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ORIGINAL RESEARCH

Qualitative Study of the Patient Experience with Venglustat for Gaucher Disease Type 3 in a Phase 2 Open-Label, Multicenter, Multinational Study (LEAP)

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ABSTRACT

Introduction: Gaucher disease type 3 (GD3) is a genetic, progressive lysosomal storage disorder characterized by visceral manifestations and chronic neurologic symptoms (e.g., horizontal ophthalmoplegia/supranuclear gaze palsy, ataxia, dystonia). The investigational agent venglustat is being studied in combination with imiglucerase as potential treatment for systemic and neuronopathic manifestations of GD3 in a single-arm, open-label, phase 2 trial (LEAP; $N=11$). To understand perceived changes in GD3 symptoms from the perspectives of patients, caregivers, and clinicians, we conducted a qualitative case study of selected LEAP participants.

Methods: Four patients in LEAP (age range, 20–28 years), four of their caregivers, and three clinicians involved in LEAP were interviewed individually by moderators using semi-structured guides. Clinicians' perceptions were based on observation of interviewed patients and those in LEAP who were not interviewed, as well as information provided by other staff involved in LEAP, patients, and caregivers.

Results: Reported changes in GD3 symptoms varied among patients and among reporters. Only eye movement was spontaneously mentioned as

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improved by at least one patient, caregiver, and clinical expert. Symptom improvement also varied in terms of time to improvement. Within the first weeks, improvements were seen in understanding new information or complex instructions, remembering the weekday, eye movement, tremor, and seizures. Changes in alertness, engagement and responsiveness, memory, and concentration appeared after months or a year. Most caregivers and all clinical experts reported greater patient independence (e.g., increased ability to perform activities of daily living or travel independently during the trial) as a perceived treatment effect on a GD3 impact. For one patient who perceived benefits from venglustat therapy, pharmacokinetic analyses during LEAP found low to undetectable venglustat levels in their plasma and cerebrospinal fluid.

***Conclusion*:** Outcomes from this study provide insights into GD3 symptoms and the early signaling of changes reported during venglustat therapy.

***Trial Registration*:** ClinicalTrials.gov identifier, NCT02843035.

Keywords: Caregiver experience; Case study; Gaucher disease type 3; Perception; Patient experience; Qualitative study; Quality of life; Venglustat

Key Summary Points

Why carry out this study?

The investigational agent venglustat, in combination with imiglucerase, has shown promise as a potential treatment for systemic and neuronopathic manifestations of Gaucher disease type 3 (GD3) in a single-arm, open-label, phase 2 trial (LEAP; $N=11$). Although LEAP has provided important insight into the efficacy and safety of venglustat in combination with imiglucerase, this study has yielded limited information on patients' and caregivers' perspectives of the effects of venglustat.

To understand perceived changes in GD3 symptoms from the perspectives of patients, caregivers, and clinicians, we conducted a qualitative case study of selected participants in LEAP (three patients, the caregiver of each of these patients, and a fourth patient represented by a caregiver).

What was learned from this study?

Participants in the qualitative study perceived a treatment benefit in cognitive, neurologic, and functional symptoms with venglustat in combination with imiglucerase in adults with GD3 whose hematologic and visceral outcomes had already been stabilized with enzyme-replacement therapy. These perceived benefits were observed from as early as 3 months after starting treatment to as late as 2 years.

Improvements in cognition in all patients were perceived but reportedly occurred in different aspects of cognition among patients, confirming the heterogeneity of neurologic manifestations of GD3. Perceived improvement in tremor was noted by one of four patients and their caregiver.

Masked (i.e., blinded) controlled trials can be important in interpreting the results of qualitative studies of patient and caregiver perceptions of treatment effect. The finding of low plasma and cerebrospinal fluid concentrations of venglustat in a patient during the LEAP trial provided context in which to analyze this patient's and caregiver's perceptions of treatment benefits.

Findings from this study provide insights into GD3 symptoms and early signaling of changes reported during venglustat therapy.

INTRODUCTION

Gaucher disease (GD) is a rare lysosomal storage disorder caused by biallelic mutations in the acid β-glucosidase (*GBA1*) gene, which lead to reduced acid β-glucosidase activity with

consequent accumulation of its primary substrate, glucosylceramide (GL-1 or Gb1), mainly in the lysosomal compartment of macrophages and, in the neuronopathic variants, in the neurons [1]. Gaucher disease type 3 (GD3) is a neuronopathic form of GD, characterized by central nervous system (CNS) involvement [2, 3].

Patients with GD3 have the same range of visceral symptoms as patients with Gaucher disease type 1, which include prominent visceral abnormalities [4, 5]. In addition, GD3 is associated with heterogenous presentation of chronic neurologic impairment of varying severity. Neurologic signs range from moderate (horizontal ophthalmoplegia/horizontal supranuclear gaze palsy, lower cognitive function) to severe (developmental delay, progressive myoclonus epilepsy, cerebellar ataxia, dystonia and spasticity, and dementia) [6–9]. The defining and most common feature of GD3 is gaze palsy associated with the slowing or absence of the horizontal saccadic eye movements [2, 8, 10].

