STATISTICAL ANALYSIS PLAN

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**
Compound number (INN/Trademark):	**Venglustat/GZ402671**
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VERSION HISTORY

This statistical analysis plan (SAP) for Study EFC15299 is based on the protocol amendment 6 dated on 31 July 2023.

A first version of the draft statistical analysis plan was finalized on 17 July 2019 and submitted to the FDA on 26 July 2019, as part of the background package for a Type B meeting (Seq 0015).

The draft SAP was updated on 30 October 2019, following written response received from the FDA on 24 September 2019. The updated version was submitted to the FDA in the initial IND (Seq 0016) on 18 November 2019 as part of the response to Agency written responses.

The draft SAP was amended on 02 March 2021 to include a proposal of interim analysis.

The draft SAP was amended on 25 May 2021 to include FDA recommendation on the proposed interim analysis.

A first version of the full SAP was finalized on 16 November 2022, including recommendation from the EMA and PMDA not to conduct an interim analysis. It also included additional analyses not described in the previous draft versions. This version of the SAP was submitted to FDA and EMA.

The full SAP was amended on 03 August 2023, including changes based on comments and recommendations from FDA, received on 10 March 2023.

The changes in the SAP are detailed in Table 1.

Table 1 - Major changes in statistical analysis plan

SAP version number	Date finalized	Description of statistical changes	Rationale
0.1	17-Jul-2019	Initial version	-
0.2	30-Oct-2019	Addition of code and results of simulations used to investigate the probability of declaring superiority of venglustat under the null hypothesis	As per FDA recommendation
		Clarification of analysis and determination of efficacy of venglustat for the secondary endpoints	As per FDA recommendation
0.3	02-Mar-2021	Addition of interim analysis	Duration and sample size of this study were based on conservative assumptions of stabilization or slight improvement on venglustat. Recent data in PDY13949 study in patients with Gaucher Type 3 disease suggest possible neurological improvement. A similar improvement may also be expected in patients with late-onset GM2 gangliosidosis. An interim analysis may allow early demonstration of efficacy and earlier approval of venglustat in patients with GM2. It would also allow patients enrolled in this study to switch to open label venglustat if efficacy is demonstrated earlier than at the planned final analysis.

SAP version number	Date finalized	Description of statistical changes	Rationale
0.3		Primary analysis of 9-HPT with Bayesian analysis using non-informative prior is replaced by a Frequentist analysis (Section 3.2.2.2)	Bayesian analysis using non-informative prior is equivalent to a Frequentist analysis. Interim analysis is however more easily conducted in a Frequentist framework, using methods developed for group sequential design. Bayesian analysis with informative prior remains a secondary analysis of the 9-HPT.
		Clarification and justification that overall Type I error rate is 0.05 one-sided (Section 3.1 and Section 4)	Previous Bayesian analysis had success criterion based on 95% posterior probability. This is equivalent to an alpha level of 0.05 one-sided in a Frequentist framework. An alpha 0.05 one-sided was selected due to the rarity of late-onset GM2 gangliosidosis, the seriousness of this disease and lack of available therapy, as per FDA draft guidance.
		Update of prior distribution of placebo slope, used as secondary analysis of the 9-HPT (Section 3.2.2.4.1 and Section 5.7)	Prior distribution in the initial SAP 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. These data are presented in Section 5.7.
		9-HPT global score not calculated if assessed for only one hand (Section 5.5.1)	9-HPT assessed from only one hand would potentially bias the analysis.
		Update of SAS and results of simulations	Modified SAS code to evaluate the probability of declaring superiority of venglustat with interim analysis and using Frequentist approach. Modified SAS code includes probabilities under different alternative hypotheses as well as under the null hypothesis.
0.4	25-May-2021	Inclusion of analysis of CSF GM2 in the interim analysis	As per FDA recommendation
1.0	16-Nov-2022	Removal of interim analysis (Section 3.8.1)	As per EMA and PMDA recommendation
		For primary and secondary endpoints, use of robust ANCOVA in case of outliers (Section 3.2.1.2, Section 3.2.2.2, Section 3.3.1.2), 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 (see Section 5.6.3).
		Addition of supportive analysis of time to worsening (Section 3.2.2.4.3) and time to improvement of 9-HPT (Section 3.2.2.4.4).	To provide supportive evidence of the efficacy of venglustat.
		Addition of subgroup analysis (Section 3.2.3)	To explore the consistency of the effect of venglustat in different subgroups.
		Two-step analysis (Section 3.8.2)	Following addition of an open-label extension period in Protocol amendment 4.
		Description of analysis of exploratory endpoints (Section 3.4), safety (Section 3.6) and other endpoints (Section 3.7)	Not included in the previous versions, that focused on the analysis of the primary and secondary endpoints.

SAP version number	Date finalized	Description of statistical changes	Rationale
2.0	03-Aug-2023	For primary population, add secondary endpoint of absolute change in CSF GM2 biomarker from baseline to Week 104 (Section 2.1.1, Section 3.3.1.1, Section 3.3.1.2.1, Section 3.3.1.3, Section 3.3.1.5).	As per FDA recommendation
		For secondary population, add secondary endpoint of acceptability and palatability assessments (Section 1.2, Section 3.6.1)	To align with PIP commitment
		For primary population, add tertiary/exploratory endpoint of "Additional plasma and CSF biomarkers may include but are not limited to: lipidomics, glycoprotein nonmetastatic protein B (gpNMB), neurofilament" (Section 1.2, Section 3.7.2)	To clarify the exploratory biomarkers endpoints of primary population according to Amendment 6 of protocol
		Add descriptive statistics and sensitivity analyses on percent change in CSF GM2 biomarker endpoint with treatment as assigned by randomization (Section 3.2.1.2, Section 3.2.1.3).	As per FDA recommendation
		For primary population the subgroup analyses will also be conducted on CSF GM2 endpoint (Section 3.2.3, Section 3.3.1.5).	As per FDA recommendation
		Add 95% confidence interval for supportive and subgroups analyses in addition to 90% confidence interval (Section 3.2.2.4, Section 3.2.3).	As per FDA recommendation
		The procedure for handling multiplicity of tests for secondary endpoints using a hierarchical approach was replaced by the Hochberg procedure (Section 3.3.1.2,Section 3.5).	To account for the new secondary efficacy endpoint that was added as per FDA recommendation
		Update to endpoint on ophthalmologic in OLE period (Section 1.2, Section 3.6.3.3).	According to Amendment 6 of protocol
		Update the PK analyses (Section 3.7.1)	According to Amendment 6 of protocol add some details about PK sub-study

1 INTRODUCTION

1.1 STUDY 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 open-label extension (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, pharmacokinetic (PK), pharmacodynamic (PD), and efficacy of venglustat once-daily administration will be determined during the 104-week treatment period.
3. Period 3 (OLE period, 104-week treatment 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.
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.

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 data monitoring committee (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).

1.2 OBJECTIVES AND ENDPOINTS

Table 2 - Objectives and endpoints

<table>
<tr><th>Objectives</th><th>Endpoints</th></tr>
<tr><td colspan="2">Primary</td></tr>
<tr><td>Primary population:
• To assess the efficacy and pharmacodynamics (PD) of daily oral dosing of venglustat when administered over a 104-week period.</td><td>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.</td></tr>
<tr><td>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.</td><td>• Plasma and CSF GL-1 biomarker and a pathway specific biomarker will be assessed as follows:
<table><tr><th>Disease</th><th>Biomarker</th></tr><tr><td>GM2 gangliosidosis</td><td>GL-1, GM2</td></tr><tr><td>GM1 gangliosidosis</td><td>GL-1, GM1</td></tr><tr><td>Sialidosis</td><td>GL-1, GM2, GM3</td></tr><tr><td>Galactosialidosis</td><td>GL-1, GM1, GM3</td></tr><tr><td>Saposin C Deficiency</td><td>GL-1 only</td></tr></table>• Additional plasma and CSF biomarkers may include but are not limited to: lipidomics, glycoprotein nonmetastatic protein B (gpNMB), neurofilament.</td></tr>
<tr><td colspan="2">Secondary</td></tr>
<tr><td>Primary population:
• To assess the PD of daily oral dosing of and effect of venglustat on selected performance test and scale over a 104-week period.</td><td>• Absolute change in CSF GM2 biomarker from baseline to Week 104.
• Change in 25-foot walk test (25-FWT) 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.</td></tr>
<tr><td>Primary population:
• To determine the safety and tolerability of venglustat when administered orally once daily over a 104-week period.</td><td>• Changes from baseline to Week 104 in the following:
- Assessment of adverse events (AEs) and concomitant medication.
- Physical examination.
- Neurological examination.
- Ophthalmological examination.
- Vital signs.
- Clinical laboratory evaluations including hematology, biochemistry, urinalysis, and serology.
- Electrocardiogram (ECG).</td></tr>
<tr><td>Primary population:
• To assess the pharmacokinetics (PK) of venglustat in plasma and CSF.</td><td>• 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}).</td></tr>
</table>

Objectives	Endpoints
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 (FARS-neuro) 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 - Physical examination. - 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]	

2 ANALYSIS POPULATIONS

The following populations for analyses are defined:

Table 3 - Populations for analyses

Period	Population	Description
Primary analysis	Screened	All participants (and/or participant's parent(s)/legal guardian(s)) who signed the Informed Consent Form (ICF).
	Randomized	All participants from screened population who have been allocated to a randomized intervention by Interactive Response Technology (IRT) regardless of whether the intervention was received or not.
	Population without trial impact (disruption) due to COVID-19	All randomized participants without any critical or major deviation related to COVID-19 and who didn't permanently discontinue treatment due to COVID-19 and who didn't permanently discontinue study due to COVID-19.
	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 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.
Open-Label extension	Enrolled population	All participants who completed the primary treatment analysis period and accept to continue.
	Efficacy population	All participants from enrolled population.
	Safety population	All participants from enrolled population who received at least one venglustat dose after the 104-week visit.

Participants exposed to study intervention before or without being randomized will not be considered randomized and will not be included in any analysis population. The safety experience of these participants will be reported separately.

Randomized participants for whom it is unclear whether they took the study intervention will be considered as exposed and will be included in the safety population as randomized.

For any participant randomized more than once, only the data associated with the first randomization will be used in any analysis population. The safety experience associated with any later randomization will be reported separately.

For participants receiving more than one study intervention during the study, the intervention group for as-treated analyses will be the one to which the participant was treated with the longest duration.

2.1.1 Estimands

Primary estimand defined for main endpoints are summarized in below Table 4. More details are provided in Section 3.

Table 4 - Summary of primary estimand for main endpoints

Endpoint Category (estimand)	Estimands			
	Endpoint	Population	Intercurrent event(s) handling strategy	Population-level summary (Analysis and missing data handling)
Primary population				
Primary objective: To assess the efficacy of daily oral dosing of venglustat when administered over a 104-week period.				
Primary endpoint (treatment policy)	Annualized rate of change in the 9-HPT from baseline to Week 104	Primary efficacy population	Regardless of adherence to study intervention	Difference in mean slope of the 9-HPT from baseline to Week 104, estimated from a linear mixed effect model after log transformation. In case of outliers, the linear mixed effect model will be replaced by a robust ANCOVA on individual slopes. No imputation of missing data due to small sample size.
Primary objective: To assess the PD of daily oral dosing of venglustat when administered over a 104-week period.				
Primary endpoint (treatment policy)	Percent change in CSF GM2 biomarker from baseline to Week 104	Primary pharmacodynamic population	Regardless of adherence to study intervention	Difference in mean percent change in CSF GM2 biomarker from baseline to Week 104, estimated from ANCOVA. In case of outliers, the ANCOVA will be replaced by a robust ANCOVA. No imputation of missing data due to small sample size.
Secondary objectives: To assess the PD of daily oral dosing of venglustat when administered over a 104-week period				
Secondary endpoint (treatment policy)	Absolute change in CSF GM2 biomarker from baseline to Week 104	Primary pharmacodynamic population	Regardless of adherence to study intervention	Difference in mean absolute change in CSF GM2 biomarker from baseline to Week 104, estimated from ANCOVA. In case of outliers, the ANCOVA will be replaced by a robust ANCOVA. No imputation of missing data due to small sample size.
Secondary objectives: To assess the effect of venglustat on selected performance test and scale over a 104-week period.				
Secondary endpoint (treatment policy)	Change in 25FWT from baseline to Week 104	Primary efficacy population (participants able to walk at baseline)	Regardless of adherence to study intervention	Difference in mean slope of change in the 25FWT from baseline to Week 104, estimated from a linear mixed effect model after log transformation. In case of outliers, the linear mixed effect model will be replaced by a robust ANCOVA on individual slopes. No imputation of missing data due to small sample size.

