A detailed test instructions and adult normative values according to hand, sex, and age were available in 1985 (20).

Manual dexterity (including hand function) is an individual's ability to coordinate the fingers and manipulate objects in a timely manner. Such ability greatly impacts a person's performance in daily activities (bathing, grooming, eating), completing work-related tasks, and engaging in leisure activities. It also serves as an indicator of academic performance (eg, handwriting), work performance (eg, machine workers, dentists, surgeons), and independent living.

Further details will be provided in the study reference manual.

8.1.2 25-Foot walk test

The 25FWT is a quantitative mobility and leg function performance test based on a timed 25-foot walk. The 25FWT has high inter-rater and test-retest reliability and shows evidence of good concurrent validity. The participant is directed to one end of a clearly marked 25-foot course and is instructed to walk 25 feet as quickly as possible, but safely. The time is calculated from the initiation of the instruction to start and ends when the participant has reached the 25-foot mark. The task is immediately administered again by having the participant walk back the same distance. Participants may use assistive devices when doing this task. Further details will be provided in the study reference manual.

8.1.3 Friedreich's Ataxia Rating Scale (excluding the 9-HPT portion and the 25FWT)

The FARS scale is a composite clinician-reported outcome (ClinRO)/patient-reported outcome (PRO)/observer-reported outcome (ObsRO)/PerfO, which measures the severity of neurologic dysfunction in patients with inherited ataxias. It includes 4 domains: functional staging for ataxia (1 item; ClinRO); ADL (9 items; PRO/ClinRO/ObsRO); FARS-Neuro (23 items; PerfO); and a battery of related tests including 25FWT, 9-HPT, and PATA rate (PerfO). It assesses not only functional staging of ataxia, but also evaluates bulbar manifestations, coordination, muscle weakness, gait, speech, and swallowing, as well as the impact of the neurological deficits on activities of daily living, all areas affected by GM2 gangliosidosis. The results are gathered with a paper questionnaire with sections for each subdomain. Further details will be provided in the study reference manual.

8.1.4 [redacted]

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8.1.5 [redacted]

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[redacted]

[redacted]

8.1.6 [redacted]

[redacted]

[redacted]

8.1.7 [redacted]

[redacted]

[redacted]

8.1.8 [redacted]

[redacted]

8.1.8.1 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

8.1.8.2 [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted]
- [redacted]

[redacted]

8.1.8.3 [redacted]

[redacted]

8.1.8.4 [redacted]

[redacted]

8.1.9 [redacted]

[redacted]

8.1.10 [redacted]

[redacted]

8.1.11 Muscle weakness of triceps and quadriceps

Muscle weakness is one of the typical clinical presentations of late onset GM2-gangliosidosis. Natural history data shows that psoas was the first and most affected muscle in the lower limbs, the quadriceps was also commonly involved. The triceps and interosseous were predominantly involved in the upper limbs (28). Psoas and interosseous weakness will be evaluated in FARS-Neuro. The muscle weakness of triceps and quadriceps will be assessed and considered a sensitivity analysis of the FARS-Neuro.

8.1.12 Regional or national emergency

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by

an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

- If onsite visits are not possible, remote visits (eg, with home nurses, home health vendor, etc) may be planned for the collection of possible safety and/or efficacy data.
- If onsite visits are not possible visit windows may be extended for assessment of safety and/or efficacy data that cannot be obtained remotely.
- Use of local clinic or laboratory locations may be allowed.

Contingencies implemented due to emergency will be documented in eCRF.

For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.11 (Appendix 11).

8.2 SAFETY ASSESSMENTS

Planned time points for all safety assessments are provided in the SoA (Section 1.3).

8.2.1 Physical examinations

- A complete/full physical examination will include, at a minimum, assessments of the general appearance, examination of the skin; head, eyes (including visual acuity), ears, nose, and throat; lymph nodes; heart, lungs, and abdomen; extremities and joints; and neurological and mental status. Height and weight will also be measured and recorded.
- An abbreviated/brief physical examination will include, at a minimum, general assessments.
- Investigators should pay special attention to clinical signs related to previous serious illnesses.
- Any new finding or worsening of previous finding should be reported as a new AE.

8.2.2 Neurological examination

- Each neurological examination will include, but not be limited to, assessments of the patient's mental status, cranial nerves, motor system (including muscle atrophy, tone and power), deep tendon reflex, sensory, and cerebellar function. The examination should be performed by the same neurologist throughout the study, if possible. When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed before the ophthalmological examination.

8.2.3 Vital signs

- Body temperature, heart rate, respiratory rate, and blood pressure will be assessed.

- Blood pressure and pulse measurements will be assessed with a completely automated device. Manual techniques will be used only if an automated device is not available.
- Blood pressure and pulse measurements should be preceded by at least 5 minutes of rest for the participant in a quiet setting without distractions (eg, television, cell phones).
- Vital signs (to be taken before blood collection for laboratory tests) will consist of 1 pulse and 3 blood pressure measurements (3 consecutive blood pressure readings will be recorded at intervals of at least 1 minute). The average of the 3 blood pressure readings will be recorded on the eCRF.
- Ideally, pulse and blood pressure should be obtained and recorded while the participant is in the supine position as well as in the standing position. If the participant is unable to stand, blood pressure may be taken while the participant is sitting with feet dangling. If the participant is unable to stand or sit, pulse and blood pressure may be taken in supine position only.

8.2.4 Electrocardiograms

- 12-lead ECG will be obtained as outlined in the SoA (see Section 1.3) using an ECG machine that automatically calculates the heart rate and measures PR, QRS, QT, and corrected QT (QTc) intervals.
- For Day 1/Week 1, triplicate ECG (3 ECGs) will be recorded within 5 minutes with at least 1 minute between 2 replicates prior to IMP administration.
- The ECG will be read centrally.

8.2.5 Ophthalmological examination

The effect of venglustat on the lens will be closely monitored throughout the whole study for all participants. The full ophthalmological examination will include slit-lamp examination, fundoscopy with pupil dilation and examination of the cornea, lens, and retina.

The evaluation of the lens by photography according to the Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System (ARLNS) will be performed during screening, Week 104, Week 208, early withdrawal or treatment discontinuation, or any time deemed medically necessary.

A conventional confrontation visual field examination such as the Donders' test can be performed by the local ophthalmologist as needed as a part of the eye examination. Systematic visual field test by perimetry is not required for this trial.

A full ophthalmological examination, photography, and ARLNS will be performed during screening (this will serve as a baseline assessment), at Week 104 and at Week 208, or at early withdrawal or treatment discontinuation for all participants.

A full ophthalmological examination will be performed at Week 26, Week 52, and Week 78 for all participants and also at Week 130, Week 156, and Week 182 for participants aged ≥2 and <18 years.

Full ophthalmological examination can be performed at any time if deemed medically necessary.

If a lens abnormality is found, the ophthalmologist at the site should perform pupil dilation, photography, and ARLNS evaluation.

The full ophthalmological examination should be performed by the same ophthalmologist throughout the study, if possible. Abnormal findings reported by the clinical sites will be reviewed by the DMC and/or the clinical site to adjudicate these findings as an adverse event of special interest (AESI) and assess their seriousness/severity.

When neurological and ophthalmological examinations are performed on the same day, the neurological examination should be performed before the ophthalmological examination.

8.2.6 Clinical safety laboratory assessments

- See Appendix 2 (Section 10.2) for the list of clinical laboratory tests to be performed and to the SoA (Section 1.3) for the timing and frequency.
- The Investigator must review the laboratory report, document this review, and record any clinically relevant changes occurring during the study in the AE section of the eCRF. The laboratory reports must be filed with the source documents. Clinically significant abnormal laboratory findings are those which are not associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- All laboratory tests with values considered clinically significantly abnormal during participation in the study or within 5 half-lives after the last dose of study intervention should be repeated until the values return to normal or baseline or are no longer considered clinically significant by the Investigator or Medical Monitor.
  - If such values do not return to normal/baseline within a period of time judged reasonable by the Investigator, the etiology should be identified and the Sponsor notified.
- All protocol-required laboratory assessments, as defined in Appendix 2 (Section 10.2), must be conducted in accordance with the laboratory manual and the SoA.
  - If laboratory values from nonprotocol-specified laboratory assessments performed at the institution’s local laboratory require a change in participant management or are considered clinically significant by the Investigator (eg, SAE or AE or dose modification), then the results must be recorded in the eCRF.

8.2.7 [redacted]

[redacted]

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[redacted]

8.2.7.1 [redacted]

[redacted]

[redacted]

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8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

Adverse event of special interest

An AESI is an AE (serious or nonserious) of scientific and medical concern specific to the Sponsor's product or program, for which ongoing monitoring and immediate notification by the Investigator to the Sponsor is required. Such events may require further investigation in order to characterize and understand them. Adverse events of special interest may be added, modified or removed during a study by protocol amendment.

- Pregnancy of a female participant entered in a study as well as pregnancy occurring in a female partner of a male participant entered in a study with IMP;

  - Pregnancy occurring in a female participant entered in the clinical trial or in a female partner of a male participant entered in the clinical trial. It will be qualified as an SAE only if it fulfills one of the seriousness criteria (see Appendix 3 [Section 10.3]).
  - In the event of pregnancy in a female participant, IMP should be discontinued.
  - Follow-up of the pregnancy in a female participant or in a female partner of a male participant is mandatory until the outcome has been determined (see Appendix 4 [Section 10.4]).
- Symptomatic overdose (serious or nonserious) with IMP;
  - An overdose (accidental or intentional) with the IMP is an event suspected by the Investigator or spontaneously notified by the participant (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug.
- Increase in ALT (see the "Increase in ALT" flow diagram in Appendix 6 [Section 10.6]).
- **Other project specific AESI(s)**
  - New or worsening lens opacities and cataracts.

The definitions of an AE or SAE can be found in Appendix 3 (Section 10.3).

Adverse events will be reported by the participant (or, when appropriate, by a caregiver, surrogate, or the participant's legally authorized representative).

The Investigator and any qualified designees are responsible for detecting, documenting, and recording events that meet the definition of an AE or SAE and remain responsible for following up AEs that are serious, considered related to the study intervention or study procedures, or that caused the participant to discontinue the study intervention and/or study (see Section 7).

8.3.1 Time period and frequency for collecting AE and SAE information

All AEs, AESIs, and SAEs will be collected from the signing of the ICF until the 6-week follow-up visit at the time points specified in the SoA (Section 1.3).

All SAEs and AESI will be recorded and reported to the Sponsor or designee immediately and under no circumstance should this exceed 24 hours, as indicated in Appendix 3 (Section 10.3). The Investigator will submit any updated SAE data to the Sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AE or SAE after conclusion of the study participation. However, if the Investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the Investigator must promptly notify the Sponsor.

8.3.2 Method of detecting AEs and SAEs

The method of recording, evaluating, and assessing causality of AE and SAE and the procedures for completing and transmitting SAE reports are provided in Appendix 3 (Section 10.3).

Care will be taken not to introduce bias when detecting AEs and/or SAEs. Open-ended and nonleading verbal questioning of the participant is the preferred method to inquire about AE occurrences.

8.3.3 Follow-up of AEs and SAEs

After the initial AE/AESI/SAE report, the Investigator is required to proactively follow each participant at subsequent visits/contacts. At the prespecified study end-date, all SAEs, and nonserious AESI (as defined in Section 8.3) will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up (as defined in Section 7.3). Further information on follow-up procedures is given in Appendix 3 (Section 10.3).

8.3.4 Regulatory reporting requirements for SAEs

- Prompt notification by the Investigator to the Sponsor of an SAE is essential so that legal obligations and ethical responsibilities towards the safety of participants and the safety of a study intervention under clinical investigation are met.
- The Sponsor has a legal responsibility to notify both the local regulatory authority and other regulatory agencies about the safety of a study intervention under clinical investigation. The Sponsor will comply with country-specific regulatory requirements relating to safety reporting to the regulatory authority, Institutional Review Boards (IRB)/Independent Ethics Committees (IEC), and Investigators.
- Investigator safety reports must be prepared for suspected unexpected serious adverse reactions (SUSAR) according to local regulatory requirements and Sponsor policy and forwarded to Investigators as necessary.
- Adverse events that are considered expected will be specified in the reference safety information.
- An Investigator who receives an Investigator safety report describing an SAE or other specific safety information (eg, summary or listing of SAEs) from the Sponsor will review and then file it along with the Investigator's Brochure and will notify the IRB/IEC, if appropriate according to local requirements.

8.3.5 Pregnancy

- Details of all pregnancies in female participants and female partners of male participants will be collected after the start of study intervention and until the 6-week follow-up visit.
- If a pregnancy is reported, the Investigator should inform the Sponsor within 24 hours of learning of the pregnancy and should follow the procedures outlined in Appendix 4 (Section 10.4).

- Abnormal pregnancy outcomes (eg, spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) are considered SAEs.

8.3.6 Guidelines for reporting product complaints

Any defect in the IMP must be reported as soon as possible by the Investigator to the monitoring team that will complete a product complaint form within required timelines.

Appropriate information (eg, samples, labels or documents like pictures or photocopies) related to product identification and to the potential deficiencies may need to be gathered. The Investigator will assess whether or not the quality issue has to be reported together with an AE or SAE.

8.4 TREATMENT OF OVERDOSE

Overdose is defined as at least twice the intended dose within the intended therapeutic interval, adjusted according to the tested drug. Sponsor does not recommend specific treatment for an overdose.

In the event of an overdose, the Investigator should:

1. Contact the Sponsor immediately.
2. Evaluate the participant to determine, in consultation with the Sponsor, whether study intervention should be interrupted or whether the dose should be reduced.
3. Closely monitor the participant for any AE/SAE and laboratory abnormalities until venglustat can no longer be detected systemically (at least 6 days).
4. Document appropriately in the case report form (CRF).

