A Safety and Efficacy Study in Late Onset Tay-Sachs Disease with a Separate Arm for Ultra-Rare Diseases in the Same Pathway, Including GM2 Gangliosidosis

Study Overview:

This is a study to evaluate the efficacy (effectiveness) and safety of a drug called venglustat in adult participants with late-onset GM2 gangliosidosis (late-onset Tay-Sachs disease and Sandhoff disease). This group of participants are referred to as the "primary" population.

The study may include participants with juvenile onset GM2 gangliosidosis and ultra-rare conditions within the same biochemical pathway as the primary population. This arm of the study is referred to as the "secondary" population.

Study Medication:

Venglustat is in a class of drugs called "GCS inhibitors". These drugs inhibit or block the production of GL-1, which is necessary for production of GM2. This study is looking at whether venglustat can decrease the production of GM2 in the nervous system and possibly slow down or stop disease progression and improve pre-existent problems.

Venglustat is a tablet given by mouth once daily.

What is the Aim of This Study?

The purpose of this study is to determine whether the study medication is safe and effective in decreasing or improving the neurologic and motor symptoms as well as slow or stop progression in participants with late-onset Tay-Sachs Disease or in juvenile GM2 gangliosidosis.

The study will also look at how well the study medication is tolerated and what changes in symptoms of the participant's disease (e.g., Tay-Sachs disease or other GM2 gangliosidosis) are experienced during the study.

Study Design:

The study will last approximately 2 years and is planned to include about 57 participants from approximately 14 countries.

The study will be divided into 3 periods:

Screening Period: Screening period is the period for determining whether a participant meets all the eligibility requirements for the study. It consists of various tests and may be done up to 2 months before the participant enters the Treatment Period.

Treatment Period: Treatment Period is the period from the start of study drug administration (e.g., venglustat or placebo) until the end of the study. For this study, the Treatment Period is two years in length.

Post-treatment Safety Observation Period, 6-week follow-up period: The post-treatment safety observation period will be for 6 weeks after the Treatment Period ends.

Participants who are eligible for the adult study will be randomly assigned (like the flip of a coin) to receive either venglustat or placebo once daily for 2 years. The ratio of patients who receive venglustat versus those who receive placebo with be 2:1 (i.e., twice as many participants will receive venglustat). This is a double-blind study, meaning neither the participant nor the study doctor will know what treatment the participant is receiving.

Participants in the juvenile arm (secondary population) will receive venglustat for 2 years in an open-label design, meaning there is no placebo and all participants will receive venglustat.

At the end of the study, all participants may be given the option to enroll in a **long-term safety (LTS)** follow-up study to assess safety and tolerability of the study medication over a longer period of time. Study participants who receive placebo may have the option to receive study medication after the 2-year Treatment Period.

Timing for Secondary Study

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. Exact timing of start will be dependent on timing of enrollment of the first 5 participants of the primary population.

Summary of Study Visits & Procedures

Phase/Procedure	Screening	Baseline/ start study drug	Treatment Period							Follow-up Period
Week (a window of ±7 days is allowed for all visits after screening)	**W-8 to D-1**	**D1**	**W12**	**W26**	**W39**	**W52**	**W65**	**W78**	**End of Study Visit W104**	**Follow-up Visit (W110)**
Visit at clinical site	X	X	X	X	X	X	X	X	X	X
Study treatment administration										
Study medication/placebo dispensed (by mouth)		X	X	X	X	X	X	X		
Safety										
Physical examination, vital signs, temperature, body weight	X	X	X	X		X		X	X	X
Electrocardiogram	X	X							X	
Blood and urine sampling	X	X	X	X		X		X	X	X
Neurologic & Opthalmological Exams	X								X	
Lumbar Puncture	X								X	
Efficacy										
Motor/Functional Assessments	X	X	X	X		X		X	X	
Pharmacokinetics and Pharmacodynamics										
Blood sample for study medication pharmacokinetic and pharmacodynamics		X (3 hours after dose)	X pre-dose and 0.5, 3, 8, 12, and 24 hrs after dose)	X (pre-dose and 3 hours after dose)		X (pre-dose and 3 hours after dose)			X (pre-dose)	X (any time)
Genetic tests										
Blood sample for Biomarkers		X	X	X		X		X	X	

Main Inclusion/Exclusion Criteria:

Inclusion Criteria:

- For the adult study (primary population), the participant may be male or female and at least 18 years of age with a diagnosis of late-onset GM2 gangliosidosis (Tay-Sachs disease and Sandhoff disease).
- For the juvenile and ultra-rare arm of the study, (secondary population) participants must be at least 2 years of age and not older than 18 years of age at the time of informed consent and must have a diagnosis of juvenile GM2 gangliosidosis; or juvenile or adult GM1 gangliosidosis, Saposin C deficiency, Sialidosis type 1, or galactosialidosis.
- The participant is able to understand and perform study assessments and is able to comply with all aspects of the study.
- If the participant has a history of seizures, they must be well-controlled under appropriate medication.
- For the juvenile and adolescent study, participants must have body weight ≥10 kg (22 lbs.) at the time of signing the informed consent.