Endpoint Category (estimand)	Estimands			
	Endpoint	**Population**	**Intercurrent event(s) handling strategy**	**Population-level summary (Analysis and missing data handling)**
Secondary endpoint (treatment policy)	Change in FARS-neuro from baseline to Week 104	Primary efficacy population	Regardless of adherence to study intervention	Difference in mean slope of estimated FARS-neuro from baseline to Week 104 using a linear mixed effect model. In case of outliers, the linear mixed effect model will be replaced by a robust ANCOVA on individual slopes. No imputation of missing data due to small sample size.
Secondary population				
Primary objective: 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.				
Primary endpoint (treatment policy)	Plasma and CSF GL-1 biomarker and a pathway specific biomarker will be assessed as described in Section 3.2.4.	Secondary PD population	Regardless of adherence to study intervention	Descriptive
Secondary objectives: To assess the effect of venglustat on selected performance tests and scale over a 104-week period				
Secondary endpoint (treatment policy)	Annualized rate of change in the 9-HPT from baseline to Week 104	Secondary efficacy population	Regardless of adherence to study intervention	Descriptive
Secondary endpoint (treatment policy)	Change in 25FWT from baseline to Week 104	Secondary efficacy population	Regardless of adherence to study intervention	Descriptive
Secondary endpoint (treatment policy)	Change in FARS-neuro from baseline to Week 104	Secondary efficacy population	regardless of adherence to study intervention	Descriptive

3 STATISTICAL ANALYSES

3.1 GENERAL CONSIDERATIONS

Statistical significance for comparison between venglustat and placebo will be assessed at the Type I error rate of 0.05 one sided. Although a typical criterion for concluding that a trial is positive is a p-value of <0.05 two-sided, a higher Type I error rate of 0.05 one-sided was selected due to the rarity of late-onset GM2 gangliosidosis, the seriousness of this disease and lack of available therapy, as per Food and Drug Administration (FDA) draft guidance (1).

In general, continuous data will be summarized using the number of observations available, mean, standard deviation (SD), median, [Q1, Q3] minimum, and maximum. Categorical and ordinal data will be summarized using the count and percentage of participants.

The baseline value is defined as the last available value before or equal to the first dose of investigational medicinal product (IMP) date in the primary analysis period. For participants randomized but not exposed, the baseline value is defined as the last available value before or equal to the date of randomization.

Unless otherwise specified, analyses will be performed by intervention group (and overall for baseline and demographics characteristics).

The two analysis periods described below are defined:

- The **primary analysis period** is defined as the period starting at the date of signed informed consent, and ending at the end of Week 104 visit, or the day before the first IMP OLE administration (whichever comes last). For participants not exposed to IMP in the OLE, the primary analysis period ends at the date of end of study.
- The **OLE period** (only for participants exposed to IMP in the OLE) is defined as the period starting the day after the end of primary analysis period, until the end of the study.

Within each analysis period, the following observation periods are defined:

During the **primary analysis period** (as defined above), the following observation periods are defined:

- **The pre-treatment period** is defined as the time from the signed informed consent date up to the first IMP administration.
- **The treatment-emergent (TE) period** is defined as the time from the first IMP administration to the last administration of IMP during the primary analysis period +6 weeks (including any temporary treatment discontinuation period, if any) or the end of the primary analysis period (whichever comes first).

The TE period includes the following 2 periods:

- **The on-treatment period** is defined as the time from the first administration of IMP to the last administration of IMP in the primary analysis period +1 day (including any temporary treatment discontinuation period, if any).
- **The residual treatment period**, if any is defined as the time from the end of the on-treatment period to the end of the TE period.

- **The post-treatment period** is defined as the period starting the day after the end of the TE period, up to the end of the primary analysis period.

During the **OLE period** (as defined above), the following observation periods are defined:

- **The treatment-emergent (TE) period** is defined as the time from the start of the OLE period to the last administration of the OLE IMP +6 weeks (including any temporary treatment discontinuation period, if any).

  The TE period includes the following 2 periods:

  - **The on-treatment period** is defined as the time from the start of the OLE period to the last administration of the OLE IMP +1 day (including any temporary treatment discontinuation period, if any).
  - **The residual treatment period** is defined as the time from the end of the on-treatment period to the end of the TE period.
- **The post-treatment period** is defined as the period starting the day after the end of the TE period up to the end of the study.

In addition, the overall venglustat treatment-emergent period will combine the primary analysis period and the OLE period:

- The **overall venglustat treatment-emergent period** is defined as the time from the first intake of venglustat to the last intake of venglustat +6 weeks (including any temporary treatment discontinuation period, if any). Depending on the treatment received during the primary analysis period (venglustat or placebo), the first intake of venglustat may be either during the primary analysis period or during the OLE period.

The on-study observation period is defined as the time from the first administration of the IMP until the end of the study (defined as the last scheduled visit for those who completed the study and the end-of-study date collected on electronic case report form (e-CRF) page “Completion of End of Study” for those who did not complete the study. If death is the end-of-study reason, date of death will be used.

3.2 PRIMARY ENDPOINT(S) ANALYSIS

The co-primary endpoints are:

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

A statistically significant effect should be demonstrated on both primary endpoints to declare superiority of venglustat.

3.2.1 Percent change in CSF GM2

3.2.1.1 Definition

The first co-primary endpoint in the primary population is the percent change in CSF GM2 from baseline to Week 104.

[redacted]

3.2.1.2 Main analytical approach

This endpoint 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.

This model will provide baseline adjusted least-squares (LS) means estimates at Week 104 for both treatment groups with their corresponding standard errors (SEs).

The difference in LS means will be used to compare the venglustat group to the placebo group. The difference in LS means will be presented with its associated SE, 90% confidence interval and one-sided p-value. Statistical significance will be assessed at the one-sided 0.05 level (see Section 3.1 for justification).

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 exact criterion to determine whether the robust ANCOVA should be used is presented in Section 5.6.1.1. The robust ANCOVA will also include the fixed effect of treatment (venglustat versus placebo) and the continuous fixed covariate of baseline value.

In case the robust ANCOVA is not used as main analysis, this robust analysis will be produced as sensitivity analysis. If the robust ANCOVA becomes the main analysis, the ANCOVA will be produced as sensitivity analysis.

The number and percentage of participants with values <LLOQ or >ULOQ will also be presented.

In addition, descriptive statistics will be presented on CSF GM2 biomarker by time points. These statistics will include mean, standard deviation (SD), [Q1, Q3], median, minimum, and maximum.

3.2.1.3 Sensitivity analyses

3.2.1.3.1 Analysis with treatment as randomized

The main analysis described in Section 3.2.1.2 will be conducted according to intervention treatment actually received by participants. In case the treatment actually received is different from the treatment assigned by randomization for at least one participant, the analysis will also be conducted according to the treatment assigned by randomization.

3.2.2 9-hole peg test endpoint for primary population

3.2.2.1 Definition

The second co-primary endpoint in the primary population is the annualized rate of change in 9-HPT from baseline to Week 104.

3.2.2.2 Main analytical approach

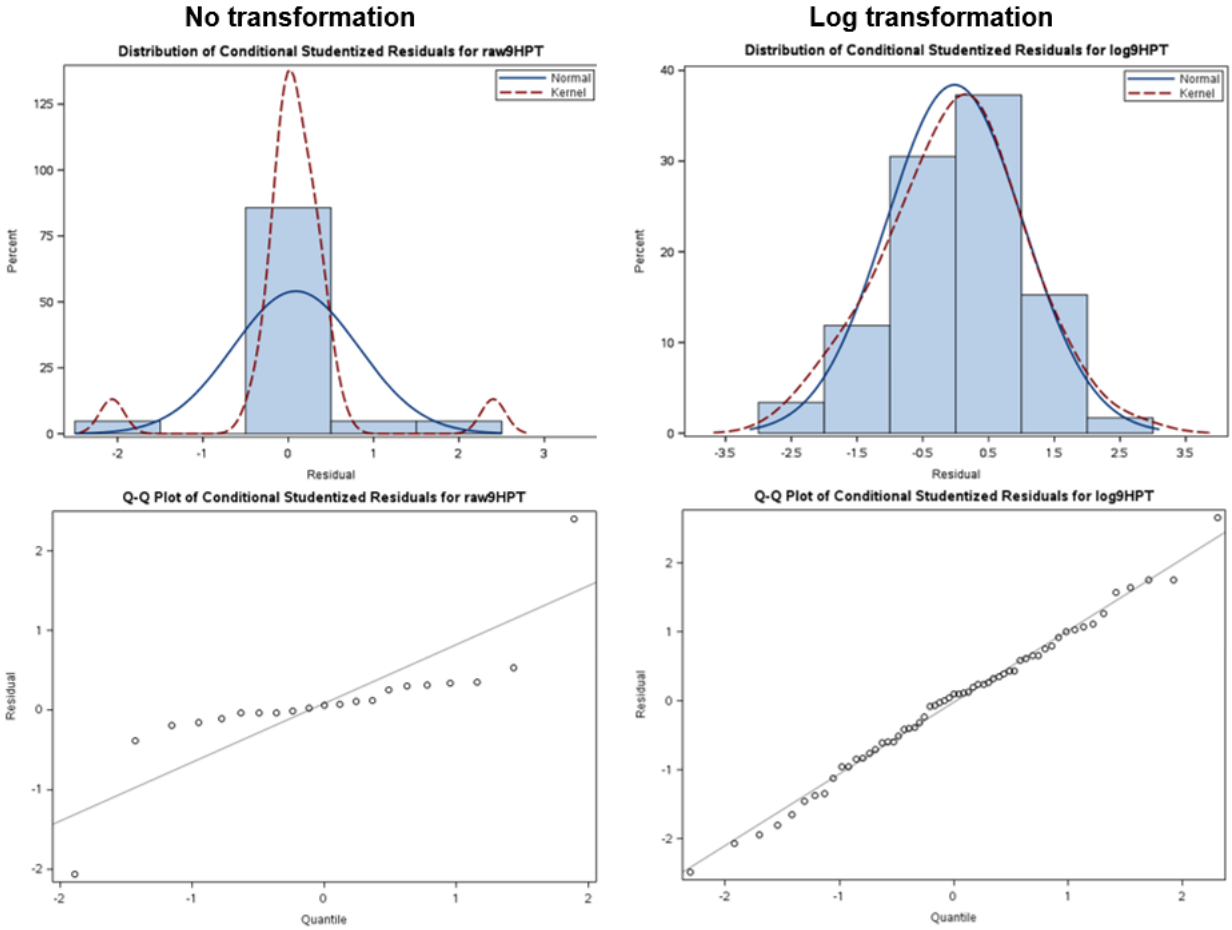
The primary analysis will include all data collected in patients from the primary population, regardless of whether or not participants completed the treatment period. Patients who prematurely and permanently discontinue study medication will be requested to continue to be assessed after treatment discontinuation, 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 9-HPT will be derived from the two trials for each hand (see Section 5.5.1 for derivation of the 9-HPT).

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 (see Figure 1). A logarithm transformation will allow interpretation in terms of relative increase in time to complete the 9-HPT (annual % increase per year).

Figure 1 - Distribution and QQ-plot of Studentized residuals from the linear mixed-effect model on natural history data - With or without log transformation



The model will include separate slopes for the venglustat and placebo arm. In addition, the model will include random intercept and slope in order to account for the between subjects variability. A residual variance will account for the within-subject variability.

The linear mixed-effect model is based on the following equation:

$$y_{ijk} = \alpha_j + \beta_j t_{ijk} + u_{1ij} + u_{2ij} t_{ijk} + \varepsilon_{ijk}$$

Where:

- y_{ijk} is the log-transformed 9-HPT of subject i from group j at the k^{th} assessment.
- t_{ijk} is the time (in years) from randomization of the k^{th} assessment of 9-HPT.
- α_j is the fixed intercept of group j.
- β_j is the fixed slope of group j.
- u_{1ij} and u_{2ij} are the random intercept and random slope of subject i from group j.
- ε_{ijk} is the residual error.

The linear mixed-effect model makes the following assumptions:

$$\begin{pmatrix} u_{1ij} \\ u_{2ij} \end{pmatrix} \sim N\left(\begin{pmatrix} 0 \\ 0 \end{pmatrix}, \begin{pmatrix} \sigma_I^2 & \rho\sigma_I\sigma_S \\ \rho\sigma_I\sigma_S & \sigma_S^2 \end{pmatrix}\right)$$

$$\varepsilon_{ijk} \sim N(0, \sigma_R^2)$$

$\begin{pmatrix} u_{1ij} \\ u_{2ij} \end{pmatrix}$ and ε_{ijk} are independent

Where:

- σ_I^2 is the variance of random intercepts.
- σ_S^2 is the variance of random slopes.
- σ_R^2 is the variance of residual errors.
- ρ is the correlation between random intercepts and random slopes.

For the primary analysis, the linear mixed-effect model will be estimated in a Frequentist framework.

This model will provide mean estimate of the slope of log-transformed 9-HPT with their corresponding SE. A back-transformation (ie, exponential transformation) will be applied to obtain annualized rate of change of 9-HPT (in % per year) within each treatment arm:

Annualized rate of change (%/year) = [exp(mean slope of log-transformed 9-HPT) – 1]×100

The difference in annualized rate of change will be used to compare the venglustat group to the placebo group. The difference in LS means will be presented with its associated 90% confidence interval (see Section 5.6.2) and one-sided p-value. Statistical significance will be assessed at the one-sided 0.05 level (see Section 3.1 for justification).

In case the results from the linear mixed-effect model may be severely impacted by the presence of 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, described in Section 3.2.2.3.1. The exact criterion to determine whether the robust ANCOVA should be used is presented in Section 5.6.1.2.

Simulations showed that the linear mixed-effect model is the most powerful approach when the distribution of individual slopes is normal but would be dramatically impacted in case a small proportion of participants exhibit an extreme slope. The Type I error rate of the linear mixed-effect model would also be inflated in presence of extreme slopes. The robust ANCOVA on individual slopes would be slightly less powerful if the distribution of individual slopes is normal, but very modestly impacted in presence of extreme slopes. The proposed approach with a pre-specified criterion for using the robust ANCOVA maintains the power close to 80% in all scenarios and protects against inflation of the Type I error rate. Details on the simulation is provided in Section 5.6.3.

If the robust ANCOVA becomes the main analysis, the linear mixed-effect model will be produced as sensitivity analysis.

