NATIONAL KIDNEY FOUNDATION®

The Voice of the Patient Report Externally Led Patient-focused Drug Development Meeting on Fabry Disease

Public Meeting: September 19, 2022
Report Date: March 11, 2025

Submitted as patient experience data for consideration pursuant to section 569C of the Federal Food, Drug and Cosmetic Act to: Center for Biologics Evaluation and Research (CBER), U.S. Food and Drug Administration (FDA).

This report reflects the National Kidney Foundation's and Fabry Support & Information Group's (FSIG) accounts of the perspectives of patients and care partners who participated in an Externally Led Patient-Focused Drug Development meeting, an effort to support the FDA's Patient-Focused Drug Development Initiative.

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REPORT ON THE EXTERNALLY LED PATIENT-FOCUSED DRUG DEVELOPMENT (EL-PFDD) MEETING ON FABRY DISEASE

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DISCLOSURES

Dr. Wallace: Sanofi, Chiesi, Idorsia, Sangamo Therapeutics, uniQure biopharma, Amicus Therapeutics, Natera Inc., Kyowa Hakko Kirin Co.

Dr. Rastogi Sanofi S.A.; Amicus Therapeutics; Chiesi Global Inc.; Idorsia Pharmaceuticals. Ltd; Protalix Biotherapeutics Ltd

FUNDING

Sponsorship for this meeting was provided by Chiesi Pharmaceuticals and Sangamo Therapeutics, Inc. Sponsorship was provided as independent grants that supported meeting logistics, including venue costs, a medical writer, and preparation of the meeting transcript.

VERSION DATE

This Voice of the Patient report has not been revised or modified since March 11, 2025.

STATEMENT OF USE

The National Kidney Foundation (NKF) and Fabry Support & Information Group (FSIG) have permission to submit this Voice of the Patient Report to the FDA External Resources webpage; linking to the FDA website will not violate the proprietary rights of others.

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INTRODUCTION

On September 19, 2022, the National Kidney Foundation (NKF) and Fabry Support & Information Group (FSIG) held an Externally Led Patient-focused Drug Development (EL-PFDD) Meeting on Fabry Disease. The goal of the meeting was to provide the U.S. Food and Drug Administration (FDA), product developers, clinicians, and academic researchers a forum in which to learn from people with Fabry disease about their experiences and perspectives on living with the disease. While Fabry disease is a multi-organ disease, discussions during this meeting focused mainly on kidney involvement from this disease. This meeting was conducted as a parallel effort to the FDA-led PFDD meetings that were first conducted under PDUFA V from 2013-2017, supporting, a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to systematically gather patient perspectives on their conditions and the available therapies to treat their conditions. To help expand the benefits of FDA's PFDD initiative, in 2015, FDA announced the opportunity of EL-PFDD meetings. EL-PFDD meetings are planned and hosted by patient organizations, with the input of FDA staff, and use the process established by FDA-led PFDD meetings as a model.

More information on this initiative can be found at: *https://www.fda.gov/industry/prescription-drug-user-fee-amendments/externally-led-patient-focused-drug-development-meetings*

OVERVIEW OF FABRY DISEASE

DEFINITION OF FABRY DISEASE

Fabry disease is a progressive life-threatening lysosomal storage disorder of X-linked inheritance caused by the deficient expression of the enzyme alpha-galactosidase. This impairment results in the accumulation of glycosphingolipids within virtually every cell in the body and is associated with multiple adverse outcomes, including those of the kidney, heart, and nervous system. Fabry disease is frequently more severe in male patients, while the disease burden in female patients is more variable.

Fabry disease can be classified as "classic" or "late-onset;" these types differ in their progression and prognosis. In classic (type 1) Fabry disease, no or little (<1% of normal mean activity) functional α-galactosidase A enzymatic activity is present,[1] while late-onset (type 2) Fabry disease is characterized by enzymatic activity that is better preserved than in classic, but still low compared to healthy individuals. Consequently, this form of the disease is less severe than classic Fabry disease.

SYMPTOMS AND CLINICAL COURSE OF FABRY DISEASE

General

The heterogeneity of the genetic defect in Fabry disease confers wide clinical variability, even within the same family. Two forms of Fabry disease are recognized: classic and late-onset, the symptoms and clinical course of which differ.

Generally, patients with classic phenotype show no residual enzyme activity and typically experience symptom onset, such as neuropathic pain or anhidrosis, in early childhood. Their condition may progress to major organ complications as early as the second or third decade of life. Symptoms of classic Fabry disease, including burning sensations in the hands and feet as a sign of neuropathic pain, an- or hypohidrosis, recurrent fever, pain crises, and the presence of angiokeratomas, usually develop in early or late childhood.

Kidney disease

Kidney involvement in Fabry disease is a major cause of morbidity and mortality, especially in males.

Microalbuminuria and then overt, progressive proteinuria typically appear in the second or third decades of life. [2,3] In some cases, chronic kidney disease (CKD) may begin as early as the second decade of life, with up to 50% of patients developing CKD by just over 43 years of age.[4]

Left untreated, kidney disease in Fabry disease patients progresses to end stage kidney disease (ESKD) in virtually all males and many females. During the later stages of kidney disease, patients experience symptom burdens that are common to those in other CKD and these are often debilitating. Dialysis and/or kidney transplantation is required in some patients.

Heart disease

In at least one study[5] cardiovascular disease was the leading cause of death in patients with Fabry disease. People with Fabry disease often experience bradycardia, left ventricular hypertrophy, short PR intervals, atrioventricular blocks, supraventricular and ventricular arrhythmias, and myocardial ischemia, and fibrosis. These manifestations may lead to cardiac insufficiency, the need for heart transplantation, or sudden cardiac death.

In contrast to classic Fabry disease, patients with late-onset Fabry disease are typically female or are males with nonclassical mutations and have a more variable disease course, in some cases presenting with only single organ involvement. Symptom onset may occur in these patients as late as the fifth decade of life.

Additional symptoms

Neurological symptoms, especially neuropathic pain are common in Fabry disease. Other symptoms include gastrointestinal issues, hypohidrosis, and fever, which may manifest as early as three years in boys and six years in girls.

TREATMENTS FOR FABRY DISEASE

There is currently no cure for Fabry disease. Management is life-long and can involve multiple medical disciplines, depending on the symptoms and manifestations of the disease.

Enzyme Replacement and Chaperone Therapies Disease

The first line treatment for Fabry disease is enzyme replacement therapy (ERT), administered by infusion of recombinant alpha-galactosidase A. The goal of this therapy is to supplement or replace the deficient or absent enzyme activity. One limitation of ERT is the development of antibodies against the recombinant enzyme in about 40% of treated males.[6] In addition, infusion reactions may occur in patients given ERT.[7]

Another treatment strategy is oral chaperone therapy, approved for patients with missense mutations that lead to misfolded, but active alpha-galactosidase A. Such mutations are “amenable” to chaperone therapy, in which the chaperone molecule binds, “refolds,” and thereby stabilizes the enzyme, permitting its full lysosomal activity.[8]

Supportive therapy

Patients also receive supportive care to control symptoms. These measures include nephroprotection and/or blood pressure management with renin angiotensin system blockers. Prophylactic anticoagulant and/or antiplatelet agents are given to patients, and antiarrhythmic agents are prescribed for cardio- and vascular protection. Analgesics, opiates, and lifestyle modifications are prescribed to manage pain[9] and non-prescription medications and lifestyle changes are used to manage gastrointestinal symptoms.[10]

Patients experiencing neuropathic pain may be treated with antidepressants or anticonvulsants. Nonpharmacologic approaches, including psychological and physical treatments, may also provide relief of pain or other comorbid disorders, including anxiety and depression.

Dialysis And Kidney Transplantation

Dialysis and kidney transplantation are options for Fabry disease patients who are approaching or experiencing ESKD. However, kidney transplantation offers better prospects than dialysis for ESKD patients with Fabry disease.[1]

MEETING OVERVIEW

This EL-PFDD Meeting on Fabry Disease provided the FDA, product developers, clinicians, and academic researchers the opportunity to hear directly from patients and their care partners about their experiences living with Fabry disease and their views on disease-related topics. Specifically, the goals of this meeting were to afford the FDA and other key stakeholders an overall understanding of:

- Patient perspectives on living with Fabry disease, especially daily disease burdens
- Factors that influence patient willingness to enter clinical trials, including patient and caregiver perspectives on how to minimize the burden of participation
- Patient experiences with, and views on, the limitations of current therapies, patient insights into desirable characteristics of potential new therapies, and risk/benefit factors that influence patients' willingness to try new therapies

MEETING FORMAT

This meeting was held in a virtual format. The proceedings were livestreamed and orchestrated by a moderator. Patient input was gathered from pre-recorded patient testimonies, dialogue with patients and care partners through live virtual panels, and from the virtual audience via emails, phone calls, and online comments submitted during and after the meeting. Only patients and care partners were asked to participate in the dialogue.

Discussions during the meeting focused on three key topics:

- Living With Fabry Disease: Disease Symptoms and Daily Impacts
- Clinical Trials In Fabry Disease
- Current Challenges of Treating Fabry Disease.
- An overview of the meeting is included in the Meeting Agenda (Appendix 2) as are the Slide Presentations and Meeting Recording. The Discussion Questions used to guide the Audience Discussions are found in Appendix 3.

Patient Panels and Moderated Discussion

Patient voices were heard through five Patient/Care Partner Panels (Appendix 4.1) and three moderated Audience Discussion sessions. Panelists were selected by NKF and FSIG representatives from their respective memberships. Criteria for selecting Panelists were set to maximize clinical and demographic diversity on each Panel. The Panels were conducted as described below.

Patient Testimony Panels

Two patient Testimony Panels were heard in which four to five patients per Panel gave five-minute pre-recorded presentations on their experiences regarding symptoms and daily burdens (Topic 1) or current treatment challenges for Fabry disease (Topic 3) (Appendix 4.2). Testimonies were not given for Topic 2.

Each Testimony Panel was followed by a three- to six-member Discussion Panel of patients and care partners and a parallel moderated Audience Discussion. During these discussions, the moderator interacted directly with the Discussion Panelists. Between these discussions, phone calls and written comments from the virtual audience were broadcast and read, respectively.

Polling Questions

Polling Questions (Appendix 5) were posed to the participants to reveal the demographics of the attendees and their perspectives on the different Discussion Topics. Only patients and care partners were asked to participate in polling. Polling questions were based on a pre-meeting survey of prospective attendees, input from the meeting co-chairs, and the literature. Care partners were asked to respond on behalf of the patients for whom they provide care (not on behalf of themselves), even if the patient also responded.

Polling was conducted via an online platform, through which attendees could respond. Responses were projected instantly for audience viewing and described simultaneously by the moderator. The results are described in the text and depicted graphically in Appendix 6.

Post-meeting Comments

To expand on the perspectives gathered at the meeting, patients and care partners were encouraged to submit comments to NKF and FSIG after the meeting. Comments were accepted until October 20, 2022.

Enduring Documentation of Meeting

The archived meeting recording, this meeting report, and the meeting transcript are available on the National Kidney Foundation and Fabry Support & Information Group websites (Appendix 2).

Attendees

A total of 96 people attended the livestreamed meeting, including 35 Fabry disease patients and seven care partners.

The profiles of the patient and care partner attendees were revealed by demographic polling questions (Appendix 5.1). Most (94%) respondents were patients living with Fabry disease and 6% were care partners of someone with Fabry disease (Appendix 6; Figure 1). The majority (58%) of attendees resided on the East Coast, followed by 26"% in the Midwest, and 11% on the Pacific Coast. Five percent were from outside of North America (Appendix 6; Figure 2).

Approximately 5% of attendees were 18-29 years old, 14% were between 30-39 years old, and 40-49 years old. Most respondents (36%) were between 50-59 years of age. Twenty-seven percent of the attendees were 60-69 years old, while 5% of respondents were 70 years or older. No respondents were under 18 years (Appendix 6; Figure 3).

Respondents were predominantly female (81%); 19% were male (Appendix 6; Figure 4). Most respondents had received their diagnosis more than 10 years ago (81%), 14% were diagnosed 6 to 10 years ago, and 5% were diagnosed in the last 3 to 5 years (Appendix 6; Figure 5).

KEY THEMES

The testimonies and answers to Polling Questions from the meeting emphasized the challenges of living with Fabry disease, its impact on daily life, patient views of clinical trials, and their perspectives on currently available therapies. Several key symptom themes emerged from this meeting:

- **Kidney disease:** While kidney involvement in Fabry disease was not a dominant issue raised by many patients in the virtual audience, for those living with kidney disease from Fabry disease, the fear of their kidney disease progressing to the need for dialysis or kidney transplantation was a major concern. Patients recounted experiences with worsening kidney function during pregnancy, history of parents dying from kidney disease, and fears of recurrence of kidney disease after a kidney transplant.
- **Cardiovascular issues:** Several patients described having suffered strokes or one or multiple TIAs. Many patients spoke of their fear of suffering a stroke or TIA, especially a debilitating event that would cause them to become a burden to their families. When speaking of ideal treatments for Fabry disease, a treatment that could prevent strokes or transient ischemic attacks (TIAs) was the most commonly selected option. Patients also spoke of their fear of heart disease progression; many already had suffered from various Fabry disease-related cardiovascular issues. Patients noted how their heart disease limited their participation in exercise or recreational activities. They also spoke of stress from even minor heart issues (eg, having a high heart rate or being out of breath) fearing that these symptoms were indicators of more serious cardiovascular health concerns.
- **Heat intolerance:** Intolerance to heat and its negative effect on daily life was commonly discussed by patients. Patients described how even minor changes in temperature can have major impacts on their daily activities.
- **Fatigue:** Fatigue is a constant in the life of a Fabry patient. For some patients, fatigue was a side effect of treatment and/or occurred because of treating other symptoms. For others, fatigue itself was a debilitating symptom that could prevent a patient from participating in regular daily activities. For all Fabry patients, fatigue added another layer of challenges to dealing with their multi-systemic symptoms.
- **Neuropathy:** Many patients discussed how living with daily pain could make it difficult to lead normal and fulfilling lives. Although limb pain decreased in some patients as they aged, it increased in others. While treatment seemed to help some patients with pain, some reported that no treatments had been effective at providing relief. Patients also reported how limb pain detracted from their daily enjoyment and participation in life.
- **Social and emotional issues:** Living with Fabry disease is isolating. Patients spoke at length of the difficulties of starting and maintaining friendships and social and romantic relationships. Patients expressed their frustration at how the unpredictability of their symptoms made them feel unreliable at school and work and when making plans with friends and family. Patients also discussed their fears regarding disease progression. They also related worries about whether their children and grandchildren would inherit Fabry disease.
- **Plans/future:** Participants described frustration with the inability to make short- and long-term plans for their or their loved ones' futures amidst worries about disease progression and treatment non-response (e.g., in patients who have developed antibodies against ERT proteins). Parents of patients with Fabry disease in particular expressed worry about sending their children to college where they would have to manage their treatments independently.
- **Clinical trials:** Patients resoundingly supported participation in clinical trials, with many noting it was their responsibility to do whatever they could to help develop better treatments options—and therefore, a better future—available for all Fabry patients. Although some patients expressed reservations about potential side effects of a test agent, and some were reluctant to try a new treatment without proven efficacy, all patients emphasized the importance of participating in trials whenever possible to help and support the Fabry community.
- **Treatments:** Patients expressed gratitude when speaking about Fabry disease treatments. However, many patients also shared their frustration about the length, frequency, and inconvenience of ERT treatments, noting the • difficulties they had in planning their lives around treatments • infusion reactions • the challenges that patients faced when they were responsible for managing their own home infusions.
- **Ideal treatment:** While most patients indicated they would like a treatment that addressed their own specific set of symptoms (i.e., pain, temperature intolerance, brain fog, stroke, or cardiovascular or kidney health, etc.), all patients agreed that the ideal therapy would address the symptoms of *all* Fabry patients.