Two available types of treatment for GD—enzyme-replacement therapy (ERT) and substrate-reduction therapy (SRT)—are effective in treating systemic manifestations of GD (i.e., hematologic, visceral, and skeletal signs and symptoms), but these therapies fail to correct neuronopathic signs and symptoms of GD [9, 11]. In contrast, the investigational compound venglustat is a potent, small-molecule, CNS-penetrant, selective inhibitor of glucosylceramide synthase that has the potential to treat systemic and neuronopathic manifestations [11].

Initial clinical trials of venglustat in the treatment of GD3 have shown promise in treating the neuronopathic features of GD3 [12–15]. Phase 1 studies of venglustat in healthy adults and a phase 2 study of venglustat in combination with imiglucerase (i.e., the LEAP study) in patients with GD3 have characterized venglustat's pharmacokinetics/pharmacodynamics and safety, and have explored its efficacy (defined as rapid, sustained, clinically meaningful decreases in plasma and cerebrospinal fluid [CSF] GL-1 and glucosylsphingosine [lyso-GL-1]). In 10 of 11 patients in LEAP, substantial reductions of plasma and CSF GL-1 were reported: the median (95% CI) concentration in plasma was reduced by 78% (46–84%) in plasma and 81% in CSF (47–83%) from baseline to week 52. Also, the median (95% CI) concentration of lyso-GL-1 was reduced by 56% (23–60%) in plasma and 70% (45–76%) in CSF. No severe adverse events (AEs) or discontinuation were reported through week 52; most AEs were mild or moderate in severity and not considered to be related to study treatment.

Effects of study treatment on patient function were also evaluated in LEAP. Ataxia was reduced at week 52; the mean (± standard deviation [SD]) total modified Scale for Assessment and Rating of Ataxia (SARA) scores for all patients were 2.68 (± 1.54) at baseline versus 1.55 (± 1.88) at week 52. Also, improvements in neurocognition were indicated by a reduction in the time to complete Trail-Making Test (TMT) Trail B minus the time to complete Trail A: the mean difference (±SD) for all patients decreased from 99.3 (± 107.5) seconds at baseline to 61.7 (± 46.2) seconds at week 52; 7 of 11 patients had a reduction. Although LEAP provided important insight into the efficacy and safety of venglustat in combination with imiglucerase, it provided limited information on patients' and caregivers' perspectives of the effects of venglustat [13]. Therefore, a standalone qualitative study is warranted to explore the patient and caregiver relevance of venglustat in combination with imiglucerase.

We have conducted semi-structured, in-depth case studies of selected patients with GD3 enrolled in LEAP, their caregivers, and selected clinicians involved in the LEAP trial to explore changes in the symptoms and impacts for patients with GD3, and to understand similarities and differences in perceptions of change among these stakeholders. The case-study approach was chosen because a small number of patients ($N = 11$) were enrolled in LEAP and because the naturalistic design of a case study allows investigation of a phenomenon or event in depth in its natural or real-life context, by

means of data collection from multiple information sources such as interviews, direct observation, archival records, and documentation [16].

METHODS

LEAP Study Design

The LEAP study (ClinicalTrials.gov identifier NCT02843035) is an ongoing, international, phase 2, open-label, single-arm, multicenter clinical study of venglustat 15 mg given orally once daily in combination with a maintenance dose of imiglucerase ERT administered intravenously every 2 weeks to adult patients with GD3 [13]. Eligibility criteria included age ≥18 years, a clinical diagnosis of GD3, a deficiency of acid β-glucosidase activity in peripheral blood leukocytes, gaze palsy, at least 3 years of imiglucerase therapy provided at a stable dose for at least 6 months. The primary endpoints of LEAP were the safety and tolerability of venglustat in combination with imiglucerase, and changes in concentration of the direct GD biomarkers GL-1 and lyso-GL-1 in CSF from baseline to weeks 26 and 52. Details about the design of LEAP and its primary results have been published [13].

Qualitative Study Design

In this standalone qualitative study, semi-structured, case-study interviews were conducted between 2018 and 2019 with three patients with GD3 participating in the LEAP trial and their respective caregivers (one per patient), one patient proxy (their caregiver), and three clinical experts involved in LEAP [17]. Patient recruitment for the interviews was limited to the United States (US) because a large proportion of patients in the LEAP trial reside there (5 of 11 patients). The trial site in Germany was considered as another location for the qualitative study, but interviews there could not be conducted in English; therefore, this site was excluded.