3.2.2.3 Sensitivity analyses

[redacted]

[redacted]

3.2.2.3.2 Sensitivity to the logarithm transformation

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, described in Section 3.2.2.3.1. The exact criterion to detect outliers is presented in Section 5.6.1.2.

Another sensitivity analysis will use the reciprocal of the 9-HPT.

3.2.2.3.3 Sensitivity to the assumption of linear change

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 covariate of log-transformed baseline 9-HPT.

This model will be run using SAS Mixed procedure with an unstructured correlation matrix to model the within-participant errors. Parameters will be estimated using restricted maximum likelihood method. Denominator degrees of freedom will be estimated using Kenward-Roger approximation. This model will provide baseline adjusted LS mean change at Week 104 for each study intervention groups with their corresponding SE.

A back-transformation (ie, exponential transformation) will be applied to obtain baseline adjusted LS mean percent change at Week 104 within each treatment arm. The difference in LS mean percent change will be presented with its associated 90% confidence interval (similar to Section 5.6.2) and one-sided p-value.

In addition, the same analysis will be repeated without log-transformation of 9-HPT.

3.2.2.4 Supportive analyses

3.2.2.4.1 Analysis in a Bayesian framework

A secondary analysis will be conducted using a Bayesian approach with an informative prior distribution for the slope in the placebo arm. This informative prior distribution is based on natural history data collected during the National Tay-Sachs & Allied Diseases (NTSAD) annual conferences between 2015 and 2019. A summary of these data is provided in Section 5.7.

In this secondary analysis, the linear mixed-effect model will be estimated in a Bayesian framework. An informative prior distribution for the slope of the placebo arm will be used, assuming the prior distribution of the slope of log-transformed 9-HPT has a normal distribution, with mean =0.0264 and standard deviation of 0.0118 (see Table 25 for details). A non-informative prior distribution will be used for all other parameters of the linear mixed-effect model.

Efficacy of venglustat will be based on the posterior probability that the slope of annualized rate of change in 9-HPT on venglustat is lower than the slope on placebo. A posterior probability of at least 95% will be considered significant.

3.2.2.4.2 While-on-treatment analysis

A secondary analysis will target a while-on-treatment estimand.

In this sensitivity analysis, the linear mixed-effect model described in Section 3.2.2.2 will be repeated, including only 9-HPT collected during the primary analysis period, up to the last IMP administration +30 days.

In case of presence of outlier, the linear mixed-effect model will be replaced by the robust ANCOVA on individual slopes, described in Section 3.2.2.3.1. The exact criterion to detect outliers is presented in Section 5.6.1.2.

3.2.2.4.3 Time to meaningful worsening in 9-HPT

A meaningful worsening in 9-HPT will be defined as an increase from baseline in 9-HPT, larger than or equal to a pre-defined threshold for meaningful worsening. The within-patient threshold for meaningful worsening will be determined from a psychometric analysis conducted on the blinded data with at least 75% of participants who completed the Week 104 assessments or withdrew from the EFC15299 study, that will be completed before the database lock.

In order to take into account within-participant fluctuations over time of the 9-HPT, a meaningful worsening in 9-HPT will be defined as an unresolved increase from baseline in 9-HPT. A meaningful worsening will therefore be defined as an increase from baseline in 9-HPT, larger or equal to the pre-defined threshold, that is observed at any visit (Week 12, 26, 52, 78 or 104), and is sustained at all subsequent visits until the Week 104 visit or study discontinuation (whichever comes first). In case an increase larger or equal to the pre-defined threshold is observed at the Week 104 visit (or at last visit in case of premature study discontinuation), the criterion for meaningful worsening will be considered met, since the worsening was not resolved during the study.

Time to meaningful worsening in 9-HPT will be defined as follows:

- For participants with meaningful worsening, time to meaningful worsening will be defined as the first visit (Week 12, 26, 52, 78 or 104) where an increase in 9-HPT larger or equal to the pre-defined threshold was observed, and not subsequently resolved.
- For participants without meaningful worsening, time to meaningful worsening will be censored at the last visit (Week 0, 12, 26, 52, 78 or 104) where 9-HPT was assessed.

An example of derivation of time to meaningful worsening and status is presented in Table 5, with 4 hypothetical participants, and assuming for illustration purpose that the threshold for meaningful worsening is a ≥20% increase in 9-HPT.

Table 5 - Examples of time to meaningful worsening in 9-HPT, assuming threshold for meaningful worsening is a ≥20% increase from baseline

	Participant #1	Participant #2	Participant #3	Participant #4
Change from baseline in 9-HPT				
Week 12	+5%	+5%	+15%	+10%
Week 26	**+25%**	**+25%**	+5%	**+25%**
Week 52	+10%	+15%	+10%	Not done
Week 78	**+25%**	**+25%**	+15%	Not done
Week 104	**+30%**	+15%	**+25%**	Not done
Time to meaningful worsening				
Status	Event	Censor	Event	Event
Time to event/censor	78 weeks	104 weeks	104 weeks	26 weeks

Numbers in **bold** represent increase ≥20%.

Visits will be defined based on the analysis window defined in Table 13.

Time to meaningful worsening in 9-HPT will be summarized graphically using Kaplan-Meier cumulative incidence curves. The proportion of participants with meaningful worsening at Week 104 will be obtained from the Kaplan-Meier estimates at Week 104 within each treatment arm. The proportion of participants with meaningful worsening at Week 104 will be informally compared between the two treatment arms, based on the SE of the Kaplan-Meier estimate using the Greenwood formula. Statistical test and (90%,95%) confidence intervals of the difference in proportion will be presented for descriptive purpose only, since not included in the procedure for handling multiplicity of tests.

In addition, in order to assess alternative thresholds for meaningful worsening, the same procedure will be repeated using different thresholds, varying from 5% increase to 100% increase in 9-HPT. Similar analysis will evaluate worsening based on absolute change from baseline, rather than relative change from baseline (with thresholds varying from 1 second increase to 60 seconds increase). The results will be presented in a cumulative graph, presenting the threshold for worsening on the X axis, and the proportion of participants with meaningful worsening at Week 104 (based on the threshold presented on the X axis) on the Y axis. The graph will present the proportions in the venglustat and placebo arm.

3.2.2.4.4 Time to meaningful improvement in 9-HPT

The same analysis will be conducted to evaluate meaningful improvement in 9-HPT.

A meaningful improvement in 9-HPT will be defined as decrease from baseline in 9-HPT, larger than or equal to a pre-defined threshold for meaningful improvement. The threshold for meaningful improvement will also be determined from the psychometric analysis. This analysis will be produced if such threshold is found with psychometric analysis.

A meaningful improvement will be defined as a decrease from baseline in 9-HPT, larger or equal to the pre-defined threshold, that is observed at any visit (Week 12, 26, 52, 78 or 104), and is sustained at all subsequent visits until the Week 104 visit. In case a decrease larger or equal to the pre-defined threshold is observed at the Week 104 visit, the criterion for meaningful improvement will be considered met. In case of missing data at Week 104, the criterion for meaningful improvement will not be considered met, even if a decrease in 9-HPT was observed at previous visits.

Time to meaningful improvement in 9-HPT will be defined as follows:

- For participants with meaningful improvement, time to meaningful improvement will be defined as the first visit (Week 12, 26, 52, 78 or 104) where a decrease in 9-HPT larger or equal to the pre-defined threshold was observed and maintained until Week 104.
- For participants without meaningful improvement, time to meaningful improvement will be censored at the last visit (Week 0, 12, 26, 52, 78 or 104) where 9-HPT was assessed.

An example of derivation of time to meaningful improvement and status is presented in Table 6, with 4 hypothetical participants, and assuming for illustration purpose that the threshold for meaningful improvement is a ≥20% decrease in 9-HPT.

Table 6 - Examples of time to meaningful improvement in 9-HPT, assuming threshold for meaningful improvement is a ≥20% decrease from baseline

	Participant #1	Participant #2	Participant #3	Participant #4
Change from baseline in 9-HPT				
Week 12	-5%	-5%	-15%	-10%
Week 26	**-25%**	**-25%**	-5%	**-25%**
Week 52	-10%	-15%	-10%	Not done
Week 78	**-25%**	**-25%**	-15%	Not done
Week 104	**-30%**	-15%	**-25%**	Not done
Time to meaningful improvement				
Status	Event	Censor	Event	Censor
Time to event/censor	78 weeks	104 weeks	104 weeks	26 weeks

Numbers in in **bold** represent decrease ≥20%

The analysis of time to meaningful improvement will be the same as for time to meaningful worsening.

3.2.2.4.5 Descriptive analysis by visit

Results will be summarized using descriptive statistics at each time point, including values, change and percent change from baseline.

Two graphs will be produced: one presenting the mean value ±SE by visit, the other presenting the mean change from baseline ±SE by visit.

Number and percentages of participants who did not complete the assessment will be described by time point.

3.2.3 Subgroup analyses

To assess the homogeneity of the treatment effect across various subgroups, analyses will be performed on the two co-primary endpoints across subgroups. Subgroup analyses will include, but not be limited to the following subgroups:

- Sex (Male, Female).
- Age group (<35, ≥35 years).
- Disease type (Tay-Sach disease versus Sandhoff disease).
- Time from diagnosis (<5 years, ≥5 years).
- Time from symptom onset (<20 years, ≥20 years).
- Age at diagnosis (<30 years, ≥30 years).
- Ability to walk (yes versus no).
- Baseline GM2 level (<median value, ≥median value).
- Baseline 9-HPT (<30 sec, ≥30 sec).
- Baseline 25-FWT (<10 sec, ≥10 sec or unable to walk).
- Baseline FARS-neuro (<50, ≥50).

Treatment-by-subgroup interaction term and the subgroup factor term will be added in the primary model.

The treatment effects (venglustat versus placebo) for the primary endpoint will be provided, as well as the corresponding 90% and 95% CI, for each subgroup, using the same method as applied to the primary analysis. Forest plots will be provided.

3.2.4 Primary endpoint for secondary population

3.2.4.1 Definition of endpoint(s)

For the secondary population, the primary endpoint is Plasma and CSF GL-1 biomarker and pathway specific biomarkers, as shown in Table 7.

Table 7 - Disease specific biomarkers for the secondary population

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

3.2.4.2 Main analytical approach

Primary endpoints 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.

The number and percentage of participants with values <LLOQ or >ULOQ will also be presented.

3.3 SECONDARY EFFICACY ENDPOINT(S) ANALYSIS

3.3.1 Primary population

3.3.1.1 Definition of endpoint(s)

Secondary efficacy endpoints include:

- 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-neuro) from baseline to Week 104.

3.3.1.2 Main analytical approach

3.3.1.2.1 Absolute change in CSF GM2

The endpoint of absolute change in CSF GM2 biormarker will be analyzed with the same approach used for percent change and described in Section 3.2.1.2.

3.3.1.2.2 Change in 25FWT

The 25FWT will be derived from the two trials (see Section 5.5.2 for derivation of the 25FWT).

Change in 25FWT will be analyzed only in participants able to walk at baseline. Participants unable to complete the 25FWT at baseline will be excluded from this analysis. To ensure balanced randomization of subjects able to walk at baseline, the randomization will be stratified based on the participant's ability to walk at the baseline visit.

Change in 25FWT will be compared between venglustat and placebo using a linear mixed-effect model with random intercept and slopes, similar to the analysis of the 9-HPT (see Section 3.2.2.2). The model will assume linear change over time in 25FWT after log transformation. The logarithm transformation was selected due to anticipated non-normal distribution of the 25FWT. A logarithm transformation will allow interpretation in terms of relative increase in time to complete the 25FWT (annual % increase per year).

Slope on venglustat and on placebo will be estimated from the linear mixed effect model. Efficacy of venglustat will be based on the comparison of slopes. The difference in slopes will be estimated and presented with its associated 90% confidence interval and p-value. Significance level will be the same as for the primary endpoint.

In case of outliers, the linear mixed-effect model will be replaced by the robust ANCOVA on individual slopes, described in Section 3.2.2.3.1. The exact criterion to determine whether the robust ANCOVA should be used is presented in Section 5.6.1.2.

3.3.1.2.3 Change in FARS-neuro

The FARS neurological score will be derived from the 23 items of the FARS-neuro (see Section 5.5.3 for the derivation of the score).

Change in FARS-neuro will be compared between venglustat and placebo using a linear mixed-effect model with random intercept and slopes, similar to the analysis of the 9-HPT (see Section 3.2.2.2). The model will assume linear change over time in the FARS-neuro. No logarithm transformation will be performed for FARS neurological score.

Slope on venglustat and on placebo will be estimated from the linear mixed effect model. Efficacy of venglustat will be based on the comparison of slopes. The difference in slopes will be estimated and presented with its associated 90% confidence interval and p-value. Significance level will be the same as for the primary endpoint.

In case of outliers, the linear mixed-effect model will be replaced by the robust ANCOVA on individual slopes, described in Section 3.2.2.3.1. The exact criterion to determine whether the robust ANCOVA should be used is presented in Section 5.6.1.2.

3.3.1.3 Sensitivity analyses

The sensitivity analyses described in Section 3.2.2.3 will also be conducted for the two secondary endpoints of 25FWT and FARS-neuro.

Since the log transformation is not applied for the FARS-neuro, sensitivity to the log transformation will not be conducted for this endpoint.