REPORT OVERVIEW

This report summarizes the perspectives shared by Fabry disease patients and care partners at the EL-PFDD Meeting on Fabry disease, including Patient Testimonies, Audience Discussions, and responses to Polling Questions posed during the meeting.

This Voice of the Patient report intends to support the understanding of Fabry disease by the FDA, product developers, clinicians, and academic researchers, and includes firsthand information on symptom burdens, views on clinical trials, and perspectives on current and future treatments for Fabry disease. This document also highlights the unmet needs of Fabry disease patients. Thus, this report may aid the FDA in considering the patient voice as the agency fulfills its role in the drug development process, such as advising sponsors on their drug development programs, including clinical trial design, evaluating products for approval to be marketed, and assessing benefit-risk for products under review.

This report may also be valuable to the drug development process more broadly. For example, it may guide pharmaceutical companies in their development process by uncovering previously unappreciated and unmet burdens of living with Fabry disease and may direct research decisions toward targeting disease mechanisms that underlie such symptoms.

In addition, this report describes some of the barriers to clinical trial participation by patients with Fabry disease and may inform the identification of clinical trial endpoints that are meaningful to patients.

In this report, patients and care partners are collectively referred to as "patients" and/or "care partners," "participants," or "attendees." To distinguish participants who responded to Polling Questions from those who did not, we use "respondents" when describing results from these questions. "Care partner" refers to a family member, partner, or friend who provides direct care for the patient.

Percentages from Polling Questions reported in the text and as numerals in the Appendix Figures are rounded off from the original data. Consequently, the sum of percentages for a given graph may not total 100% and the bar heights may not always precisely reflect the percentages within. In addition, not all attendees responded to all Polling Questions. Therefore, the total number of responses varied across these questions. Consequently, even when an identical number of attendees chose a response option for say, two questions, the computed percentages may differ between questions.

We note that, while the participants at this meeting represented a clinically and demographically diverse group, the extent to which this group reflected the Fabry disease patient population at large is unknown, in part due to the lack of quality epidemiology and natural history information on Fabry disease. Moreover, there may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the narrative. Therefore, this report is not meant to represent the views and experiences of any specific group of individuals or entities. The terms and language used in this report to describe Fabry disease symptoms and impacts, views of participating in clinical trials, and treatment experiences reflect only those of the meeting attendees.

Quotes from patients and care partners in this report were taken from Patient Testimonies, remarks from Discussion Panelists, online comments, and statements transcribed from phone calls; they have been edited for grammar, clarity, and punctuation.

PERSPECTIVES FROM PATIENTS

TOPIC 1. LIVING WITH FABRY DISEASE: DISEASE SYMPTOMS AND DAILY IMPACTS

The first Discussion Topic focused on Fabry disease symptoms and their impact on the daily lives of patients and their families. The session began with video presentations from four patients living with Fabry disease. The patients described their symptoms and the daily burdens from Fabry disease. Noteworthy excerpts from these presentations are below. Full testimonies are found in Appendix 4.2.

KK (adult female patient and parent of a child patient)

"Fabry disease is multi-generational, ***and I'm just one of seven in my family known to have or are suffering from this disease****."*

" I watched my father in a constant state of health crisis, endless pain and suffering with his body and mind deteriorating. ***At age 52, he called me at college to tell me that he was giving up to suicide****."*

"...at age 48, I had a brain MRI that showed white matter changes. Six months later, I suffered an acute ischemic stroke... ***to this day, I have some lingering memory, word recall, and processing deficiencies****."*

RMC (adult female patient and parent of child patients)

"As a child, I had fever and chills often. ***Doctors often misdiagnosed me*** *with having juvenile arthritis or thought it was just growing pains."*

"Without his daily dose of pain medicine, my son has difficulty going about his day. ***Something as simple as getting up to go to work [can] be quite the chore****,* ***[even]*** *more when he delivers packages to multiple businesses.* ***Throughout the day, he [will] feel aches and pains from every joint****."*

PG (female teenage patient)

"My dad was diagnosed with Fabry before I was born so ***my parents always knew I had the gene****. When I was born, the geneticist told my parents I would be an asymptomatic carrier and would live a normal life.* ***I started having unexplained fevers, crying spells, and abdominal pain at just a year and a half.*** *My parents, who* ***[are]*** *both doctors, believed what the geneticist had told them and searched for other causes of my symptoms. This led to a lot of doctor and hospital visits with no real answers."*

"My symptoms were so nonspecific... that my coaches, my teachers, and even my family questioned ***whether this was really Fabry or if I was just doing things for attention****."*

"...when I was 14 years old, I started with a ***fever crisis that lasted for 35 days****..."*

"...I became so sick that I couldn't even do virtual school and I almost failed out*. I had previously been a straight-A student in honors classes. I missed out on normal high school experiences and even had to* ***cancel my own birthday party two years in a row****."*

"Having Fabry complicates my decisions. ***There are so many factors that normal kids don't have to take into account****."*

KS (adult female patient and parent of child patient)

"...I am 37 years old. ***For as long as I can remember, Fabry disease has been a part of my life****."*

*"...****I still experience similar symptoms that have progressed since childhood****."*

*"****I've had ringing in my ears for as long as I can remember****."*

"One of the most substantial ways that Fabry affects my everyday life is the constant responsibility of staying on top of my health.... ***[it's] like a second full-time job.****"*

*"****[My eight-year-old]*** *has been on Fabrazyme® for almost two years. This means that every two weeks,* ***this eight-year-old child has to sit for hours with an IV in his arm****, causing him to miss school, interrupting his life, and* ***affecting his ability to live as a typical eight-year-old****."*

Polling Questions, Discussion Panel, and Audience Discussion

After the Panel presentations, Polling Questions (Appendix 5.2) were posed to the audience to gather broader patient input on the symptoms and daily impacts of Fabry disease. This was followed by a moderated Audience Discussion structured around the Discussion Questions (Appendix 3), which were shared with the audience. This discussion included a dialogue with five Discussion Panelists (Appendix 4.1). During the Moderated Discussion, patients and care partners in the audience provided verbal (phoned-in) and written (emailed) comments on their perspectives on the physical, emotional, and social impacts of Fabry disease on their daily lives. Participants also discussed their worries about Fabry disease, how it has affected their immediate and extended families, and what it means for their or their loved ones' futures.

Described below are the results of the Polling Questions, portions of the Panel Discussion, quotes from testimonies, and examples of phoned-in and written comments during the discussion.

Effect of Most Significant Symptoms on Daily Life

Patients were asked to select from a panel of symptoms that they may have experienced (Appendix 5.2; Topic 1: Question 1). The nine symptoms most frequently cited (7% to 10% of respondents) were heart problems or stroke (10%); fatigue (10%); pain in feet or hands (neuropathic pain) (9%); heat or cold intolerance (9%); gastrointestinal issues (nausea/

vomiting, pain, constipation, diarrhea 9%); hearing problems; anxiety or depression; "brain fog" (forgetfulness, poor concentration) (all 8%); and kidney problems (proteinuria, reduced kidney function) (7%) . These were followed by skin issues (such as angiokeratomas) (6%), swelling (such as in ankles, face) (5%), high blood pressure (4%), and lung/breathing problems (4%). Three percent of respondents indicated they experienced "other" symptoms that were not listed; 1% responded that they do not have symptoms (Appendix 6; Figure 6).

When attendees were presented with a panel of symptoms or conditions and asked to select the three that most negatively affect their daily life (Appendix 5.2; Topic 1; Question 2), they identified heart problems or stroke (16%), heat or cold intolerance (15%), and fatigue; (13%), followed by pains in feet or hands, hearing problems; and anxiety or depression (all 9%) and kidney problems and "brain fog" (both 7%) (Appendix 6; Figure 7).

When asked about the daily impact of Fabry disease (Appendix 5.2; Topic 1: Question 3), the majority (61%) of the participants indicated that Fabry disease moderately impacts their daily life while nearly a third (28%) reported that it affects their lives significantly and 6% each indicated that Fabry disease affects their lives minimally or not at all (Appendix 6; Figure 8).

The daily impact of Fabry varied from patient to patient and from day to day. Some patients reported that, on good days, they could accomplish their goals and interact with friends, coworkers, and loved ones normally. However, many participants noted that, on bad days, even the most basic tasks became too challenging, due to heat or cold intolerance, pain, fatigue, or gastrointestinal symptoms. These symptoms affected several aspects of patients' lives, including their jobs and social lives. Patients reported the need to plan cautiously their daily activities, with consideration of how they might be affected by the occurrence of symptoms. Many patients and care partners noted that they limited their plans toward minimizing risks and impacts.

The discussion with the Discussion Panelists and audience members further explored the impact of major and other symptoms in greater detail. Patients' experiences and the effects of these symptoms uncovered by these discussions are detailed below.

Heart problems or stroke

Cardiovascular issues were reported by several participants as both impediments to routine daily life and to participation in physical activities. Cardiovascular health and disease progression were also a constant source of worry for Fabry patients.

> *"I also experience* ***heart palpitations that can come out of nowhere*** *and* ***catch me off guard at my job or during a work meeting****. I also have an* ***incomplete right bundle branch block*** *and a* ***low heart rate...****"*

> *"I had medical procedures, but still experienced* ***hundreds of premature atrial and ventricular contractions daily.*** *And constantly I worry when I feel out of breath. I also have* ***stage one heart block, some dizziness and mild left ventricle hypertrophy****, according to my regular testing."*

> *"...I have* ***even more difficulty exerting myself*** *now in exercise and recreational activities, particularly with* ***progressive lung obstruction from Fabry that causes daily coughing****."*

> *"My second pregnancy... came with* ***more heart rhythm irregularities, like frequent low and high heart rate changes, dizziness, and arrhythmia, as well as sharp stabbing pain[s] in my heart and brain****."*

> *"...what's really hard for me right now is my heart health. I've been having a lot of issues with AFib* ***[atrial fibrillation]****. Of course, the left chamber of my heart is enlarged.* ***It's the one that makes me worry the most...****"*

> *"****[Because of my heart condition from Fabry disease,]*** *there are physical things I cannot do. My family and I just went on a vacation to Colorado, and* ***it's very hard that I can't hike with the rest of them... or just do what they do****.*

Heat and cold intolerance

Temperature intolerance was reported by multiple participants as having a negative impact on their ability to participate in regular daily life. Some participants noted that heat or cold intolerance prevented them from participating in exercise or physical activities; while one Panelist spoke at length about how even the slightest fluctuations in temperature can push her internal temperature off balance. She and others noted that repeated or extended exposure to even mild temperature changes could cause exhaustion and the onset of other Fabry symptoms.

> *"The slightest change in temperature...* ***even two to four degrees, will upset my body****. As I get older, I've noticed that* ***heat and cold intolerance worsens over time****. It takes longer for me to balance out."*

> *"A normal person can warm up or cool down in less than five minutes.* ***For me, it will take hours****."*

> *"****I have a really difficult time playing outdoor sports... when it's very cold out****. The neuropathy in my hand is what really bothers me, to the point where it's hard for me to play."*

> *"...between the kidney damage, hearing loss, infusions, temperature insensitivity...* ***everything we plan... with [our seven-year-old son] is around temperature and weather****."*

"My symptoms continued on and off. As a competitive cheerleader, I would get overheated very easily. I loved cheerleading, but ***the older I got, the less I was able to tolerate the strenuous exercise. I eventually quit, due to the stress on my body****."*

"While my body tries to recover from an episode of temperature fluctuation, ***it works overtime and causes fatigue."***

"Sometimes, ***[when]*** *I am chilled for too long,* ***I feel the onset of flu-like symptoms, along with arthritic-like pain in my hands and feet****."*

"This past summer... we were extremely warm... There were days where ***[sic] I would take two steps out of my house to check my mail and that was it****. Just being inside in the air conditioning, I could tell that I was just more fatigued, and* ***it just zapped all of my energy****."*

*"****There were a few stretches this summer that—literally—I was inside my house for days because of the heat****."*

*"****I can't be [depended] on [for making plans]... if it's a hot day****, I might have to go slow."*

"...the ***temperature sensitivity*** *I experience from Fabry...* ***is the symptom that bothers me most, as it is a daily reminder that I have Fabry disease****."*

Fatigue

Most patients mentioned fatigue as an ever-present symptom. For some patients, fatigue had a major impact on their daily activities and social lives.

*"****One of the most significant symptoms I struggle with is fatigue****. In the one to two days leading up to* ***[ERT]*** *treatment,* ***my body feels like it has been unplugged from its energy source****. To say I am* ***tired does not come close to the level of exhaustion I feel****. Everything is a struggle, from getting my kids dinner to getting up off the couch to use the bathroom."*

"...the ***fatigue [has been the most troublesome of my symptoms].*** *Just going through school and having a hard time in gym class and not being able to play outside with the kids."*

"Imagine waking up every day tired and staying tired throughout that day."