Patient and Caregiver Interviews

This qualitative study was not included in the LEAP trial protocol. The study was approved by a third-party institutional review board (Advarra, Columbia, MD) and conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. With permission from a participating clinical trial site in the US, patients enrolled in the LEAP trial in the US were approached by the site's research coordinator to determine interest in participating in face-to-face interviews. A project team member explained the details of the study to patients and caregivers, and those who expressed interest in participating provided informed consent to the team member. Informed consent was recorded in writing on an online or paper consent form. Patients and caregivers were also asked to provide verbal confirmation of their consent before the start of their interviews. Patient enrollment was independent of the duration of their venglustat treatment. The caregivers who participated in the interviews were parents of patients in the LEAP study.

First-round patient and caregiver interviews were 75 minutes long, from December 2018 to February 2019, and focused on a range of previously defined GD3 symptoms (e.g., symptoms related to cognitive function and other functions or abnormalities such as eye movement, tremors, fatigue, or shortness of breath) before and during the study [18]. In addition, caregiver interviews were designed to provide insights and perspectives on the patient experience before and during LEAP, explore the caregiver experience (results not reported here), and identify other impacts from GD3 symptoms and their treatment. The first-round interviews were conducted and recorded in person at a designated location convenient for the patient and caregiver. Patients and caregivers were compensated per fair market value for their time during the first round of interviews.

A second round of interviews with the same patients was conducted between March and May 2019, focusing on exploring additional concepts of change around eye-movement difficulties and cognitive impairment. The second-round interviews, lasting 40 minutes,

were conducted and recorded via telephone. Patients and caregivers were compensated per fair market value for their time during the second round of interviews.

Using standardized guides for the patient and caregiver interviews (Tables S1 and S2, respectively, in the electronic Supplementary Material), one moderator trained in interviewing techniques for concept elicitation and cognitive debriefing conducted both rounds of interviews with the two groups. The interview approach was in line with recommended guidelines of the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices Task Force [19].

Clinical Expert Interviews

With the permission of the LEAP sponsor, three clinical experts involved in the trial (one principal investigator from the US, one from Germany, and a research nurse from the US) were asked to participate in individual telephone interviews designed to last 40–60 minutes. These experts were selected because of their investigative roles in LEAP at the US and German study sites, and their extensive knowledge and experience in diagnosing and treating GD3. The interviews were conducted via telephone by a second moderator and, with the permission of the clinicians, the audio was recorded. A clinician-specific structured interview guide (Table S3) and stimulus material consisting of a preliminary GD3 conceptual model and instruments considered for use in GD3 clinical trials were used to gain clinical expert insights and perspectives on the patient experience among all patients at the experts' sites in LEAP.

Analysis Approach

To identify changes in the GD3 experience of patients during their enrollment in the LEAP trial, de-identified transcripts of recorded interviews were analyzed, and relevant data (including reported signs, symptoms, impacts, and changes over time) were tracked in Microsoft Excel. Soft coding of the de-identified interviews was performed to systematically identify relevant concepts at an individual level and the change over time during the clinical trial. Relevant quotes supporting the findings were also tracked and listed. Any sign, symptom, or impact indicated as changed since enrollment in the LEAP trial was noted. After coding was completed, quantitative outputs were generated to determine the salience of concepts and provide detailed overviews for reporting. Supporting quotes were selected to provide individual-level context to the quantified data.

RESULTS

Patients and Caregivers

Demographic and Clinical Information

Of the nine patients enrolled in LEAP at the time of the interviews, four provided consent to participate in the interviews. All four patients were between the ages of 20 and 29 and had been diagnosed with GD3 between 16 and 24 months of age (Table 1). Each patient had the L444P/L444P (p.Leu483Pro/p.Leu483Pro) mutation in *GBA1*. The *CYP3A4* genotype was *CYP3A4*1/*1* for three patients and ambiguous for the fourth (patient 3), but this patient did carry one *CYP3A4*15* allele. Patients' duration of venglustat and imiglucerase treatment during LEAP ranged from 3 months to 2 years.

Four caregivers were interviewed, and their ages were between 40 and 59 years (Table 1). All caregivers were providing care for the patients interviewed.

Patient Profiles

While all patients capable of reporting for themselves (excluding patient 2 because of cognitive deficits) and all caregivers noted improvements in some symptoms, to varying degrees, the two cohorts differed in their view of the impact of these improvements. None of the patients reported positive changes in their independence or confidence, while all caregivers observed steady improvement in these areas throughout

Table 1 Patient and caregiver demographics

Patient or caregiver number in qualitative study	Patient number in LEAP[a]	Characteristic	Patient	Caregiver
1	7	Age range (years)	20–28	50–59
		Relationship to patient	–	Parent
		Age at diagnosis of GD3 (months)	18	–
		Time on LEAP trial (years)	2	–
2	8	Age range (years)	20–28	50–59
		Relationship to patient	–	Parent
		Age at diagnosis of GD3 (months)	24	–
		Time on LEAP trial (years)	2	–
3	9	Age range (years)	20–28	40–49
		Relationship to patient	–	Parent
		Age at diagnosis of GD3 (months)	18–24	–
		Time on LEAP trial (years)	1–1.50	–
4	11	Age range (years)	20–28	50–59
		Relationship to patient	–	Parent
		Age at diagnosis of GD3 (months)	15	–
		Time on LEAP trial (years)	0.25	–

GD3 Gaucher disease type 3

[a]These patient numbers correspond to those reported in the manuscript describing week 52 results from LEAP [13]

the trial. Profiles of each patient and their caregiver are presented below.