In addition, a sensitivity analysis of the FARS-neuro will be conducted, using the muscle weakness of triceps and quadriceps. In this sensitivity analysis, the score from the two items "Muscle Weakness - Right side" and "Muscle Weakness - left side" from the Peripheral Nervous System section of FARS-neuro (see Table 15 for details) will be replaced by the scores from the muscle weakness of triceps and quadriceps (right and left side).

The sensitivity analyses described in Section 3.2.1.3 will also be conducted on absolute change in CSF GM2 biomarker endpoint.

3.3.1.4 Supportive analyses

Time to meaningful worsening in 25FWT and in FARS-neuro will be conducted, using the method described in Section 3.2.2.4.3.

Time to meaningful improvement in 25FWT and in FARS-neuro will be conducted, using the method described in Section 3.2.2.4.4.

Descriptive analysis will be conducted on 25FWT and FARS-neuro, using the method described in Section 3.2.2.4.5.

3.3.1.5 Subgroup analyses

The subgroup analyses described in Section 3.2.3 will also be conducted for the three secondary endpoints presented above.

3.3.2 Secondary population

3.3.2.1 Definition of endpoint(s)

- 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 FARS-neuro from baseline to Week 104.

3.3.2.2 Main analytical approach

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.

For the descriptive analysis of 9-HPT, participants with maximum score (300 seconds) at baseline or unable to complete the test at baseline will be excluded.

Similarly, for the descriptive analysis of 25FWT, participants with maximum score (180 seconds) at baseline or unable to complete the test at baseline will be excluded.

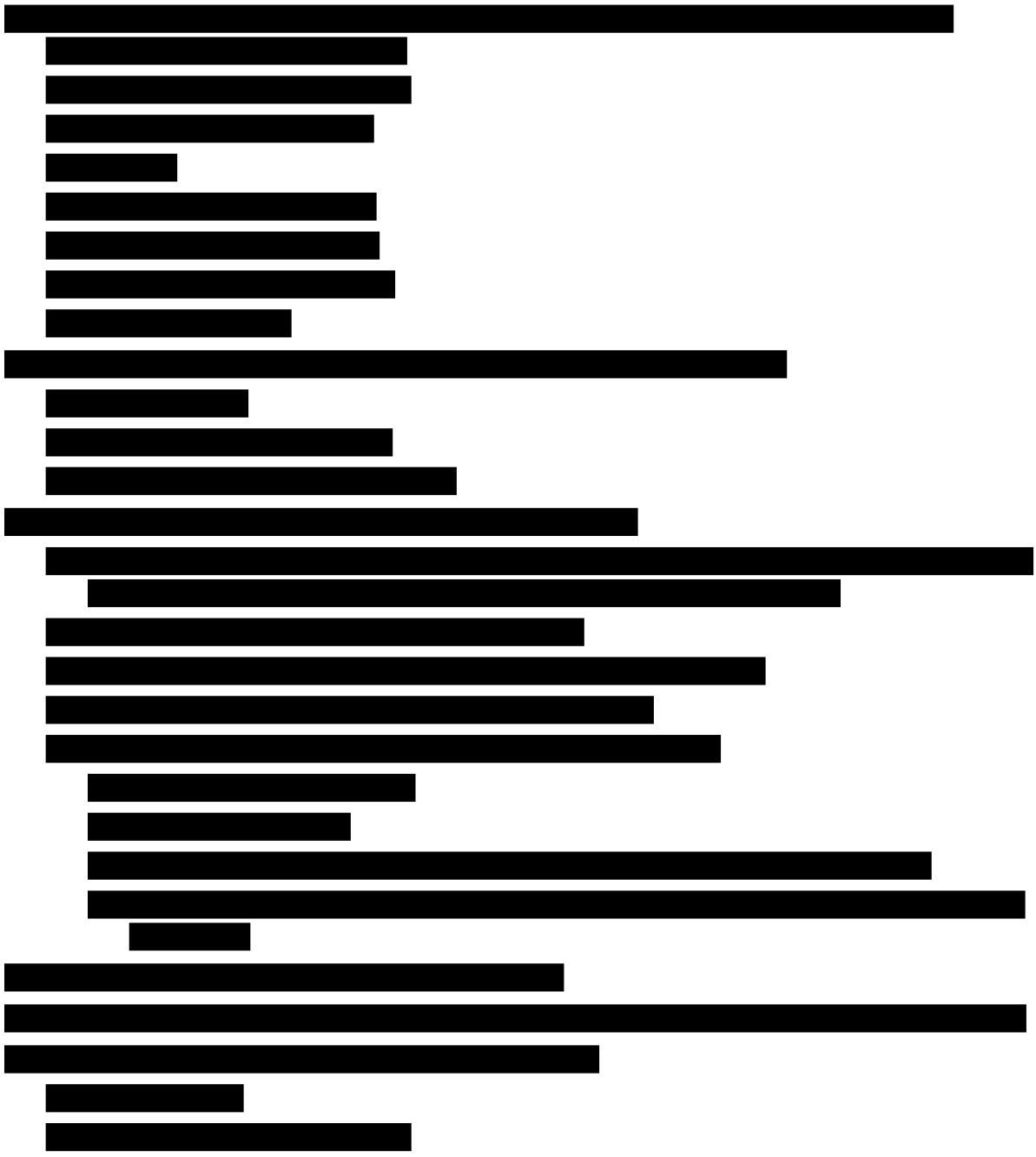
Number and percentage of participants who did not complete the assessments will be described by time point.

3.4 TERTIARY/EXPLORATORY EFFICACY ENDPOINT(S) ANALYSIS

The analysis will be conducted in two steps (see Section 3.8.2). The exploratory endpoints at Week 104 will be presented in the first step analysis. The exploratory endpoints at Week 208 will be presented in the second step analysis.

The exploratory efficacy endpoints are the same for the primary and secondary populations.

3.4.1 Definition of endpoint(s)



[redacted]

3.4.2 Main analytical approach

For all exploratory efficacy endpoints, the analyses will be descriptive, and no testing are planned. Continuous data will be summarized by treatment group using the number of observations available, mean, standard deviation (SD), median, [Q1, Q3], minimum, and maximum. Categorical and ordinal data will also be summarized by treatment group using the count and percentage of participants. If applicable the change and percent change from baseline will be presented.

3.4.2.1 [redacted]

[redacted]

[redacted]

3.4.2.2 [redacted]

[redacted]

3.4.2.3 [redacted]

[redacted]

[redacted]

[redacted]

3.4.2.4 [redacted]

[redacted]

3.4.2.5 [redacted]

[redacted]

Table 8 - [redacted]

[redacted]

[redacted]

3.5 MULTIPLICITY ISSUES

No adjustment for multiplicity will be considered for the co-primary endpoints (percent change in CSF GM2 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 endpoints to conclude to efficacy.

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.

No further adjustments will be made for exploratory endpoints for which p-values may be provided for descriptive purpose only.

3.6 SAFETY ANALYSES

All safety analyses will be performed on the safety populations as defined in Section 2 for the two steps analysis, unless otherwise specified, using the following common rules:

- The analysis of the safety variables will be essentially descriptive, and no testing is planned.
- Safety data in participants who do not belong to the safety population (eg, exposed but not randomized) will be provided separately if any.

In the first step analysis, safety data will be presented for the following period:

- Safety analysis of the primary analysis period. This analysis will present safety data collected during the primary analysis period (as defined in Section 3.1). Safety analyses will present safety data in the following arms:
  - Primary population – Placebo: participants from the primary population, having received placebo during the primary analysis period.
  - Primary population – Venglustat: participants from the primary population, having received venglustat during the primary analysis period.
  - Secondary population – Venglustat: participants from the secondary population, having received venglustat during the primary analysis period.

In the second step analysis, safety data will be presented separately for the two following periods:

- Safety analysis of the OLE period. This analysis will present safety data collected during the OLE period (as defined in Section 3.1). Only participants having received venglustat during the OLE period will be included in this analysis. Safety analyses will present safety data from the following groups:
  - Primary population - Delayed venglustat: participants from the primary population, having received placebo during the primary analysis period, then having received venglustat during the OLE period.
  - Primary population - Early venglustat: participants from the primary population, having received venglustat during the primary analysis period, then having continued to receive venglustat during the OLE period.

- Primary population - All venglustat: all participants from the primary population having received venglustat during the OLE period.
- Secondary population – Venglustat: participants from the secondary population having received venglustat during the OLE period.

- Safety analysis of the overall venglustat treatment period. This analysis will present adverse event occurring from the first intake of venglustat to the last intake of venglustat plus 6 weeks. All participants having received venglustat (either during the primary analysis period or during the OLE period) will be included in this analysis. Safety analyses will present safety data from the following groups:
  - Primary population - Venglustat: participants from the primary population having received venglustat during the primary analysis period and/or during the OLE period.
  - Secondary population - Venglustat: participants from the secondary population having received venglustat during the primary analysis period and/or during the OLE period.
  - All - Venglustat: all participants from the primary or secondary population, having received venglustat during the primary analysis period and/or during the OLE period.

3.6.1 Extent of exposure

The extent of IMP exposure will be assessed for the two steps analysis by the duration of IMP exposure and compliance and summarized within the safety populations.

Duration of IMP exposure

Duration of IMP exposure is defined as last IMP administration date – first IMP administration date +1 day, regardless of unplanned intermittent discontinuations. If the date of the last dose of IMP is missing, the duration of IMP will be left as missing.

The duration is defined differently for the two steps of the analysis (see Section 3.8.2):

Duration of IMP exposure for the primary analysis period is defined as:

- The last IMP administration date during the primary analysis period - first IMP administration date +1.

Duration of IMP exposure for the OLE period is defined as:

- The last IMP administration date during the OLE period - first IMP administration date during the OLE period +1 day.

In addition, overall duration of exposure to venglustat is defined as:

- The last venglustat administration date (either during the primary analysis period or OLE period) - first IMP administration date (either during the primary analysis period or OLE period) +1 day.

Duration of IMP exposure will be summarized quantitatively and categorically:

- ≥1 day.
- ≥4 weeks (1 month).
- ≥12 weeks (3 months).
- ≥26 weeks (6 months).
- ≥52 weeks (12 months).
- ≥78 weeks (18 months).
- ≥104 weeks (24 months).
- ≥130 weeks (30 months).
- ≥156 weeks (36 months).
- ≥182 weeks (42 months).
- ≥208 weeks (48 months).

Additionally, the cumulative duration of treatment exposure (expressed in participant-years) will be provided.

Summary of extent of exposure will be provided for the safety population as well as for the population with trial impact (disruption) due to COVID-19.

Treatment compliance

A given administration will be considered noncompliant if the participant did not receive the number of days of IMP as required by the protocol. No imputation will be made for participants with missing or incomplete data.

Percentage of treatment compliance for a participant will be defined as the number of days of IMP administered divided by the total number of days that the participant was planned to take from the first administration of IMP up to the actual last administration of IMP.

Treatment compliance will be summarized quantitatively and categorically: <80%, ≥80%.

Cases of overdose are reported in the adverse event (AE) e-CRF pages as Adverse Event of Special Interest (AESI) if symptomatic or AE if asymptomatic. The reported cases of overdose will be described in the AE analysis (see Section 3.6.2).

Acceptability and palatability

For pediatric secondary population, the acceptability and palatability of venglustat tablets will be assessed for the two steps analysis by the route of venglustat administration collected in the eCRF and the treatment compliance (as defined in the above section).

Treatment compliance of participants from the pediatric secondary population will be summarized quantitatively and categorically (<80%, ≥80%) according to the route of venglustat administration (Swallowed the Tablet as Whole, Chewed and Swallowed) within the secondary safety population.

[redacted]

3.6.2 Adverse events

General common rules for adverse events

All adverse events (AEs) will be coded to a lower-level term (LLT), preferred term (PT), high-level term (HLT), high-level group term (HLGT), and associated primary system organ class (SOC) using the Medical Dictionary for Regulatory Activities (MedDRA) version currently in effect at Sanofi at the time of database lock.

The AEs will be analyzed in the following 3 categories:

- Pre-treatment AEs: AEs that developed, worsened or became serious during the pre-treatment period.
- Treatment-emergent adverse events (TEAE)s: AEs that developed, worsened or became serious during the treatment-emergent period.
- Post-treatment AEs: AEs that developed, worsened or became serious during the post-treatment period.

Similarly, the deaths will be analyzed in the pre-treatment, treatment-emergent and post-treatment periods.

The primary focus of AE reporting will be on TEAEs. Pre-treatment and post-treatment AEs will be described separately.

An AE with incomplete or missing date/time of onset (occurrence, worsening, or becoming serious) will be classified as a TEAE unless there is definitive information to determine it is a pre-treatment or a post-treatment AE.

If the assessment of the relationship to IMP is missing for an AE, this AE will be assumed as related to IMP. If the severity is missing for 1 of the treatment-emergent occurrences of an AE, the severity will be imputed with the maximal severity of the other occurrences. If the severity is missing for all the occurrences, the severity will be left as missing.

The AE tables will be sorted as indicated in Table 9.

Table 9 - Sorting of AE tables

AE presentation	Sorting rules
SOC, HLGT, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLGTs, HLTs and PTs.
SOC, HLT and PT	By the internationally agreed SOC order and by alphabetic order of HLTs and PTs.
SOC and PT	By the internationally agreed SOC order and decreasing frequency of PTs[a, b]
SMQ/CMQ and PT	By decreasing frequency of SMQs/CMQs and PTs[a]
PT	By decreasing frequency of PTs[a]

a Sorting will be based on the venglustat 15 mg dose group.
b The table of all TEAEs presented by primary SOC and PT will define the presentation order for all other tables (eg, treatment-emergent SAE) presented by SOC and PT, unless otherwise specified.