*"****I know immediately, if I've not had a nine-hour solid sleep, that I'm going to be dragging through the day.*** *In the... past few years now, I've had to work part-time, and sometimes I'll work for a few hours and then just sit on the couch, and* ***I'll fall asleep in the middle of the day****."*

"The fatigue is always something that I just plan around, or try to plan around, ***because I never know how in the morning I'm going to feel*** *or what the weather is going to trigger..."*

"With the chronic fatigue, ***I fall asleep at work while on the phone sometimes while talking to people, sometimes while on hold****."*

"As a physician ***[and mother of Fabry disease patient]****, you downplay* ***[fatigue]*** *and you're like, 'Oh, fatigue, you're fine. You can get up and do it.' But when you watch one of these* ***[Fabry]*** *patients do this, all of a sudden, it's very impactful to see them go* ***from perfectly fine to just absolutely miserable and nonfunctional****."*

*"****Fatigue doesn't really describe or encompass what these patients have to go through****."*

Neuropathic pain

A significant portion of patients reported experiencing burning pain in their extremities that started at an early age and, in some patients, continues into adulthood. Some reported this burning sensation as having progressed beyond their feet and hands, and many noted it has a significantly negative impact on their daily lives.

"[As a teen]*, I was often out sick and unable to participate in sports teams or even my gym class.* ***My pediatrician didn't believe me****, and* ***some thought I was just lazy and unmotivated****.* ***I was told to just push through [the] pain and keep going****."*

"I still experience burning hands and feet during a fever, but now in addition, ***[I also experience] full body pain, that significantly limits what I'm able to do until it passes****."*

*"****T****he first symptom that I remember experiencing was* ***burning in my hands and feet*** *when I was sick and when I had a fever."*

"I experienced ***terrible burning pain in my hands and feet*** *and unexplained fevers then, when I was a teen, as well."*

*"****[My husband]*** *is very active recreationally, and I try to keep up, but* ***the burning pain and fatigue keep me from the more rigorous activities****."*

"We'd try to get the schedule switched once ***[our son]*** *got to high school and there was flexibility in that schedule to get his gym class at the end of the day, so that* ***he could attend all his academics right before he did physical activity that would give him a lot of pain****."*

Hearing problems

Several patients and caregivers remarked on the difficulties that Fabry disease-associated hearing loss brings to them and their children at home, work/school, and in their social lives. Although only 9% of respondents reported hearing problems as an important symptom (Appendix 6; Figure 7), for those patients, the impact on their lives is significant.

*"**The hearing part is really, really hard for me**."*

*"I—finally—about 10 years ago had to get two hearing aids for my ears because I couldn't hear very well. **It impacts my job**. I am a teacher, so **I need to be able to hear when people are talking to me**."*

*"It was hard with my two children. **When I couldn't hear what [they] were saying, that was really difficult for me**."*

*"**[When you can't hear, people will]** speak louder, but **it gives you a sense of incompleteness or you're not quite as good as the other kids** because you can't hear as well."*

*"**[My seven-year-old son] has hearing loss...**. The doctors have said they're absolutely open to putting a hearing aid in his ear for school. We opted to not do that quite yet. So, his teacher last year wore... a microphone during class."*

Kidney problems

Despite the significant advances made in the control of kidney disease and preservation of kidney function with ERT, kidney issues remain key problems for many Fabry patients. In particular, Fabry disease can put an additional strain on the kidney during pregnancy.

*"**[During]** my second pregnancy... I also started **spilling more protein in my urine** and had **unrelenting fatigue.**"*

*"**[M]**y wife was **spilling protein while she was pregnant**, so they **had to [deliver] my son early**, so, he has mild cerebral palsy, so he's weak on his left side, which... adds on to **[sic]** how everything affects our daily lives."*

*"I've had three **[kidney]** transplants since **[1987]... stretches of dialysis ranging from six months to upwards of four years**... **that's been the biggest impact on my life and my family and my friends** who have supported me and dealt with all **[of]** that with me."*

*"Sometimes it's hard to **distinguish where the kidney symptoms or conditions start and the Fabry symptoms end** or vice versa... but, **definitely for me, [the kidney issues have] been the biggest challenge**."*

*"**[My seven-year-old] son already has kidney damage**. He had kidney damage early on, so he started Fabrazyme® at four years old."*

Brain fog

About eight percent of respondents to polling cited experience with "Brain fog" (forgetfulness, poor concentration) and about seven percent reported this symptom negatively impacting their daily lives. One patient noted that "brain fog" and associated problems with memory recall caused low self-confidence.

GI issues (nausea, vomiting, pain, constipation, diarrhea)

Gastrointestinal symptoms such as nausea, vomiting, diarrhea, and constipation were noted as having a considerable impact on patients' lives. Several participants cited the difficulty they have planning around unpredictable episodes of gastrointestinal disturbances, and the effect such episodes have on their daily activities.

*"I cannot tell my neighbor I will babysit on Friday because **I may be vomiting uncontrollably**. I cannot plan to go to the movies with my friends next weekend, because **I never know what tomorrow will bring**."*

*"I have occasional gastrointestinal symptoms, including **severe stomach pain, diarrhea, and constipation**. **During these episodes, I'm hesitant to leave my house or even to eat**."*

*"My son... still has a lot of gastrointestinal disruption that is plaguing for him **[sic]** to get to school. There were times where **he'd just be late because he was in the bathroom and his stomach was upset just from eating a little bit of breakfast**, so his first class had a lot of attendance issues."*

*"There were times where I had to pick **[my son]** up and take him home because he **either had an accident or he just didn't want to go to the bathroom there at the public school**."*

Additional Symptoms

Living with multiple organ symptoms

One patient remarked on the impossibility of knowing which issues are symptoms of an ailing organ, given the multisystemic effects of Fabry disease, and which might be side effects from medications being taken and how that complicates dealing with symptoms. Others reported that balancing the combination of symptoms makes certain aspects of life more challenging—or, in some cases, insurmountably challenging.

*"...**Blood pressure, GI [gastrointestinal] issues, related heart issues. The kidneys are so involved in your entire body that my heart symptoms could be family [history of heart disease]; it could be Fabry; it could be kidney related**... the fatigue could be Fabry **[or]** the medicine I'm taking. **It could be all of the [above]...**"*

*"The number one thing is the combination of two symptoms. **Because of the enlarged heart and the insufficient perspiration,** heat and exertion are out of the question. As a result, **I don't take those physical fitness classes that are so important to aging well, and that's a concern to me that I'm not doing the right things for myself because it's the 'wrong' thing for myself to do the 'right' thing[s]**."*

*"I feel **if my fatigue, pain, and depression could be controlled** that it would **significantly improve my life**."*

SOCIAL AND PSYCHOLOGICAL EFFECTS OF FABRY DISEASE

Social Isolation, limitations on daily function, family stress, and participation in activities

Patients were invited to select from a list of eight responses to describe the impact of living with Fabry disease (Appendix 5.2: Topic 1: Question 4). Respondents most frequently (26%) noted that others do not know what it is like to live with Fabry disease. This was followed by not being able to fully participate in sports or other physical activities (20%), feelings of social isolation (15%), and limitations in daily function (13%). Several respondents indicated they are not as independent as they would like to be (10%) and that they are restricted in their level of participation in hobbies (8%). Five percent of respondents reported missing work or school more than they would like or not being able to go at all; 3% of participants indicated that their lives are not impacted by Fabry disease (Appendix 6; Figure 9).

During the Audience Discussion, participants noted that the cumulative effects of having Fabry disease, experiencing its symptoms and treatments lead to a range of social and psychological manifestations, including a sense of social isolation and effects on their relationships with family and friends. Several participants described how their symptoms affected their ability to work at their job or at school. Pain and gastrointestinal issues were noted as challenges to being able to fully participate in work, school, and social activities.

> *"I had previously been a straight-A student in honors classes.* ***I missed out on normal high school experiences****."*

> *"...****Fabry defines my daily life****, meaning not in a bad way, that over these long years of Fabry disease****, I have tailored a life that excludes the things that I can't do... those people I can't enjoy life with****."*

> *"The answer is* ***[that Fabry disease]*** *is very defining of who you're with, and it* ***becomes a 'deal- breaker' that you can't be with certain people****."*

> *"I happen to like to see the world, and I travel as far as I can, as often as I can, but* ***my immersion into those places I go is fairly limited to the more sedentary ways [I] experience it****."*

> *"I don't hike. I don't bike.* ***I don't even walk with exertion. My good day is when it's cool, I can walk a certain amount at a certain pace****, and the distance is correlated to the pace."*

> *"In general, I'm a very organized 'type-A' person. I like to be on time.* ***I'm a planner, but Fabry has made my life unpredictable.****"*

> *"****I'm the person in your tour group who's always at the end****, huffing and puffing when you're thinking, 'Why doesn't she keep herself in shape?'* ***And I'm a drag on a tour. I'm a drag with people who are outdoor people.*** *As a consequence,* ***my friendships are defined by those who are not bikers or not athletic... I can't be in activities with others****."*

> *"I played field hockey in high school, 9th through 12th grade, and invariably****, once per season, I passed out****. It was so commonplace that I would actually hear people on the team yelling, 'She's going down again!"*

> *"The feeling that you need to keep up, you need to keep up appearances because* ***we don't want to let Fabry disease define us, but it is a very real part of us****."*

> *"I have a very visible position at my work... dealing with a lot of people every day and I... feel that I* ***[must]*** *have a smile on my face... be... on top of things, organizing everything. And* ***some days are just so, so difficult****."*

> *"...while I am fortunate to have a very supportive work environment,* ***it's just very difficult for me to always be saying, 'Oh, I need this time off,' or 'I need to work from home****.'"*

Care partners reported about the challenges of supporting a child with Fabry disease at home during elementary school and high school, as well as preparing their children for managing their disease independently for the first time at college or university.

> *"She's incredibly intelligent. She's a National Merit finalist, but* ***we cannot send her off to a good college next year*** *because we can't let her go.* ***She can't even make it to school two days a week right now****."*

> *"We forged the way in our school district for remote attendance before the pandemic happened.* ***So, that was another thing that we had to do****... when he either couldn't make it, or he had treatment."*

> *"****I've had to have my son's school put a 504 plan in place [Section 504, federal law designed to protect the rights of individuals with disabilities] to protect him from failing due to missing school and needing more time for assignments, [because of]*** *missing* ***[school]*** *for infusions or doctor's appointments.* ***You see immediately how this disease is affecting multiple areas of people's lives****."*

> *"****[Because of Fabry, our son] met the maximum of 20 absences in a year*** *and there were a lot of "late"... you could have 15 "lates" that equated to an absence, and he just met the max."*

> *"With college, making those decisions... where to apply,* ***you have to factor in things like, what schools can I work with to help [my son] manage this disease remotely****? He is taking on that responsibility for the first time himself,* ***[managing]*** *all the supplies, and medication, and ordering.* ***It's a lot for any new college freshmen****."*

> *"**I think you can't underestimate what it takes to be a parent in caring for a Fabry patient**, going through a schooling system and whether it's primary school or college, **trying to figure out how to manage a chronic illness and accommodations**."*

Participants remarked about the social isolation they felt with Fabry disease, because the unpredictability of their symptoms makes planning difficult.

> *"As I got older, not going to football games during high school because I was in bed, and during college **having a very limited social life** because I would go to classes and do my schoolwork and be in bed early. **That really has [continued] through my adulthood in socializing with people.**"*

> *"**Now I have to cancel dinner plans or don't make dinner plans** because I know I'm going to have a busy week and I'm just going to have to **take care of myself and rest.**"*

> *"...there was a **prospective romantic situation**, but the man was an outdoors man—couldn't wait for the moment the sun came up—he was outside, hiking, biking, doing as much as he could. **I couldn't participate.** I made the attempt to, **[but] it was a 'deal-breaker**.'"*

> *"The larger impact of all this, and **maybe what's the most important to me, [is] the time I [have] lost with my family and my friends**."*

Participants also noted the isolating effect of having an "invisible" disease that many people do not know about and how that affects mental health.

> *"...**people just don't understand Fabry**. If I said that I had a broken leg or I had some other very well-known disease, then I think people are more understanding. But **[when people do not understand,] it can be very wearing and just cause a lot of frustration and lead to depression as well**."*

> ***"I look normal, but I'm not, and it's very hard for people to understand that**."*

Anxiety and depression

Participants commonly reported experiencing anger, anxiety, and/or depression while coping with Fabry disease and that these symptoms significantly affected their daily lives. For many patients, anxiety and depression were related to the uncertainty surrounding their prognosis, including the unpredictability of recurrence of symptoms, the risk of recurrence of kidney disease after kidney transplant, and how Fabry affects their ability to work or to take care of themselves or their families. They also discussed difficulties in planning for the future and the negative outlook for their quality of life.

> *"**Currently, my mental health symptoms are much more impactful on my everyday life than my physical symptoms**. I suffer from anxiety, and every single day, I wonder, 'What if? What if my kidneys fail? What if I need a pacemaker in my 30s? What if I have a stroke?'"*

> *"**Not being with people is isolating**, which **can also lead to and make my depression worse**, just not being around people."*

> *"**I think it's difficult when you become that person that is constantly missing**, whether as a teen, missing school, missing class, missing certain activities, but also just missing work or just slowing down in your work production. I think that's a difficult point. And I think that **that leads to isolation, that leads to anxiety**."*

> ***"There are days I'm in so much pain or [have so much nausea] or doubled over because of stomach issues, that even when I was working from home, I would have to miss [work]. Employers aren't willing to keep people, so then the depression hits worse. [I'll have]** no job, **[I] can't take care of myself or my family**. And for some unknown reason, you can't get disability for Fabry disease."*

> *"I have found that anxiety and depression are also dependent on many of these other physical manifestations that we experience. **It's very hard to be a positive person if you're experiencing 'brain fog,' exhaustion, and chronic pain**."*

> *"It is an anxiety **[sic]**... when I'm traveling and I know there are going to be group tours and excursions, **I get a lot of anxiety about, 'Will I be that one at the end of the trip again, dragging, people waiting for me while I'm huffing, puffing, turning red?'**"*

Two participants pointed to the lack of perceived importance of mental health relative to physical symptoms.

> *"**Mental health symptoms** are symptoms that **don't seem to be on the radar** as much when it comes to Fabry disease..."*

> *"**For many years physicians and providers have been focusing on the physical manifestations of Fabry disease and not the social/emotional aspect[s] of the disease**."*

Fears and worries

Participants also discussed their concerns about the future (Appendix 5.2; Topic 1: Question 5). Respondents were equally concerned about the following: that their symptoms will get worse (21%); that they will not be able to live independently (19%), they will experience end-stage kidney or heart disease/failure (19%); or that they will experience a TIA or stroke (19%). Respondents also indicated their concern regarding being able to attend school or work or to pursue

a career (10%); that their social and familial relationships will suffer (6%); and that new symptoms will appear (4%) (Appendix 6; Figure 10).