Each profile describes GD3 symptoms that were present at enrollment in LEAP and were perceived by one or more patients and/or caregivers to have changed after the start of study treatment. Quotations from patients and their caregivers that describe their perceptions of symptom change are given in Table 2. Symptoms at enrollment that were perceived to be unaffected by study treatment are summarized for each patient in Table 3.

Patient 1 Patient 1 (patient 7 in the article reporting LEAP results [13]) was diagnosed with GD3 at 18 months of age. According to the caregiver, during infancy the patient experienced symptoms such as an "enlarged belly" and impaired eye movement. The caregiver confirmed the patient's report of "learning problems" at school. Although several issues during childhood (e.g., sleep apnea, spine curvature, vision impairment) resolved or were corrected before the trial, issues with cognition (e.g., difficulty understanding new or multiple pieces of information and slowness processing new information) remained at the time of study enrollment.

At the time of the interview, the patient had been participating in the LEAP trial for approximately 2 years. When asked about symptom changes, the patient and caregiver mentioned improvement in eye movement, which began "a couple of months" after starting the trial. The patient described the improvement as "moving more… like further to the left and right, I guess." The caregiver reported seeing more eye

Table 2 Quotes from patients, caregivers, and clinical experts about symptom concepts of GD3

Type of function	Selected symptom concept	Representative quotes[a]
Cognitive	Understanding new information quickly	Caregiver 2: "That's a good question, because he... we have seen [the patient] drawing and making things that we're like, 'Wow, [the patient] can do that?' Before, [the patient] could never do that because [the patient] didn't have that focus, or that drive, or even have the ability to move and do it"
		Caregiver 4: "Sometimes I think [the patient] maybe will understand a little bit clearer when you're telling [the patient] something. [Before start of the trial 3 months ago] You kind of had to tell [the patient] over and over and over, maybe five or six times. Now it's maybe three or four times. It's a little bit better"
		Clinical Expert 2: "[The patient] seemed to process the requests made of [the patient] more quickly and be able to comply with what was being asked of [the patient], show [the patient] idea, whatever, with less help from the caregivers. [...] There's not multiple steps, but it does seem as though [the patient] doesn't require as much processing time to comply with instructions like that involved with the testing"
	Understanding complex instructions	Patient [answering questions on a PRO questionnaire]: "I don't understand this. If I was to take a test and I didn't have you reading, I would be stuck on still the same... and then I'll frustrate myself because I don't understand it"
	Remembering the day of the week/ability to plan	Clinical Expert 2: "Knowing what the date is and what kinds of things should be going on around that date. 'I don't want to come then because it's going to be Halloween.' Or, 'Gee, do I have to come back? That's only going to be 6 weeks.' Those kinds of things where I'm not sure that always clicked with this patient. [...] I know that happened at week 52"

Table 2 continued

Type of function	Selected symptom concept	Representative quotes[a]
	Alertness, engagement, and responsiveness	Clinical Expert 1: "[The improvement in alertness] could be as soon as 3 months, anything before that. [...] It continues to be present. I don't know if the improvement continues or reaches a plateau" Clinical Expert 3: "...when I have a call with [the patient], usually [the patient] could follow just only a few sentences and then it was attention deficits, and now you can speak with [the patient] over a long time and the answers are adequate"
	Memory	Caregiver 2: [*Moderator: What have you noticed that has changed over the past 2 years?*] "It seems to be helping. It's helping your memory. [...] [*Moderator: When do you think that focusing on a conversation got better?]* That seemed to happen about the same time, around last year of November. [*Moderator: Same thing with the memory?*] Yeah. [*Moderator: Was it all of a sudden that you noticed this?*] It just happened"
	Decision-making	Caregiver 1: "I think that [the patient] getting better. I think that, to me, that fell in with the processing. [...] Now if [the patient] needs to call the mechanic, [the patient will] do it, instead of saying, '...do I need to call the mechanic?' Those kinds of things, [the patient is] starting to think..."
	Organizing what to say/carrying on a conversation/speech output	Caregiver 2: "[The patient] does, yeah. [The patient] talks a lot more now, but like I said, if [the patient's] eating a gummy, [NAME] will sit there and have a conversation with you for hours. I think it's because of the energy that it gives [the patient], and the comfort, and the relaxation, because [the patient] will be so stressed out with pain and so fatigued sometimes and just miserable"
	Concentration	Clinical Expert 3: *[Moderator: For the patient who experienced some of the changes in concentration, how long after the start of treatment did that first start to happen, would you say?]* "6 to 9 months. After 6 months. On the last visit, [the patient] told me that it's further improved, so it's a gradual improvement"