Analysis of all adverse events

The overview of TEAE with the details below will be generated:

- Any TEAE.
- Any treatment emergent serious adverse events (SAEs).
- TEAE leading to death.
- Any TEAE leading to permanent intervention discontinuation.
- Any treatment emergent AESI.

The AE summaries of Table 10 will be generated with number (%) of participants experiencing at least one event.

Table 10 - Analyses of adverse events

Type of AE	MedDRA levels
All TEAE	Primary SOC, HGLT, HLT and PT
	Primary SOC and PT
All TEAE by trial impact (disruption) due to COVID-19	Primary SOC and PT
TEAE related to IMP as per Investigator's judgment	Primary SOC and PT
TEAE by maximal intensity	Primary SOC and PT
Treatment emergent SAE	Primary SOC and PT
TEAE leading to permanent intervention discontinuation	Primary SOC and PT
TEAE leading to death (death as an outcome of the AE as reported by the Investigator in the AE page)	Primary SOC and PT
Treatment emergent COVID-19 related AE	Primary SOC and PT
Pretreatment AE	Overview[a]
Pretreatment AESI	Primary SOC and PT
Treatment-emergent AESI	Primary SOC and PT
Post-treatment AE	Overview[a]

a Will include the following AE categories: any AEs, any serious AEs, any AEs leading to death, any AEs leading to permanent intervention discontinuation.

Analysis of deaths

In addition to the analyses of deaths included in Table 10 the number (%) of participants in the following categories will be provided:

- Deaths during the treatment-emergent and post-treatment periods by reason for death.
- Deaths in non-randomized participants or randomized but not exposed participants.

Analysis of adverse events of special interest (AESIs)

Adverse events of special interest (AESIs) and other AEs of interest will be selected for analyses as indicated in Table 11. Number (%) of participants experiencing at least one event will be provided for each event of interest. Tables will be sorted as indicated in Table 9.

Table 11 - Selections for AESIs

AESIs and other AEs of interest	Selection
Pregnancy of a female subject	e-CRF specific tick box on the AE page / specific e-CRF page
Symptomatic overdose (serious or non-serious) with IMP	e-CRF specific tick box on the AE page / specific e-CRF page
Increase in alanine transaminase (ALT)	e-CRF specific tick box on the AE page
New or worsening lenticular opacities and cataracts	e-CRF specific tick box on the AE page

3.6.3 Additional safety assessments

3.6.3.1 Laboratory variables, vital signs and electrocardiograms (ECGs)

The following laboratory variables, vital signs and electrocardiogram (ECG) variables will be analyzed. They will be converted into standard international units.

- Hematology:
  - Red blood cells and platelets and coagulation: hemoglobin, hematocrit, erythrocyte count, platelet count.
  - White blood cells: white blood cell count, neutrophils, lymphocytes, monocytes, basophils, eosinophils.
- Clinical chemistry:
  - Metabolism: glucose, protein.
  - Electrolytes: sodium, potassium.
  - Renal function: creatinine, blood urea nitrogen, estimated Glomerular Filtration Rate (eGFR).
  - Liver function: alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, total and direct bilirubin.
  - Pregnancy test: Serum β-human chorionic gonadotropin (all female participants).
- Urinalysis:
  - Urinalysis for quantitative analysis: pH, proteins, and glucose.

- Vital signs: heart rate, systolic and diastolic blood pressure, weight.
  - For all Blood Pressure (BP) and Heart Rate (HR) measurements, will be analyzed using the supine measurements at each visit.
- ECG variables: heart rate, PR, QRS, QT, and corrected QTc (according to Bazett/Fridericia).

[redacted]

For ECG at baseline visit (V2) a triplicate of data is collected. For calculation of baseline value, the average of all available data will be calculated.

eGFR will be derived using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) creatinine equation for adult participants and the Schwartz formula for pediatric participants.

Quantitative analyses

For all laboratory variables, vital signs and ECG variables above, descriptive statistics for results and changes from baseline will be provided for each visit, the last value and the worst value (minimum and/or maximum value depending on the parameter) during the on-treatment period.

All laboratory parameters and vital signs parameters will be summarized using the analysis windows as defined in Section 5.4, Table 13 and into account planned visit in the protocol.

When appropriate, plots of mean ±SE over time will be presented. Plots of mean change from baseline ±SE will also be presented.

Analyses according to PCSA

Potentially clinically significant abnormality (PCSA) analyses will be performed based on the PCSA list currently in effect at Sanofi at the time of the database lock. For parameters for which no PCSA criteria are defined, similar analyses will be done using the normal range, if applicable.

For parameters defined as efficacy endpoints, PCSA summaries will not be provided.

Analyses according to PCSA except for ECG data, will be performed based on the worst value during the treatment-emergent period, using all measurements (either local or central, either scheduled, nonscheduled or repeated).

For ECG parameter the analyses according to PCSA will used central data only.

For laboratory variables, vital signs and ECG variables above, the incidence of participants with at least one PCSA during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal according to PCSA criterion or criteria.

For ECG, the incidence of participants with at least one abnormal ECG during the treatment-emergent period will be summarized regardless of the baseline level and according to the following baseline status categories:

- Normal/missing.
- Abnormal.

Additional analyses for drug-induced liver injury

The following additional analyses will be performed for drug-induced liver injury:

- A graph of the distribution of peak values of ALT versus peak values of total bilirubin during the treatment-emergent period will be provided.
- For each liver function test (eg, ALT), participants having experienced a PCSA (eg, ALT >5 ULN) will be summarized using the following categories: Returned to baseline PCSA status (or returned to value ≤ULN in case of missing baseline) before last IMP dose, returned to baseline PCSA status after last IMP dose, Never returned to baseline PCSA status, No assessment after elevation. This summary will be performed by categories of elevation (ALT >3, >5, >10, >20 ULN).

The incidence of liver related AEs will be summarized by study intervention group. The selection of PT will be based on SMQ Hepatic disorder.

3.6.3.2 Neurological examination

Each neurological examination will include, but are not limited to:

- Cranial nerve examination: olfactory, optic, oculomotor, trochlear, trigeminal, abducens, facial, vestibulocochlear, glossopharyngeal, vagus, accessory, hypoglossal).
- Extrapyramidal features: postural tremor, rest tremor, intention tremor, cogwheel rigidity, lead pipe rigidity, bradykinesia, postural deficit, dystonia, other.
- Gait examination: antalgic, staggering, steppage, waddle, difficulty initiating, glue footed, toe walking, other.
- Coordination examination: finger to nose test, rapid alternating movements, heel to shin, tandem gait.
- Motor examination (tone): spasticity, rigidity, paratonia, other, decreased muscle tone.
- Peripheral nervous system (sensory disturbances).
- Reflexes examination.
- Strength examination: heel walking, sit to stand test, toe walking, other motor abnormality.

These examination findings will be assessed as normal or abnormal.

Number and percentage of participants with abnormal neurological examination will be summarized by location (cranial nerve, Extrapyramidal features, motor, Peripheral nervous system strength, reflex, sensory, coordination, gait) at each planned visit during the treatment emergent period.

3.6.3.3 Ophthalmological examination

The effect of venglustat on the lens will be closely monitored throughout the primary analysis period for all participants and throughout the whole study for participants <18 years of age. The full ophthalmological examination will include slit-lamp examination, fundoscopy with pupil dilation and examination of the cornea, lens, and retina.

So, the results will be presented for all participants in the first step analysis. In the second step, only participants in secondary population younger than 18 years will be included.

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 for all participants.

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.

Secondary safety endpoints in first step, include change in the lens opacity by ophthalmological examination during the treatment emergent period.

Number and percentages of participants with abnormal ophthalmological examination on any eye at any time (whether present at screening or not) as well as number and percentages of participants with any new onset of abnormal ophthalmological examination on any eye during the treatment emergent period as per investigator (site ophthalmologist) assessment will be summarized along with a description of lens opacity according to the WHO classification.

The decrease in Best Corrected Visual Acuity (BCVA) will also be presented on any eye at any time (whether present at screening or not). This decrease will be presented according to 1, 2 or 3 lines.

3.6.3.4 Depression [redacted] examination

[redacted]

[redacted]

3.7 OTHER ANALYSES

3.7.1 PK analyses

The PK analyses will be produced only in the first step analysis (see Section 3.8.2).

A PK sub study is planned on 15 participants in primary population. Some supplementary time points was collected at D1 visit for these specific participants. The details of time points are presented in Table 14.

Plasma and CSF venglustat concentrations will be summarized as per analysis window (see Table 14) and by theoretical time (Day 1 and Week 12) using the following descriptive stats: mean, geometric mean, median, standard deviation, coefficient of variation, minimum, and maximum.

PK samples collected outside of the sampling time window or PK samples collected as unscheduled samples will be classified as “undefined concentrations”. No descriptive statistics will be performed on these concentrations. Plasma venglustat PK parameters will be determined

using noncompartmental methods (when data permits) on Day 1 and Week 12 visits and summarized using descriptive statistics mentioned above. Plasma PK parameters will be estimated and summarized under the responsibility of Pharmacokinetics, Dynamics and Metabolism (PKDM) function, Sanofi.

The PK results will be presented separately in the primary and secondary population. For the secondary population an analysis according to the weight group at baseline will also be described.

All concentration values below the lower limit of quantitation (LLOQ) will be treated as zero in all summary statistics excepted for the geometric mean and associated coefficient of variation for which they will be considered as missing.

Mean values below lower limit of quantification (LLOQ) will be reported as LLOQ in the tables and not plotted in the figures if after C_{max}. Mean calculations and their associated statistics will be generated from unrounded numbers and may differ slightly from those values that would be determined using the rounded numbers displayed in the tables.

Plasma parameters during the primary analysis period will include, but may not be limited to:

- Day 1 (single dose administration): maximum plasma concentration observed (C_{max}), and in the PK sub study when data permits, maximum plasma concentration observed (C_{max}), time to reach 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}).
- Week 12: Maximum plasma concentration observed (C_{max}), time to reach 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}). In the PK sub study if data permits the accumulation ratio at Week 12/Day 1 will be presented for C_{max} and AUC_{0-24} (individual listings and descriptive statistics).
- Week 26: C_{trough} and C_{max} (such that C_{max}: Venglustat concentration sample taken 2 to 4 hours after IMP administration and - C_{trough}: Venglustat concentration sample taken just prior to IMP administration).
- Week 52: C_{trough} and C_{max} (such that C_{max}: Venglustat concentration sample taken 2 to 4 hours after IMP administration and - C_{trough}: Venglustat concentration sample taken just prior to IMP administration).
- Week 104: C_{trough} (such that C_{trough}: Venglustat concentration sample taken just prior to IMP administration).

Cerebrospinal fluid parameters during the primary analysis period will include:

- Week 104: predose concentration.

3.7.2 Pharmacodynamic analyses

In the first step analysis for the secondary population, the pharmacodynamic endpoint correspond to the primary endpoint and is described in Section 3.2.4.

In the first step analysis for the primary population, the CSF GM2 parameter correspond to the primary and secondary endpoint. It is described in Section 3.2.1 and Section 3.3.1.2.1.

In the second step analysis for the secondary population, plasma samples for GL-1 and other biomarkers according to the disease (see Section 1.2) will be summarized on the PD population.

[redacted]

Plasma samples for GL-1, GM2 and CSF sample for GL-1 will be summarized on the pharmacodynamics primary population.

The CSF sample is only available in the primary analysis period. So, the measurement in CSF will be presented only in first step analysis.

Exploratory endpoints include percent change in:

- GL-1 from baseline to Week 104 (primary population in CSF and Plasma sample).
- GM2 from baseline to Week 104 (primary population in Plasma sample).
- GL-1 from baseline to Week 208 (primary and secondary population in Plasma sample).
- GM2 from baseline to Week 208 (primary population and secondary if applicable in Plasma sample).
- GM1 or GM3 from baseline to Week 208 (secondary population when applicable in Plasma sample).

Additional plasma and CSF biomarkers that may include lipidomics, glycoprotein nonmetastatic protein B (gpNMB) and neurofilament will be summarized on the PD primary and secondary populations if any.

Each PD variable will be summarized using descriptive statistics at each time point, including assessment of observed values, change and percent change from baseline.

3.8 INTERIM AND FINAL ANALYSIS

3.8.1 Interim analysis

No interim analysis is planned.

3.8.2 Final analysis

The final analysis will be conducted in two steps:

First step: Primary analysis period:

- The 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.

- The cut-off date for the first step analysis will be the date of the last visit of the last participant during the primary analysis period.
- The analysis of the primary analysis period of the study will include all data collected up to the Week 104 visit. Any data collected during the open-label extension treatment period will not be included in this first step analysis.
- In order to further document safety for regulatory purpose, an overview of adverse events occurring during the open-label extension, up to the cut-off date of the primary analysis period will be provided.

Second step: analysis of the open-label extension treatment period:

- The analysis of the open-label extension 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.

3.9 CHANGES TO PROTOCOL-PLANNED ANALYSES

This section summarizes major statistical changes in the protocol amendment(s).

Table 12 - Major statistical changes in protocol amendment(s)

Amendment Number	Approval Date	Changes	Rationale
01	05-Nov-2019	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.
04	20-Apr-2022	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 period.	Addition of OLE to the study.

4 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.

Sample size and power calculations were based on simulations (see Section 5.6.3 for details).

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.