A common theme among participants' remarks was the constant sense of worry that they felt with their disease and the inability to plan for the future, especially in the context of their disease progression, and how increasing disease severity might affect their families, and loss of treatment efficacy.

> *"...my grandmother who had Fabry, she died of a stroke, so I'm always wondering,* ***when is that going to happen?****"*

> *"Knowing how critical the fifth and sixth decades of life are for progression of women with Fabry and* ***knowing that I've hit all the unfortunate milestones so far makes the fear paralyzing at times with this terminal illness****."*

> ***I'm fearful that my body's just going to—all of a sudden—realize that, 'Okay, well, we're just going to go on the decline again because your system is used to this [chaperone therapy].'"***

> *"I've seen the decline with the other enzyme therapies, and* ***I'm very fearful that my body will decline again****."*

> *"Neither one of my children has Fabry disease, so that's my huge blessing.* ***But I do worry about them when I get older, what they feel they're going to have to do for me****."*

> *"****I guess my greatest fear is to be incapacitated and have to have somebody care for me****. I think they would do it, willingly and lovingly. It's not that, but* ***you just hate to think that that would be something that your children would have to do later in your life****."*

> *"...that left ventricular hypertrophy doubles the risk* ***[of heart failure and stroke]*** *makes me cognizant that* ***I must make the plans now with an assumption of that outcome, so that I am not going to become a burden to my family****."*

Fabry disease can also negatively affect the self-image of patients.

> *"****The worst part of having Fabry is*** *not all of the pain or the things I miss out on, but* ***being unreliable... I'm not a reliable student, a reliable employee, or even a reliable friend, even when I try my best to be****."*

Care partners of patients reported worrying about what disease progression will look like for their children with Fabry disease and what they can hope for them in the future. Guilt was also mentioned as an important factor for parents.

> ***"****...all of these worries that I talked about before, I worry for* ***[my child]****, too. I wonder what his years will look like, how his social life will be, but more so his mental health, if there will be effective treatments and a cure in his lifetime.* ***That feeling of guilt that I have every single day can be crippling."***

Children and Family

Many patients reported being one of several individuals in their families with Fabry disease. They discussed the current and generational effects of the disease on their families.

> *"Within my family, there are a* ***double-digit... number of people that have been diagnosed [with Fabry disease]*** *in the last seven or eight years."*

> *"Growing up, there were* ***over 15 family members of mine that had Fabry. I watched my father suffer daily with pain, life-altering GI symptoms, extreme fatigue, hearing loss, and more****. I watched as he received two kidney transplants from family members."*

> *"Raising my teenagers and one having Fabry...* ***I see the same frustrations with them where they've had to tell their boyfriend or their friends that they can't do something and it's because of Fabry and it's very difficult just trying to re-explain it all in all."***

> *"...on the group Fabry support pages, people are* ***hesitating to seek treatment for their kids, [because of] the difficulty [and] disruption that it will cause****."*

> *"****[As]*** *a patient and caregiver, I agree that it* ***is very hard to try to allow your child a normal life and manage this disease****."*

> *"Due to Fabry,* ***[my father] had to miss out on events and activities in our lives****. And now* ***[that he's passed away]*** *he'll* ***miss out on watching his grandchildren grow up, too****."*

> *"My father died when I was 17; had a heart attack when he was 40; died of kidney failure at 43....* ***Nobody knew [why] my daddy died****...now 40 years later, at age 57, I was diagnosed with Fabry disease, and* ***that's when I began to see the symptoms looking back****."*

> *"My sister* ***[and I have]*** *Fabry disease because our father did... My mother would say, 'Donna has lousy lungs and Debbie has loose bowels.'* ***It was just how we were defined****."*

> *"****[I have]*** *four children. We live in Northern Michigan, and* ***all five of us have been diagnosed with Fabry disease****. So, I'm a patient as well as a caregiver."*

TOPIC 2: CLINICAL TRIALS IN FABRY DISEASE

Polling Questions and Audience Discussion

Following a presentation about the challenges of designing clinical trials for Fabry disease, Polling Questions (Appendix 5.2; Topic 2) and Moderated Audience Discussion disclosed patients' experiences with and preferences for participating

in clinical trials, their concerns about participation, and what factors would be important to them when deciding whether to participate in such studies. A Testimony Panel was not implemented for this topic.

Participation in clinical trials for Fabry disease treatments

Participants reported they considered clinical trial participation an important service to the eventual betterment of their own lives, the lives of their children and grandchildren, and to the wider Fabry disease community. Discussion Panelists expressed interest in participating in clinical trials and noted the importance of clinical trials in shaping future treatments. They also noted their eagerness awaiting trials for pediatric patients and those investigating possible gene therapy treatments.

Enthusiasm and preferences for enrolling in clinical trials

> *"**[I am interested in] clinical trials for pediatric patients**, especially in cases **in which patients have developed antibodies to the only available treatment**..."*
>
> *"...**my hope is to get into [a] stem cell study before I retire and not need ERT**."*
>
> *"**Gene therapy trials** need to be expanded, if possible."*
>
> *"...I feel that **by participating in these clinical trials that we're advocating, and we are trying to get something better for our community**."*
>
> ***A sense of altruism was conveyed by several patients when they spoke about participating in clinical trials for Fabray disease.***
>
> *"...**we all have to participate, and unless we participate, we're not going to find help for one another**."*
>
> *"...**we all have to join together and get this done**."*
>
> *"**It's our duty as humans if we qualify [to] do what's necessary to help mankind**. There is no magic solution; research takes time."*

Major factors influencing a decision to enroll in a clinical trial

During the Moderated Audience Discussion, patients noted a spectrum of issues that would influence whether they would enroll in a clinical trial. These ranged from matters of convenience to concerns about physical safety.

When asked in a Polling Question (Appendix 5.2; Topic 2: Question 1) about the top five factors that would affect a respondent's decision to participate in a clinical trial, potential side effects from the trial drug were the most common factor (15%) selected. Respondents indicated as the second most important factors whether they might receive a placebo and whether their physician recommends enrolling in the trial (both 11%), followed by whether their current treatment would need to be stopped before the trial (10%) (Appendix 6; Topic 2; Figure 11).

Also noted as important factors for respondents were whether current treatment would need to be stopped during the trial, the route of drug administration, and how entering one trial may affect their eligibility for a future trial (each 7%). Other factors were the frequency of exam appointments (6%), the length of the trial (6%), whether a kidney, heart, or skin biopsy would be required (5%), the distance to the trial site (5%), and whether specific benefits from the drug have been seen in earlier trials (4%). Few respondents selected the option of participating in an extension trial (3%) (Appendix 6; Figure 11).

Side effects

Panelists spoke about their concerns regarding potential side effects from a study drug. However, side effects that may be similar to those already experienced by Fabry disease patients would not necessarily be a deterrent to participating in a clinical trial. One Panelist who expressed concern about potential side effects conceded such effects would probably not be sufficient to discourage participation in a trial. However, participants noted the importance of being informed before the trial of potential side effects, in particular, ones that may be serious.

Several patients recounted previous adverse reactions to infusion treatments as factors that would influence a decision to enroll in a clinical trial:

> *"I have really bad infusion reactions to Fabrazyme®, so that's **one of the major things—what could the possible side effects be for this [experimental] drug that I am going to take**?"*
>
> *"I don't think that the side effects would be a 'deal breaker'... when I had the **[infusion]** reactions, my throat closed... So, if it's a few added headaches, I take medication daily for migraines. But **if, ultimately, it's going to better my life or my children's lives, then I definitely would be okay with participating**."*

Doctor recommendations

Participants indicated that the opinion of their doctor was very important when deciding whether to join a clinical trial.

> *"**My doctor knows what's best for me. I feel like he cares for me and he knows my disease**. So, I definitely look to see what he has to say."*
>
> *"As a patient, **I would be most interested in a clinical trial option that my doctor believes has potential better results for me than my current treatment**."*
>
> *"**I was not interested in being treated** for Fabry... I didn't think I was severe enough... **but after the insistence of my primary provider... being in a trial has given me a lot more insight [into] how bad the disease has progressed...**"*

*"**[Being in a clinical trial was helpful because], ordinarily, I would not have that kind of information [about my disease]**."*

Barriers in a clinical trial

Patients noted the importance of reducing or removing logistical barriers for entering a clinical trial, particularly considering the other challenges that patients with rare disease face. One caller noted that being excluded from a clinical trial actually resulted in her taking the initiative to make decisions about her treatment that she otherwise might not have considered.

*"...**removing the barriers for patients [is important]**, because**... Fabry patients in particular, want to participate, but if they can't because of simple barriers, just the logistics of the trial, I think it's quite difficult**."*

*"Going into a clinical trial, you really have to consider so many different things. My first was getting on the trial, because **the inclusion and exclusion criteria... can sometimes be difficult**."*

*"**[For]** several of the visits, I would fly down to **[a]** different state... and I would, literally, be in the clinic for an hour just to get a medical history, do an EKG and a blood draw. **Very simple things that could have been done in my hometown** would have saved time, money, and again, **would have reduced the barriers that are put up for so many participants**."*

Therapeutic benefit

Panelists were asked in a Polling Question (Appendix 5.2; Topic 2: Question 2) whether they would be interested in a clinical trial for a drug designed to achieve benefit for the kidney alone, heart alone, or symptoms alone. Thirty-nine percent of respondents reported a preference for benefits to only the kidney, while 28% indicated a treatment that provided benefit to the heart alone would be enough to consider clinical trial participation, followed by a reduction in a specific symptom (e.g., pain, gastrointestinal symptoms, fatigue) alone (25%). Eight percent of respondents indicated that none of these possible treatment benefits would be enough to convince them to enter a trial (Appendix 6; Figure 12).

Respondents indicated that selecting such a clinical benefit for a study drug was difficult, **because the symptoms of the disease vary so widely between individuals, even among family members**.

*"It's kind of difficult to answer that question, because **within my own family, all our symptoms [vary] considerably**. Some members, their kidney function is impacted greatly; others **[it's]** their heart, and other, cerebrovascular issues. We all seem to fall under the umbrella of all these other issues, GI issues, cold and heat intolerance. So, **it's a really difficult question to answer if you're trying to zone in on [just] one [clinical benefit]**."*

*"Probably the kidney function is one of the highest **[priorities]**, for my other family members... for me... and **[for]** one other family member, **[their priority is]** the heart."*

*"...my kidneys are more involved than my heart. So, **if I had to choose one of those, I would say [I'm] probably geared more towards kidney, but I really would want a study that is for the entire progression of Fabry, and not just geared towards one [organ]... or just symptoms**."*

*"**...I would pick neuropathy [as the target of the trial drug]**. That would reduce the symptoms... **I continue to suffer with every single day**."*

Requirement for kidney biopsy

The requirement of a kidney biopsy would influence the decision to enroll in a clinical trial for a Fabry disease treatment in about 5% of patients (Figure 11). One patient independently pursued a kidney biopsy to help her decide on starting ERT.

During the Audience Discussion, patients with experiences in clinical trials voiced their support for these studies and many indicated that they would be willing to participate in another trial, citing a better understanding of their disease and a desire to improve the chances of developing better treatment options for patients with Fabry disease. One Panelist emphasized the importance of lowering barriers to participation that might prevent otherwise willing Fabry disease patients from considering a trial.

TOPIC 3: CURRENT CHALLENGES OF TREATING FABRY DISEASE

The third Discussion Topic focused on patient experiences with treatments for Fabry disease, including challenges of infusions, limitations of treatment options, and their hopes and desires for future treatments. The session began with video presentations from five Fabry disease patients who described their experiences with their Fabry disease treatments (Appendix 4; Topic 3; Testimony Panelists). After these presentations, four Discussion Panelists provided further insights into the challenges of treating Fabry disease (Appendix 4; Topic 3; Discussion Panelists). This conversation was structured around Discussion Questions (Appendix 3) to initiate dialogue with the remote audience. Audience members echoed many of the points made by Testimony and Discussion Panelists and offered additional perspectives on what is needed in the Fabry disease treatment landscape.

Noteworthy excerpts from the patient testimonies are below.

PR (adult male patient)

*"**On the fourth treatment, almost at the end of the infusion, I had an adverse event, where my blood pressure began to rise, my throat began to swell, and my body experienced rigors... Eventually, after nine months of experiencing infusion reactions [and] working with***

my prescribing physician, we came up with a correct premedication regimen of Tylenol®, Claritin®, and prednisone."

CM (adult male patient)

"*Combined,* ***these therapies over two decades amounted to approximately 2,400 hours of treatment, which equals 300 eight-hour workdays****. That's almost a year, and doesn't include time spent at doctor visits, varied and numerous surgeries, dialysis treatment, or* ***the time lost due to the everyday life of a Fabry patient.***"

TW (adult female patient and parent of child patients)

"*Although the burning in my hands* ***never fully subsides****, it's* ***easier to deal with after treatment.***"

JOB (adult female patient)

"*I continue on treatment, and I live on the precipice, hoping not to move into more severe kidney disease and multisystem decline.*"

LW (adult female patient)

"*Each time a new nurse is assigned, I contact my Genzyme rep to do an assessment with the nurse to make sure that they know how to mix and administer the Fabrazyme® properly.* ***Most of the nurses I've had... never heard of Fabrazyme before****... having* ***someone unsure on how to mix it properly is not something I want to deal with when I'm already dealing with my symptoms****. Also, considering how expensive the Fabrazyme is and how badly I need it at infusion time,* ***I need a nurse who knows how to mix the medicine quickly and properly with no waste.***"

Polling Questions and Audience Discussion

In the discussions that followed the Patient Testimonies, participants described their experiences during treatment of their Fabry disease by recounting the successes, limitations, and effects of their current treatment regimens. Many patients indicated that they endured multiple drug regimens.

Polling of the audience revealed that, among the treatments patients were receiving or had taken, the medications most commonly used to treat Fabry disease were ERT (Fabrazyme®, Replagal®) (16% of respondents), ACE inhibitors, ARBs, beta-blockers, diuretics, and other blood pressure drugs (11%), drugs for high cholesterol (11%), and anticoagulants to prevent blood clots (11%) (Appendix 5.2; Topic 3: Question 1; Appendix 6; Figure 13).