Decisions regarding dose interruptions or modifications will be made by the Investigator in consultation with the Medical Monitor based on the clinical evaluation of the participant.

8.5 PHARMACOKINETICS

- Sampling time: Blood and CSF samples for plasma and CSF venglustat concentration assessment will be collected from all participants throughout the study according to the time points shown in the SoA (Section 1.3). Exact date and time of IMP administration and PK sampling are to be recorded in eCRF. For PK sample collected at end-of-treatment visit in case of premature treatment discontinuation, time of last dose and time of PK sample collected should be accurately recorded in eCRF.
- Pharmacokinetics sample handling procedure: Special procedures for collection, storage, and shipment of plasma and CSF samples will be described in a separate laboratory manual provided by the central laboratory. Approximately 2 mL of blood sample and 0.5 mL of CSF sample will be collected at each time point.
- Bioanalytical method: Venglustat plasma concentrations will be determined using a validated liquid chromatography tandem mass spectrometry (LC-MS/MS) method

(DMPK15-R012) with a lower limit of quantification (LLOQ) of 0.5 ng/mL under the responsibility of QPS, Newark, Delaware, USA. Venglustat CSF concentrations will be determined using a validated LC-MS/MS method (DMPK15-R016) with a LLOQ of 0.1 ng/mL under the responsibility of QPS, Newark, Delaware, USA.

- Pharmacokinetic parameters: Plasma PK parameters including, C_{max}, t_{max}, and AUC_{0-24} will be determined using noncompartmental methods (when data permits). In addition, PK variables will include plasma and CSF venglustat concentrations determined at each time point described in the SoA (Section 1.3). Depending on the timing of the PK sample collection versus the previous dose, venglustat PK parameters will be defined as follows:
  - C_{max}: Venglustat concentration sample taken 2 to 4 hours after IMP administration
  - C_{trough}: Venglustat concentration sample taken just prior to IMP administration
- Exploratory venglustat metabolite profiling and/or metabolite exposure analysis may be conducted in the collected plasma samples.

Drug concentration information that may unblind the study will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6 PHARMACODYNAMICS

Cerebrospinal fluid and plasma will be collected at the times specified in the SoA (Section 1.3) for the assessment of PD markers. Special procedures for collection, storage, and shipment of plasma and CSF samples will be described in a separate laboratory manual provided by the central laboratory. Approximately 7-8 mL of whole blood and 3-4 mL of CSF will be collected at each time point.

GM2 and GL-1 biomarkers will be assessed from plasma and CSF from all participants in the primary population using validated methods performed at the Sponsor's laboratory or at a subcontracted laboratory.

For the secondary population participants only, GL-1 biomarker and a pathway specific biomarker will be assessed from CSF and plasma as follows:

Disease	Biomarker
GM2 gangliosidosis	GL-1, GM2
GM1 gangliosidosis	GL-1, GM1
Sialidosis	GL-1, GM2, GM3
Galactosialidosis	GL-1, GM1, GM3
Saposin C Deficiency	GL-1 only

Additional plasma and CSF biomarkers may include but are not limited to the following: lipidomics, gpNMB, and neurofilament.

Biomarker results may unblind the study; they will not be reported to investigative sites or blinded personnel until the study has been unblinded.

8.6.1 Lumbar puncture

The lumbar puncture (LP) will be performed by the site Investigator or another qualified clinician appointed by the Investigator.

An LP for the collection of approximately 7 to 8 mL of CSF at each collection will be conducted for participants per the visit schedule, unless there is evidence of clinically significant coagulopathy or thrombocytopenia or other relevant reason that would interfere with the safe conduct of the procedure. It is expected that all participants will undergo an LP at baseline and W104. The baseline LP can be done within 14 days prior to the day of randomization (pre-dose).

The first 1 to 2 mL of CSF may be discarded; the subsequent 2 mL will be processed at the site's local laboratory facility (unless the laboratory is not able to process the CSF within 4 hours) to conduct standard analyses on cell count, including red blood cell counts, protein and glucose. The remaining CSF will be processed and shipped to a central laboratory for biomarker (approximate 3 mL) and PK assessments (approximate 0.5 mL). For pediatric participants, the CSF sampling is prioritized for biomarker and PK. Please refer to the laboratory manual provided by the central laboratory.

Participants will be closely monitored during the procedure and lying flat in bed rest for at least 1 hour following the procedure.

8.7 ACCEPTABILITY AND PALATABILITY

For the secondary pediatric population, the acceptability and palatability of venglustat tablets will be assessed through the route of venglustat administration collected in the eCRF and study intervention compliance (see Section 6.4) throughout the whole study.

8.8 [redacted]

[redacted]

[redacted]

8.9 [redacted]

[redacted]

Refer to Section 8.11 for further details regarding use of biological samples and data for future use.

8.10 [redacted]

[redacted]

8.11 USE OF BIOLOGICAL SAMPLES AND DATA FOR FUTURE RESEARCH

Future research may help further the understanding of disease subtypes, disease biology, related conditions, mechanism of action, or possible toxicity, and can help identify new drug targets or biomarkers that predict participant response to treatment. Therefore, data and biological samples will be stored and used for future research when consented to by participants (see Section 10.1.3) unless prohibited by local laws or IRBs/IECs (in such case, consent for future use of sample will not be included in the local ICF).

For participants who consent to the storage and use of their data and remaining (leftover) and/or extra (additional) clinical samples, data and samples may be used for future research related either to the drug, the mechanism of action, and the disease or its associated conditions. Such research may include, but is not limited to, performing assessments on DNA, RNA, proteins or metabolites. If future research on genetic material is performed, this will also be limited to the purpose of addressing research questions related to the drug, the mechanism of action, the disease or its associated conditions.

Remaining leftover samples will be used only after the study ends, ie, end of study as defined in the study protocol. Additional/extra samples can be collected and used during the study conduct at a given timepoint (eg, at randomization visit) as defined in the study protocol.

In the event future research is conducted for other purposes, the study participants will be informed of those purposes and will be given means to object to those research projects. Data and samples will be used in alignment with the information provided to participants in the ICF Part 2 (future research). For future research projects, all biological samples and relating data to be used will be coded such that no participant direct identifiers will be linked to them. These coded data and samples may be transferred to a Sponsor site (or a subcontractor site), which may be located outside of the country where the study is conducted. The Sponsor adopts safeguards for protecting participant confidentiality and personal data (see Section 10.1.4).

Relating data and biological samples for future research will be stored for up to 25 years after the end of the study. Any samples remaining at the end of retention period will be destroyed. If a participant requests destruction of his/her samples before the end of the retention period, the Investigator must notify the Sponsor (or its contract organization) in writing. In such case, samples will be destroyed and related coded data will be anonymized unless otherwise required by applicable laws.

Participant's coded datasets provided to researchers for a specific research project will be available to the researchers for a maximum of 2 years after the end of their specific project (end of project is defined by publication of the results or finalization of the future research project report).

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

The study is designed to test the following hypotheses for the 2 co-primary endpoints in the primary population:

- Percent change in CSF GM2 biomarker:
  - Null hypothesis: No difference between venglustat and placebo with regards to mean percent change in CSF GM2 biomarker from baseline to Week 104
  - Alternative hypothesis: Venglustat has higher reduction in CSF GM2 biomarker from baseline to Week 104 compared to placebo
- Annualized rate of change in 9-HPT:
  - Null hypothesis: No difference between venglustat and placebo with regards to mean annualized rate of change in 9-HPT
  - Alternative hypothesis: Venglustat has lower mean annualized rate of change in 9-HPT compared to placebo

9.2 SAMPLE SIZE DETERMINATION

In the primary population, approximately 57 participants will be randomly assigned with a 2:1 randomization ratio to venglustat (n=38) or placebo (n=19). This sample size will provide approximately 80% power to detect a difference between venglustat and placebo with regards to the primary efficacy endpoint of annualized rate of change in 9-HPT.

[redacted]

The sample size for the secondary population (up to 20) is not based on statistical power calculation, but on empirical considerations. The Sponsor will attempt to enroll at least 1 participant, aged 2 years or older (or aged 2 to <18 years for juvenile/adolescent late-onset GM2 gangliosidosis), in each disorder. This is in addition to the 57 participants from the primary population.

9.3 POPULATIONS FOR ANALYSES

For purposes of analysis, the following populations are defined (Table 5):

Table 5 - Populations for analyses

Population	Description
Screened	All participants who sign the ICF
Randomized population	All participants who have been allocated a treatment kit based on the randomization process and recorded in the IRT database, regardless of whether the treatment kit was used or not
Primary efficacy population	All randomized participants with diagnosis of late-onset GM2 gangliosidosis aged ≥18 years. Participants will be analyzed according to the intervention assigned by randomization.
Primary PD population	All randomized participants with diagnosis of late-onset GM2 gangliosidosis aged ≥18 years who received at least 1 dose of study medication and who have baseline and postbaseline assessments of PD. Participants will be analyzed according to the intervention they actually received.
Primary PK population	All randomized participants with diagnosis of late-onset GM2 gangliosidosis aged ≥18 years who received at least 1 dose of study medication and who have at least 1 PK assessment
Primary safety population	All randomized participants with diagnosis of late-onset GM2 gangliosidosis aged ≥18 years who received at least 1 dose of study medication. Participants will be analyzed according to the intervention they actually received.
Secondary efficacy population	All enrolled participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis.
Secondary PD population	All enrolled participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis, who received at least 1 dose of study medication and who have baseline and postbaseline assessments of PD.
Secondary PK population	All enrolled participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis, who received at least 1 dose of study medication and who have who have at least one PK assessment
Secondary safety population	All enrolled participants with a clinical diagnosis of juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, or juvenile/adult galactosialidosis, who received at least 1 dose of study medication.

Abbreviations: ICF, informed consent form; IRT, interactive response technology; PD, pharmacodynamics; PK, pharmacokinetics.

9.4 STATISTICAL ANALYSES

The statistical analysis plan will be developed and finalized before the analysis of the primary analysis treatment period and will describe the participant populations to be included in the analyses, and procedures for accounting for missing, unused, and spurious data. This section is a summary of the planned statistical analyses of the primary and secondary endpoints.

9.4.1 Efficacy analyses

Table 6 - Efficacy analyses

ndpoint	Statistical Analysis Methods
Primary	**Coprimary endpoint in the primary population:** **Percent change in CSF GM2 biomarker from baseline to Week 104** Percent change in CSF GM2 biomarker from baseline to Week 104 will be analyzed using an ANCOVA including the fixed effect of treatment (venglustat versus placebo) and the continuous fixed covariate of baseline value. In case the results from the ANCOVA may be severely impacted by the presence of outliers (participants with extremely low or high percent change in CSF GM2), the ANCOVA will be replaced by a robust ANCOVA, using Huber's M estimation. The robust ANCOVA will also include the fixed effect of treatment (venglustat vs. placebo) and the continuous fixed covariate of baseline value. The exact criterion to determine whether the robust ANCOVA should be used will be described in the Statistical Analysis Plan (SAP). **Annualized rate of change in 9-HPT from baseline to Week 104** Annualized rate of change in 9-HPT will be compared between venglustat and placebo using a linear mixed-effect model. The model will assume linear change over time in 9-HPT (after log transformation). The logarithm transformation was selected due to anticipated non-normal distribution of the 9-HPT. Analysis of natural history data showed that logarithm transformation improved the normality of the distribution and reduced the impact of outliers. A logarithm transformation will allow interpretation in terms of relative increase in time to complete the 9-HPT (annual % increase per year). The model will include separate slopes for the venglustat and placebo arms. Actual time relative to randomization of all planned assessments at Week 12, Week 26, Week 52, Week 78, and Week 104 will be taken into account in the model. In addition, the model will include a random intercept and slope in order to account for the between participants variability. A residual variance will account for the within-participant variability. The linear mixed-effect model will be estimated in a Frequentist framework. If the results from the linear mixed-effect model are severely impacted by the presence of data outliers (participants with extremely low or extremely high slope of log-transformed 9-HPT), the linear mixed-effect model will be replaced by the robust ANCOVA on individual slopes. [redacted]

ndpoint	Statistical Analysis Methods
	The exact criterion to determine whether the robust ANCOVA should be used will be described in the SAP. A secondary analysis will be estimated in a Bayesian framework with an informative prior distribution for the slope in the placebo arm. This informative prior distribution was determined based on the annualized rate of change in 9-HPT observed in a natural history study. The prior distribution will assume a normal distribution for the annual slope of 9-HPT (on a logarithm scale) in the placebo arm, with mean of 0.0264 and standard deviation of 0.0118. A sensitivity analysis will assess the impact of the assumption of joint multivariate normal distribution for the random intercept and slope. In this sensitivity analysis, individual slopes of each participant will be estimated from a linear model fitted separately in each participant, with log-transformed 9-HPT as dependent variable and time (in years) as explanatory variable. A comparison of mean slopes between the venglustat and the placebo arm will then be conducted using a robust ANCOVA of individual slopes using Huber's M estimation, including the fixed effect of treatment (venglustat versus placebo) and the continuous fixed covariate of baseline value. In order to take into account potential differences between participants with regards to the number of assessments and duration of follow-up, the ANCOVA will be weighted by the sum of squares of centered time of assessment of each participant. This sensitivity analysis will be conducted in a Frequentist framework and correspond to the analysis planned in case of outliers. A sensitivity analysis will assess the impact of the logarithm transformation. In this sensitivity analysis, the linear mixed-effect model will be fitted to the 9-HPT without logarithm transformation. In case of presence of outlier, the linear mixed-effect model will be replaced by the robust ANCOVA on individual slopes as for the primary analysis. Another sensitivity analysis will use the reciprocal of the 9-HPT.These sensitivity analyses will be conducted in a Frequentist framework. A sensitivity analysis will assess the impact of the assumption of linearity of change. A mixed effect model with repeated measures (MMRM) with the categorical fixed factor of time (representing scheduled visits) will be used. Change from baseline in log-transformed 9-HPT at the different time-points will be included in this model, with the fixed effects of treatment group (venglustat versus placebo), time point (Week 12, Week 26, Week 52, Week 78, and Week 104) treatment-by-time point interaction as well as the continuous fixed covariates of baseline log-transformed 9-HPT. This sensitivity analysis will be conducted in a Frequentist framework. Handling of missing data The primary analysis will include all data collected in participants from the primary population, regardless of whether or not participants completed the treatment period. Participants who prematurely and permanently discontinue study medication will be requested to continue to be assessed after treatment discontinuation, up to the Week 104 visit. Data collected after treatment discontinuation will be included in the primary analysis. All efforts will be made to minimize the amount of missing data. The linear mixed effect model described for the primary analysis will be run on all observed data, including data collected after treatment discontinuation. Missing data will be handled by the model assuming a Missing At Random mechanism. Due to the small sample size in this study, it is expected that a model based imputation of missing data will not be feasible. In particular, imputation of missing data based on a model estimated from participants from the same treatment arm who discontinued the study treatment but continued to have their data collected will likely be unfeasible, due to the small number of participants in this category. Multiplicity of primary endpoints: No adjustment for multiplicity will be considered for the co-primary endpoints (percent change in CSF GM2 biomarker from baseline to Week 104 and annualized rate of change in 9-HPT) since it will be necessary to demonstrate an effect on both co-primary endpoint to conclude to efficacy. **Primary endpoints in the secondary population:** Plasma and CSF GL 1 biomarker and pathway specific biomarkers in the secondary population will be summarized descriptively. Percent change from baseline in plasma and CSF GL-1 biomarker will be described for the entire secondary population. The pathway specific biomarker will be described separately for each disease in the secondary population. When at least 5 participants have available data in the entire