Exclusion Criteria:

- Participant has clinical features of Tay-Sachs or Sandhoff disease, but a completely negative result on a genetic test for GM2 gangliosidosis (primary population only).
- Any significant illness that could make it too difficult or unsafe for participation in the study
- A documented diagnosis of any of the following infections: hepatitis B, hepatitis C, human immunodeficiency virus 1 or 2.
- Significantly elevated liver enzymes or renal failure
- The participant has a cataract known either as a Grade cortical cataract-2 or a Grade posterior subcapsular cataract-2.
- Receiving current treatment with anticoagulants (e.g., coumadin, heparin).

Frequently Asked Questions:

What are Clinical Research Studies?

- Clinical research studies are used to find out whether an experimental medication works and is safe
- They involve healthy human volunteers or patients with an illness to answer specific health questions
- Clinical trials are conducted according to a protocol that describes the tests and procedures, how the study drug will be given, the length of the study and how the outcome of the study will be assessed and measured
- Each person participating in the study must voluntarily agree to be in the study and follow the instructions of the study doctor. They are free to withdraw from the study at any time
- Independent committees made up of medical and nonmedical people also watch over clinical trials to make sure the people who join are told everything they need to know and are protected

Why is a placebo being used in the primary population but is not required for the secondary population?
Placebo is required by Health Authorities (such as the FDA) to demonstrate the study medication is more effective than no treatment in improving the symptoms of the disease. However, this is not the case when participant numbers are very small, as is expected in the secondary arm of the study. Requiring a placebo in a very small number of participants will not affect the measurement of potential response to the study drug versus placebo. Therefore, it is not being required by Health Authorities.

What will happen at the end of this study?
Depending on the results of the study, all participants may be given the option to enroll in a **long-term safety (LTS)** study to assess safety and tolerability of the study medication over a longer time period.

Do I have to pay for any of the tests or procedures while I'm in the study?
No. All tests and procedures associated with the study are at no charge to the participant.

Do I have to have health insurance to participate?
No. You do not have to have health insurance to participate in this study.

Will I be paid to participate in the study?
You will not be paid for participation. However, the Sponsor will pay for visits, medical care and treatments other than those of your regular medical care. Transportation and accommodation can also be reimbursed. The study team will discuss this in more detail at your first visit when you review the informed consent document

Will my travel to and from the study site be covered, including hotel, meals and transportation?
Yes. Again, the study doctor or their team will discuss travel assistance.

How long will the clinical trial last? And how many times do I need to travel back?
This trial will last two years, with participants given the option to enter a long-term safety study (LTS). All participants in the LTS will receive venglustat. You will make about ten visits to the study site during the two years.

Frequently Asked Questions (cont.):

Can I talk about it on Facebook to let people know what I'm doing?
Because sharing your experience while you're on the study medication (e.g., side effects, whether you think the study medication is working, etc.) can potentially affect another participant's experience, we ask that you refrain from posting about your experience on any type of social media or even speaking with other participants about the study.

Will I qualify if I was in another clinical trial? If so, how long do I need to be off the previous medication before I can participate?
Yes. It must be at least 30 days between trials, depending on what drug you received in the previous trial.

Is this clinical trial part of why I was participating in the assessments at the conferences?
No. This trial is not associated with the assessments conducted at the conferences.

Is there an expanded access program for this drug?
We understand that many patients and their families may have an interest in accessing venglustat. It is important to understand that venglustat is still in the early stages of development. After carefully considering the limited available data (including extremely limited safety and efficacy data in patients with CNS indications at this time) and weighing the risks and benefits, the decision has been made that at this time it is too early to allow expanded access to venglustat. As you know, further systematic study of safety and efficacy, in a controlled manner, must take place before allowing access outside of clinical trials. We can assure you that as the trials progress and we have more information and a better understanding of the safety profile and efficacy of the drug, we will continually reassess the options for expanded access as well as the possibility of studying venglustat in patients with DLB and a GBA stop-gain mutation. More info on compassionate use at Sanofi is available here: **http://en.sanofi.com/Innovation/clinical-trials-and-results/compassionate-use-expanded-access/compassionate-use-expanded-access.aspx.**