Eight percent of participants reported using gabapentin or other anti-seizure drugs for pain, or other drugs, including non-prescription remedies, which were not listed (8%). Some patients had taken anti-depressants or anti-anxiety drugs (6%), an oral chaperone therapy (Galafold®) (5%), drugs to treat gastrointestinal issues (5%), drugs to treat abnormal heart rhythm (5%), or anti-inflammatories or immunosuppressants (5%). Five percent had used hearing aids or drugs for hearing issues (5%). Two percent reported taking treatment for high potassium or high phosphate levels or being on dialysis or having received a kidney transplant. One patient (1%) reported having a heart transplant (Appendix 5.2; Topic 3: Question 1; Appendix 6; Figure 13).

In response to another polling question (Appendix 5.2; Topic 3: Question 2), 44% of respondents indicated that their current treatment regimen reduced their most significant symptoms minimally well, while 33% considered their symptoms are reduced moderately well. Seventeen percent of respondents reported feeling their symptoms are reduced extremely well by their Fabry-specific treatments (Appendix 6; Figure 14) One (6%) respondent felt that their treatment(s) do not reduce their symptoms at all. No respondents said that they did not take any treatment.

Perspectives on Current Treatments

In discussions, patients described the everyday and long-term challenges of enduring ERT treatments for Fabry disease. Although participants expressed gratitude for having access to treatments, and some participants felt the treatments improved their lives significantly, many participants also expressed their frustration about several aspects associated with currently available Fabry disease treatments.

Decision to start treatment

Two patients spoke about their or their sibling's decision to start ERT.

"*My physician's assistant encouraged me to start enzyme therapy, but I was hesitant.* ***The cost and the effort to treat was extensive, and would it really benefit me****?*"

"*...****[my sister]*** *continued to spill protein in her urine, had neuropathy and fevers with overexertion, and... hypertension with ventricular hypertrophy.... **[she] was concerned about her health and decided to start ERT.***"

Current pharmacological treatments taken by patients

Patients spoke about their therapies, which consisted of ERT and numerous medicines for this multi-organ disease.

"*Currently,* ***in addition to Fabrazyme®, I take carbamazepine for pain associated with intolerance to heat, ginger pills to assist with my GI issues, and Eliquis® for reducing blood clots from AFib, Lipitor® [for high cholesterol], and baby aspirin for heart health and prevention of additional strokes.***"

"*I was started on a low dose of valsartan to protect my kidneys.*"

"***[I have taken]*** *immunosuppressants such as* ***tacrolimus, Myfortic®, Imuran®****, and* ***cyclosporine****, steroids such as* ***prednisone****, blood pressure pills like* ***carvedilol, losartan****, and* ***amlodipine****, and a host of other drugs.*"

*"I took **ibuprofen, Aleve®**, and **Tylenol®** every day...."*

*"It's ironic that prednisone, which helps take care of my kidney, can also lead to increased blood sugar levels, **the result of which can bring real damage to that same organ**."*

Benefits of current pharmacological treatments

Panelists spoke about the relief from their many Fabry disease-related symptoms and issues that their current drug treatment regimens bring them. They expressed appreciation for these treatments and spoke about how these therapies improved their lives.

*"...**once I started the [ERT] treatment, I had no idea how bad I actually felt [before treatment]**."*

*"I do also have a heart condition and [with] Fabrazyme® in the last year, **nothing has [progressed].** And **[as for]** my kidneys, the numbers are better, and it's just amazing to me, so I'm so grateful to Fabrazyme®. "*

*"I really think, right now, **the chaperone drug is helping immensely** because I don't have that 'up-and-down' on day 10 or 12, when people would say at work, 'Oh, you're due for infusion, aren't you?' And it's like, how do you know? And they go, 'We can tell it by your eyes. You're exhausted.' I was like, 'Oh my gosh.' It hit me weird, but then when I got on chaperone, there's no ups and downs. **There's not that wave**."*

*"**[With Fabrazyme®]**, I had many TIAs, I was going every two to three months... to the hospital. And **[while on the chaperone], I've seldom had TIAs now** and it's been three years."*

*"Just the pain crises alone—**I can manage them so much better**."*

*"I feel now that **the only way I know that I have Fabry disease is that I'm taking a [chaperone therapy] pill every other evening**, otherwise I don't have to remember it. The fatigue is so much less."*

*"The plus side to it is that **[Fabrazyme®]** has helped alleviate the pain in my hands and my feet. I had a **strange rash on my hands and my feet for 10 years**, and **it's gone**. I mean, it's just amazing."*

*"**I can participate in a lot more things now because of the enzyme replacement therapy...** it's been really great."*

*"**In part, ERT has provided me with the opportunity to not only survive, but to live a fulfilling life**."*

Challenges of current pharmacological treatments

Although grateful for the availability of ERT treatments, many patients often voiced displeasure with various aspects of this therapy, including inconvenience, issues related to efficacy and duration of effect, and physical effects of the therapy and its related procedures.

When polled about what they considered to be the biggest drawbacks of their current treatments (Appendix 5.2; Topic 3: Question 3), 27% of participants indicated that their treatment addresses some but not all their symptoms and health issues. Many (18%) indicated that the route of administration is a challenge, while others noted that their treatments require too much effort and/or time commitment (15%), have too high a cost or co-pay that is not covered by insurance (13%), and/or are not very effective at treating target symptoms or health issues (12%). Five percent of respondents indicated the most significant drawbacks of their current treatments were the limited availability or accessibility of the treatment, side effects, and/or other aspects not listed (Appendix 6; Figure 15).

(In)convenience of current pharmacological treatments

*"...**the reality of spending a full day, every other week, for the rest of our lives, hooked up to an IV is disheartening and overwhelming**."*

*"I'm happy to have the treatment, but **I feel like my life is centered around Fabry and infusions**."*

*"The **time involved** on a biweekly basis for ERT is **very difficult and interferes with life's plans,** as well causes damage to veins."*

Physical effects of current pharmacological treatments

*"**After many years of infusing, the veins start to collapse and become scarred**. This makes it harder to access them. I wouldn't want to go through getting a venous access port because it might create more issues to deal with, like infection along with pain."*

*"I have lived with the side effects of medications that help support my kidney health, treat my heart disease, and manage related conditions... All of these and other **medications** have been necessary and life-sustaining for me, but they also **have had an impact on my body** that includes **arthritis, enduring foot pain, blood sugar challenges, gastrointestinal issues, and fatigue,** just to name a few."*

*"I've had **three ports replaced in four and a half years**, and my **daughters have had their ports repaired or replaced twice each**."*

Efficacy, duration of effect of current pharmacological treatments

*"The **fatigue [on Fabrazyme®] was just extreme** on days 10 through 14 **[following treatment]** and even the day after infusion because of the Benadryl® **[to mitigate infusion/allergic reactions]**"*

*"…. the days **leading up to treatment, my hands become beet red with white splotches, very hot to the touch, swollen, and it's painful to bend my fingers at the joints**."*

*"The one downside is… **[that]** at **about 10, 11 days after the enzyme [treatment], I start to have the fatigue again**."*

*"**While taking Galafold®, I had more energy and my gastrointestinal symptoms improved**. However, although I have a mutation that helps Galafold® to be effective, **it appears that the enzyme activity in my body was still not increased sufficiently. My Lyso-GL-3 level was still high**."*

*"Between the stroke and my rise in the Lyso-GL-3 level while on Galafold®, my physician urged me to transition back to Fabrazyme®. Without an agreed upon set of parameters to monitor in order to determine if the Galafold® is effective, **she was skeptical that it was working for me."***

*" **I don't feel Fabrazyme® or Galafold® have improved my Fabry symptoms**, except for sweating."*
*"Fortunately, I'm able to work remotely while receiving ERT, because **immediately after, I feel run down and don't have the energy to do much of anything**. I have noticed, **while being back on Fabrazyme® that my overall energy level has decreased as well, compared to when I was on Galafold®**."*

*"The infusions help ease some of the pains in my hands and feet a little bit**. I usually feel a difference in how I feel within 24 hours after the infusion, and it helps for about 10 to 12 days**, but **the infusions haven't made too much difference with the 'brain fog,' as that continues to be an issue**."*

*"**[Fabrazyme®] was great** for the first couple years, and **then, I just noticed a decline. [I]**t worries me now, even with a chaperone **[therapy]**."*

*"**[My teenage daughter]** initially made some progress with the Fabrazyme®, but now she's **developed antibodies [to the enzyme] and is symptomatic again**."*

In-center infusions of current pharmacological treatments

Patients described in detail the challenges of scheduling their lives around infusion treatments. Many described long treatment days (6 to 8 hours) that were compounded by long travel times to and from the treatment clinic.

*"The treatments were every two weeks… they had me in **[the treatment]** center for **over eight hours, not counting that 30-to-45-minute commute each way**."*

*"**[Switching to ERT was]** a challenging change, as **it involved a much lengthier infusion process**, which was upwards of four hours, as compared to the one-and-a-half hours on Replagal® **[during clinical trial]**. All in, I was looking at a **six-hour process every other week**."*

*"The treatment **[was originally]** an infusion every two weeks. We began our treatment at a short stay unit in a hospital about two hours away. Once we arrived, the nurses could order our medication and we were prepped for infusion. **The entire process, from start to finish, usually took about five hours. Combine that with a four-hour round-trip drive, and [the] treatment day was very exhausting**."*

*"Currently I'm seeking to switch my treatment to Galafold oral therapy. This change would **potentially vastly improve my work/life balance, as well as eliminate the need to travel to an infusion center and endure a multi-hour treatment**."*

*"**The eight-hour infusion consumed my entire day**. The ambulance service would pick me up at 7:00am… and I would finish around 6:00pm. Once… **[back]** home, I would just eat something and go to bed."*

Home infusions of current pharmacological treatments

Participants who are able to have home infusions expressed their appreciation for this option. However, many participants also noted that, while home infusions save travel time, in-home treatments come with their own set of frustrations and challenges.

*"**Home infusions are a lot more convenient than going to an infusion center**."*

*"My infusions are every two weeks… now they are conducted at my home by my infusion nurse… **I don't have to drive the two and a half hours to my infusion center and can have them done in the privacy of my own home**."*

"It's more work compared to the short stay unit. But… staying home, I don't have to stay awake for the drive home after a five-hour infusion."

*"**Being responsible for ordering all the supplies for three people, as well as medications, can be stressful**."*

*"**On two different occasions, Fabrazyme® has not made it in time for our infusion day**. On one occasion, the meds went to Australia. By the time the med**[s]** reached our home, they had to be discarded because they hadn't been kept cold."*

*"**While my two non-treated children understand that we have Fabry and we are well aware of treatment days, it is difficult for them because [even though we are at home during treatment]**, our lives are limited,*

no walks to the park, no swimming in the pool because I'm not there to watch them, no friends over. Constant reminders to ***watch our [infusion] tubes and poles****."*

"Sometimes ***UPS*** *would come back to our house two and three times a day because they've* ***missed boxes in our delivery****."*

*"****If our home nurse isn't qualified or able to resolve the issue, then we're forced to go to the local emergency room****."*

*"****Sometimes the venous access ports cannot be accessed for whatever reason. Then we can't get our treatment****. Whereas if that happened at a facility, other nurses or professionals might be able to help resolve the issue."*

"Anytime I want to plan something or schedule anything, ***I have to be mindful to make sure that it's not on a supply delivery day or an infusion day****. And infusion days are subject to change,* ***which creates even more uncertainty****."*

*"****A lot of supplies are also required to do home infusions****. This means a lot of storage space is necessary."*

Infusion reactions from current pharmacological treatments

Some participants spoke about infusion reactions they have experienced during their ERT infusions.

"Almost at the end of the infusion... ***I would get rigors*** *and the nurse would put a heated blanket on me. This didn't help the situation because I wasn't cold, and my heat intolerance made having a heated blanket on me even more uncomfortable."*

"For the first two years, about an hour into treatment, ***I would experience gut-wrenching cramps, followed by diarrhea. It would last the entirety of the treatment and into the evening, once I was home****. Thankfully, this symptom has since stopped."*

"I felt ***extremely tired after the infusions****, due to the Benadryl® and Tylenol®, but these pre-infusion medications are* ***necessary to reduce the possibility of allergic reactions****."*

Current non-pharmacological treatments and remedies

Patients also shared non-pharmacological approaches they have found helpful in managing their Fabry disease symptoms. These included: integrated medicine, functional medicine, [non-medicinal] supplements under medical guidance, some regenerative medicine, anti-aging [treatments], Pilates, lifting weights, yoga, and diet.

Kidney transplants and dialysis

Participants who had or who had loved ones who received a kidney transplant(s) or endured dialysis spoke of their experiences and the varied impacts of these procedures.

Perspectives on an Ideal Treatment for Fabry Disease

Polling Questions assessed participants' views on an ideal future treatment for Fabry disease. To a Polling Question that asked the audience to select attributes of a future ideal treatment for Fabry disease, without regard to side effects (Appendix 5.2; Topic 3: Question 4), 25% of patients desired a drug that would prevent stroke (Appendix 6; Figure 16). The preference of 18% of respondents was for an agent that slows or stops progression of their overall condition (without improving symptoms), while another 18% reported a preference for slowing the decline in heart function. Sixteen percent preferred a treatment that improved their symptoms.

Fourteen percent of respondents chose a drug that would prolong their life. Five percent of respondents responded that an ideal future drug would slow the decline in kidney function (Appendix 6; Figure 16).

During the Audience Discussion, patients expressed a spectrum of preferences for an ideal future drug for Fabry disease. These amplified the responses to Polling Questions and extended into topics such as route of administration, duration of action, genetic treatments, cures, and improvements in quality of life.

Preventing stroke

A treatment that can cross the blood-brain barrier and prevent strokes and TIAs *is very, very important to me."*

"I think ***preventing stroke is something for all of Fabry patients****. That would be a wonderful thing to see developed."*

Slowing progression

*"The most important things to me are****, will the treatment slow the progression of the disease? Is it safe?*** *While life would be easier with a simpler treatment option,* ***I'm unwilling to sacrifice effectiveness****."*

*"****Slowing or stopping organ involvement (including brain) would be important factors****."*

"I have a ***13-year-old son****. He* ***started infusions when he was five****, so* ***anything that prevents him from losing kidney function and having to be on a kidney transplant list... anything that can keep him where he is and keep that disease from progressing in his major organs****."*

Several patients and parents voiced their passion for new treatments to prevent disease progress in young people.