Table 2 continued

Type of function	Selected symptom concept	Representative quotes[a]
Other	Eye movement	Patient 1: "I've noticed my eyes have gotten a little bit better too since I've been on the trial. Probably a couple months after I started. [*Moderator: Like 2 months in?*] Yeah. It seems like it's just easier to move them back and forth than it was before. [...] I guess it would be moving more further to the left and right, I guess. [...] Especially like going down the road looking out the window, it's a lot easier" Caregiver 1: "I don't see as much head movement as I did" Clinical Expert 2: "[The patient] felt like when... driving, [the patient] was better able to focus. I don't know. It felt like [the patient's] eye movements were improved. [...] What I'm remembering is when [the patient] was driving it seemed as though it was easier to focus on the road ahead. This is the only patient that we have that is driving now, I believe"
	Fatty lump	Patient 3[b]: "But then once it started getting dark and irritated or somebody hit it, I'll get shortness of breath and it hurts. Because usually, like if I lean, sit back on it, or I'll be carrying my backpack, it'll irritate it. But now it doesn't. Ever since August, the study is helping it"
	Tremor	Patient 4: "Yes, it's more neurological. It's like the nerves, I guess. [...] Part of it is like when you get nervous meeting new people. Shooting my gun, I don't have tremors at all. It's my head and my hands. [...] It's worse in the morning than it is in the afternoon. [...] I think when I was a child it was a little worse, and once I got older it wasn't as noticeable. I don't know if it's the medicine or if it's me. [...] Once the medicines work, and my brain is thinking that it's doing that and the tremors are slowing down to make me feel like that. Less severity. Probably a week into the medicine" Caregiver 4: "...mainly the tremors seem a little less." [...] [The patient] still has them, and [the patient's] had them forever, but [...] now it's a little bit less"

Table 2 continued

Type of function	Selected symptom concept	Representative quotes[a]
	Seizure	Clinical Expert 1: "There is one patient who seems to have fewer seizures, fewer types of epilepsy, even though there was no change in [the patient's] seizure medication. But I can't say this is due to the treatment itself. I mean, with the experimental drug"
	Shortness of breath	Caregiver 2: "I used to have to sleep with [the patient] a lot because [the patient] would literally gag off of... saliva and choke basically if I didn't be in there. Since [the patient's] been on the trial medication, I'm comfortable with leaving [the patient] in a room now without having to sleep with [the patient] all night"
	Vision	Patient 4: "My vision is not as blurry. Meaning I used to have difficulty with very small words, I would have to squint to see them. Like the words on that board, I can see those, but I would have to squint to see it. [*Moderator: Now you can just keep your eyes open and see it?*] Right. [*Moderator: And that would have been an issue for you 3 months ago, to not be able see that?*] I could see it, but I would have to squint to see it"

The patient and their caregiver have the same number, e.g., the caregiver for Patient 1 is Caregiver 1
CSF cerebrospinal fluid, *GD3* Gaucher disease type 3

[a]To protect patient identities, personal pronouns were not used

[b]This is Patient 3, whose plasma and CSF concentrations of venglustat were low to undetectable at weeks 26 and 52 in LEAP

movement and less head movement than before the trial.

Improvements in decision-making and independence were reported by the patient and caregiver. According to the patient, improvement in memory and in processing multiple instructions or performing multiple tasks started approximately 2 months after beginning the study therapy. During the 2 years of study treatment, the caregiver had observed greater independence; for example, the patient had traveled independently, developed skills to cope with unforeseen difficulties, and made significant improvements in decision-making and concentration (Table 2).

Both the patient and caregiver reported that symptoms unchanged since the start of the clinical trial included understanding new information (which the patient distinguished from decision-making), and symptoms such as shortness of breath, tremors, and pain, which were not relevant to the patient at the time of trial enrollment. This patient and caregiver did not report any worsening of signs or symptoms attributed to GD3.

Patient 2 Patient 2 (Patient 8 in the article reporting LEAP results [13]) was diagnosed with GD3 at 2 years of age. This patient was the most symptomatic of those interviewed. Because of cognitive deficits, this patient's contributions to the interviews were limited; the caregiver served as a proxy and gave perceptions of this patient's experience.