ndpoint	Statistical Analysis Methods
	secondary population or within a specific disease, a 95% confidence interval for the percent change from baseline will be provided. In addition, biomarker data will be summarized descriptively with individual plots and listings. No formal comparison will be performed in the secondary population.
Secondary	**Secondary endpoints in the primary population:** **Absolute change in CSF GM2 biomarker from baseline to Week 104** Absolute change in CSF GM2 biomarker will be analyzed with the similar approach used for the percent change in CSF GM2 biomarker. **Change in 25FWT from baseline to Week 104 (in participants able to walk at baseline)** Change in 25FWT will be analyzed only in participants able to walk at baseline. Participants who did not complete the 25FWT at baseline will be excluded from this analysis. Change in 25FWT will be compared between venglustat and placebo using a linear mixed-effect model with random intercept and slopes or using a robust ANCOVA on individual slopes, similar to the model used for the primary analysis of 9-HPT. **Change in the neurological examination of the FARS from baseline to Week 104** Change in the neurological examination of the FARS will be compared between venglustat and placebo using the same statistical model described for the primary analysis of 9-HPT. Multiplicity of secondary endpoints: In order to handle multiple secondary endpoints, the overall type-I error will be controlled by the Hochberg procedure. Statistical significance of the two co-primary endpoints is required before drawing inferential conclusions about secondary endpoints. **Secondary endpoints in the secondary population:** Secondary endpoints in the secondary population will be summarized descriptively with individual plots and listings. When at least 5 participants have available data at baseline and Week 104, mean change from baseline to Week 104 will be provided with 95% confidence interval. No formal comparison will be performed in the secondary population.
Exploratory	Will be described in the statistical analysis plan finalized before database lock.

Abbreviations: 25FWT, 25-foot walk test; 9-HPT, 9-hole peg test; ANCOVA, analysis of covariance; CSF, cerebrospinal fluid; FARS, Friedreich's Ataxia Rating Scale.

9.4.2 Safety analyses

Primary safety analyses will be performed on the primary safety population.

Safety data will be described separately for the participants in the secondary safety population.

9.4.3 Pharmacokinetic analyses

Plasma PK parameters will be determined using noncompartmental methods (when data permits) and summarized using descriptive statistics. Plasma and CSF venglustat concentrations will be summarized separately using descriptive stats, by visit and will be described in the statistical analysis plan. PK data will be described separately in the secondary population.

Plasma and CSF venglustat concentration data might be used for population PK modeling if considered necessary and the results for population PK modeling will be reported separately from the clinical study report (CSR). The population PK analyses will characterize the inter- and intra-participant variability in pharmacokinetic parameters and evaluate the effect of covariates such as, renal function status (creatinine clearance) on the venglustat PK.

An evaluation of the correlation between exposure and efficacy and safety may be performed to evaluate exposure-response relationships. Plasma PK parameters may be estimated for metabolites using noncompartmental methods and reported for individual participants and summarized using descriptive statistics.

9.4.4 Other analyses

Pharmacodynamic and biomarker exploratory analyses will be described in the statistical analysis plan finalized before database lock.

The impact of the regional or national emergency declared by a governmental agency on study conduct will be summarized (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency). Any additional analyses and methods required to evaluate the impact on efficacy (eg, missing data due to the emergency) and safety will be detailed in the SAP. For a regional or national emergency declared by a governmental agency that results in travel restrictions, confinement, or restricted site access, contingency measures are included in Section 10.11 (Appendix 11).

9.5 INTERIM ANALYSES

No interim analyses are planned.

The analysis will be conducted in two steps:

- First step: Primary analysis treatment period:
  The final analysis of the primary analysis period of the study will be conducted when all participants have completed the primary analysis period of the study. It will consist in the final analysis of the primary, secondary, and exploratory endpoints at 104 weeks. The analysis of the primary analysis period will be conducted when all participants have completed the Week 104 visit or have prematurely discontinued the study.
- Second step: analysis of the OLE treatment period:
  The final analysis of the OLE treatment period of the study will be conducted when all participants have completed the Week 208 visit and safety follow up visit or have prematurely discontinued the study.

9.5.1 Data Monitoring Committee (DMC)

An independent DMC will be used to monitor safety of the study. Unblinded DMC reports will be prepared by an independent unblinded statistician. Timing of such reviews as well as the specific responsibilities and mode of operation of the DMC will be described in the DMC charter.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 APPENDIX 1: REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 Regulatory and ethical considerations

- This study will be conducted in accordance with the protocol and with the following:
  - Consensus ethical principles derived from international guidelines including the Declaration of Helsinki and the applicable amendments and Council for International Organizations of Medical Sciences (CIOMS) International Ethical Guidelines
  - Applicable ICH GCP Guidelines
  - Applicable laws and regulations
- The protocol, protocol amendments, ICF, Investigator Brochure, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the Investigator and reviewed and approved by the IRB/IEC before the study is initiated.
- Any amendments to the protocol will require IRB/IEC approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.
- The Investigator will be responsible for the following:
  - Providing written summaries of the status of the study to the IRB/IEC annually or more frequently in accordance with the requirements, policies, and procedures established by the IRB/IEC
  - Notifying the IRB/IEC of SAEs or other significant safety findings as required by IRB/IEC procedures
  - Providing oversight of the conduct of the study at the site and adherence to requirements of 21 Code of Federal Regulation (CFR), ICH guidelines, the IRB/IEC, European regulation 536/2014 for clinical studies (if applicable), and all other applicable local regulations

10.1.2 Financial disclosure

Investigators and sub-Investigators will provide the Sponsor with sufficient, accurate financial information as requested to allow the Sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

10.1.3 Informed consent process

- The Investigator or his/her representative will explain the nature of the study to the participant and/or participant's parent(s)/legal guardian(s) and answer all questions regarding the study.
- Participant and/or participant's parent(s)/legal guardian(s) must be informed that their participation is voluntary. Participant and/or participant's parent(s)/legal guardian(s) will be required to sign a statement of informed consent that meets the requirements of 21 CFR 50, local regulations, ICH guidelines, Health Insurance Portability and Accountability Act (HIPAA) requirements, where applicable, and the IRB/IEC or study center.
- The medical record must include a statement that written informed consent was obtained before the participant was enrolled in the study and the date the written consent was obtained. The authorized person obtaining the informed consent must also sign the ICF.
- Participant and/or participant's parent(s)/legal guardian(s) must be re-consented to the most current version of the ICF(s) during their participation in the study.
- A copy of the ICF(s) must be provided to the participant and/or participant's parent(s)/legal guardian(s).

Participants who are rescreened are required to sign a new ICF.

The ICF will contain a separate section that addresses the use of remaining mandatory samples for optional exploratory research. The Investigator or authorized designee will explain to each participant the objectives of the exploratory research. Participants will be told that they are free to refuse to participate and may withdraw their consent at any time and for any reason during the storage period. A separate signature will be required to document a participant's agreement to allow any remaining specimens to be used for exploratory research. Participants who decline to participate in this optional research will not provide this separate signature.

10.1.4 Data protection

All personal data collected related to participants, Investigators, or any person involved in the study, which may be included in the Sponsor's databases, shall be treated in compliance with all applicable laws and regulations including the Global Data Protection Regulation (GDPR).

Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective.

"Participant race and ethnicity will be collected in this study because these data are required by regulatory agencies (eg, on afro American population for the FDA or on Japanese population for the Pharmaceuticals and Medical Devices Agency in Japan)".

- Participants will be assigned a unique identifier by the Sponsor. Any participant records or datasets that are transferred to the Sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred.

- The participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.
- The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Sponsor, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
- When archiving or processing personal data pertaining to the Investigator and/or to the participants, the Sponsor shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.1.5 Committees structure

Study committees

A DMC, operating independently from the Sponsor and Clinical Investigators, will be responsible for overseeing the safety of participants and the risk/benefit ratio throughout the study. This committee is composed of externally based individuals with expertise in the disease under study, biostatistics, and/or clinical research. The primary responsibilities of the DMC are to ensure the participant's welfare as well as to evaluate and review the safety and other applicable data throughout the course of the study and make appropriate recommendations to the Sponsor regarding the conduct of the clinical trial. The specific responsibilities of the DMC will be described in the DMC Charter.

10.1.6 Dissemination of clinical study data

Sanofi shares information about clinical trials and results on publicly accessible websites, based on company commitments, international and local legal and regulatory requirements, and other clinical trial disclosure commitments established by pharmaceutical industry associations. These websites include clinicaltrials.gov, European Union clinicaltrialregister (eu.ctr), and sanofi.com, as well as some national registries.

In addition, results from clinical trials in participants are required to be submitted to peer-reviewed journals following internal company review for accuracy, fair balance and intellectual property. For those journals that request sharing of the analyzable data sets that are reported in the publication, interested researchers are directed to submit their request to clinicalstudydatarequest.com.

Individual participant data and supporting clinical documents are available for request at clinicalstudydatarequest.com. While making information available we continue to protect the privacy of participants in our clinical trials. Details on data sharing criteria and process for requesting access can be found at this web address: clinicalstudydatarequest.com.

10.1.7 Data quality assurance

- All participant data relating to the study will be recorded on printed or electronic CRF unless transmitted to the Sponsor or designee electronically (eg, laboratory data). The Investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.
- The Investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.
- The Investigator must permit study-related monitoring, audits, IRB/IEC review, and regulatory agency inspections and provide direct access to source data documents.
- Monitoring details describing strategy (eg, risk-based initiatives in operations and quality such as Risk Management and Mitigation Strategies and Analytical Risk-Based Monitoring), methods, responsibilities and requirements, including handling of noncompliance issues and monitoring techniques (central, remote, or on-site monitoring) are provided in separate study documents.
- The Sponsor or designee is responsible for the data management of this study including quality checking of the data.
- The Sponsor assumes accountability for actions delegated to other individuals (eg, Contract Research Organizations).
- Study monitors will perform ongoing source data verification to confirm that data entered into the CRF by authorized site personnel are accurate, complete, and verifiable from source documents; that the safety and rights of participants are being protected; and that the study is being conducted in accordance with the currently approved protocol and any other study agreements, ICH GCP, and all applicable regulatory requirements.
- Records and documents, including signed ICFs, pertaining to the conduct of this study must be retained by the Investigator for 25 years after the signature of the final study report unless local regulations or institutional policies require a longer retention period. No records may be destroyed during the retention period without the written approval of the Sponsor. No records may be transferred to another location or party without written notification to the Sponsor.

10.1.8 Source documents

- Source documents provide evidence for the existence of the participant and substantiate the integrity of the data collected. Source documents are filed at the Investigator's site.
- Data reported on the CRF or entered in the eCRF that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The Investigator may need to request previous medical records or transfer records, depending on the study. Also, current medical records must be available.
- Definition of what constitutes source data can be found in study reference manual.

10.1.9 Study and site closure

The Sponsor or designee reserves the right to close the study site or terminate the study at any time for any reason at the sole discretion of the Sponsor. Study sites will be closed upon study completion. A study site is considered closed when all required documents and study supplies have been collected and a study-site closure visit has been performed.

The Investigator may initiate study-site closure at any time, provided there is reasonable cause and sufficient notice is given in advance of the intended termination.

Reasons for the early closure of a study site by the Sponsor or Investigator may include but are not limited to:

- The information on the product leads to doubt as to the benefit/risk ratio.
- Participant enrollment is unsatisfactory.
- Noncompliance of the Investigator or Sub-Investigator, delegated staff with any provision of the clinical trial protocol, and breach of the applicable laws and regulations or breach of the ICH GCP.
- The Investigator has received from the Sponsor all IMP, means, and information necessary to perform the clinical trial and has not included any participant after a reasonable period of time mutually agreed upon.
- The total number of participants are included earlier than expected.
- If the study no longer meets the development needs of the compound or business needs of the company.

10.1.10 Publication policy

- The results of this study may be published or presented at scientific meetings. If this is foreseen, the Investigator agrees to submit all manuscripts or abstracts to the Sponsor before submission. This allows the Sponsor to protect proprietary information and to provide comments.
- The Sponsor will comply with the requirements for publication of study results. In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating Investigator will be designated by mutual agreement.
- Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors authorship requirements.