"A cure would be amazing. ***I would love to be able to see my son's children grow up.****"*

*"I would love a cure... my daughter and my grandson have Fabry. My grandson has been on infusions since age seven. My biological father died of kidney disease in his forties... **I want a cure for the young people**."*

Improving symptoms

*"We need **medications that... address all, or at least most, of our symptoms**."*

*"Something that **doesn't require being premedicated,** a treatment that's going to help **eliminate more pain and reach the brain**."*

*"I would love to... make my GI symptoms go away **[and]** be able to handle heat and cold intolerance, but I don't feel like I may lose my life over **[them]**. I think that **[treating]** those would make my life better... **but the kidney and the heart really can lead to the morbidity.**"*

*"...I would **hope [for] something... that would dull my pain**, because that's something that hasn't gone away."*

Genetic treatments

*"...I would like **an oral treatment that is not specific to the genetic mutation of a patient**."*

*"...**I would sign her [daughter] up [for gene therapy if it were available] knowing the risks... we would start tomorrow**."*

*"I am very **interested in the gene experiments** now going on. I'm looking for a cure. Even at my age, I think **it's not too late to look for maybe not having to take medicine again**."*

*"**[I want] to expand [gene therapy] treatment to kids**. Watching **[my daughter] has** been the worst thing in my life. **It's very frustrating that [the gene therapy trials are] not expanded to children**."*

Route of administration and duration of action

*"A treatment that could be done **one [month apart or further]** would be extremely helpful in reducing the amount of medical appointments per week/month."*

*"**Extending the drug's half-life to allow monthly infusions would be a significant improvement to my life**."*

*"**I would like to have a treatment that doesn't require accessing a vein for each infusion**."*

*"I would like to have something like a **daily pill or something monthly**."*

*"For infusions, we need **more medications that do not create adverse events**."*

Quality of life

*" **Being able to travel while not missing treatments** is very important to me."*

*"A treatment that doesn't require **so many supplies**."*

*"Beyond the heart and kidney challenges I face; **I want to worry less** about my GI issues during a car trip or when visiting friends. **I want to have increased confidence** that my 'brain fog' has been reduced to a level which allows me to be more confident in my memory recall. **I want the chance to spend more quality time with loved ones** and fully enjoy the life that my donated kidney has brought me."*

*"As I look to the future, I pray for Fabry **treatment options that will allow me to just be more normal**."*

*"I want a treatment that will let me see my daughter, who also has Fabry disease, graduate from college, begin a career, and maybe get married... **I want to hold her child in my lap**."*

CONCLUSIONS

This EL-PFDD Meeting on Fabry disease, held by the National Kidney Foundation and Fabry Support & Information Group, provided the FDA, product developers, clinicians, and academic researchers an opportunity to hear in-depth patient views on the challenges of living with Fabry disease, the impact on patients' daily lives, their experiences with, and views on, clinical trials, and their experiences with currently available treatment options.

Major themes that emerged from patient discussions in the meeting were:

Symptoms from **cardiovascular, neurological, kidney, and gastrointestinal involvements** associated with Fabry disease cause enormous **daily burdens** to patients living with Fabry disease.

- Patients often expressed a fear of **progressing to more serious heart or kidney disease** and shared their concerns about **having a debilitating neurological event**, with particular concern for the possibility of becoming even more of burden to their families.
- Patients shared their experiences with **kidney transplant(s)** and noted that this procedure sometimes addressed only kidney involvement and did not alleviate other Fabry-associated symptoms.
- The above concerns, coupled with **constant pain** and **unpredictability of symptom onset** in Fabry disease contribute to **depression, anxiety**, and a sense of **hopelessness** in patients. Accordingly, patients expressed the importance of **treating and supporting mental health** together with treating the disease.
- The **fatigue** associated with Fabry disease and some treatments significantly affect patients' daily lives and their ability to participate in work, school, and social activities.
- The invisible nature of Fabry disease and unpredictability of its symptoms causes **social isolation** and a disconnect between patients and their friends, families, coworkers, and peers.
- Patients emphasized their feelings of commitment and responsibility to the **Fabry community as a reason to participate** in clinical trials. Although there were some **concerns about potential side effects or efficacy**, overall, Fabry patients shared a strong conviction about the importance of contributing to futures of all Fabry patients by helping further research into better treatment options.
- The majority of patients reported that **currently available treatments do not adequately address their symptoms**. All patients emphasized the negative impact that **frequent and lengthy treatment infusions** have on living and planning their lives. An ideal treatment for most patients would be **more convenient, less time-consuming**, less costly, and would **allow more flexibility for planning**.
- Patients expressed their **fears about their children's disease progression** and their worries about their children's transition to independent management of their own disease. Patients shared their wishes for better treatment options and better lives for their offspring and their families as well as their desires to be **able to manage their own disease for as long and as well as possible**. They also expressed **fears of not being able to be a part of their children's and grandchildren's lives** as they grow.

The FDA expressed sincere thanks and admiration for the patients' courage and willingness to share their experiences and insights at the EL-PFDD meeting.

INCORPORATING PATIENT INPUT INTO A BENEFIT-RISK ASSESSMENT FRAMEWORK FOR FABRY DISEASE

In recent years, the FDA has adopted an enhanced approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics to support certain regulatory decisions about NDAs or BLAs, from pre-market approval through the post-market setting.[11] The Benefit-Risk Assessment Framework involves assessing four key benefit-risk dimensions: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, and *Risk and Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains the FDA's rationale for its regulatory decision.

In the Framework table, the *Analysis of Condition* and *Current Treatment Options* rows summarize both the severity of the condition as well as the nature and impact of the therapies currently available to treat the condition. The assessment provides an important context for drug regulatory decision making, providing information that can help inform the weighing of specific benefits and risks of a particular medical product under review.

The information for *Analysis of Condition* and *Current Treatment Options* in the following sample Framework table for Fabry disease draws from patient contributions at the EL-PFDD Meeting on Fabry disease held on September 19, 2022. This sample Framework table contains the kind of information that may be anticipated to be included in a Framework completed for a Fabry disease drug treatment under review.

Dimension Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Fabry disease affects children and adults, males and females. • The symptoms that most negatively affect daily life of Fabry disease patients include: • Heart problems/stroke • Heat/cold intolerance • Fatigue • Pain • Hearing problems • Anxiety/depression • Kidney problems • "Brain fog" • GI issues • Disease symptoms and current treatments prevent patients with Fabry disease from fully engaging in work, school, physical, and social activities. • Anxiety, depression, other emotional difficulties derive from: » Feelings of social isolation » Patient's current symptoms » Fears and uncertainties regarding unpredictability of disease progression of kidney and cardiovascular disease, and long-term efficacy of treatments. » Low empathy from others » Limited daily function/ability to fully engage in personal and work life » Curative treatment options for Fabry disease do not exist.	• Fabry disease is a debilitating disease, affecting mainly heart, kidneys, and the nervous system. • Males and females, all ages are affected. • Patients experience reductions in quality of life; reduced ability to fully participate in life. • Currently available treatments for Fabry disease: » Do not fully meet the efficacy expectations of patients. » Rely on infusions (disliked by patients). » Are lengthy (infusion time). » Infusion reactions and side effects of medications for managing infusion reactions compound disease symptoms. » Include chaperone therapies that are available only for patients with a specific genetic mutation. » May induce antibodies against the replacement enzyme. » Patients feel infusions are too frequent and lengthy and may involve long travel distances to treatment center. » Home infusions eliminate travel but add complexity and uncertainty (managing delivery, supplies, and unexpected treatment events).
Current Treatment Options	• Current treatments (enzyme replacement therapy; ERT) do not fully address Fabry disease symptoms. • Infusion treatments are time consuming, frequent, and benefits may wane toward the end of the treatment cycle. • ERT infusion reactions are of significant concern to patients. • ERT may induce antibodies to the replacement enzyme. • Patients often also receive ACE inhibitors, ARBs, diuretics, statins, and anti-coagulants to control multisystemic disease factors. • Kidney transplantation is a viable option for Fabry disease patients who have reached ESKD.	• Patients seek more convenient (i.e., daily oral or injection) and/or less frequent treatment options that would give them more flexibility to live and plan their lives. • Ideal treatments would be designed for all Fabry patients, not just to target specific symptoms or genetic mutations. • In particular, patients expressed hope for the potential of gene therapy. » Patients are willing to participate in clinical trials for Fabry in part if: • Chance of side effects from test drug are low » They will not receive placebo » Trial is recommended by nephrologist » No need to stop current treatment before or during the trial » Route of administration of drug is acceptable » Eligibility for future trials is not jeopardized

APPENDIX 1: REFERENCES

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APPENDIX 2: RESOURCE MATERIALS

MEETING AGENDA AND PRESENTATIONS

PDFs of the meeting agenda and presentations can be downloaded from: *https://nkf.egnyte.com/fl/1c7IpmyVuP*

MEETING RECORDINGS

The meeting recording can be viewed on the *Externally-Led Patient-focused Drug Development Meeting on Fabry Disease* page of the websites of the National Kidney Foundation *https://www.kidney.org/externally-led-patient-focused-drug-development-el-pfdd-meeting-fabry-disease* and Fabry Support & Information Group

https://fabry.org/

APPENDIX 3: DISCUSSION QUESTIONS

TOPIC 1: LIVING WITH FABRY DISEASE: DISEASE SYMPTOMS AND DAILY IMPACTS

1. Of all the symptoms that you experience because of your condition, which 1-3 symptoms have the most significant impact on your life?
2. Are there specific activities that are important to you but that you cannot do at all, or as fully as you would like, because of your condition?
    a. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
3. How have your condition and its symptoms changed over time?
4. What worries you most about your condition?

TOPIC 2: CLINICAL TRIALS IN FABRY DISEASE

5. If you knew a clinical trial was planned for Fabry disease, what information would you want to know to inform your decision on enrolling in the trial?
6. In which type of clinical trial would you be more likely to enroll:
    a. A trial that studies safety of a new drug for Fabry disease
    b. A trial that studies how well a new drug manages the underlying cause of kidney damage in Fabry disease but does not study symptoms or progression
    c. A trial for a drug designed to do one of the following even if it did not slow or stop the overall disease progression:
        i. Benefit to the kidney alone
        ii. Benefit to the heart alone
        iii. Reduce symptoms (eg, pain, GI involvement, fatigue) alone
    d. A trial to study if and how well a new drug reduces symptoms of Fabry disease
    e. A trial to study if and how well a new drug reduces progression of Fabry disease
7. For parents of pediatric patients: Are you interested in enrolling your child in a clinical trial? If so, what factors would you consider in deciding whether to participate (e.g., age, whether symptoms have begun, whether already on ERT)? If not interested, why?

TOPIC 3: CURRENT CHALLENGES OF TREATING FABRY DISEASE

8. 1. What are you currently doing to help treat your condition or its symptoms?
    a. How has your treatment regimen changed over time, and why?
9. How well does your current treatment regimen treat the most significant symptoms of your disease?
    a. How well do your treatments address specific symptoms?
    b. Which symptoms are not addressed as well?
10. What are the most significant downsides to your current treatments and how do they affect your daily life?
11. What factors would be most important to you if you were considering participation in a clinical trial for Fabry disease?
12. Assuming there is no complete cure for your condition, what specific things would you look for in an ideal treatment for your condition?

APPENDIX 4: PATIENT PARTICIPANTS, TESTIMONIES

APPENDIX 4.1: PATIENT PARTICIPANTS

Topic 1. Living With Fabry Disease: Disease Symptoms and Daily Impacts

Testimony Panelists

KK — Adult female patient and parent of child patient

RMC — Adult female patient and parent of child patients

PG — Female teenage patient

KS — Adult female patient and parent of child patient

Discussion Panelists

DH — Adult female patient

CM — Adult male patient

MN — Adult female patient

DVF — Adult female patient

CD — Adult female patient

Topic 2. Clinical Trials in Fabry Disease

Discussion Panelists

SK — Adult patient

KL — Adult patient

KG — Adult patient and caregiver of adult patient

Topic 3. Current Challenges to Treating Fabry Disease

Testimony Panelists

PR — Adult male patient

JO'B — Adult female patient

LW — Adult female patient

CM — Adult male patient

TW — Adult female patient and parent of child patients

Discussion Panelists

LT — Adult female patient

CB — Adult female patient

JG-V — Adult female patient

MFH — Adult female patient

APPENDIX 4.2: PATIENT TESTIMONIES

Topic 1: Living With Fabry Disease: Disease Symptoms and Daily Impacts

KK (adult female patient and parent of child patient)

My name is KK. I'm 53 years old and live outside of New York City in Maplewood, New Jersey, with my husband and two boys. For work, I'm a leader of human resources for an investment bank in the city. I was diagnosed with Fabry disease at birth in 1969 because my father was diagnosed when my mother was pregnant with me. He was referred to a dermatologist due to a large amount of the angiokeratomas on his trunk and that led to his own diagnosis. All his teen symptoms of pain and fever finally made sense. It quickly progressed to kidney failure in his early 30s. His brother also died suddenly from Fabry at age 34 of a stroke.

Fabry disease is multi-generational, and I'm just one of seven in my family known to have or are suffering from this disease. I watched my father in a constant state of health crisis, endless pain and suffering, with his body and mind deteriorating. At age 52, he called ma at college to tell me he was giving up to suicide.

In my early 30s, I was told that my symptoms meant that I was not just a carrier, I'm also burdened with the progression of the disease. It all made more sense for me as well that I experienced terrible burning pain in my hands and feet and unexplained fevers then, when I was a teen, as well. I often took very uncomfortable cold baths to bring down my temperature, which would relieve the burning. And I was often out sick and unable to participate in sports teams, even my gym class. My pediatrician didn't believe me, and some thought I was just lazy and unmotivated. I was told to just push through [the] pain and keep going.

I married in my 30s and shared a love for being outdoors, hiking, skiing, camping, and fishing with my husband. He's very active recreationally, and I try to keep up, but the burning pain and fatigue keep me from the more rigorous activities. We started a family, and in my first pregnancy, I had the baby tested in utero for the disease. I'll never forget receiving the devastating call that he had Fabry. We hope[d] that treatment would be available for him early as a child.

We didn't want to take a chance with our second. So, I went through the arduous and expensive process of IVF and pre-implantation genetic diagnosis to ensure that he wouldn't have it. And I'm happy to say it worked. My second pregnancy, however, came with more heart rhythm irregularities, like frequent low and high heart rate changes, dizziness, and arrhythmia, as well as sharp stabbing pain[s] in my heart and brain. I also started spilling more protein in my urine and had unrelenting fatigue.

In 2010, after multiple emergency room visits for heart rhythm problems, I was diagnosed with atrial fibrillation. I had medical procedures, but still experienced hundreds of premature atrial and ventricular contractions daily. And constantly I worry when I feel out of breath. I also have stage-one heart block, some dizziness and mild left ventricle hypertrophy, according to my regular testing. And I have even more difficulty exerting myself now in exercise and recreational activities, particularly with progressive lung obstruction from Fabry that causes daily coughing.