Table 3 GD3 symptoms that were present at enrollment in LEAP but were not perceived as improved after the start of venglustat in combination with imiglucerase therapy

Patient number	Symptoms
1	None reported[a]
2	Difficulty climbing stairs
	Difficulty controlling leg movements when trying to walk
	Frequent nose bleeding
	Frequent bleeding
	Frequent falling
	Balance difficulty
	Fatigue
	Muscle twitch, jerk, or spasm
	Sensitive skin (itching/scratching)
	Chronic pain
	Anxiety
3	Bone issues that required surgery and bone pain
	Nerve pain in legs
	Spine curvature
	Poor balance
	Difficulty climbing stairs
	Bruising easily
	Enlarged liver and spleen
4	Scoliosis
	Narcolepsy
	Teeth sensitivity
	Muscle and back pain
	Uncontrolled muscle contractions causing changes in posture or movement

GD3 Gaucher disease type 3

[a]The primary issues that patient 1 had at the time of the initial interview were cognitive

Many symptoms were reported at study baseline by the patient and caregiver and included the following: breathing difficulties, lung problems, misalignment of eyes (inward or outward), saccadic eye movement, seizures, tremor, fatigue, frequent falling, loss of balance, and vision impairment. Behavioral and neurocognitive symptoms at baseline were difficulties in the following: making decisions, understanding and processing new information quickly, memory (e.g., retaining information), social engagement, following directions, and concentration. The patient had undergone surgeries to treat kyphosis, saccades, and strabismus.

At the time of the interview, the patient had been participating in LEAP for 2 years. The caregiver noted substantial improvement in other GD3 symptoms; most improvements began approximately 18 months after starting the study. Symptom changes were improved lung function/breathing; improved ability to stretch and better arm movement; improved cognition, such as better memory (Table 2), greater focus, increased ability to learn, and better recall of the current day of the week; a reduction in seizures (but the dose of antiseizure medications had been increased during the trial); and improved eye movement, which may have been due to recent surgery to correct strabismus. No worsening of signs or symptoms attributed to GD3 was reported for this patient.

Patient 3 Patient 3 (Patient 9 in the article reporting LEAP results [13]) was diagnosed with GD3 between 18 months and 2 years of age. During childhood and adolescence, Patient 3 experienced nose bleeds and chest pain, respectively, but these symptoms resolved before the trial. Breathing difficulties began around 2 years of age and continued until this patient was 19 or 20 years old; at that time, their breathing improved, according to the caregiver, but sleep apnea continued. Before entering the trial, Patient 3 was experiencing bone issues that required surgery, nerve pain in both legs, bone pain, spine curvature, poor balance, difficulty climbing stairs, bruising easily, hepatosplenomegaly, and abnormal eye function. The patient reported having a "great" memory, although

the caregiver said that the patient's memory function varied daily.

At the time of the interview, the patient had been participating in LEAP for approximately 18 months. Both the patient and caregiver noted slight improvements in the patient's eye movement. The patient described eye movement before the trial as "a 10" (on a scale of 0 to 10 with 10 being the worst eye movement in the prior 24 h) and that "everything's going so fast!" In contrast, the patient said eye movement had improved during the trial to the point where "I sort of can focus on moving." The caregiver noted better eye movement, the impact of which would be important to this patient's daily life: "Oh, yeah, especially if [the patient's] talking about getting a driver's license." The patient also mentioned feeling less shy and more talkative since beginning the study therapy. In addition, the caregiver acknowledged the patient's memory improvement. The patient and caregiver reported no worsening of signs or symptoms related to GD3.

Of note, this patient had low to undetectable plasma and CSF concentrations of venglustat at weeks 26 and 52 in LEAP [13, 15]. The reason for these results was not identified; the patient reported no challenges with treatment adherence, and no drug–drug interactions were found. The patient's and caregiver's perceptions of treatment benefits cannot be explained by the patient's low to undetectable plasma and CSF concentrations of venglustat.

Patient 4 Patient 4 (Patient 11 in the article reporting LEAP results [13]) was diagnosed with GD3 at the age of 15 months. During early childhood, the patient experienced hepatosplenomegaly, asthma, and breathing difficulty. The patient and caregiver reported a lifelong difficulty with balance, and both attributed this problem to impaired depth perception. Other vision problems included "a lazy eye," reading difficulty that required increased font size, and impaired eye movement that eventually led to the patient's discontinuation of driving. At the time of study enrollment, the patient also had tremors, difficulty understanding instructions, and difficulty in processing new information.

Patient 4 had been involved in LEAP and receiving venglustat in combination with imiglucerase treatment for 3 months at the time of the interview. Despite this brief duration, both the patient and caregiver reported changes in some GD3 symptoms, such as a reduction in tremor severity. The patient reported observing this reduction "probably a week into the medicine," but noted, "I don't know if that's the medicine or it's me wanting it to work and my brain is slowing it down to make me feel that way." In addition, the patient noticed an improvement in their vision (Table 2). Improvement in cognitive processing (e.g., concentration and focus) was observed by the caregiver only. In particular, the caregiver noted that the patient was better at tracking time, such as the schedule for medication use. This patient and caregiver did not report any worsening of symptoms attributed to GD3.

Clinical Experts

Background and Experience

Three clinical experts were interviewed. Clinical Expert 1 is the principal investigator at a US site participating in the LEAP trial and is responsible for assessing patients every 1–3 months, including all patients interviewed. This expert specializes in neurology and has more than 21 years of experience treating patients with GD. Clinical Expert 2 was a research coordinator at the same US trial site and is responsible for the day-to-day operations of the ongoing LEAP trial. As a result, she is familiar with the experiences of patients with GD3 and their caregivers. Clinical Expert 3 was the principal investigator at the German site at the time of the LEAP trial.