10.2 APPENDIX 2: CLINICAL LABORATORY TESTS

- The tests detailed in Table 7 will be performed by the central laboratory, except urinalysis by dipstick and “other tests” as listed in Table 7.

- , which will be performed at the study site. If local laboratory results are used to make a study treatment decision, response evaluation, or to diagnose/follow-up an AE, the results must be entered into the eCRF.
- Protocol-specific requirements for inclusion or exclusion of participants are detailed in Section 5 of the protocol.
- Additional tests may be performed at any time during the study as determined necessary by the Investigator or required by local regulations.
- The first 1 to 2 mL of CSF may be discarded; the subsequent 2 to 4 mL will be processed at the site's local laboratory facility (unless the laboratory is not able to process the CSF within 4 hours) to conduct standard analyses on cell count (including red blood cell counts), protein and glucose levels. The remaining CSF will be processed and shipped to a central laboratory for biomarker and PK assessments. Further details will be in the laboratory manual provided by the central laboratory.

Table 7 - Protocol-required laboratory assessments

Laboratory assessments	Parameters
Hematology	Platelet count
	Red blood cell (RBC) count
	Hemoglobin
	Hematocrit
	RBC indices:
	Mean corpuscular volume (MCV)
	Mean corpuscular hemoglobin (MCH)
	% Reticulocytes
	White blood cell (WBC) count with differential:
	Neutrophils
	Lymphocytes
	Monocytes
	Eosinophils
	Basophils
Clinical chemistry[a]	Blood urea nitrogen (BUN)
	Creatinine, estimated glomerular filtration rate
	Glucose
	Potassium
	Sodium
	Calcium
	Aspartate aminotransferase (AST)/Serum glutamic-oxaloacetic transaminase (SGOT)
	Alanine aminotransferase (ALT)/Serum glutamic-pyruvic transaminase (SGPT)

Laboratory assessments	Parameters
	Alkaline phosphatase
	Total and direct bilirubin
	Total protein
Routine urinalysis[b]	Specific gravity
	pH, glucose, protein, blood, ketones, bilirubin, urobilinogen, nitrite, leukocyte esterase by dipstick
	Microscopic examination (if blood or protein is abnormal)
Urine biochemistry	Creatinine
	Total protein
	Albumin
	UPCR
	UACR
Other screening tests	Human chorionic gonadotropin (hCG) pregnancy test (as needed for women of childbearing potential)[c]
	The results of each test must be entered into the eCRF.
	Serology (HIV antibody, hepatitis B surface antigen (HBsAg), and hepatitis C virus antibody, other infectious disease or other tests) if locally required.

Abbreviations: eCRF, electronic case report form; IRB/IEC, Institutional Review Board/Independent Ethics Committee; SAE, serious adverse event.

NOTES :

a Details of liver chemistry stopping criteria and required actions and follow-up assessments after liver stopping or monitoring event are given in Section 10.6 (Appendix 6). All events which may indicate severe liver injury (possible Hy's Law) must be reported as an SAE (excluding studies of hepatic impairment or cirrhosis).

b Urinalysis by dipstick will be performed at the site. If abnormal, a complete urinalysis will be performed by the central laboratory.

c Urinalysis by dipstick will be performed at the site and home. Local urine testing will be standard for the protocol unless serum testing is required by local regulation or the IRB/IEC.

Investigators must document their review of each laboratory safety report.

10.3 APPENDIX 3: ADVERSE EVENTS: DEFINITIONS AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

DEFINITION OF AE

AE definition

- An AE is any untoward medical occurrence in a participant or clinical study participant, temporally associated with the use of study intervention, whether or not considered related to the study intervention.
- NOTE: An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of study intervention.

Events meeting the AE definition

- Any abnormal laboratory test results (hematology, clinical chemistry, or urinalysis) or other safety assessments (eg, ECG, radiological scans, vital signs measurements),

including those that worsen from baseline, considered clinically significant in the medical and scientific judgment of the Investigator (ie, not related to progression of underlying disease), eg:

- Symptomatic and/or
- Requiring either corrective treatment or consultation, and/or
- Leading to IMP discontinuation or modification of dosing, and/or
- Fulfilling a seriousness criterion, and/or
- Defined as an AESI

- Exacerbation of a chronic or intermittent pre-existing condition including either an increase in frequency and/or intensity of the condition.
- New conditions detected or diagnosed after study intervention administration even though it may have been present before the start of the study.
- Signs, symptoms, or the clinical sequelae of a suspected drug-drug interaction.
- Signs, symptoms, or the clinical sequelae of a suspected overdose of either study intervention or a concomitant medication.
- "Lack of efficacy" or "failure of expected pharmacological action" per se will not be reported as an AE or SAE. Such instances will be captured in the efficacy assessments. However, the signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE.
- The signs, symptoms, and/or clinical sequelae resulting from lack of efficacy will be reported as AE or SAE if they fulfil the definition of an AE or SAE. Also, "lack of efficacy" or "failure of expected pharmacological action" also constitutes an AE or SAE.

Events NOT meeting the AE definition

- Any clinically significant abnormal laboratory findings or other abnormal safety assessments which are associated with the underlying disease, unless judged by the Investigator to be more severe than expected for the participant's condition.
- The disease/disorder being studied or expected progression, signs, or symptoms of the disease/disorder being studied, unless more severe than expected for the participant's condition.
- Medical or surgical procedure (eg, endoscopy, appendectomy): the condition that leads to the procedure is the AE.
- Situations in which an untoward medical occurrence did not occur (social and/or convenience admission to a hospital).
- Anticipated day-to-day fluctuations of pre-existing disease(s) or condition(s) present or detected at the start of the study that do not worsen.

DEFINITION OF SAE

If an event is not an AE per definition above, then it cannot be an SAE even if serious conditions are met (eg, hospitalization for signs/symptoms of the disease under study, death due to progression of disease).

A SAE is defined as any untoward medical occurrence that, at any dose:

A) Results in death

B) Is life-threatening

The term "life-threatening" in the definition of "serious" refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death, if it were more severe.

C) Requires inpatient hospitalization or prolongation of existing hospitalization

In general, hospitalization signifies that the participant has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in the physician's office or outpatients setting. Complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. When in doubt as to whether "hospitalization" occurred or was necessary, the AE should be considered serious.

Hospitalization for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

D) Results in persistent disability/incapacity

- The term disability means a substantial disruption of a person's ability to conduct normal life functions.
- This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (eg, sprained ankle) which may interfere with or prevent everyday life functions but do not constitute a substantial disruption.

E) Is a congenital anomaly/birth defect

F) Other situations:

- Medical or scientific judgment should be exercised in deciding whether SAE reporting is appropriate in other situations such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the participant or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These events should usually be considered serious.
- Examples of such events include invasive or malignant cancers, intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalization, or development of drug dependency or drug abuse.

RECORDING AND FOLLOW-UP OF AE AND/OR SAE

AE and SAE recording

- When an AE/SAE occurs, it is the responsibility of the Investigator to review all documentation (eg, hospital progress notes, laboratory reports, and diagnostics reports) related to the event.
- The Investigator will then record all relevant AE/SAE information in the eCRF.
- It is **not** acceptable for the Investigator to send photocopies of the participant's medical records to the Sponsor or its designee in lieu of completion of the AE/SAE eCRF page.
- There may be instances when copies of medical records for certain cases are requested by the Sponsor or its designee. In this case, all participant identifiers, with the exception of the participant number, will be redacted on the copies of the medical records before submission to the Sponsor or its designee.
- The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. Whenever possible, the diagnosis (not the individual signs/symptoms) will be documented as the AE/SAE.

Assessment of intensity

The Investigator will make an assessment of intensity for each AE and SAE reported during the study and assign it to 1 of the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

An event is defined as "serious" when it meets at least 1 of the predefined outcomes as described in the definition of an SAE, NOT when it is rated as severe.

Assessment of causality

- The Investigator is obligated to assess the relationship between study intervention and each occurrence of each AE/SAE.
- A "reasonable possibility" of a relationship conveys that there are facts, evidence, and/or arguments to suggest a causal relationship, rather than a relationship cannot be ruled out.
- The Investigator will use clinical judgment to determine the relationship.
- Alternative causes, such as underlying disease(s), concomitant therapy, and other risk factors, as well as the temporal relationship of the event to study intervention administration will be considered and investigated.

- The Investigator will also consult the Investigator's Brochure (IB) and/or Product Information, for marketed products, in his/her assessment.
- For each AE/SAE, the Investigator **must** document in the medical notes that he/she has reviewed the AE/SAE and has provided an assessment of causality.
- There may be situations in which an SAE has occurred and the Investigator has minimal information to include in the initial report to the Sponsor or its designee. However, **it is very important that the Investigator always make an assessment of causality for every event before the initial transmission of the SAE data to the Sponsor or its designee.**
- The Investigator may change his/her opinion of causality in light of follow-up information and send a SAE follow-up report with the updated causality assessment.
- The causality assessment is one of the criteria used when determining regulatory reporting requirements.

Follow-up of AEs and SAEs

- The Investigator is obligated to perform or arrange for the conduct of supplemental measurements and/or evaluations as medically indicated or as requested by the Sponsor or its designee to elucidate the nature and/or causality of the AE or SAE as fully as possible. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals.
- If a participant dies during participation in the study or during a recognized follow-up period, the Investigator will provide the Sponsor or its designee with a copy of any postmortem findings including histopathology.
- New or updated information will be recorded in the originally completed eCRF.
- The Investigator will submit any updated SAE data to the Sponsor or its designee within 24 hours of receipt of the information.

REPORTING OF SAES

SAE reporting to the Sponsor or its designee via an electronic data collection tool

- The primary mechanism for reporting an SAE to the Sponsor or its designee will be the electronic data collection tool.
- If the electronic system is unavailable, then the site will use the paper SAE data collection tool (see next section) in order to report the event within 24 hours.
- The site will enter the SAE data into the electronic system as soon as it becomes available.
- After the study is completed at a given site, the electronic data collection tool will be taken off-line to prevent the entry of new data or changes to existing data.
- If a site receives a report of a new SAE from a study participant or receives updated data on a previously reported SAE after the electronic data collection tool has been taken off-line, then the site can report this information on a paper SAE form (see next section) or to the Sponsor or its designee by telephone.
- Contacts for SAE reporting can be found in study reference manual.

SAE reporting to the Sponsor or its designee via paper CRF

- Facsimile transmission of the SAE paper CRF is the preferred method to transmit this information to the Sponsor or its designee.
- In rare circumstances and in the absence of facsimile equipment, notification by telephone is acceptable with a copy of the SAE data collection tool sent by overnight mail or courier service.
- Initial notification via telephone does not replace the need for the Investigator to complete and sign the SAE CRF pages within the designated reporting time frames.
- Contacts for SAE reporting can be found in study reference manual.

10.4 APPENDIX 4: CONTRACEPTIVE GUIDANCE AND COLLECTION OF PREGNANCY INFORMATION

DEFINITIONS:

Woman of childbearing potential (WOCBP)

A woman is considered fertile following menarche and until becoming postmenopausal unless permanently sterile (see below).

If fertility is unclear (eg, amenorrhea in adolescents or athletes) and a menstrual cycle cannot be confirmed before first dose of study intervention, additional evaluation should be considered.

Women in the following categories are not considered WOCBP

1. Premenarchal
2. Premenopausal female with 1 of the following:
   - Documented hysterectomy
   - Documented bilateral salpingectomy
   - Documented bilateral oophorectomy

   For individuals with permanent infertility due to an alternate medical cause other than the above, (eg, mullerian agenesis, androgen insensitivity), Investigator discretion should be applied to determining study entry.

   Note: Documentation can come from the site personnel's: review of the participant's medical records, medical examination, or medical history interview.
3. Postmenopausal female
   - A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

- A high follicle-stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a postmenopausal state in women not using hormonal contraception or hormone replacement therapy (HRT). However, in the absence of 12 months of amenorrhea, confirmation with more than one FSH measurement is required.
- Females on HRT and whose menopausal status is in doubt will be required to use one of the nonestrogen hormonal highly effective contraception methods if they wish to continue their HRT during the study. Otherwise, they must discontinue HRT to allow confirmation of postmenopausal status before study enrollment.

CONTRACEPTION GUIDANCE:

Male participants

- Male participants with female partners of childbearing potential are eligible to participate if they agree to ONE of the following (during the protocol-defined time frame in Section 5.1):
  - Are abstinent from penile-vaginal intercourse as their usual and preferred lifestyle (abstinent on a long term and persistent basis) and agree to remain abstinent
  - Agree to use a male condom plus partner use of a contraceptive method with a failure rate of <1% per year as described in Table 8 when having penile-vaginal intercourse with a WOCBP who is not currently pregnant
- In addition, male participants must refrain from donating sperm for the duration of the study and for 90 days after the last dose of study intervention.
- Male participants with a pregnant or breastfeeding partner must agree to remain abstinent from penile-vaginal intercourse or use a male condom during each episode of penile penetration during the protocol-defined time frame.

Female participants

Female participants of childbearing potential are eligible to participate if they agree to use a highly effective method of contraception consistently and correctly for the duration of the study and for at least 6 weeks following their last dose of study drug as described in Table 8.