5 SUPPORTING DOCUMENTATION

5.1 APPENDIX 1 LIST OF ABBREVIATIONS

25-FWT: 25-foot walk test
9-HPT: 9-hole peg test
AE: adverse event
AESI: adverse event of special interest
[redacted]
ALT: alanine transaminase
ANCOVA: analysis of covariance
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)
[redacted]
C_{max}: maximum plasma concentration observed
CRF: electronic case report form
CSF: cerebrospinal fluid
DMC: data monitoring committee
ECG: electrocardiogram
[redacted]
FARS: Friedreich's ataxia rating scale
FARS-neuro: neurological examination of FARS
FDA: Food and Drug Administration
GL-1: glucosylceramide
GM3: monosialodihexosylganglioside
HGLT: high level group term
HLT: high level term
ICF: inform consent form
IMP: investigational medicinal product
IRT: interactive response technology
IWPM: intelligible words per minute
LLOQ: lower limit of quantification
LLT: lower level term
MedDRA: Mecical Dictionary for Regulatory Activities
[redacted]
MMRM: mixed model with repeated measures
MSFC: multiple sclerosis functional composite
[redacted]
OLE: open-label extension
PCSA: potentially clinically significant abnormality
PD: pharmacodynamic
[redacted]

[redacted]

PK:	pharmacokinetic
PKDM:	pharmacokinetics dynamics and metabolism
PRO:	patient reported outcome

[redacted]

PT:	preferred term
SAE:	serious adverse event
SAP:	statistical snalysis plan
SD:	standard deviation
SOC:	system organ class
TE:	treatment-emergent
TEAE:	treatment-emergent adverse event
t_{max}:	time to reach maximum plasma concentration

[redacted]

ULOQ:	upper limit of quantification
WHO-DD:	World Health Organization-drug dictionary

5.2 APPENDIX 2 PARTICIPANT DISPOSITIONS

The number (%) of participants included in each of the analysis populations listed in Table 3 will be summarized. The reasons for exclusion from the population without trial impact (disruption) due to COVID-19 will be also summarized.

Screen failures are defined as participants who consent to participate in the study but are not subsequently randomized. The number (%) of screen failures and reasons for screen failures will be provided in the screened population.

The number (%) of participants in the following categories will be provided:

- Randomized participants.
- Randomized but not exposed participants.
- Randomized and exposed participants.
- Participants who completed the study treatment period as per protocol.
- Participants who did not complete the study treatment period as per protocol and main reason for permanent intervention discontinuation.
- Participants who completed the study period as per protocol.
- Participants who did not complete the study period as per protocol and main reason for study discontinuation.

The number (%) of exposed and not randomized participants will also be summarized.

In addition, the number (%) of participants screened, screened-failed, randomized, with permanent intervention discontinuation and with early study discontinuation will be provided by country and site.

Protocol deviations

Critical and major protocol deviations (automatic or manual) will be summarized in the randomized population as well as displayed separately according to their relation to COVID-19.

Dispostion by visit

Participant disposition by visit will be provided according to trial impact (disruption) due to COVID-19, as reported in CRF.

5.3 APPENDIX 3 DEMOGRAPHICS AND BASELINE CHARACTERISTICS, PRIOR OR CONCOMITANT MEDICATIONS

The following demographics and baseline characteristics, medical and surgical history and disease characteristics will be summarized using descriptive statistics in the randomized population.

Demographic and baseline characteristics

- Gender (Male, Female).
- Age in years (quantitative and categorical variable: Children (2-11 years), Adolescents (12-17 years), 18 to <65, 65 to<85 and ≥85 years), the two first categories are applicable only to participants in the secondary population.
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or other Pacific Island, other).
- Ethnicity (Hispanic, non-Hispanic).
- Weight in kilograms (quantitative and categorical variable: 10 to <15, 15 to <30, 30 to <50, 50 to <100, ≥100).
- Body mass index (BMI) in kg/m² (quantitative and categorical variable: <18.5, 18.5 to <25, 25 to <30, ≥30).

Randomization strata

The randomization strata is only applicable for primary population. The two categories will be presented: able to walk, unable to walk.

Disease characteristics

The time since diagnosis and time since symptom onset will be derived from the subtraction between two years: year of randomization and year of diagnosis or symptom onset. A value of zero means that diagnosis or symptom were occurred the year of randomization.

Based on the same principle, the age at diagnosis and age at symptom onset will be derived from the difference between the year of diagnosis or symptom onset and the year of birth.

Medical or surgical history

Medical (or surgical) history includes previous relevant medical and surgery history collected at baseline. Medical and surgical history will be coded to a LLT, PT, HLT, HLGT, and associated to

a primary SOC using the MedDRA version currently in effect at Sanofi at the time of database lock.

Medical/ surgical history will be summarized in each treatment arm by primary SOC and PT. Events will be sorted by SOC internationally agreed order and decreasing frequency of PT based on the incidence in the primary population.

Alcohol habits at baseline

Alcohol habits include:

- Frequency of alcoholic drinks in the last 12 months (Never/Occasional/At least monthly/At least weekly/At least daily).
- Number of standard drinks (1 or 2/Greater than 2, where standard drink means 1 pint/bottle of beer, 1 glass of wine, 1 shot of hard liquor…) per day when drinking alcohol.

Prior or concomitant medications

All medications will be coded using the World Health Organization-Drug Dictionary (WHO-DD) using the version currently in effect at Sanofi at the time of database lock:

- Prior medications are those the participant used prior to first IMP intake. Prior medications can be discontinued before first administration or can be ongoing during treatment period.
- Concomitant medications are any medications received by the participant concomitantly to the IMP during the on-treatment period.
- Post-treatment medications are those the participant took in the period running from the end of the concomitant medications period up to the end of the study.
- A given medication can be classified as a prior medication and/or as a concomitant medication and/or as post-treatment medication. If it cannot be determined whether a given medication was taken prior or concomitantly or post, it will be considered as prior, concomitant, and post-treatment medication.

The prior and concomitant medications will be summarized for the randomized and exposed population, by anatomic and therapeutic level. The summaries for prior medications will be sorted by decreasing frequency of anatomic category (ATC) based on the overall incidence across study intervention group. The summaries for concomitant medications will be sorted by decreasing frequency of ATC based on the incidence in the venglustat group of the primary population. In case of equal frequency, alphabetical order will be used.

Participants will be counted once in each ATC category (anatomic or therapeutic).

5.4 APPENDIX 4 DATA HANDLING CONVENTIONS

General conventions

The following formulas will be used for computation of parameters.

Demographic formulas

- $\text{BMI} = \frac{\text{weight(kg)}}{\text{height(m)}^{2}}$

Missing data for primary/secondary efficacy endpoints

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 in Section 3.2.2.2 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.

Age for children/adolescents participants for derivation of PCSA

For children/adolescents participants, the PCSA definition depends on the category of age. Therefore, it is necessary to derive the age during the study. For this purpose, the age during the study will be defined as the age at screening plus the time (in years) since randomization.

Analysis windows for time points

For all analyses, D1 will be defined as the reference date of the participant. For treated participant, the reference date will be the day of first IMP intake. For the other participants, randomized but not treated the reference date will be the day of randomization.

For endpoints not collected at each visit (CSF biomarkers, neurological examination), analysis by time points will be summarized using the protocol planned visits.

For other endpoints collected at multiple visits, the following analysis windows (see Table 13) will decide how the scheduled and/or unscheduled visits will be used in the by-visit analyses of efficacy data, laboratory safety data, vital signs, ophthalmological examination, patient reported outcome variables as well as PK variables.

A measurement (scheduled or unscheduled) will be used if it is available and measurement date is within the analysis window.

After applying these time windows, if multiple assessments are associated to the same time point, the value collected at the scheduled visit will be used, if any. Otherwise, the closest from the targeted study day will be used. If the difference is a tie, the value after the targeted study day will be used. For all endpoints except PK, if multiple valid values exist within a same day, then the first value of the day will be selected.

If there is no measurement for a given parameter in an analysis window, data will be considered missing for the corresponding visit. For laboratory data, only central measurements will be taken into account by default. Nevertheless, due to COVID-19 situation, in case of high number of missing central assessments by analysis window, local assessments may be taken into account.

Table 13 - Analyses window definition

Time point	Targeted study day	Analysis window in study days
Week 12	D84	D2 - D133
Week 26	D182	D134 - D273
Week 52	D364	D274 to D455
Week 78	D546	D456 to D637
Week 104	D728	D638 to D819
Week 130	D910	D820 to D1001
Week 156	D1092	D1002 to D1183
Week 182	D1274	D1184 to D1365
Week 208	D1456	D1366 to D1547

Table 14 - Analyses window definition for PK analyses

Time point	Target study day	Analysis window
Day 1/ Pre dose*	Day 1 / Pre dose	Before Day 1 dose
Day 1/ 1st Post dose*	Day 1 / 0.5 hours Post dose	20 min to 40 min after Day 1 dose
Day 1/ 2nd Post dose	Day 1 / 3 hours Post dose	2 h to 4 h after Day 1 dose
Day 1/ 3rd Post dose*	Day 1 / 8 hours Post dose	6 h 45 to 9 h 15 after Day 1 dose
Day 1/ 4th Post dose*	Day 1 / 12 hours Post dose	10 h to 14 h after Day 1 dose
Day 1/ 5th Post dose*	Day 1 / 24 hours Post dose	20 h to 28 h after Day 1 dose
Week 12/ Pre dose	Week 12 / Pre dose	Before Week 12 dose
Week 12/ 1st Post dose	Week 12 / 0.5 hours Post dose	20 min to 40 min after Week 12 dose
Week 12/ 2nd Post dose	Week 12 / 3 hours Post dose	2 h to 4 h after Week 12 dose
Week 12/ 3rd Post dose	Week 12 / 8 hours Post dose	6 h 45 to 9 h 15 after Week 12 dose
Week 12/ 4th Post dose	Week 12 / 12 hours Post dose	10 h to 14 h after Week 12 dose
Week 12/ 5th Post dose	Week 12 / 24 hours post dose	20 h to 28 h after Week 12 dose
Week 26/ Pre-dose	Week 26 / Pre-dose	Before Week 26 dose
Week 26/ Post dose	Week 26 / 3 hours post dose	2 h to 4 h after Week 26 dose

Time point	Target study day	Analysis window
Week 52 / Pre-dose	Week 52 / Pre-dose	Before Week 52 dose
Week 52/ Post dose	Week 52 / 3 hours post dose	2 h to 4 h after Week 52 dose
Week 104 / Pre-dose	Week 104 / Pre-dose	Before Week 104 dose

*Time points only applicable for participants included in PK sub-study

Unscheduled visits

Unscheduled visit measurements will be used for computation of baseline, the last on-treatment value and worst on-treatment value. For parameters summarized according to analysis time windows, unscheduled visit measurements may also be used to provide a measurement for a timepoint.

For laboratory data, vital signs and ECG analysis unscheduled visit measurements will be used to provide the analysis according to the PCSA and the shift summaries for safety.

5.5 APPENDIX 5 SCORING

5.5.1 Scoring of 9-HPT

The 9-HPT is a standardized, quantitative test of upper extremity (arm and hand) function. Both the dominant and non-dominant hands are tested twice (two consecutive trials of the dominant hand, followed immediately by two consecutive trials of the non-dominant hand). In brief, the participant is seated at a table with a small, shallow container holding the pegs and a block containing nine empty holes. On a start command when a stopwatch is started, the participant picks up the nine pegs one at a time as quickly as possible, puts them in the nine holes, and, once they are in the holes, removes them again as quickly as possible one at a time, replacing them into the shallow container. The total time to complete the task is recorded.

9-HPT will be scored according to Multiple Sclerosis Functional Composite (MSFC) instructions (2).

The two trials for each hand will be averaged, converted to the reciprocals of the mean times for each hand and then the two reciprocals will be averaged. The average of the two reciprocals will then be back-transformed in order to obtain the global 9-HPT on the original scale (in seconds).

Let D_1 and D_2 be the time to complete the 9-HPT for the dominant hand for the two trials and let ND_1 and ND_2 be the time to complete the 9-HPT for the non-dominant hand for the two trials. The overall 9-HPT is calculated as:

$$9HPT = \frac{2}{\left(\frac{2}{D_1 + D_2}\right) + \left(\frac{2}{ND_1 + ND_2}\right)}$$

In case a participant needs more than 5 minutes to complete in any trial (or was unable to complete trial due to physical limitations), the maximal time of 5 minutes (300 seconds) will be assigned.

Investigators will be reminded that missing data should be avoided. However, in case of missing data for other reason than inability to complete the test, missing data will be treated as follows:

- In case only 1 trial was done for a hand, the average of the two trials will be replaced by the time for the available trial.
- In case 9-HPT was assessed for only one hand, the overall 9-HPT will not be calculated and considered missing.

A higher value on the 9-HPT is indicative of higher disability.

5.5.2 Scoring of 25FWT

The 25FWT is a quantitative mobility and leg function performance test based on a timed 25-foot walk. 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.

The 25FWT score is defined as the average of two trials.

In case a participant needs more than 3 minutes to complete a single trial (or was unable to complete trial due to physical limitations), the maximal time of 3 minutes (180 seconds) will be assigned.

Investigators will be reminded that missing data should be avoided. However, in case only 1 trial was done for other reason than inability to complete the test, the average of the two trials will be replaced by the time for the available trial.

A higher value on the 25FWT is indicative of higher disability.

5.5.3 Scoring of FARS

The FARS-neuro includes 23 items, each item being scored as shown in Table 15. Increments of 0.5 may be used if examiner feels an item falls between 2 defined severities).