Perceptions from the clinical experts were based on observation of all patients who were interviewed, observation of those in the LEAP trial who were not interviewed, and information provided by other staff involved in LEAP, patients, and caregivers.

Perceived Treatment Effect on GD3 Symptoms

All three clinical experts reported improvement in patients' alertness, engagement, and/or responsiveness with their surroundings, and in general conversations. Before treatment with venglustat in combination with imiglucerase, the clinical experts stated that patients would passively respond to questions in a conversation, be "parrot-like," and not show an understanding of the subject. During treatment, these patients seemed to be more spontaneous and alert in their responses; these improvements were perceived as early as 3 months after the start of therapy and appeared to be sustained through 52 weeks.

Other perceptions from the clinical experts were a better awareness of dates and ability to plan, a greater understanding of complex instructions (e.g., following instruction for spirometry testing), and improved memory and concentration (Table 2), each of which began to improve gradually at 6–9 months after trial enrollment. In addition, Clinical Experts 1 and 2 stated that one patient was having fewer seizures, but Clinical Expert 1 was hesitant to connect the improvement to study treatment. None of the clinical experts observed improvement in eye movement, but Clinical Expert 2 noted one patient had subjectively described improved eye movement that allowed better focus on the road while driving. Clinical Expert 1 noted improvements in speech and stated that improvement in gait was possible in one or two patients, but additional evidence was needed to support this possibility. In addition, Clinical Expert 3 had hoped that ataxia would improve in one particular patient in Germany, but this patient's participation in LEAP had begun recently and, by the time of the interview, the clinical expert had observed no improvement in ataxia for this patient.

Perceived Treatment Effect on GD3 Impacts

All three clinical experts reported improved independence of patients and improved ability of these patients to take care of activities of daily living, such as getting the mail, taking the dog out, and traveling on their own. Quotations describing each clinical expert's perceptions about greater patient independence are provided in Table 4.

DISCUSSION

Overall, all patients, caregivers, and clinical experts perceived either maintenance or improvement of GD3 symptoms after initiating venglustat in combination with imiglucerase. There were no reports of worsening GD3 symptoms or the appearance of new symptoms related to GD3 by patients, caregivers, or the clinical experts at the time of their interviews.

Reported changes in GD3 symptoms varied from patient to patient and from reporter to reporter. Only one symptom—eye movement—was spontaneously mentioned as improved by at least one patient, caregiver, and clinical expert (the expert's report was subjective). Perceived improvement in symptoms also varied in terms of time to improvement; first perceived improvements (e.g., understanding new information, understanding complex instructions, remembering the day of the week, eye movement, tremor, and seizures) occurred within the first weeks, whereas changes in alertness, engagement and responsiveness, memory, and concentration appeared after months or a year; this variation in time of appearance highlights the importance of more frequent assessments throughout treatment. These perceived improvements in our qualitative study are consistent with findings for several exploratory endpoints regarding executive function, brain volume, and brain activity in LEAP at 1 year [13]. Given that the specific changes seem to vary depending on the patient's baseline profile and the reporter, a broad approach for measuring the full range of symptoms is recommended in clinical trials—by patients (via patient-reported outcome instruments) when possible, and by caregivers (via observer-reported outcome instruments) when required.

In the present study, perceived improvements or stabilization in motor and coordination

Table 4 Clinical experts' perceptions of the effects of venglustat in combination with imiglucerase on the GD3 impact of independence

Clinical expert number	Representative quotes[a]
1	"One patient who was already quite independent really became more independent. Before [study drug therapy], [the patient] came to us with [the patient's] parents. [The patient] is now coming to see us alone; [the patient's] taking a flight..."
2	"...[The patient's] family had reported [the patient's] better able to—[the patient's] got children—[the patient's] better able to care for [the patient's] children, take care of household chores..."
3	"The... patient was a [person] with cognitive deficits, especially in memory, and also in concentration and attention. The caregivers of the patient, they feel that this [patient] was not able to manage... daily life and... needs... parents and [the patient's] sisters and brothers, which help [the patient] to manage daily life. In this [patient], that improved"

GD3 Gaucher disease type 3

[a]To protect patient identities, personal pronouns were not used

deficits, and speech, which are characteristic of ataxia, were not reported by patients, caregivers, or clinical experts. However, results for the modified SARA at weeks 26 and 52 in LEAP showed that ataxia had improved for Patients 1, 3, and 4 (Patients 7, 9, and 11 in the article by Schiffmann et al. [13]) but worsened for Patient 2 (Patient 8 in [13]). The discrepancy in measured improvement and perceived improvement may have been because 10 of the 11 patients in LEAP had mild ataxia (total modified SARA score ≥ 0.5) at baseline, and one patient had a score of 0 at baseline [13].