Table 8 - Highly effective contraceptive methods

Highly effective contraceptive methods that are user dependent[a] *Failure rate of <1% per year when used consistently and correctly.*
Combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation[b] • Oral • Intravaginal • Transdermal
Progestogen only hormonal contraception associated with inhibition of ovulation • Oral • Injectable

Highly effective methods that are user independent
Implantable progestogen only hormonal contraception associated with inhibition of ovulation • Intrauterine device (IUD) • Intrauterine hormone-releasing system (IUS) • Bilateral tubal occlusion
Vasectomized partner *A vasectomized partner is a highly effective contraception method provided that the partner is the sole male sexual partner of the woman of childbearing potential (WOCBP) and the absence of sperm has been confirmed. If not, an additional highly effective method of contraception should be used.*
Sexual abstinence *Sexual abstinence is considered a highly effective method only if defined as refraining from heterosexual intercourse during the entire period of risk associated with the study intervention. The reliability of sexual abstinence needs to be evaluated in relation to the duration of the study and the preferred and usual lifestyle of the participant.*

a Typical use failure rates may differ from those when used consistently and correctly. Use should be consistent with local regulations regarding the use of contraceptive methods for participants participating in clinical studies.

b Hormonal contraception may be susceptible to interaction with the study intervention, which may reduce the efficacy of the contraceptive method. In this case, 2 highly effective methods of contraception should be utilized during the intervention period and for at least 6 weeks after the last dose of study intervention.

PREGNANCY TESTING:

- WOCBP should only be included after a negative serum pregnancy test.
- Additional pregnancy testing should be performed at monthly intervals during the intervention period and as required locally.
- Pregnancy testing will be performed whenever a menstrual cycle is missed or when pregnancy is otherwise suspected.

COLLECTION OF PREGNANCY INFORMATION:

Male participants with partners who become pregnant

- The Investigator will attempt to collect pregnancy information on any male participant's female partner who becomes pregnant while the male participant is in this study. This applies only to male participants who receive study intervention.
- After obtaining the necessary signed informed consent from the pregnant female partner directly, the Investigator will record pregnancy information on the appropriate form and submit it to the Sponsor within 24 hours of learning of the partner's pregnancy. The female partner will also be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the neonate (Note: follow-up to 1 year after birth) and the information will be forwarded to the Sponsor. Information on the status of the mother and child will be forwarded to the Sponsor. Generally, the follow-up will be no longer than 6 to 8 weeks following the estimated delivery date. Any termination of the pregnancy will be reported regardless of fetal status (presence or absence of anomalies) or indication for the procedure.

Female participants who become pregnant

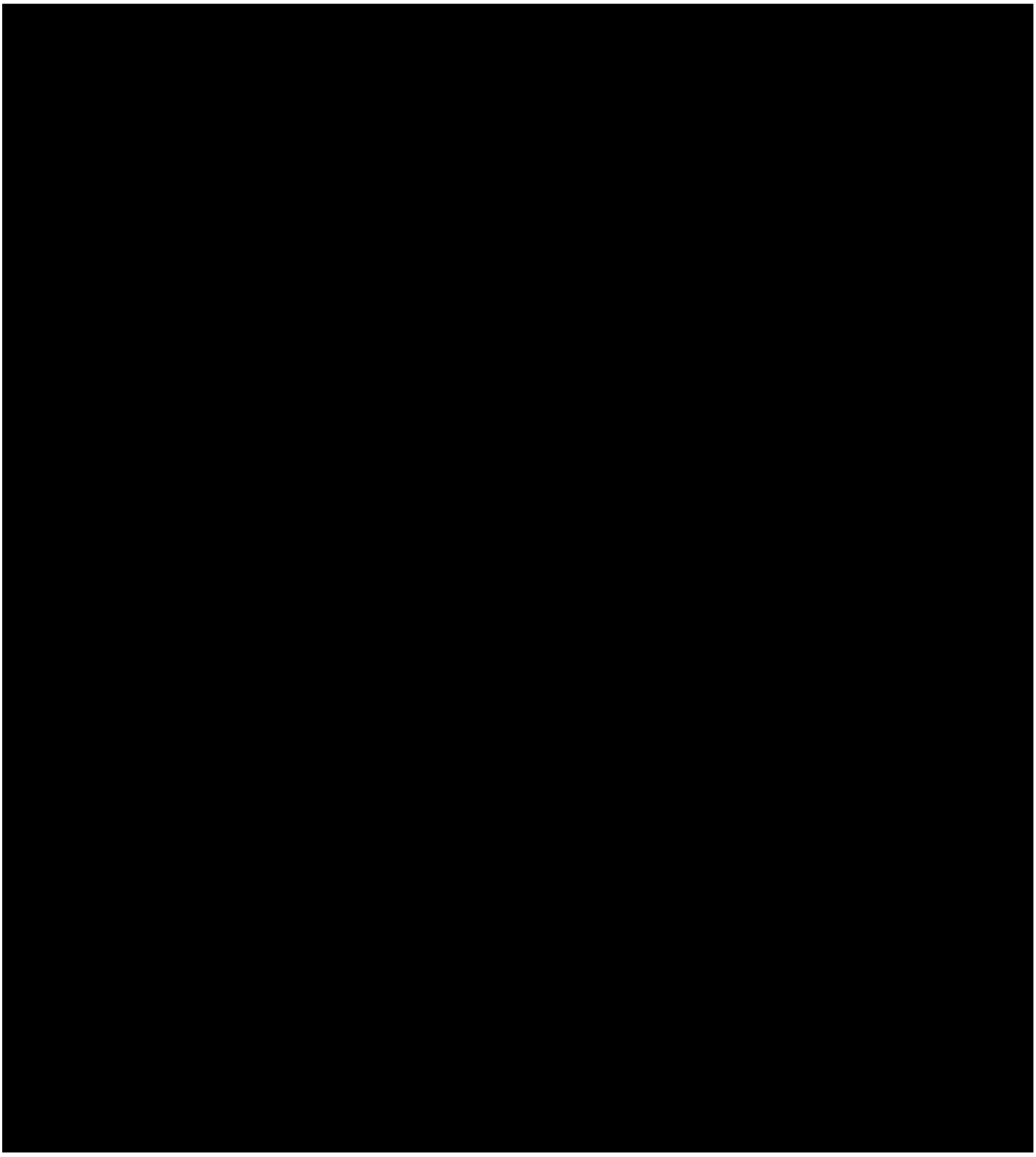
- The Investigator will collect pregnancy information on any female participant who becomes pregnant while participating in this study. Information will be recorded on the appropriate form and submitted to the Sponsor within 24 hours of learning of a participant's pregnancy. The participant will be followed to determine the outcome of the pregnancy. The Investigator will collect follow-up information on the participant and the neonate (Note: follow-up to 1 year after birth) and the information will be forwarded to the Sponsor. Generally, follow-up will not be required for longer than 6 to 8 weeks beyond the estimated delivery date. Any termination of pregnancy will be reported, regardless of fetal status (presence or absence of anomalies) or indication for the procedure.
- Any pregnancy complication or elective termination of a pregnancy will be reported as an AE or SAE. A spontaneous abortion is always considered to be an SAE and will be reported as such. Any poststudy pregnancy related SAE considered reasonably related to the study intervention by the Investigator will be reported to the Sponsor as described in Section 8.3.4. While the Investigator is not obligated to actively seek this information in former study participants, he or she may learn of an SAE through spontaneous reporting.
- Any female participant who becomes pregnant while participating in the study will discontinue study intervention or be withdrawn from the study.

10.5 APPENDIX 5: [redacted]

[redacted]

[redacted]

10.6 APPENDIX 6: LIVER SAFETY: SUGGESTED ACTIONS AND FOLLOW-UP ASSESSMENTS



10.7 APPENDIX 7: MEDICAL DEVICE INCIDENTS: DEFINITION AND PROCEDURES FOR RECORDING, EVALUATING, FOLLOW-UP, AND REPORTING

Not applicable.

10.8 APPENDIX 8: COUNTRY-SPECIFIC REQUIREMENTS

For Canadian participants enrolled in US:

The IMP will be dispensed every 13 weeks at site or through DTP.

Table 9 - Schedule of Activities (SoA) addition for Canadian participants

Study Period/ Procedure	Screening	Primary analysis treatment period										Open-label extension treatment period							FU Period
Day or Week	Up to 60 d before D1	W1 /D1	W12 (±7d)	W26 (±7d)	W39 (±7d)	W52 (±7d)	W65 (±7d)	W78 (±7d)	W91 (±7d)	W104 (±7d)/ EW[a]	W117 (±7d)/ EW	W130 (±14d)	W143 (±14d)	W156 (±14d)	W169 (±14d)	W182 (±14d)	W195 (±14d)	W208 (±14d)/ EOT/EW[b]	W214 (±7d) SFU after EOT
Visit number	1	2	3	4	4.1[c]	5	5.1[c]	6	6.1 [c*]	7	7.1 [c*]	8	8.1[c*]	9	9.1 [c*]	10	10.1[c*]	11	12
IRT contact	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Dispense IMP		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

a In case of early treatment withdrawal before W104, and if participant does not wish to stay in the study, assessments mentioned in the W104 visit will be performed, followed by safety follow-up visit 6 weeks after the W104/EW visit.

b In case of early treatment withdrawal after W104, and if participant does not wish to stay in the study after W104, assessments mentioned in the W208 will be performed, followed by safety follow-up visit 6 weeks after the W208/EOT/EW visit.

c The IMP can be dispensed and sent to participants at Visits 4.1 (W39) and 5.1 (W65) via DTP shipment except if the local regulatory authority requires the IMP dispensed at site. No other study assessments are planned during these 2 visits.

c* For Canadian participants, the IMP will be dispensed and sent to participants at Visits 6.1 (W91), 7.1 (W117), 8.1 (W143), 9.1 (W169), and 10.1 (W195) via DTP shipment or the IMP will be dispensed at site per local regulatory authority requirements. No other study assessments are planned during these visits.

For participants enrolled in Japan:

Inclusion Criterion 08: The participant or if appropriate parent(s) or legal guardian(s) must provide written informed assent/consent prior to any study-related procedures being performed as described in Appendix 1 (Section 10.1). For Japanese participants 18 and 19 years old, the informed consent is required from both parent/guardian and the participant.

For participants enrolled in France:

I 08: For patients ≥18 years of age: the patient must provide written informed consent prior to any study-related procedures being performed, as described in Appendix 1 (Section 10.1).

OR

French Public Health Code

For patients ≥18 years of age who are the subject of a legal protection measure or who are unable to express their consent, as per Article L1121-8 of French Public Health Code, the patient can only be requested for research mentioned in 1° or 2° of Article L1121-1 if research of comparable effectiveness cannot be carried out on another category of the population and under one of the two following conditions:

- Either the importance of the expected benefit for these persons is such as to justify the foreseeable risk incurred.
- Or this research is justified in terms of the expected benefit for other people in the same situation. In this case, the foreseeable risks and constraints involved in the research must be minimal.

In view of the research concerned and the regulations cited above, the inclusion criteria I08(a), I08(b) and exclusion criteria E24(a), E24(b) have been added for France.

Inclusion criteria

- I08(a): For patient under tutorship, the legal representative must provide written informed consent prior to any study-related procedures being performed.
- I08(b): For patient under curatorship, the patient and the curator must provide written informed consent prior to any study-related procedures being performed.

Exclusion criteria

- E24(a): the participant is under safeguard of justice or deprived of his/her liberty by a court decision.
- E24(b): the participant is unable to express his/her consent.

10.9 APPENDIX 9: ABBREVIATIONS

25FWT: 25-foot walk test
9-HPT: 9-hole peg test
ADL: activities of daily living
ADME: absorption, distribution, metabolism, excretion
AE: adverse event
AESI: adverse event of special interest
[redacted]
ALT: alanine aminotransferase
ANCOVA: analysis of covariance
AREDS: Age-Related Eye Disease Study
ARLNS: Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System
AST: aspartate aminotransferase
AUC_{0-24}: area under the plasma concentration versus time curve calculated using the trapezoidal method over a predefined time period (0 to 24 hours)
BBB: blood brain barrier
[redacted]
CFR: Code of Federal Regulation
[redacted]
ClinRO: clinician-reported outcome
C_{max}: maximum plasma concentration observed
CNS: central nervous system
CNS: central nervous system
CSF: cerebrospinal fluid
CSR: clinical study report
CYP: cytochrome P450
ECG: electrocardiogram
ERT: enzyme-replacement therapy
FARS: Friedreich's Ataxia Rating Scale
FD: Fabry disease
FDA: Food and Drug Administration
FES: falls efficacy scale
FSH: follicle-stimulating hormone
GBA-PD: Parkinson's disease and a glucocerebrosidase mutation
GCP: Good Clinical Practice
GCS: glucosylceramide synthase
GD1: Gaucher disease type 1
GD3: Gaucher disease type 3
GL-1: glucosylceramide
GM3: monosialodihexosylganglioside
gpNMB: glycoprotein nonmetastatic protein B
HRT: hormone replacement therapy

ICF:	informed consent form
ICH:	International Council for Harmonisation
IEC:	Independent Ethics Committee
IMP:	investigational medicinal product
IRB:	Institutional Review Board
IRT:	interactive response technology
LC-MS/MS:	liquid chromatography tandem mass spectrometry
LLOQ:	lower limit of quantification
LP:	lumbar puncture
[redacted]	
NTSAD:	National Tay-Sachs & Allied Diseases Associations
ObsRO:	observer-reported outcome
OLE:	open-label extension
PD:	pharmacodynamic
PerfO:	performance outcome
[redacted]	
PK:	pharmacokinetic
PRO:	patient-reported outcome
[redacted]	
SAE:	serious adverse event
SAP:	Statistical Analysis Plan
SoA:	schedule of activities
SRT:	substrate reduction therapy
SUSAR:	suspected unexpected serious adverse reaction
t_{max}:	time to reach maximum plasma concentration
[redacted]	
UACR:	urine albumin creatinine ratio
ULN:	upper limit of normal
UPCR:	urine protein creatinine ratio
WOCBP:	woman of childbearing potential
β-hCG:	beta human chorionic gonadotropin

10.10 APPENDIX 10: PROTOCOL AMENDMENT HISTORY

The Protocol Amendment Summary of Changes Table for the current amendment is located directly before the Table of Contents (TOC).