In 2018 My husband found me that awful morning unable to speak with limited movement on my right side. It was very fortunate that it was within the critical window of time, but I was unable to work for six months while in rehab. And still to this day, I have some lingering memory, word recall, and processing deficiencies.

My professional life and maintaining some income security and insurance for the family has been a big part of my life. I suffer from extremity pain and relentless fatigue daily, and most days feel like a zombie. My work performance at times has suffered and I overcompensate with a strong work ethic but wonder really how long can I keep it up. Knowing how critical the fifth and sixth decades of life are for progression of women with Fabry and knowing that I've hit all the unfortunate milestones so far makes the fear paralyzing at times with this terminal illness.

My 18-year-old son represents hope. He's never missed a dose of ERT since he was a toddler and has managed to find the energy to play moderate sports and achieve at school. But he's more tired than his peers. He has plaguing gastrointestinal problems common with Fabry, and he worries what will come with the disease. For me, having just turned one year older than my father made it with this disease, I hope to be here longer to see a better future for my son.

RM (adult female patient and parent of child patients)

Hello, my name is RM. My husband and I have been married for 16 years. Our blended family has a total of seven kids. My 24-year-old son from a previous marriage and my 10-year-old daughter that my husband and I share also have this disease. Fortunately, my daughter currently shows no signs of Fabry. My son's symptoms differ from mine. He started feeling symptoms of tiredness and stomach aches when he was a teenager, but at 18 years old started to experience a higher level of pain, often treated with prescribed pain medication. Without his daily dose of pain medicine, my son has difficulty going about his day. Something as simple as getting up to go to work [can] be quite the chore, [even] more when he delivers packages to multiple businesses. Throughout the day, he [will] feel aches and pains from every joint.

As a child, I had fever and chills often. Doctors often misdiagnosed me with having juvenile arthritis or thought it was just growing pains. Finally, I was officially diagnosed 15 years ago when I had a Fabry crisis. It was a cold day in December and snow had fallen the day before. I remember going to the store dressed in sweatpants and boots. I remember feeling chilled to the bone and could not get warm. Suddenly, I felt drained and had to close my eyes and lay down. The next thing I knew, I had a fever. I could barely move [and] drifted in and out of sleep. When I looked in the mirror, my entire face was swollen. That had never happened before. That was when my primary care doctor introduced me to my nephrologist.

My husband and I work full time and our lives are very busy. A typical day for me begins as early as 9:00 AM when I reach for The Weather Channel, so I know how to dress for the day. This sounds really trivial, but it is very important for me, because of the temperature sensitivity I experience from Fabry. This is the symptom that bothers me most, as it is a daily reminder that I have Fabry disease.

The weather here in Washington State is mild with a lot of rain mixed throughout the year. 75 degrees with a mixture of sunshine and a little cloud [cover] is ideal for me. The slightest change in temperature, however—even two to four degrees—will upset my body. As I get older, I've noticed that [the] heat and cold intolerance worsens over time. It takes longer for me to balance out. Although I rarely sweat, I find that it is easier to cool down from being too hot than to warm up after being cold. I can take a wet towel over my neck and grab an ice-cold drink to cool down and stay out of the heat. However, being in an air-conditioned room for me too long gets tricky. A normal person can warm up or cool down in less than five minutes. For me, it will take hours.

Washingtonians are often advised, especially those new to the state, to dress in layers so you can take off and put on clothing as needed. I do that and more. In my car, I have a heavy jacket with gloves stored inside the pockets. And in my classroom, a blazer hangs over my chair. I'm often seen wearing cardigan, even during summer. While my body tries to recover from an episode of temperature fluctuation, it works overtime and causes fatigue. Sometimes, [when] I am chilled for too long, I feel the onset of flu-like symptoms, along with arthritic-like pain in my hands and feet. Eventually, whatever I have planned for the rest of the day starts to fall off my schedule. I cancel planned dinners [or] outings with my kids. I go home, take a nap if I have to, and shut the world away. Fabry has impacted my life with something as simple as feeling a draft when someone walks into the room while I am in the shower. Being diagnosed so many years ago and regularly going for six-hour infusions of Fabrazyme every two weeks has helped minimize the worsening of symptoms. When I miss a scheduled infusion, my body reacts. I become more sensitive to temperature changes, easily fatigued, and pain becomes heightened. I used to overextend myself and attend every activity, every event so as to not disappoint myself, my family, and my friends. However, that did me no good. My body would rebel. It takes time, even years, to learn these lessons. So, I do what I can by being prepared first thing in the morning. I reach for my Weather [Channel], dress in layers, check off my daily to-dos, and go about my day.

PG (female teenage patient)

Hi, my name is PG. I'm 17 years old and live in Baton Rouge, Louisiana. I am a senior in high school. My dad was diagnosed with Fabry before I was born so my parents always knew I had the gene. When I was born, the geneticist told my parents I would be an asymptomatic carrier and would live a normal life. I started having unexplained fevers, crying spells, and abdominal pain at just a year and a half. My parents, who [are] both doctors, believed what the geneticist had told them and searched for other causes of my symptoms. This led to a lot of doctor and hospital visits with no real answers. I was diagnosed with strep, flu kidney infections, and many other illnesses that didn't seem to fit just right. It got to the point that my parents and the doctors all thought I had anxiety or psychological problems and sent me to see a psychiatrist.

My symptoms continued on and off. As a competitive cheerleader, I would get overheated very easily. I loved cheerleading, but the older I got, the less I was able to tolerate the strenuous exercise. I eventually quit, due to the stress on my body. My symptoms were so nonspecific and hard to pinpoint that my coaches, my teachers, and even my family questioned whether this was really Fabry or if I was just doing things for attention.

In 2020, when I was 14 years old, I started with a fever crisis that lasted for 35 days. For an entire month, I had fevers. I took ibuprofen, Aleve, and Tylenol every day, but nothing brought down my fever. I saw doctors and went to the hospital, but no one could find anything wrong. I didn't leave the house and I missed a month of school. Every time I would try and go to school, my fever would go up and I would have to go home.

Luckily for me, a few weeks later, everyone got sent home from school due to COVID. This is when my parents suspected that the geneticist who told them I would be an asymptomatic carrier was wrong. I wasn't crazy and just a difficult child, I was really sick. I started Fabrazyme infusions. No one could say for sure if my symptoms were due to Fabry. My local geneticist said the fevers weren't related. I became so sick that I couldn't even do virtual school and I almost failed out. I had previously been a straight-A student in honors classes. I missed out on normal high school experiences and even had to cancel my own birthday party two years in a row. I ran fever while taking the ACT for my high school and had to go home immediately after. I became so consistently sick that I felt like I would never get better. It took about 18 months on Fabrazyme for me to be somewhat normal again. We do my infusions at home, so I won't miss school. I am back to in-person school and missed only 20 days last year. That is a huge accomplishment for me. I still have fevers, vomiting, and headaches several days per week, but at least they aren't every day.

The worst part of having Fabry is not all of the pain or the things I miss out on, but being unreliable. In general, I'm a very organized, "type-A" person. I like to be on time. I'm a planner, but Fabry has made my life unpredictable. I cannot tell my neighbor I will babysit on Friday because I may be vomiting uncontrollably. I cannot plan to go to the movies with my friends next weekend, because I never know what tomorrow will bring.

I'm not a reliable student, a reliable employee, or even a reliable friend, even when I try my best to be. Right now, I'm looking at colleges. Having Fabry complicates my decisions. There are so many factors that normal kids don't have to take into account. Like will my insurance cover me at college? Who will do my infusions? Will the infusions work out with my schedule? As I look to the future, I pray for Fabry treatment options that will allow me to just be more normal.

KS (adult patient and parent of child patient)

My name is KS. I live in Massachusetts with my husband, my two sons ages eight and six, and my two dogs. And I am 37 years old. For as long as I can remember, Fabry disease has been a part of my life. Growing up, there were over 15 family members of mine that had Fabry. I watched my father suffer daily with pain, life-altering GI symptoms, extreme fatigue, hearing loss, and more. I watched as he received two kidney transplants from family members. And I watched as he passed away from heart failure on Christmas Eve 2016 at the age of 59.

Due to Fabry, he had to miss out on events and activities in our lives. And now he'll miss out on watching his grandchildren grow up, too. When I was younger, the first symptom that I remember experiencing was burning in my hands and feet when I was sick and when I had a fever. I remember standing in my kitchen during one of those episodes and accidentally dropping a cold sponge on my foot. That sponge felt like a knife going straight through to the floor because of the sensitivity in my burning feet and the cold temperature coming into contact with them.

Growing up, I had mild symptoms and was still able to participate in the activities that I wanted to. And today at age 37, I still experience similar symptoms that have progressed since childhood. I still experience burning hands and feet during a fever, but now in addition, [I also experience] full body pain, that significantly limits what I'm able to do until it passes. I've had ringing in my ears for as long as I can remember. I thought it was normal actually, and that everyone had those sounds in their head. I have occasional gastrointestinal symptoms, including severe stomach pain, diarrhea, and constipation. During these episodes, I'm hesitant to leave my house or even to eat. I also experience occasional headaches and migraines that can last for two to three days and leave me laying down with my eyes closed until they pass. My organs are also affected. In the past, I've had protein in my urine, but five years of Fabrazyme has seemed to stabilize my kidney function for the time being. I also experience heart palpitations that can come out of nowhere and catch me off guard at my job or during a work meeting. I also have an incomplete right bundle branch block and a low heart rate that may or may not cause issues in the future.

One of the most substantial ways that Fabry affects my everyday life is the constant responsibility of staying on top of my health. I see a geneticist, a cardiologist, a nephrologist, a neurologist, a therapist, and an ophthalmologist, in addition to the regular doctors for somebody my age. Calling these offices to schedule appointments, waiting to hear back from the doctors, keeping track of my tests and procedures and when and how often I need to have them done is like a second full-time job. It's exhausting, and Fabry is always on my mind. Currently, my mental health symptoms are much more impactful on my everyday life than my physical symptoms. I suffer from anxiety, and every single day, I wonder, "What if? What if my kidneys fail? What if I need a pacemaker in my 30s? What if I have a stroke? What if the pain gets worse and I'm unable to work since that's the only way that I can get life insurance?"

I'm always waiting for lab results and test results. It produces a constant state of worry that something's going to come back this time and something's going to be really wrong.

Mental health symptoms are symptoms that don't seem to be on the radar as much when it comes to Fabry disease, but I know I'm not the only one who asks myself these questions.

My eight-year-old also has Fabry. He has been on Fabrazyme for almost two years. This means that every two weeks, this eight-year-old child has to sit for hours with an IV in his arm, causing him to miss school, interrupting his life, and affecting his ability to live as a typical eight-year-old. Even with the early treatment, his symptoms are starting to evolve. He has occasional hand and foot pain, especially when he is outside in cold weather and comes in to warm up. His sweating is minimal, so flushed cheeks and overheating are things that we have to constantly watch out for, especially in these hot months. He sometimes needs to use the bathroom soon after eating for a bowel movement, and he has stomach pain occasionally. He already has some angiokeratomas on his belly button.

He's also an amazing person, and he is the strongest eight-year-old that I have ever met. So, all of these worries that I talked about before, I worry for him, too. I wonder what his years will look like, how his social life will be, but more so his mental health, if there will be effective treatments and a cure in his lifetime. That feeling of guilt that I have every single day can be crippling.

Topic 2: Clinical Trials in Fabry Disease

There were no patient testimonies in this session.

Topic 3: Current Challenges to Treating Fabry Disease

PR (adult male patient)

Hello, my name is PR, and I am 46 years old. I live in New Hampshire with my wife and our dog, where I work as a program analyst for the Department of Defense. After battling typical symptoms of Fabry disease for years, and after numerous misdiagnoses, I had a kidney biopsy and genetic testing that confirmed Fabry disease in 2007 at the age of 31.

Less than two months after diagnosis, I started enzyme replacement therapy, or ERT, on a medication known as Fabrazyme, at Johns Hopkins Hospital. The treatments were every two weeks, and began at an infusion rate, they had me in [the treatment] center for over eight hours, not counting that 30- to 45-minute commute each way. On the fourth treatment, almost at the end of the infusion, I had an adverse event, where my blood pressure began to rise, my throat began to swell, and my body experienced rigors. Over the next year, we relocated from Maryland to New England. In the new infusion clinic, the infusions still lasted six hours with the same adverse events occurring, but even sooner after the infusion started. I would get rigors, and the nurse would put a heated blanket on me. This didn't help the situation because I wasn't cold, and my heat intolerance made having a heated blanket on me even more uncomfortable. Eventually, after nine months of experiencing infusion reactions [and] working with my prescribing physician, we came up with a correct premedication regimen of Tylenol®, Claritin®, and prednisone. As a result, the adverse reaction stopped. The infusion rate slowly increased, and my time in the infusion center decreased. Less time in the center meant more time [for me], either working or with family and friends. I now also had the flexibility to schedule infusions at different times of my infusion day, because less time was needed to be hooked up to an infusion pump. ERT wasn't stopping the worst of the damage to my kidneys, and I began searching for an organ donor.

In 2009, a college classmate and friend donated one of her kidneys to me and my life was instantly changed for the better. I was very fortunate to have a preemptive transplant and not have to be on dialysis. I continued on Fabrazyme after the transplant, but never noticed the marked improvement in my non-kidney symptoms. GI issues and pain associated with heat intolerance continued. Shortly after my kidney transplant, problems with the production of Fabrazyme reduced its availability to patients for approximately three years. For me, this meant longer periods between treatments, and at points I received only one infusion instead of the usual two per month.

I also noticed an increase in the severity of my symptoms, specifically GI issues such as diarrhea. The diarrhea was occurring more often than when I was receiving my infusions at the prescribed interval. When I was diagnosed in 2007, I underwent genetic testing that showed a mutation in my alpha-gal gene. In 2018, the genetic information was used to justify prescribing Galafold which is an oral therapy. I took one pill every other day and took this treatment until May of this year. While taking Galafold, I had more energy and my gastrointestinal symptoms improved. However, although I have a mutation that helps Galafold to be effective, it appears that the enzyme activity in my body was still not increased sufficiently. My Lyso-GL-3 level was still high. In February of this year, I suffered a stroke. As a result, I underwent a procedure to insert a heart monitor to help identify potential causes of the stroke, such as atrial fibrillation, or AFib. Between the stroke and my rise in the Lyso-GL-3 level while on Galafold, my physician urged me to transition back to Fabrazyme. Without an agreed upon set of parameters to monitor in order to determine if the Galafold is effective, she was skeptical that it was working for me. I don't feel Fabrazyme or Galafold have improved my Fabry symptoms, except for sweating. I do sweat more now, but not what I would consider equivalent to one of my healthy family members or friends. Fortunately, I'm able to work remotely while receiving ERT, because immediately after I feel run down and don't have the energy to do much of anything. I have noticed, while being back on Fabrazyme, that my overall energy level has decreased as well, compared to when I was on Galafold. Many days, I feel as though I need a nap in mid-afternoon even after a good night's rest.