The FARS-neuro is a PerfRO, composed of 4 sections that assess different neurological faculties: bulbar activity (4 items), upper limb coordination (5 items assessed right and left side), lower limb coordination (2 items assessed right and left side), peripheral nervous system (5 items assessed right and left side) and upright stability (7 items).

The FARS-neuro is defined as the sum of the different items. The total score varies from 0 to 117. A higher value is indicative of higher disability.

Table 15 - Scoring of neurological examination of the FARS (FARS-neuro)

Section	Item	Range of score
Bulbar	Facial Atrophy, Fasciculation, Action Myoclonus, and Weakness	0-3
	Tongue Atrophy, Fasciculation, Action Myoclonus and Weakness	0-3
	Cough	0-2
	Spontaneous Speech	0-3
Upper limb coordination	Finger to Finger Test – Right and left side	0-3
	Nose-Finger Test - Right and left side	0-4
	Dysmetria - Right and left side	0-4
	Rapid Alternating Movements of Hands – Right and left side	0-3
	Finger Taps - Right and left side	0-4
Lower limb coordination	Heel Along Shin Slide - Right and left side	0-4
	Heel-to-Shin Tap – Right and left side	0-4
Peripheral nervous system	Muscle Atrophy – Right and left side	0-2
	Muscle Weakness – Right and left side	0-5
	Vibratory Sense - Right and left side	0-2
	Position Sense - Right and left side	0-2
	DTR – Right and left side	0-2
Upright stability	Sitting Posture	0-4
	Stance feet apart	0-4
	Stance - Feet Together	0-4
	Tandem Stance	0-4
	Stance on Dominant Foot	0-4
	Tandem Walk	0-3
	Gait	0-5

The activities of daily living score of the FARS includes 9 items, each item being scored as shown in Table 16. Increments of 0.5 may be used if examiner feels an item falls between 2 defined severities).

The activities of daily living score of the FARS is defined as the sum of the different items. The total score varies from 0 to 36. A higher value is indicative of higher disability.

Table 16 - Scoring of activities of daily living of the FARS

Section	Item	Range of score
Activities of daily living	Speech	0-4
	Swallowing	0-4
	Cutting Food and Handling Utensils	0-4
	Dressing	0-4
	Personal Hygiene	0-4
	Falling	0-4

Section	Item	Range of score
	Walking	0-4
	Quality of Sitting Position	0-4
	Bladder Function	0-4

For each section, the score is calculated as the sum of the scores on the items of the section. In case up to 25% of items are missing, a prorated score will be calculated, defined as:

$$\text{Score} = \text{Sum of scores of non-missing items} \times \frac{\text{Maximal score if no item is missing}}{\text{Sum of maximum scores of non-missing items}}$$

Maximal number of allowable missing items and maximal score if no item is missing for each section is presented in Table 17.

Table 17 - Maximal number of allowable missing items to calculate FARS scores

Section	Number of items	Maximal number of allowable missing items to calculate score	Maximal score if no item is missing
I. Functional staging of ataxia	1	0	6
II. Activities of daily living	9	2	36
III. Neurological examination			
A. Bulbar	4	1	11
B. Upper limb coordination	10	2	36
C. Lower limb coordination	4	1	16
D. Peripheral nervous system	10	2	26
E. Upright stability	7	1	28
Total neurological examination	35	8	117

5.5.4 [redacted]

[redacted]

[redacted]

[redacted]

5.5.5 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.5.6 [redacted]

[redacted]

Table 18 - [redacted]

[redacted]

Table 19 - [redacted]

[redacted]

5.6 APPENDIX 6 STATISTICAL TECHNICAL DETAILS

5.6.1 Criteria for using robust ANCOVA

The procedure to detect outliers will be based on the robust regression with Huber M estimation. The procedure will slightly differ for CSF GM2 (with a single measurement) and for 9-HPT, 25FWT and FARS-neuro (with repeated measurements, analyzed using a slope analysis).

5.6.1.1 Criterion for CSF GM2

Potential outliers will be identified from the standardized residuals, estimated from a robust ANCOVA of percent change in CSF GM2 from baseline to Week 104, with treatment effect (venglustat versus. placebo) as factor and the continuous fixed covariate of baseline value.

The robust ANCOVA will be used as primary analysis for the percent change in CSF GM2 [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

5.6.1.2 Criteria for 9-HPT, 25FWT and FARS-neuro

Potential outliers will be identified from the weighted standardized residuals, estimated from a robust ANCOVA on individual slopes, with treatment effect (venglustat versus placebo) as factor and the continuous fixed covariate of baseline value.

The robust ANCOVA will be used as primary analysis for the slope analysis [redacted]

[redacted]

[redacted]

[redacted]

- [redacted]
- [redacted].

5.6.2 Confidence interval for the difference in annualized rate of change in 9-HPT

The estimated difference in annualized rate of change in 9-HPT is defined as:

$$\hat{\delta} = \exp\left(\widehat{\beta_1}\right) - \exp\left(\widehat{\beta_0}\right)$$

where $\widehat{\beta_1}$ and $\widehat{\beta_0}$ are the estimated slopes of log-transformed 9-HPT, for the venglustat and placebo arm respectively.

Using the properties of the log-normal distribution, it can be shown that $\exp\left(\widehat{\beta_i}\right)$ have mean and variance m_i and v_i respectively, equal to:

$$m_i = \exp\left(\widehat{\beta_i} + \frac{Var\left(\widehat{\beta_i}\right)}{2}\right)$$

$$v_i = \left(exp\left(Var\left(\widehat{\beta_i}\right)\right) - 1\right) \times \exp\left(\widehat{2\beta_i} + Var\left(\widehat{\beta_i}\right)\right)$$

The 90% confidence interval of the difference in annualized rate of change in 9-HPT can be calculated as:

$$m_1 - m_0 \pm z_{0.95} \times \sqrt{v_1 + v_0}$$

where $z_{0.95}$ is the 95th quantile of the normal distribution.

5.6.3 Simulations

5.6.3.1 Method

[redacted]

5.6.3.2 Results of simulations

[redacted]

Table 20 - Power: Probability of detecting a difference in slopes under the hypothesis δ =-0.0374

Table 21 - Type I error: Probability of detecting a difference in slopes under the hypothesis δ =0

Table 22 - Root mean squared error (rMSE) for the estimated difference in slopes

Table 23 - Hybrid approach: probability of using the robust ANCOVA, under the different scenarios