10.10.1 Amended protocol 01 (05 November 2019)

This amended protocol (Amendment 01) is considered to be not substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union because it does not significantly impact the safety or physical/mental integrity of participants, nor the scientific value of the study.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to include clarifications requested by the U.S. Food and Drug Administration (FDA). Other modifications or editorial changes are included to correct inconsistencies and improve operational feasibility.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis and Section 4.1 Overall Design	Added "Randomization will be stratified on the participant's ability to walk at the baseline visit (yes/no)."	To ensure balanced randomization of subjects able to walk at baseline.
Section1.1 Synopsis and Section 6.1 Study intervention(s) administered	The sentences "The investigational medicinal product (IMP) can be chewed or swallowed whole. Whether the IMP is swallowed or chewed should be as consistent as possible throughout the whole study treatment duration, and the method should be documented in the electronic case report form (eCRF)" were modified to "investigational medicinal product (IMP) should be swallowed whole."	Waiting bioavailability (BA) study results to support the administration of the tablets by chewing.
Section 1.1 Synopsis/ Section 3 Objective and endpoints/Section 8.6 Pharmacodynamics	Deleted "LDH" from "Additional plasma and CSF biomarkers may include but are not limited to: lactate dehydrogenase (LDH), lipidomics, glycoprotein nonmetastatic protein B (gpNMB), neurofilament."	Remove LDH.
Section 1.1 Synopsis (Statistical considerations)	Added "It will also provide >99% power to detect a difference between venglustat and placebo with regards to the co-primary endpoint of percent change in CSF GM2 biomarker from baseline to Week 104."	Clarify the power on the co-primary endpoint.
[redacted]	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 1.3 Schedule of Activities (SoA)	The sentence "The IMP will be dispensed and sent to participants at Visits 4.1 (W39) and 5.1 (W65) via DTP shipment," was modified to "The IMP can be dispensed and sent to participants at Visits 4.1 (W39) and 5.1 (W65) via DTP shipment, except if the local regulatory authority requires the IMP dispensed at site."	To meet the local regulatory requirement.
Section 1.3 Schedule of Activities (SoA)	Added 12-lead ECG at W26, W52 and W78 visits.	To evaluate the ECG more frequently considering that this represents the first clinical exposure in this patient population.
Section 1.3 Schedule of Activities (SoA)	For PK plasma sample notes: Added "(Plasma sample ID P00, P01, P02, P03, P04, P05 respectively)." to "For primary population, sampling will be performed predose and 0.5, 3, 8, 12, and 24 hours postdose in 15 participants". Added "(P02)" to "For all other participants, sampling will be performed only at 3 hours postdose". Added (Plasma sample ID P06, P07, P08, P09, P10, P11 respectively)" to "Sampling will be performed predose and 0.5, 3, 8, 12, and 24 hours postdose". Added "(Plasma sample ID P12, P13 at Visit 4/Week 26 and P14 and P15 at Visit 5/week 52 respectively)" to "Sampling will be performed predose and 3 hours postdose". Added "(plasma sample ID P16)" to "Sampling will be performed predose". Added "(Plasma sample ID P17)" to" Sample may be collected at any time and the time of sample collection should be recorded". For PK CSF sample notes: Added "(CSF sample ID C00)" to" Sampling will be performed predose".	Sample ID is a required field for doing PK analysis within PKDMS (PK data management system). Adding sample IDs in protocol will help to provide a single source of information for PK samples analyzed at BA lab and PK sampling data to be collected in clinical database and avoids any errors.
Section 1.3 Schedule of Activities (SoA)/Section 10.8	Deleted "Optional for participants in Japan".	TMT A/B is now available in Japanese.
Section 1.3 Schedule of Activities (SoA) and Section 8.1.11	Added text to footnote and in 8.1.11 "Qualitative structured interviews will be conducted between Week 104 and Week 106 or within the 2 weeks following the participant's end of treatment or early withdrawal last visit." Replaced "For English-speaking participants only" by "For participants from primarily English-Speaking countries".	To clarify when the exit interview is conducted. To clarify participants who will be interviewed.

Section # and Name	Description of Change	Brief Rationale
[redacted]		
Section 5.1 Inclusion Criteria	Deleted “or chew and swallow” from I 05.	Waiting bioavailability (BA) study results to support the administration of the tablets by chewing.
Section 5.1 Inclusion Criteria	Deleted “Note: the participant must have bilateral antigravity ability in upper extremities.” In I 03.	The note is not necessary.
Section 5.2 Exclusion Criteria E 01	“completely asymptomatic” was modified to “without clinical features”.	Correction.
Section 5.2 Exclusion Criteria E 15	Added “and maintains a level of total bilirubin <5 mg/dl and direct bilirubin <1 mg/dl (20%) of total bilirubin level” to “Gilbert syndrome”.	To clarify the limits of total and direct bilirubin that are allowed for patients with Gilbert’s syndrome.
[redacted]	[redacted]	[redacted]
Section 6.3	Added a paragraph regarding “Randomization code breaking”.	To clarify the procedure of code unbinding.
Section 6.5 Concomitant therapy	Added “The participants must abstain from taking pyrimethamine and/or acetyl-leucine throughout this clinical study” Replaced “the follow up visit” by “the final safety follow-up visit (Week 110 or 6 weeks after EOT)”.	To clarify the prohibition of using pyrimethamine and acetyl-leucine in this study. To clarify “the follow up visit”.
Section 7.1.2 Temporary discontinuation	Added “If an SAE or ≥ Grade 3 AE (NCI, CTCAE v4.03) that is considered by the Investigator to be related to GZ/SAR402671 and not to underlying disease or concomitant medication, the dose may be temporarily discontinued”.	To clarify the temporary discontinuation criteria.
Section 8 Study assessments and procedures	Added a paragraph regarding the procedure of “lumbar puncture”.	To clarify the procedure of lumbar puncture.

Section # and Name	Description of Change	Brief Rationale
Section 8 Study assessments and procedures	Replaced “120 mL” by “130 mL”, replaced “135 mL” by “145 mL” regarding the maximum amount of blood collected.	To correct the blood volume collected in this study.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 8.2.4	Added “The ECG will be read centrally.”	To clarify the central reading of ECG.

Section # and Name	Description of Change	Brief Rationale
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Section 8.6	Replaced “Approximately 4 mL of whole blood” by “Approximately 6 mL of whole blood”.	To correct the blood volume collected for the assessment of PD markers.
Section 9.2 Sample size determination	Added a paragraph regarding power for the co-primary endpoint of percent change in CSF GM2 from baseline to Week 104.	Clarify the power on the co-primary endpoint.
Section 9.3 Populations for analyses	Deleted “who received at least 1 dose of study medication” in the definition of Primary efficacy population and Secondary efficacy population.	Clarify that primary and secondary efficacy populations will include all randomized patients, not only those who received at least one dose of study medication.
Section 9.4.1 Efficacy analyses	Added a paragraph regarding handling of missing data.	Clarify the strategy for handling of missing data.
Section 10.2 Appendix 2: Clinical laboratory tests	Deleted “(fasted)” for glucose test.	“Fasted” is not necessary for glucose test in this study population.
Section 10.2	Deleted “If abnormal, a complete urinalysis will be performed by the central laboratory” in footnote “*b*” of Table 6. Replaced “will” with “may” in the sentence “The first 1 to 2 mL of CSF will be discarded”	Correction.
Section 10. 4	Deleted “a” from “Highly effective methods that are user independent[a]” in Table 7. Deleted “b” from “Implantable progestogen only hormonal contraception associated with inhibition of ovulation[b]” in Table 7.	Correction.

10.10.2 Amended protocol 02 (09 March 2020)

This amended protocol (Amendment 02) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

The main reason for this amendment is to update safety monitoring per regulatory guidance.

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis (Number of Participants) and Section 4.1, Overall Design (last paragraph)	Added the following text (**in bold**) to the paragraph as follows: "In addition to the primary population, **approximately 5 participants in total are planned for the secondary population.** An attempt will be made **and first prioritized** to enroll at least 1 participant (age 2 years or older) in each of the following disorders: juvenile/adolescent late-onset GM2 gangliosidosis, GM1 gangliosidosis, Saposin C deficiency, Sialidosis Type 1, and juvenile/adult galactosialidosis."	To clarify the recruitment of the secondary population.
Section 1.1 Synopsis (Intervention groups and duration, Study interventions, investigational medicinal products: Venglustat or placebo, first bullet), and Section 6.1, Study intervention(s) administered (Table 3)	Added 2 sentences to this bullet as follows: "The placebo is only for 15 mg venglustat tablets. Strength refers to the free base corresponding to the active moiety." Added text regarding venglustat placebo and venglustat strength to a new footnotes "a" and "b" under table.	Clarification regarding venglustat placebo tablets and venglustat strength.
Section 1.1 Synopsis (Intervention groups and duration), Study Interventions, Investigational medicinal products: Venglustat or placebo, third bullet, first sub-bullet, and Section 6.1, Study intervention(s) administered (Table 3)	Added explanation regarding swallowing the investigational medicinal product (IMP) whole or chewing and then swallowing as follows: "Assessment of relative bioavailability following chewing and then swallowing of the tablet is ongoing in a Phase 1 study. Based on the results from this study, this mode of tablet administration may be allowed. Once the administration by chewing is available, administration of IMP by chewing and swallowing or swallowing whole should be as consistent as possible throughout study treatment, and the method should be documented in the electronic case report form."	Some patients are not able to swallow pills whole (such as younger children); responds to Food and drug administration (FDA) request. The tablet is designed to be able to be chewed; however, per FDA requirement, administration by chewing and then swallowing the tablet will not begin until the bioavailability results are available.
Section 1.1 Synopsis (Intervention groups and duration, Study Interventions, Investigational medicinal products: Venglustat or placebo, third bullet, table), and Section 6.1, Study intervention(s) administered, Table 3, Dosage levels, table	The table was updated to include revised weight groups as follows: [redacted]	Additional pharmacokinetic (PK) simulations run to predict venglustat exposure in pediatrics showed that the revised weight bins based dosing (table of 4 weight bins compared to 5 weight bins in earlier pediatric dosing table) still provides exposures in each pediatric weight bin matching the adult exposure following 15 mg QD dose.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedules of Activities	Row "Visit at clinical site", Notes column: the first sentence was revised to state "For participants in United States only; up to 2 visits (Visits 3 and 8) can be provided remotely under a decentralized clinical trial (DCT) model (optional)."	Patients previously were able to have remote assessments at Visits 3, 4, 5, 6, and 8 under a DCT model; however because of the addition of a full ophthalmological examination at Visits 4, 5, and 6, a clinic visit will now be required at those visits.
	Row "Medical/surgical/treatment history": added "alcohol use history."	To clarify the collection of alcohol use history.
	Row "Hexosaminidase enzyme activity": Revised notes column text as follows: For primary population, samples will be collected for all participants during screening or at D1 (predose). Only 1 sample will be collected, during screening or at D1. For those with historical results, they may begin the study without waiting for results. Also added an "X" to this row on D1.	Per FDA comments, this is in order to test the samples using the same methodology to ensure consistency in study results that will be used to assess the relationship between residual enzyme activity and PK, pharmacodynamic (PD), and efficacy. The sample will be collected for the primary population. The sample may be collected during screening or at D1 for convenience.
	[redacted]	[redacted].
	Row "Lumbar puncture" and row "CSF sample": Added statement in notes column that "The LP (lumbar puncture) should be done successfully before the first dose and/or randomization." Also, removed the requirement for lumbar puncture on Day 1.	Clarification of timing of lumbar puncture.
	Row "12-lead ECG": Revised footnote "a" to read as follows: "ECG in triplicate **will be performed prior to IMP administration**."	Clarification.
	Row "Ophthalmological examination": Added 2 footnotes to the notes section as follows: *a* Full ophthalmological examination (including slit lamp fundoscopy with dilation), photography, and ARLNS. *b* Full ophthalmological examination (including slit lamp fundoscopy with dilation). "X"s were added to columns for Visits 4, 5, and 6 and footnoted (with "a" or "b") appropriately.	Solution to FDA feedback.
	New row added for the following: "Muscle weakness of triceps and quadriceps." "Xs were added for Visits 2, 3, 4, 5, 6, and 7.	Muscle weakness is one of the typical clinical presentations of late onset GM2 gangliosidosis. The muscle weakness of triceps and quadriceps will be assessed and considered a sensitivity analysis of the FARS-Neuro.
	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 5.1, Inclusion Criteria	E 01: Removed the following sentence from this criterion as it is not applicable here: "~~Note: For criteria specific to participants enrolled in Japan, see Appendix 8 (Section 10.8).~~"	Correction.
	E 03: Added the phrase "For primary population" to the beginning of the criterion as follows: "For primary population, the participant has the ability to . . . "	Clarification that this inclusion criterion applies to participants in the primary population.
	E08: Added the following sentence to this criterion as it is applicable here: "**Note: For criteria specific to participants enrolled in Japan, see Appendix 8 (Section 10.8).**"	Correction.
Section 5.2, Exclusion Criteria	E 02: Added "For primary population and participants with juvenile/adolescent late onset GM2 gangliosidosis and GM1 gangliosidosis" to the beginning of the criterion.	Clarify the study population for this criterion.
	Added "age-appropriate" in front the "study assessments."	Clarification.
	E 02: [redacted] and added "25FWT" (25-foot walk test) as an exception to age-appropriate assessments.	Clarify exceptions to the age-appropriate assessments.
	E 14: Added note as follows: "Note: For participants using N-acetyl-leucine as IMP, within 5 half-lives before study enrollment."	Due to the very short half-life, patients taking N-acetyl-leucine will not have to wait 3 months to start this study.
Section 6.3, Measures to minimize bias: randomization and blinding	In the section "Randomization code breaking," next to last paragraph: changed "will not be" to "may or may not be."	To clarify the treatment with code breaking.
Section 6.5, Concomitant therapy	The previous text regarding prescription or nonprescription drugs was removed from the last paragraph and replaced with text to specify that concomitant medications and changes in concomitant medications should be kept to a minimum. Excluded prescription or nonprescription medication that are considered necessary for the patient's welfare may be provided as long as it is unlikely to significantly interfere with the IMP. Patients may be given such therapy as rescue mediation at the discretion of the Investigator.	Response to agency request.
Section 7.1.2, Temporary discontinuation (now Discontinuation criteria)	The previous heading "Temporary Discontinuation" was changed to "Discontinuation Criteria." A paragraph was added to this section to provide rules for continued dosing in the event of a serious adverse event or ≥Grade 3 adverse event is observed that is considered by the Investigator to be related to venglustat, which will be applied with recommendations from the data monitoring committee.	Response to agency request. Stopping criteria added as response to FDA.