Although improvements in eye movement were perceived by patients and caregivers, no improvement was detected clinically [13]. In addition, Patient 3, whose reports of improved eye movement and improved memory were confirmed by the patient's caregiver, had low plasma and CSF concentrations of venglustat at week 26 and undetectable concentrations at week 52 of the LEAP trial [13]. However, no specific rationale for this effect could be established. Other patients who were interviewed for the qualitative study and reported improvements had adequate blood and CSF venglustat levels; plasma venglustat concentrations reached steady state by week 4, as did CSF venglustat concentrations [13].

Our qualitative study has several strengths. The study was based on patient interviews, which are an effective method of evoking the patient voice and thus provide important data about the patient experience in a clinical trial. Interviewing permitted the collection of first-hand accounts of change in GD3 symptoms and impacts from the patient's, caregiver's, and clinician's points of view during a phase 2 trial. The variety of GD3 signs and symptoms in the four patients was substantial and representative of the heterogeneity of signs and symptoms within the larger population of patients with GD3. Those findings regarding patient experience before venglustat treatment are aligned with those from other studies, and our findings provide additional details about several cognitive concepts. In addition, the interviews provided insights based on different perspectives in areas that exploratory instruments were not able to identify; for example, caregivers observed changes in patient cognition, whereas patients expressed less awareness of such changes.

Limitations of our qualitative study include the use of a small sample size, which was due to the rare occurrence of GD3 (prevalence of neuronopathic GD, < 1 in 100,000) [20], the design of the LEAP trial, and the interview of US patients only. Differing durations of treatment (3 months to 2 years) for the interviewed

patients also made it difficult to assess similarities and differences in perceived symptom changes and to compare with the results on the exploratory instruments. In addition, the open-label, single-arm design of the LEAP trial may have introduced a bias toward positive drug effects during the interviews, especially in regard to the perceptions of treatment effect reported by patient 3 and the caregiver. An additional limitation is the possible effect of cognitive deficits on patient interviews—patients with documented cognitive deficits were asked to recall events or personal traits from as long ago as 2 years; their recall may not have been entirely accurate. Nevertheless, the interview of caregivers could have limited this bias.

CONCLUSIONS

Findings from this qualitative study provide insights into GD3 symptoms and early signaling of changes reported during venglustat therapy. A treatment benefit in cognitive and neurologic symptoms with venglustat in combination with imiglucerase in adults with GD3 whose hematologic and visceral outcomes had already been stabilized with ERT was perceived by adults living with the disease as well as caregivers. Differences in perceived improvement in cognitive functioning were reported by participants: improvements in cognition in all patients were perceived but reportedly occurred in different aspects of cognition among patients, confirming the heterogeneity of neurologic manifestations of GD3. A perceived improvement in tremor was noted by one patient and caregiver. Perceived benefits were observed from as early as 3 months after starting treatment to as late as 2 years. One clinical expert noted improvement in speech and possible improvement in gait. However, further confirmation of benefits in this population is needed in a randomized controlled trial with a larger sample size. Quantitative and qualitative instruments should be integrated in a phase 3 trial to capture the different perspectives from patients and caregivers.

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Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request. Qualified researchers may request access to patient level data and related

study documents including the clinical study report, study protocol with any amendments, blank case report form, statistical analysis plan, and dataset specifications. Patient level data will be anonymized and study documents will be redacted to protect the privacy of our trial participants. Further details on Sanofi's data sharing criteria, eligible studies, and process for requesting access can be found at: https://www.vivli.org/.

Declarations

Conflict of Interest. Raphael Schiffmann is the Lead Principal Investigator on the venglustat LEAP trial and receives research support and honoraria from Sanofi, Chiesi Pharmaceuticals, and Protalix Biotherapeutics. Eugen Mengel is a Principal Investigator on the venglustat LEAP trial and reports receiving fees and consultant honoraria from Actelion, Alexion, Avrobio, Cyclo Therapeutics, Freeline Therapeutics, Idorsia, Orphazyme A/S, Sanofi, and Takeda. Mary Wallace was the Clinical Study Coordinator on the venglustat LEAP trial. Ruth Pulikottil-Jacob, Camille Rochmann, Isabela Batsu, Riliang Zheng, and Alaa Hamed are employees of Sanofi; Isabela Batsu and Riliang Zheng hold shares and/or stock options in this company. James Turnbull and Robert Krupnick are employees of IQVIA, Inc., which received fees for this study. Chad Gwaltney is an employee of Gwaltney Consulting and was a paid consultant of Sanofi for this study; however, this author did not receive any payment related to authoring this manuscript.

Ethical Approval. This standalone qualitative study was not included in the LEAP trial protocol. The study was approved by a third-party institutional review board (Advarra, Columbia, MD) and was conducted in accordance with the Helsinki Declaration of 1964 and its later amendments. Patients and caregivers provided informed consent to participate online or on paper after being approached by the research coordinator from a participating clinical trial site in the US. Patients and caregivers were also asked for verbal confirmation of their consent before the start of their interviews.

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