5.6.3.3 SAS code used to conduct the simulations

```
/************************************************/
/* STEP 1 : Definition of simulation parameters */
/************************************************/

* Number of simulations;
%let Nsim = 10;

* Total number of patients on venglustat and placebo;
%let NpatV = 38;
%let NpatP = 19;

* List of time-points (in years) ;
%let listtime = 0,0.25,0.50,1,1.50,2.0;

* Seed of simulations ;
%let seed = 15299;

* Drop out rate (at time tdrop) ;
%let rdrop = 0.1;
```

```
%let tdrop = 2;

* Mean and SD of intercept ;
%let mI = 3.5551;
%let sdI = 0.4841;

* Mean slopes on Placebo ;
%let mS_P = 0.0273;

* SD of random slopes (between subject SD) ;
%let sdS = 0.0192;

* SD of residual error (within subject SD) ;
%let sdR = 0.0791;

* Scenarios for the difference in slope (list separated by commas);
%let diff = -0.0374,0;

* Number of scenarios for extreme values;
%let Nsce = 10;

* Base scenario (protocol assumption, no extreme patient ;
%let pE1 = 0;
%let mE1 = 0;
%let sE1 = 1;

* Scenario with 1% extreme patients having mean slope = 0.4;
%let pE2 = 0.01;
%let mE2 = 0.4;
%let sE2 = 0.0192;

* Scenario with 1% extreme patients having mean slope = 0.7;
%let pE3 = 0.01;
%let mE3 = 0.7;
%let sE3 = 0.0192;

* Scenario with 1% extreme patients having mean slope = 0.9;
%let pE4 = 0.01;
%let mE4 = 0.9;
%let sE4 = 0.0192;

* Scenario with 2% extreme patients having mean slope = 0.4;
%let pE5 = 0.02;
%let mE5 = 0.4;
%let sE5 = 0.0192;

* Scenario with 2% extreme patients having mean slope = 0.7;
%let pE6 = 0.02;
%let mE6 = 0.7;
%let sE6 = 0.0192;

* Scenario with 2% patients having mean slope = 0.9;
%let pE7 = 0.02;
%let mE7 = 0.9;
%let sE7 = 0.0192;
```

```
* Scenario with 5% extreme patients having mean slope = 0.4;
%let pE8 = 0.05;
%let mE8 = 0.4;
%let sE8 = 0.0192;

* Scenario with 5% extreme patients having mean slope = 0.7;
%let pE9 = 0.05;
%let mE9 = 0.7;
%let sE9 = 0.0192;

* Scenario with 5% extreme patients having mean slope = 0.9;
%let pE10 = 0.05;
%let mE10 = 0.9;
%let sE10 = 0.0192;
/*********************************************************************/
/* STEP 2 : Simulation of clinical trial data under different scenarios */
/*********************************************************************/

/* Simulation of clinical trial data */
data SimData(keep=diff sce pE mE sE sim subject group base time log9hpt);
  length diff sce pE mE sE sim subject group base time log9hpt 8;

  retain seed &seed;

  * Assess different scenarios for difference and extreme patients ;
  do diff = &diff;
  do sce = 1 to &Nsce;

    * Get proportion of extreme patients in the current scenario ;
    pE = input(symget("pE"||compress(put(sce,best.))),best.);

    * Get mean slope of placebo for extreme patients in the current scenario ;
    mE = input(symget("mE"||compress(put(sce,best.))),best.);

    * Get SD of slope for extreme patients in the current scenario ;
    sE = input(symget("sE"||compress(put(sce,best.))),best.);

    * Generate simulated clinical trial data for the current scenario;
    do sim=1 to &Nsim;
    do subject = 1 to &NpatV+&NpatP;

      * Assign patients to venglustat or placebo arm ;
      if subject <= &NpatV then group = 1;
      else group = 0;

      * Randomly determine if patient is normal or extreme, and determine mean
and SD of slope of this patient ;
      call ranuni(seed,u);
      if u > pE then do; mS = &ms_P + group*diff; sdS = &sdS; end;
      if u < pE then do; mS = mE + group*diff; sdS = sE; end;

      * Simulate time to dropout (assuming exponential time to drop-out and
rate at time &tdrop is &rdrop) ;
      call ranuni(seed,x);
      tdrop = log(x)*&tdrop/log(1-&rdrop);
```

```
      * Generate a random intercept for the current patient ;
      call rannor(seed,int);
      int = &mI + int*&sdI;

      * Generate a random slope for the current patient ;
      call rannor(seed,slope);
      slope = mS + slope*sdS;

      * Create observations at each time-point ;
      do time=&listtime;

        * Generate a residual error for the current observation ;
        call rannor(seed,e);
        e = &sdR*e;

        * Generate a log(9-HPT) measurement at the given time-point ;
        log9hpt = int + slope*time + e;

        * Baseline value;
        if time = 0 then base = log9hpt;

        * Keep only observations before patient drops out ;
        if time<tdrop then output;
      end;

    end;
    end;

  end;
  end;
run;


/* Calculate number observations per subject */
proc means data=SimData noprint nway;
  class diff sce pE mE sE sim subject;
  var log9hpt;
  output out=nobs(keep=diff sce pE mE sE sim subject nobs) n=nobs;
run;
data Simdata;
  merge simdata nobs;
  by diff sce pE mE sE sim subject;
run;

/* Calculate individual slopes (for patients with at least 2 observations) */
ods listing close;
options nonotes;
proc mixed data=SimData;
  where nobs >= 2;
  by diff sce pE mE sE sim subject group base;
  model log9hpt = time / s;
      ods output solutionF=indSlope(where=(effect="time")
rename=(estimate=slope));
run;
ods listing;
options notes;
```

```
/* Calculate weights and standardize them (so that mean weight = 1 and sum of
weights = n) */
proc means data=SimData noprint nway;
  where nobs >= 2;
  class diff sce pE mE sE sim subject group base;
  var time;
  output out=css(keep=diff sce pE mE sE sim subject group base css) css=css;
run;
proc means data=css noprint nway;
  class diff sce pE mE sE sim;
  var css;
  output out=meancss(keep=diff sce pE mE sE sim meancss) mean=meancss;
run;
data weight;
  merge css meancss;
  by diff sce pE mE sE sim;
  W = css/meancss;
run;


/* Include weights in the simulation dataset */
data indSlope;
  merge indSlope(keep=diff sce pE mE sE sim subject group base slope)
weight(keep=diff sce pE mE sE sim subject group base w);
  by diff sce pE mE sE sim subject group base;
run;

/* Create observations from both groups, with baseline = mean baseline   */
/* In order to obtain predicted mean slope from the PROC ROBUSTREG       */
/* (this is because PROC ROBUSTREG has no LSMEANS or ESTIMATE statement) */
proc means data=simdata noprint nway;
  where time = 0;
  class diff sce pE mE sE sim;
  var base;
  output out=meanbase(keep=diff sce pE mE sE sim base) mean=base;
run;
data pred;
  set meanbase;
  subject = 99.1; group = 0; W=1; output;
  subject = 99.2; group = 1; W=1; output;
run;

/* Include additional observations in the dataset for PROC ROBUSTREG */
data dataRobust;
  set indSlope pred;
run;
proc sort data=dataRobust;
  by diff sce pE mE sE sim subject;
run;

/*****************************************************************/
/* STEP 3 : Analysis of simulated data with linear mixed-effect model */
/*****************************************************************/

ods listing close;
```

```
options nonotes;

/* Linear mixed-effect model */
proc mixed data=SimData;
  by diff sce pE mE sE sim;
  class subject group;
  model log9hpt = group time group*time;
  random int time / sub=subject type=un;
  estimate "Diff" int 0 group 0 0 time 0 group*time -1 1 / cl;
  ods output estimates=LMMestimates;
run;

ods listing;
options notes;

/* Get estimate of difference of slopes and calculate 1-sided p-value */
data LMM;
  set LMMestimates;
  LMMPvalue1S = probt(estimate/stderr,DF);
  keep diff sce pE mE sE sim estimate stderr lower upper LMMPvalue1S;
  rename estimate = LMMEst
         stderr   = LMMSE
         lower    = LMMLower
         upper    = LMMUpper;
run;

/*********************************************************/
/* STEP 4 : Analysis of simulated data with robust ANCOVA */
/*********************************************************/

ods listing close;
options nonotes;

proc robustreg data=dataRobust order=data method=M(maxiter=100000);
  by diff sce pE mE sE sim;
  class group;
  id subject;
  model slope = group base;
  weight w;
  ods output ParameterEstimates=RobustParameterEstimates;
  output out=RobustPred predicted=pred stdp=SE sr=stdres;
run;

ods listing;
options notes;

/* Get estimate of difference of slopes and calculate 1-sided p-value */
data Robust;
  set RobustParameterEstimates;
  where parameter = "group" and Level1 = "1";
  RobustPvalue1S = probnorm(estimate/stderr);
  keep diff sce pE mE sE sim estimate stderr lowerCL upperCL RobustPvalue1S;
  rename estimate = RobustEst
         stderr   = RobustSE
         lowerCL  = RobustLower
         upperCL  = RobustUpper;
```

```
run;

/* Calculate number of patients with weighted standardized residual greater
than 3 and greater than 4 */
data outlier;
  set RobustPred;
  where subject notin (99.1,99.2);
  outlier3 = (abs(W*stdres) > 3);
  outlier4 = (abs(W*stdres) > 4);
run;
proc means data=outlier noprint nway;
  class diff sce pE mE sE sim;
  var outlier3 outlier4;
  output out=Noutlier(keep=diff sce pE mE sE sim nOutlier3 nOutlier4)
sum=nOutlier3 nOutlier4;
run;

/*********************************************************/
/* STEP 5 : Combine results and report simulation results */
/*********************************************************/

/* Combine results from the linear mixed model and from robust ANCOVA */
data AllResults;
  merge LMM Robust Noutlier;
  by diff sce pE mE sE sim;

  * Hybrid approach: use robust ANCOVA if at least one patient with
standardized residual > 4 or at least 2 patients with standardized residual >
3;
  *                  otherwise, use linear mixed-effect model ;
  if nOutlier4 >= 1 or nOutlier3 >= 2 then do;
    Robust         = 1;
    HybridEst      = RobustEst;
    HybridSE       = RobustSE;
    HybridLower    = RobustLower;
    HybridUpper    = RobustUpper;
    HybridPvalue1S = RobustPvalue1S;
  end;
  else do;
    Robust         = 0;
    HybridEst      = LMMEst;
    HybridSE       = LMMSE;
    HybridLower    = LMMLower;
    HybridUpper    = LMMUpper;
    HybridPvalue1S = LMMPvalue1S;
  end;

  * Determine if significant at 0.05 one-sided level ;
  LMMSign     = (LMMPvalue1S < 0.05);
  RobustSign  = (RobustPvalue1S < 0.05);
  HybridSign  = (HybridPvalue1S < 0.05);

  * Coverage of 95% confidence interval ;
  LMMCover     = (LMMLower < diff < LMMUpper);
  RobustCover  = (RobustLower < diff < RobustUpper);
  HybridCover  = (HybridLower < diff < HybridUpper);
```

```
  * Bias in difference ;
  LMMBias    = LMMEst - diff;
  RobustBias = RobustEst - diff;
  HybridBias = HybridEst - diff;

  * Squared Error ;
  LMMBias2    = LMMBias**2;
  RobustBias2 = RobustBias**2;
  HybridBias2 = HybridBias**2;

run;

/* Calculate simulation results */
proc means data=AllResults noprint nway;
  class diff sce pE mE sE;
  var Robust LMMSign RobustSign HybridSign LMMCover RobustCover HybridCover
LMMBias RobustBias HybridBias LMMBias2 RobustBias2 HybridBias2;
  output out=SimResults(keep=diff sce pE mE sE pRobust LMMpSign RobustpSign
HybridpSign LMMpCover RobustpCover HybridpCover LMMMeanBias RobustMeanBias
HybridMeanBias LMMMSE RobustMSE HybridMSE LMMRatepCover RobustRatepCover
HybridRatepCover)
          mean=pRobust LMMpSign RobustpSign HybridpSign LMMpCover RobustpCover
HybridpCover LMMMeanBias RobustMeanBias HybridMeanBias LMMMSE RobustMSE
HybridMSE;
run;

/* Prepare dataset for reporting */
data SimResults;
  set SimResults;
  by diff sce pE mE sE;
  retain num 0;
  if first.diff then num = 0;
  if pE ne lag(pE) then num = num + 1;

  if pE = 0 then mE = .;

  * Calculate root MSE ;
  LMMRMSE    = sqrt(LMMMSE);
  RobustRMSE = sqrt(RobustMSE);
  HybridRMSE = sqrt(HybridMSE);

run;

/* Report simulation results */
option ps=250 ls=250;

title "Results of simulation, based on &Nsim simulations";

proc report data=SimResults headline headskip nowd split = "@" formchar(2)="-
";
  column diff num ("Scenario" "---" pE mE)
         ("Probability of significant@difference of slopes" "---" LMMpSign
RobustpSign HybridpSign)
         ("Coverage of 95% CI@of difference of slopes" "---" LMMpCover
RobustpCover HybridpCover)
```

```
         ("Mean bias in@ difference of slopes" "---" LMMMeanBias
RobustMeanBias HybridMeanBias)
         ("Root mean squared error in@difference of slopes" "---" LMMRMSE
RobustRMSE HybridRMSE)
         pRobust
         ;

  define diff           / "Difference"     group center width=10 f=7.4
order=data;
  define num            / group noprint;
  define pE             / "Proportion of extreme patients" display center
width=18 f=percent8.0;
  define mE             / "Mean slope in extreme patients" display center
width=18 f=4.1;
  define LMMpSign       / "LMM"    display center width=8 f=percent8.1;
  define RobustpSign    / "Robust" display center width=8 f=percent8.1;
  define HybridpSign    / "Hybrid" display center width=8 f=percent8.1;
  define LMMpCover      / "LMM"    display center width=8 f=percent8.1;
  define RobustpCover   / "Robust" display center width=8 f=percent8.1;
  define HybridpCover   / "Hybrid" display center width=8 f=percent8.1;
  define LMMMeanBias    / "LMM"    display center width=8 f=8.5;
  define RobustMeanBias / "Robust" display center width=8 f=8.5;
  define HybridMeanBias / "Hybrid" display center width=8 f=8.5;
  define LMMRMSE        / "LMM"    display center width=8 f=8.4;
  define RobustRMSE     / "Robust" display center width=8 f=8.4;
  define HybridRMSE     / "Hybrid" display center width=8 f=8.4;
  define pRobust        / "Probability@of using@robust ANCOVA" display center
width=15 f=percent8.1;

  break after diff / skip;
  break after num / skip;

run;
```

5.7 APPENDIX 7 NATURAL HISTORY DATA

Sanofi Genzyme has collected 5 years of data on an annual basis in an observational study of patients with late-onset TSD or SD who attended the annual NTSAD family conference from 2015 to 2019. Patients were recruited by NTSAD for participation in the study. Consent was requested for the interview, to allow audio recording of the interview, to undergo neurological assessments (patients only), to permit audio recording and/or video recording of some neurological assessments, and to enable data-maintenance and transfer to proceed as designed. Participants were asked to sign a hardcopy version of the informed consent form at the conference. All participants were offered the opportunity to review the consent form with an investigator to review study-related questions.

A total of 23 patients participated in the study. Table 24 provides an overview of patients who participated in this study.

Table 24 - Patients who attended the NTSAD conferences

Patient ID	Gender	Age	Diagnosis	2015	2016	2017	2018	2019
1	F	41	LOTS	Yes	Yes	Yes	Yes	Yes
4	M	24	LOTS	Yes	Yes	No	Yes	No
5	F	25	LOTS	Yes	No	No	No	Yes
6	F	56	LOTS	Yes	Yes	No	Yes	Yes
7	F	60	Sandhoff	Yes	Yes	Yes	Yes	Yes
8	M	49	Sandhoff	Yes	Yes	Yes	Yes	Yes
9	M	62	LOTS	Yes	Yes	No	Yes	Yes
10	M	56	LOTS	Yes	No	No	No	No
11	F	35	LOTS	Yes	Yes	Yes	Yes	No
12	M	51	LOTS	Yes	Yes	Yes	Yes	Yes
13	M	68	LOTS	Yes	No	No	No	No
14	M	36	LOTS	Yes	Yes	No	Yes	Yes
15	M	41	LOTS	No	Yes	Yes	Yes	Yes
16	M	33	LOTS	No	Yes	Yes	No	Yes
17	F	41	Sandhoff	No	Yes	Yes	Yes	Yes
18	M	47	LOTS	No	Yes	No	Yes	No
19	M	47	LOTS	No	Yes	No	Yes	No
20	M	55	Sandhoff	No	Yes	Yes	Yes	Yes
21	M	42	LOTS	No	No	Yes	No	No
22	M	50	LOTS	No	No	Yes	Yes	Yes
23	M	46	LOTS	No	No	Yes	Yes	Yes
24	F	40	LOTS	No	No	No	Yes	Yes
25	F	53	LOTS	No	No	No	Yes	No

LOTS = late onset Tay-Sachs, NTSAD = National Tay-Sachs and Allied Diseases.

This database allowed Sanofi Genzyme to prospectively assess the natural rate of change of the co-primary endpoint of the 9-HPT. Table 25 provides a summary of number of assessments available and the rate of change in this endpoint. Individual data are presented in Table 26.

It is to be noted that data from 2019 were not available when the initial protocol and sample size were determined. In addition, some data from 2015-2018 were corrected. [redacted]

No assessment was conducted in 2020.

Table 25 - Annualized change in 9-HPT in natural history study (NTSAD) from 2015 to 2019

	9-HPT
Number of patients with	
Baseline and ≥1 post-baseline assessment	16
Baseline and ≥2 post-baseline assessments	13
Baseline and ≥3 post-baseline assessments	10
Baseline and ≥4 post-baseline assessments	4
≥1-year follow-up	16
≥2-year follow-up	15
≥3-year follow-up	13
≥4-year follow-up	7
Slope of log(9-HPT)	
Estimate (SE)	0.0264 (0.0118)
Annualized rate of change of 9-HPT	
Estimate	2.68% per year
95% CI	(0.13% to 5.29%)

Note: Analysis including patients with a baseline and at least one post-baseline assessment.
Note: Patients with baseline value >240 seconds were excluded from the analysis, since such patients would not be eligible for participation in EFC15299 study.
Note: Annualized rate of change was estimated from a linear mixed-effect model with random intercept and slope.
A log-transformation was applied prior to analysis, and slope on the log scale was back-transformed to express rate of change as percentage change from baseline.
Average of dominant and non-dominant hand was calculated as the mean of reciprocal of dominant and non-dominant hand, then the inverse of mean was calculated.

Table 26 - Individual listing of 9-HPT in natural history study (NTSAD) from 2015 to 2019

Patient ID	Gender	Age	Diagnosis	9-HPT (sec)				
				2015	2016	2017	2018	2019
1	F	41	LOTS	37.59	41.99	50.32	49.51	54.60
4	M	24	LOTS	41.00	42.75	.	45.05	.
5	F	25	LOTS	29.31	.	.	.	41.92
6	F	56	LOTS	23.50	24.91	.	23.99	26.82
7	F	60	Sandhoff	27.64	38.62	37.23	37.04	38.12
8	M	49	Sandhoff	23.22	22.89	24.43	23.60	25.49
9	M	62	LOTS	196.39	300.00	.	300.00	300.00
10	M	56	LOTS	42.79	.	.	.	.
11	F	35	LOTS	25.63	29.47	27.91	25.97	.
12	M	51	LOTS	24.12	27.41	26.40	27.36	25.29
13	M	68	LOTS	39.06	.	.	.	.
14	M	36	LOTS	300.00	300.00	.	300.00	300.00
15	M	41	LOTS	.	34.98	33.73	34.73	29.07
16	M	33	LOTS	.	25.49	28.95	.	25.11
17	F	41	Sandhoff	.	22.69	20.25	21.57	19.64
18	M	47	LOTS	.	.	.	121.47	.
19	M	47	LOTS	.	141.71	.	131.12	.
20	M	55	Sandhoff	.	28.80	34.43	30.97	28.35
21	M	42	LOTS	.	.	49.58	.	.

Patient ID	Gender	Age	Diagnosis	9-HPT (sec)				
				2015	2016	2017	2018	2019
22	M	50	LOTS	.	.	31.95	26.82	32.05
23	M	46	LOTS	.	.	.	.	.
24	F	40	LOTS	.	.	.	33.40	33.29
25	F	53	LOTS	.	.	.	45.59	.

F = Female, M = Male, LOTS = Late-onset Tay-Sachs.

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