Section # and Name	Description of Change	Brief Rationale
Section 8.1.12, Muscle weakness of triceps and quadriceps	The new efficacy assessment of muscle weakness was added, and the relevant information was inserted in a new Section 8.1.12. A new reference cited in this section was inserted into Section 11 (Marion, 2020) as new reference #31.	The most involved muscle groups in GM2 patients are triceps and quadriceps. These muscle groups are not tested in FARS-Neuro. Thus, this efficacy assessment was added and will be considered a sensitivity analysis of the FARS-Neuro.
Section 8.2.5, ophthalmological examination	Updated ophthalmological examination information for adult and pediatric patients in paragraphs 1, 2, 4, 5, and 6, as follows: Paragraph 1: The effect of venglustat on the lens will be closely monitored throughout the study. The full ophthalmological examination will include slit-lamp examination, fundoscopy with pupil dilation, and examination of the cornea, lens, and retina. Paragraph 2: The evaluation of the lens by photography according to Age-Related Eye Disease Study (AREDS) Clinical Lens Grading System (ARLNS) will be performed during screening, Week 104, early withdrawal or treatment discontinuation, or any timed deemed medically necessary. Paragraph 4: A full ophthalmological examination, photography, and ARLNS will be performed during screening (this will serve as a baseline assessment) and at Week 104 or at early withdrawal or treatment discontinuation. Paragraph 5: A full ophthalmological examination will be performed at Week 26, Week 52, and Week 78. Paragraph 6: If a lens abnormality is found, the ophthalmologist at the site should perform pupil dilation, photography, and ARLNS evaluation.	Solution to FDA feedback.
Section 8.8, Biomarkers.	Last paragraph: remove “separate” in the phrase “separate consent.”	A separate consent form is not mandatory.
Section 8.9, Lumbar Puncture	Paragraph 2: The last sentence was revised to state the following: The baseline LP can be done within 14 days prior to ~~or on~~ the day of randomization (predose). Specifically, the phrase “or on” was removed.	Clarification of timing of the lumbar puncture.
Section 10.2 Appendix 2: Clinical Laboratory Tests	Other screening tests: Removed follicle stimulating hormone. Other screening tests: Added serology tests.	Follicle stimulating hormone is not required in this protocol. For consistency with Section 1.3, Schedule of Activities.

Section # and Name	Description of Change	Brief Rationale
Section 10.8 Appendix 8: Country-specific requirements	Revised appendix to state the following: "For participants enrolled in Japan: Inclusion Criterion 08: The participant or if appropriate parent(s) or legal guardian(s) must provide written informed assent/consent prior to any study-related procedures being performed as described in Appendix 1 (Section 10.1). For Japanese participants 18 and 19 years old, the informed consent is required from both parent/guardian and the participant."	Correction.
Section 10.10 Appendix 10: Protocol Amendment History	New appendix added and protocol amendment 1 rationale and summary of changes table moved to this appendix.	Per Sanofi template.

10.10.3 Amended protocol 03 (08 March 2021)

This amended protocol 03 (Amendment 03) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to update contingency measures for a regional or national emergency as declared by a governmental agency, to update sample size for secondary population, to update inclusion/exclusion criteria, and to improve operational efficiency.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Section 1.1 Synopsis	Based on the results of a bioavailability study, chewable tablet option may be allowed	Clarification. In a Phase 1 relative bioavailability study that was recently completed (PKM16157), the bioavailability of the 15 mg venglustat tablet (planned commercial dosage form) chewed and then swallowed without water was similar to that for the tablet swallowed whole with water. Therefore, this protocol amendment includes information to allow for the use of either modes of administration.
Section 1.2 Schema	Schema update to show up to 20 participants in the secondary population	Update.
Section 1.3 Schedules of Activities (SoA)	Following text added (bold font) for hexosaminidase enzymatic activity measurement: For primary population, samples will be collected for all participants during screening or at D1 (predose). Only 1 sample will be collected, during screening or at D1 **after 4 hr**	Clarification.

Section # and Name	Description of Change	Brief Rationale
	fasting. For those with historical results, they may begin the study without waiting for results. Following telephone call clarification added: except for scheduled follow up phone calls which would fall within a few days (up to 10 days) from a site visit. Monthly pregnancy test will be performed between Week 1 and Week 104. [redacted] [redacted] Annotation 'b' is newly inserted for W26 and W78 Ophthalmological examination.	
Section 1.1 Synopsis: Number of participants, Statistical considerations, Section 4.1 Overall Study Design, Section 9.2 Sample size determination, Section 9.4.1 Efficacy analyses Table 5	Approximately 20 participants are planned for secondary population. Primary analysis time point added.	Update.
Section 5.1 Inclusion Criteria	I01: for juvenile secondary population the ICF must be signed by parent(s)/guardian(s). I07: Contraception related text added. I08: France specific criterion added.	Update.
Section 5.2, Exclusion Criteria	E02: Criterion updated to add the following text: and GM1 gangliosidosis, the participant cannot understand and perform all age-appropriate study assessments, with the exception of 25FWT and PROs. [redacted]	Exclusion criteria update, country specific criteria provided.
Section 6 Study intervention	Venglustat tablets can be chewed or swallowed.	Clarification and update.
Section 6.1 Study intervention(s) administered	Added a sentence "*Venglustat or matching placebo is to be taken daily, around the same time each day throughout the study.*"	To clarify the time of intake of IMP.
Section 6.2 Preparation/ Handling/ Storage/Accountability	Reference to a pharmacy manual added.	Update.
Section 6.1 Study Intervention(s) administered, Section 7.1.2 Discontinuation criteria, Section 7.1.2.1 Rechallenge, 8.1.12 Regional or national emergency, Section 9.4.4 Other analyses,	Contingency measures during a national emergency added.	The management of the clinical trial during a national emergency.

Section # and Name	Description of Change	Brief Rationale
Section 8.1 Efficacy assessments	Subsections in Section 8.1 were resequenced from subsection 8.1.5	Update.
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted].
Section 8.2.2 Neurological examination, Section 8.2.5 Ophthalmological examination	Added the following text: When neurological and ophthalmological examinations are performed on the same day (Visit 1 and Visit 7) the neurological examination should be performed before the ophthalmological examination.	Operational clarification.
Section 8.3 Adverse events and serious adverse events	The sentence "*Of note, asymptomatic overdose has to be reported as a standard AE"* deleted.	Update.
Section 8.6.1 Lumbar puncture	The original Section 8.9 has been renumbered Section 8.6.1.	Renumbered a section.
[redacted]	[redacted]	[redacted]
Section 10.2 Appendix 2 Table 6	A footnote added "*Urinalysis by dipstick will be performed at the site. If abnormal, a complete urinalysis will be performed by the central laboratory.*"	Clarification.
Section 10.4 Appendix 4 Contraceptive Guidance and Collection of Pregnancy Information	Clarified that babies born to the participants or partners of participants will be followed up to 1 year after birth.	Update.
[redacted]	[redacted]	[redacted]
Section 10.8 Appendix 8 Country-Specific Requirements	France specific criteria added.	Updated country specific criteria based on the ethics committee recommendations.

Section # and Name	Description of Change	Brief Rationale
Section 10.10.2 Protocol Amendment 02 (09 March 2020)	New section for protocol amendment 02 history added.	Template required section added.
Section 10.11 Appendix 11 Contingency measures for a regional or national emergency as declared by a governmental agency	A new Appendix 10.11 added to specify contingency measures for a regional or national emergency as declared by a governmental agency.	Contingency measures added to cover COVID-19 and other potential emergencies.
Section 1.2 Schema, Section 1.3 Footnote, Section 4.2 Scientific rationale for study design, Section 5.3.1 Meals and dietary restrictions, Section 5.4 Screen failures, Section 6.1 Study interventions administered, Section 6.2 Preparation/ handling/storage/ accountability, Section [redacted]	Minor edits for clarification and or updates made.	Minor editorial changes and or updates for clarity.

10.10.4 Amended protocol 04 (20 April 2022)

This amended protocol 04 (Amendment 04) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to add an open-label extension (OLE) treatment phase to the study. The OLE period is an extended treatment phase to obtain the long-term efficacy and safety of additional 24-month treatment with venglustat in patients with late-onset GM2 gangliosidosis and patients with juvenile/adolescent late-onset GM2 gangliosidosis or ultra-rare diseases within the same and similar glucosylceramide-based sphingolipid pathway who completed the 104-week primary analysis period of the study.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Document history table	Revised to include amended protocol 4 information and date.	Per Sanofi template.
Section 1.1, Synopsis, Objectives and endpoints; Section 3, Objectives and endpoints	Removed "physical examination" from secondary endpoints, primary population and secondary population at 104 weeks.	Physical examination is overlapping with visual acuity assessments that are collected separately with ophthalmological data as a separate item, and any abnormal finding will be collected as an adverse event.
Section 1.1, Synopsis, Overall design; Section 4.1, Overall design	Added text to specify that the study is a 2-arm, 104-week study (primary population only) of venglustat compared with placebo, and venglustat received in an open-label design in the secondary population. Added "text to specify that the 104-week treatment period (primary analysis period) will be followed by an OLE period with venglustat treatment for all patients. Updated "3 main periods" to "4 main periods"; clarified that Period 2 is the primary analysis period; added description of Period 3 (104-week OLE period); and updated previous Period "3" to Period "4." Updated text regarding post-trial access to venglustat.	Addition of OLE to study. With addition of the OLE to the study, the long-term study (LTS) is no longer applicable; thus, updated text for clarification.
Section 1.1, Synopsis, Disclosure statement, Intervention groups and duration	Clarified that the primary analysis will occur at 104 weeks.	Addition of OLE to study.
Section 1.1, Synopsis, Intervention groups and duration	Added text to specify that during the 104-week OLE, all participants in the primary and secondary populations will receive venglustat in an open-label manner, specifically 15 mg tablet once daily for adult participants; clarified that for adolescents and juvenile participants in the secondary population ≥2 years of age, venglustat dosing will be adjusted in the primary analysis period and the OLE treatment period.	
Section 1.1, Synopsis, Statistical considerations; Section 9.4.1, Efficacy analysis	Added details about descriptive analyses conduction in the secondary population. Added text regarding analysis of plasma and CSF GL-1 biomarker data.	Clarification.
Section 1.2, Schema	Inserted updated graphical study design.	Addition of OLE to study.
Section 1.3, Schedule of activities (SOA)	Added columns for the OLE (W130, W156, W182, W208) (also Visits 9, 10, 11, and 12); modified EOT from W104 to W208; modified "treatment period" to "primary analysis treatment period"; revised FU period visit from W110 to W214; added/revised assessments as needed; revised/added to notes column as applicable; added note "b" to provide instructions regarding early treatment withdrawal after W104. Updated notes regarding the decentralized clinical trial (DTC) model as appropriate. Added note to clarify that full ophthalmological examination (including slit lamp fundoscopy with dilation) in the OLE will be performed for participants ≥2 and <12 years of age only.	Addition of OLE to study.
	Moved notes in repeated header rows ("a," "b", and "c") to end of table to reduce length of table.	Clarification, and editorial for readability.
	[redacted]	[redacted]

Section # and Name	Description of Change	Brief Rationale
Section 2.3, Benefit/risk assessment	Updated text regarding ongoing studies. Added new text regarding potential risk of new or worsening lens opacities/cataracts in human with rationale for discontinuing ophthalmological examinations for participants ≥12 years of age who continue in the OLE. Added new text regarding the potential risk of [redacted] in ADPKD indication. Added new text regarding the potential risk of transient increase in blood pressure at the beginning of venglustat treatment.	New safety information for venglustat per updated Investigator's Brochure (v17.0, 08-Mar-2022).
Section 3, Objectives and endpoints	Added tertiary/exploratory endpoints for the primary population and for the secondary population at Week 208.	Addition of OLE to the study.
Section 6.1, Study intervention(s) administered; Section 1.3, Schedule of activities	Added text to clarify packing and labeling of IMP during the primary analysis period and the OLE.	
Section 6.3, Measures to minimize bias: randomization and blinding	Randomization and code breaking: Added the following text as a new second paragraph: **"Participant safety must always be the first consideration in making such a determination. If the Investigator decides that unblinding is warranted, the investigator must make every effort to contact the Sponsor to discuss the situation prior to unblinding a participant's intervention assignment unless this could delay emergency treatment of the participant."**	Sanofi template update.
Section 6.5.1.3, Medications with risk to cause cataract	Revised text to specify that listed medications are prohibited **for participants age <12** (rather than for all participants).	Updated for consistency with other safety information regarding cataract risks.
Section 6.5.2, COVID-19 vaccination	Added new section for COVID-19 vaccination.	Sanofi template update.
Section 8, Study assessments and procedures, Section 8.6, Pharmacodynamics, Section 8.7, Genetics	Updated blood volumes as applicable.	Addition of OLE to the study.
[redacted]	[redacted]	[redacted]
Section 8.2.5, Ophthalmological examination	Revised text to clarify timing of ophthalmological examinations for all participants and for participants <12 years of age.	No ophthalmological examinations required in OLE for participants age ≥12 years.
Section 8.8, Biomarkers; Section 8.10, Use of biological samples and data for future research	Replaced last paragraph of Section 8.8 with the following: "**Refer to Section 8.10 for further details regarding use of biological samples and data for future use."** Added new Section 8.10 with details use of biological samples and data for future research.	Sanofi template update.

Section # and Name	Description of Change	Brief Rationale
Section 9.4, Statistical analyses	Revised text to specify that the statistical analysis plan will be developed and finalized before the analysis of the primary analysis treatment period.	Clarification.
Section 9.5, Interim analyses	Added a 2-step analysis for the study, first step for the final analysis of the primary analysis period and second step for the final analysis of the OLE treatment period.	Addition of OLE to the study.
Section 10.11, Appendix 11, Contingency Measures for a regional or national emergency as declared by a government agency	Updated text regarding visit windows to include V3 to V12 (rather than V3 to V8).	
Section 11, References	Updated reference #14 as a newer version is available.	Editorial change.
Throughout the document	Minor editorial and formatting changes were made for clarity and consistency	Consistency with document edits.

10.10.5 Amended protocol 05 (11 November 2022)

This amended protocol 05 (Amendment 05) is considered to be substantial based on the criteria set forth in Article 10(a) of Directive 2001/20/EC of the European Parliament and the Council of the European Union.

OVERALL RATIONALE FOR THE AMENDMENT

The main reason for this amendment is to add urine albumin creatinine ratio (UACR) and urine protein creatinine ratio (UPCR) assessments in the renal monitoring per FDA requirement.

Protocol amendment summary of changes table

Section # and Name	Description of Change	Brief Rationale
Document history table	Revised to include amended protocol 5 information and date.	Per Sanofi template.
Sponsor name	Revised Sponsor address from “50 Binney Street Cambridge MA 02142 USA” to “450 Water Street Cambridge MA 02141 USA.”	Updated Sanofi address.
Table of Contents	Updated entries for the following new sections and subsections “2.3.1 Risk assessment," “2.3.1.1 Potential risks specific for pediatric population,” “2.3.1.2 Depression,” “2.3.1.3 Syncope,” “[redacted]” “2.3.1.5 Transient increase in blood pressure, “2.3.1.6 Embryo-fetal toxicity,” and “10.10.4 Amended protocol 04 (20 April 2022).”	Consistency with document edits.
List of Figures	Added new entry for “Table 2 - Risk mitigation strategy.”	Consistency with new table added in Section 2.3.1, Risk Assessment.

Section # and Name	Description of Change	Brief Rationale
Section 1.3, Schedule of Activities (SOA)	Added the note “For Canadian participants enrolled in the US, see Section 10.8.” for the “IRT contact” and “Dispense IMP” study procedures.	Updated for new country-specific requirement in Appendix 8.
	New annotation ‘k’ was added for urine biochemistry test for measurement of UACR and UPCR for Visits 2-10 with subsequent footnotes renamed, and the footnote was updated with the following text: "Three second-voided morning urine samples to be collected on successive days (2 days preceding a visit, plus the day of the visit. Urine sample should be sent to the central laboratory for quantitative measurement of creatinine, total protein and albumin which will be used to calculate the urine albumin/creatinine ratio and urine protein/creatinine ratio.	Per FDA requirement.
	“Dipstick only” removed from from procedure "Hematology, biochemistry, urinalysis" and corresponding note "Urinalysis by dipstick will be performed at the site. If abnormal, a complete urinalysis will be performed by the central laboratory." has been newly added.	Revised to align with updated laboratory procedures.
	Included full ophthalmology examinations for all participants, and not only for participants ≥2 and <12 years of age, at Week 208 (end of the open-label extension treatment period).	To align with all venglustat studies following FDA feedback on lens monitoring to be done at the end of the treatment period. This will be conducted as a conservative approach. There was no new safety information on this potential risk since protocol amendment 4.
	Added “The LP should be done after all other assessments if possible.” to footnote ‘e’ and ‘q”.	To clarify the order of assessments to avoid any impact of LP on other clinical assessments.
Section 2.3, Benefit/Risk Assessment	Updated this section per template to update the risk assessment and include the following subsections: “2.3.1 Risk assessment," “2.3.1.1 Potential risks specific for pediatric population,” “2.3.1.2 Depression,” “2.3.1.3 Syncope,” “2.3.1.4 [redacted],” “2.3.1.5 Transient increase in blood pressure,” and “2.3.1.6 Embryo-fetal toxicity.”	Updated the potential risks for venglustat in Section 2.3 Benefit/Risk Assessment to align with IB 18.
Section 3.1, Appropriateness of Measurements	Changed “30% of patients who participated in the NTSAD study” to “21% of patients who participated in the NTSAD study.”	Updated the percentage of wheelchair bound patients who participated in the National Tay-Sachs & Allied Diseases Associations (NTSAD) Study based on the natural history data collected from the study.
Section 8, Study Assessments and Procedures	Changed maximum amount of blood volume collected from each adult participant over the duration of the study from “175 mL” to “208 mL” for participants of the main study and “185 mL” to “216 mL for participants of the W1/D1 PK profile evaluation substudy.	Updated volumes to reflect changes in the new pharmacy manual.

Section # and Name	Description of Change	Brief Rationale
Section 8.2.5, Ophthalmological examination	Text was revised to update the timing of ophthalmological examination and clarify that the effect of venglustat on the lens will be closely monitored throughout the study including Week 208 for all participants and not only for participants <12 years of age.	To align with all venglustat studies following FDA feedback on lens monitoring to be done at the end of the treatment period. This will be conducted as a conservative approach. There was no new safety information of this risk since protocol amendment 4.
[redacted]	[redacted]	[redacted]
Section 8.6, Pharmacodynamics	Revised “8 mL of whole blood” to “7-8 mL of whole blood” and “3 mL of CSF” to “3-4 mL of CSF.”	Correction of blood volume collected in this study based on the new pharmacy manual
Section 10.2, Appendix 2: Clinical Laboratory Tests	In Table 7 - Protocol-required laboratory assessments, the laboratory assessment “Urine biochemistry” and its parameters “Creatinine,” “Total protein,” “Albumin,” “UPCR,” and “UACR” are added.	Consistency with addition of urine biochemistry as a laboratory procedure.
Section 10.8, Appendix 8: Country-Specific Requirements	Added country-specific criteria for Canadian participants enrolled in the US and expanded on Schedule of Activities for these participants to include additional IRT contact and Dispense IMP procedure to be conducted at Visits 6.1, 7.1, 8.1, 9.1, and 10.1.	Introduced additional dispensation in protocol for Canadian participants enrolled in US to meet customs restrictions limiting IMP dispensation to a 90-day supply. After Visit 6 of study, the number of weeks between IMP dispensation increases from 13 weeks to 26 weeks. Thus, additional IRT contact and IMP dispensation dates were included to ensure Canadian participants have adequate IMP supply between visits.
Section 10.9, Appendix 9: Abbreviations	Added abbreviations for urine albumin-to-creatinine ratio (UACR) and urine protein-to-creatinine ratio (UPCR).	Consistency with document edits.
Section 10.10, Appendix 10: Protocol Amendment History	Appendix 10 is updated to reflect the document history of previous amendment ie, amendment 04 in newly added as Subsection 10.10.4.	Consistency with document edits.
Section 11, References	Reference number 18, 19 and 20 from amended protocol 4 were deleted in current amendment and subsequent references were re-numbered in body-text and in Section 11.	Consistency with document edits.
Throughout the document	Minor editorial and formatting changes were made for clarity and consistency.	Consistency with document edits.

10.11 APPENDIX 11: CONTINGENCY MEASURES FOR A REGIONAL OR NATIONAL EMERGENCY AS DECLARED BY A GOVERNMENTAL AGENCY

A regional or national emergency declared by a governmental agency (eg, public health emergency, natural disaster, pandemic, terrorist attack) may prevent access to the clinical trial site.

Investigators may be unable to adequately follow protocol-mandated procedures, eg, for performance of on-site visits, screening, enrollment, randomization, administration of study IMP, imaging procedures or other study assessments.

Contingency procedures are suggested in the respective sections (Section 6.1, Section 7.1.2, Section 7.1.2.1, Section 8.1.12, Section 10.10.3) for such an emergency, to ensure the safety of the participants, to consider continuity of the clinical study conduct, protect trial integrity, and assist in maintaining compliance with Good Clinical Practice in Conduct of Clinical Trials Guidance. Sponsor's agreement MUST be obtained prior to the implementation of these procedures for the duration of the emergency.

The following contingency may be applied for the duration of the emergency (after Sponsor's agreement is obtained) to make clinical supplies available to the study participants for the duration of the emergency:

The IMP may be supplied at the site or from the PI/site/Sponsor to the participant via a Sponsor-approved courier company (direct-to-patient [DTP]) supply of IMP) where allowed by local regulations.

Attempts should be made to perform all assessments in accordance with the approved protocol to the extent possible. In case this is not possible due to a temporary disruption caused by an emergency, focus should be given to assessments necessary to ensure the safety of participants and those important to preserving the main scientific value of the study.

- Postponement of visits is preferred to cancellation of visits, if possible. Visit window (V3 toV12) can be extended up to 3 months. In this case, IMP can be dispensed to the patient at the planned visit dates (via direct-to-patient) for a maximum duration of 6 months until V4, and thereafter for a maximum duration of 9 months without on-site visit, but with a follow-up by phone every 2 weeks. In general, no patient should continue IMP for >9 months without an on-site visit for safety assessments or without laboratory safety assessments being performed (eg, at the local practitioner). The safety laboratory parameters at least include hematology, biochemistry, urinalysis according to protocol.
- If Week 104 visit is delayed, the blinded treatment will be continued until Week 104 visit is performed.
- To reduce the time spent on-site during a study visit, the focus should be on the following safety assessments and if scheduled for the concerned visit (applicable to V3 to V12):
  - laboratory assessments (biochemistry, hematology and urinalysis)
  - urine pregnancy test

- ECG
- Physical (including vital signs), neurological and ophthalmological examinations (if required). For patients with existing cataracts at baseline, full eye exams with pupil dilation, photography and ARLNS evaluation at pre-specified visits should be carried out, to detect any worsening.

[redacted]

For efficacy assessments, should be prioritized to perform primary endpoints: CSF biomarker test (baseline and W104 only) and 9-HPT. [redacted].

For D1/W1 visit (V2), if it is within 2 weeks of V1, no need to redo the exams already performed at V1 except 9-HPT, 25-FWT and FARS Part III neurological examination and weight (for participants age <18). If D1/W1 visit (V2) is 2 to 4 weeks from the screening visit, assessments with the same request at screening and V2 may use the results at screening as baseline, except 9-HPT, 25-FWT, FARS Part III neurological examination, [redacted], chemistry, hematology, urinalysis and weight (for participants age <18).

During the emergency, if the site is unable to adequately follow protocol-mandated procedures, alternative treatment outside the clinical trial should be proposed, and screening/enrollment/randomization/administration of study intervention etc may be (temporarily) delayed/halted.

The participant and/or their legally authorized representative should be verbally informed prior to initiating any emergency-related changes that are to be implemented (eg, study visit delays/treatment extension, use of local labs).

Treatment extension after temporary treatment discontinuation may be considered, depending on Sponsor agreement.

Procedures to be considered in the event of a regional or national emergency declared by a governmental agency:

If on-site visits are not possible, remote visits (eg, with Telemedicine, etc if locally agreed) may be planned for safety and efficacy assessments; home nurses/home health vendor, etc may be planned for the collection of blood samples for safety assessments and efficacy data.

If onsite visits are not possible, visit windows may be extended up to 3 months for assessment of safety and/or efficacy data that cannot be obtained remotely.

Phone contacts can be performed in place of an onsite study visits and per study protocol schedule. Essential data (that can be checked via interview to evaluate patient safety) to be captured via phone contact and documented in the source records include, but is not limited to, AEs, SAEs, change in or new concomitant medications, urine pregnancy test results, IMP compliance, potential signs of depressed mood, complaints about changes in vision, vital signs (if patients can measure temperature and BP at home).

When phone contact is performed in place of an onsite study visits, assessments of efficacy and safety data that cannot be obtained remotely (eg, ECG, ophthalmological and neurological examination) will be performed when patients are able to resume normal site visits. Safety assessment that cannot be obtained remotely may be performed prior to next regular onsite visit if Investigator considers that this is clinically indicated and feasible, and that this will not involve an additional risk for a patient from the hazard that led to declaration of national emergency.

Remote collection of ObsROs and PROs by sites will be attempted via telephone using a secure line (eg, teleconference line), including videoconference if possible to aid in the accuracy of data collection and increase the quality of data, with the prioritization of ObsROs that contribute to secondary endpoints. If none of the options above can be achieved, the PROs and ObsROs should not be collected for the visit.

Use of local clinic or laboratory locations may be allowed.

New screenings during a regional or national emergency declared by a governmental agency can be performed only if allowed by local competent authorities and after Sponsor`s agreement is obtained.

If a rescreened patient was screen-failed during a regional or national emergency for reasons not related to eligibility, rescreening shall be permitted when the situation normalizes.

Contingencies implemented due to emergency will be documented, eg, in the eCRF.

The impact of the regional or national emergency declared by a governmental agency on study conduct (eg, study discontinuation or discontinuation/delay/omission of the intervention due to the emergency, missing data) needs to be closely monitored and summarized by each study site in a dedicated document. Monitoring will ensure comprehensive and correct documentation of the site-specific impact of the emergency on the study conduct.

It will be important to capture specific information in the case report form (eCRF) that explains rationale for why protocol-specified data is missing, including whether it is attributable to the emergency precautions/measures taken by governmental agencies, or due to the patient directly being affected (such as by COVID-19).

If a patient is infected or displays symptoms that could be attributed to COVID-19, the investigator should determine whether to maintain the patient on treatment, to temporarily discontinue treatment, to pause the study visits/assessments (to be pushed out until recuperation allows it), or to withdraw the patient from the study.

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