Currently, in addition to Fabrazyme, I take carbamazepine for pain associated with intolerance to heat, ginger pills to assist with my GI issues, ad Eliquis for reducing blood clots from AFib, Lipitor [for cholesterol], and baby aspirin

for heart health and prevention of additional strokes. As far as new treatments for Fabry disease, I would like an oral treatment that is not specific to the genetic mutation of a patient. Being able to travel while not missing treatments is very important to me. Also, a treatment that can cross the blood-brain barrier and prevent strokes and TIAs is very, very important to me as well. For infusions, we need more medications that do not create adverse events. We need medications that are available to the entire community and that address all, or at least most, of our symptoms. Thank you.

JO'B (adult female patient)

My name is JO'B. I am 56 years old and live in Winterset, Iowa, with my husband and my 18-year-old daughter. I am a same-day surgery nurse at our local county hospital, and I work part-time. My sister and I have a unique perspective on Fabry disease as children. It's been a constant threat in our lives, has ebbed in and out of our consciousness. Our father was diagnosed with Fabry around 1970. The whole extended family was tested, and our grandmother, aunt, our cousin, her son, and my sister and I were tested positive for Fabry. Our father died six months after receiving a cadaver kidney transplant in 1972. Debbie [sister] and I exhibited symptoms of Fabry as pre-pubescents. We both had the neuropathy, or pain, in our hands and feet when overheated. Debbie had some hearing loss and spilled protein in her urine. As a child, I experienced neuropathy that would only occur under extreme conditions, like at basketball camp, in 95-degree heat, with little air conditioning.

In 1984, our male cousin, also diagnosed with Fabry as a child, committed suicide. The family was devastated. As young adults we knew we were carriers and the possibility of a male or female with Fabry is 50%. We knew the inheritance pattern and the ramifications of having a male child with Fabry. Debbie got married a few years later. She had two sons. With each pregnancy she had chorionic villus sampling done, and each child was negative for Fabry. At this time, she continued to spill protein in her urine, had neuropathy and fevers with overexertion, and now had hypertension with ventricular hypertrophy.

Our first pregnancy was terminated after our CVS result was a male with Fabry. In 2008, I had an eye exam that showed whirls in my cornea and was sent to an appointment with the nearest Fabry expert. I had a series of detailed testing, and one of them showed shadows on my brain MRI. My physician's assistant encouraged me to start enzyme therapy, but I was hesitant. The cost and the effort to treat was extensive, and would it really benefit me? My sister was concerned about her health and decided to start enzyme replacement therapy with her protein spillage.

I was started on a low dose of valsartan to protect my kidneys. I knew that, even if I was asymptomatic, that the accumulation of the GL-3 is irreversible and damaging but questioned really how much I was affected. The phase one trial of Protalix offered extensive testing, including a kidney biopsy at their cost. My baseline organ damage did not appear significant, so I was not accepted into [this] trial and did not have the kidney biopsy done. My Fabry provider helped me independently to get a kidney biopsy, to help me decide whether I needed enzyme replacement therapy, and that biopsy showed that I had a moderate amount of GL-3 bodies in the kidney. I started on Fabrazyme and have been on treatment for the last four-and-a-half years. My blood pressure dips only in the first 15 to 30 minutes of the infusion; otherwise, I can't tell a difference.

I was on Fabrazyme for two years. Then, in 2019, I was accepted into the phase-two Protalix Fabrazyme blind study. My infusions are every two weeks, and initially they were done at the infusion center under close observation, but now they are conducted at my home by my infusion nurse. I feel really fortunate that I don't have to drive the two and a half hours to my infusion center and can have them done in the privacy of my own home. However, there is the hassle of jockeying vacation and travel time around these infusions. Extending the drug's half-life to allow monthly infusions would be a significant improvement to my life. I continue on treatment, and I live on the precipice, hoping not to move into more severe kidney disease and multisystem decline. Thank you.

LW (adult female patient)

My name is LW. I live in East Stroudsburg, Pennsylvania, with my retired husband, adult son, and daughter. I was diagnosed with Fabry disease in April of 2015, at the age of 49, after experiencing severe debilitating pain in my legs. It felt like severe cramping, along with weakness. It prevented me from holding myself up, which resulted [in] me needing a walker. After having my children tested first and confirming that they did not have Fabry, I started treatment in June of 2015. Prior to diagnosis, I worked in the customer service and management field for over 30 years. Now disabled due to pains in my legs, hands, and feet, I spend my time learning and advocating about this rare disease. When I feel up to it, I enjoy being outdoors, gardening, traveling, listening to music, cooking, and helping others. Fabry disease runs on my mother's side of the family. Along with [my mother], I have two living siblings, nieces, and cousins with Fabry. My oldest brother passed away before being diagnosed. But now that I know the symptoms, I know he had it, and I lost my youngest brother last year due to kidney failure.

I've been on Fabrazyme infusion for seven years, every two weeks. The treatment started slowly as an eight-hour infusion at Mount Sinai Hospital in New York City, and [they] gradually increased the infusion rate until the whole procedure is down to two-and-a-half hour infusions at home. The eight-hour infusion consumed my entire day. The ambulance service would pick me up at 7:00am, I would arrive at the hospital at 9:00am, and I would finish around 6:00pm. Once picked up and arrived home, I would just eat something and go to bed. I felt extremely tired after the infusions, due to the Benadryl® and Tylenol®, but these pre-infusion medications are necessary to reduce the possibility of allergic

reactions. Even though I spent eight hours at the hospital, I was comfortable in a bed. I would spend that time reading, resting, and watching TV.

Another important change in my treatment now is the [in-] fusions are done at home. Home infusions are a lot more convenient than going to an infusion center. The infusions help ease some of the pains in my hands and feet a little bit. I usually feel a difference in how I feel within 24 hours after the infusion, and it helps for about 10 to 12 days, but the infusions haven't made too much difference with the "brain fog," as that continues to be an issue. I'm happy to have the treatment, but I feel like my life is centered around Fabry and infusions. Anytime I want to plan something or schedule anything, I have to be mindful to make sure that it's not on a supply delivery day or an infusion day. And infusion days are subject to change, which creates even more uncertainty. It's difficult living with a disease that's unpredictable. I never know how I'm going to feel each day. It's also hard because I do not have a choice of treatment. I would like to have a treatment that doesn't require accessing a vein for each infusion. After many years of infusing, the veins start to collapse and become scarred. This makes it harder to access them. I wouldn't want to go through getting a venous access port because it might create more issues to deal with, like infection along with pain. A lot of supplies are also required to do home infusions. This means a lot of storage space is necessary.

There are also concerns about issues with the infusion nurse. I have been through four infusion nurses in the last four years due to various reasons. Each time a new nurse is assigned, I contact my Genzyme rep to do an assessment with the nurse to make sure that they know how to mix and administer the Fabrazyme properly. Most of the nurses I've had never heard of Fabrazyme before. And then having someone unsure on how to mix it properly is not something I want to deal with when I'm already dealing with my symptoms. Also, considering how expensive the Fabrazyme is and how badly I need it at infusion time, I need a nurse who knows how to mix the medicine quickly and properly with no waste.

I would like to have better options for treatment. Something that doesn't require being premedicated, a treatment that's going to help eliminate more pain and reach the brain. A treatment that doesn't require so many supplies. I would like to have something like a daily pill or something monthly. We need a treatment that will be good for all mutations, a treatment that will give us back some type of freedom and normalcy to our lives.

CM (adult male patient)

Hello, my name's CM. I'm 51 years old, and I live in Fairfield, Connecticut, with my wife, Margaret, and my 15-year-old daughter, Lucy. During my work career, I spent time as a salesperson and sales leader in the information technology field. In 1986, at age 15, went to my doctor for a pre-summer camp physical and blood test. My results showed protein in my urine. Within a year of that finding, at age 16, I was diagnosed with Fabry disease. Since that time, I've been through three kidney transplants. My first, in 1992, lasted for four years, and the second in 2000 lasted for 20 years. Both of these ultimately failed. My most recent transplant occurred in September 2021. Beyond this, I've endured three periods of dialysis, ranging in duration from six months to four years, triple bypass heart surgery, and a host of other procedures and complications.

Along with my kidney and heart issues, I've experienced enduring brain fog, neuropathy, fatigue, and GI issues that have, to lesser or greater degrees, impacted my life. In the summer of 2002, I began enzyme replacement therapy with the experimental medication Replagal®. This involved visits every other week to Manhattan for a roughly one-and-a-half-hour-long infusion. I underwent this treatment for 10 years, making the two hours plus roundtrip commute, holding down a full-time job and trying to fulfill my responsibilities as a husband and a father. In 2012, I switched my treatment to Fabrazyme, when Shire removed its application with the FDA. This is a challenging change, as it involved a much lengthier infusion process, which was upwards of four hours, as compared to the one-and-a-half hours on Replagal®. All in, I was looking at a six-hour process every other week. Combined, these therapies over two decades amounted to approximately 2,400 hours of treatment, which equals 300 eight-hour workdays. That's almost a year, and doesn't include time spent at doctor visits, varied and numerous surgeries, dialysis treatment, or the time lost due to the everyday life of a Fabry patient.

The larger impact of all this, and maybe what's the most important to me, was the time I lost with my family and my friends. Currently, I'm seeking to switch my treatment to Galafold® oral therapy. This change would potentially vastly improve my work/life balance, as well as eliminate the need to travel to an infusion center and endure a multi-hour treatment. On a particular note, this medicine has the potential to cross the blood-brain barrier, hopefully allowing for treatment of and relief from the brain fog that is the result of Fabry disease. It is also potentially effective in reducing heart wall thickness, which is attractive to me due to my Fabry and family-related cardiac issues.

On top of the two decades plus of ERT and the challenges this entailed, I have lived with the side effects of medications that help support my kidney health, treat my heart disease, and manage related conditions. These include immunosuppressants such as tacrolimus, Myfortic, Imuran, and cyclosporine, steroids such as prednisone, blood pressure pills like carvedilol, losartan and amlodipine, and a host of other drugs. All of these and other medications have been necessary and life-sustaining for me, but they also have had an impact on my body that includes arthritis, enduring foot pain, blood sugar challenges, gastrointestinal issues and fatigue, just to name a few. The fatigue from Fabry, as well as from some of the medications I've taken has proven to be an ongoing struggle. Imagine waking up every day tired and staying tired throughout that day. Or think about taking prednisone and the related side effects to a person's bones

and blood sugar. It's ironic that prednisone, which helps take care of my kidney, can also lead to increased blood sugar levels, the result of which can bring real damage to that same organ.

Personally, an ideal treatment would more effectively address the symptoms I deal with every day from Fabry disease. Beyond the heart and kidney challenges I face, I want to worry less about my GI issues during a car trip or when visiting friends. I want to have increased confidence that my "brain fog" has been reduced to a level which allows me to be more confident in my memory recall. I want the chance to spend more quality time with loved ones and fully enjoy the life that my donated kidney has brought me. Maybe most importantly, I want my family and friends, those who have done so much for me over the past 35 years, to worry a little bit less about me and to let me take care of them for a change.

I want a treatment that will help those of my family afflicted with this disease live fuller lives. I want a treatment that will let me see my daughter, who also has Fabry disease, graduate from college, begin a career, and maybe get married. Hoping against hope, I want to hold her child in my lap. In part, ERT has provided me with the opportunity to not only survive, but to live a fulfilling life. While taking nothing away from the treatments I've received, my hope is that more effective medicines will be developed, and that they will offer all Fabry patients, as much as possible, a future free from pain, sickness, and health challenges. Thank you.

TW (adult female patient and parent of child patients)

Hi, my name is TW. I'm 37 years old with four children. We live in Northern Michigan, and all five of us have been diagnosed with Fabry disease. So, I'm a patient as well as a caregiver. My 15- and 16-year-old daughters and myself have taken Fabrazyme for about five years. Because we have a genetic deletion, Fabrazyme is the only current[ly] available option for us. The treatment [was originally] an infusion every two weeks. We began our treatment at a short-stay unit in a hospital about two hours away. Once we arrived, the nurses could order our medication and we were prepped for infusion. The entire process, from start to finish, usually took about five hours. Combine that with a four-hour round-trip drive, and [the] treatment day was very exhausting.

Recently, we started home infusions, which have their own difficulties. Every other Thursday, the three of us infuse at home. Being responsible for ordering all the supplies for three people, as well as medications, can be stressful. On two different occasions, Fabrazyme has not made it in time for our infusion day. On one occasion, the meds went to Australia. By the time the med reached our home, they had to be discarded because they hadn't been kept cold. Sometimes UPS would come back to our house two and three times a day because they've missed boxes in our delivery. It's more work compared to the short-stay unit, but on the other hand, staying home, I don't have to stay awake for the drive home after a five-hour infusion. It feels like trying to weigh the lesser of two evils, balancing a lot of unknowns, and hoping I've made the right decision. For instance, during a home infusion, anything can happen. And if our home nurse isn't qualified or able to resolve the issue, then we're forced to go to the local emergency room.

As it stands, I've had three ports replaced in four and a half years, and my daughters have had their ports repaired or replaced twice each. Also, sometimes the venous access ports cannot be accessed for whatever reason. Then we can't get our treatment. Whereas if that happened at a facility, other nurses or professionals might be able to help resolve the issue. Over the years, some significant changes have occurred regarding my treatment-related symptoms. For the first two years, about an hour into treatment, I would experience gut-wrenching cramps, followed by diarrhea. It would last the entirety of the treatment and into the evening, once I was home. Thankfully, this symptom has since stopped.

One of the most significant symptoms I struggle with is fatigue. In the one to two days leading up to treatment, my body feels like it has been unplugged from its energy source. To say I am tired does not come close to the level of exhaustion I feel. Everything is a struggle, from getting my kids dinner, to getting up off the couch to use the bathroom.

Usually within a few hours of treatment, I notice a significant change in my energy level. During treatment, I'm able to catch up on tasks around the house that have been left unattended due to my inability to function for the two days prior to treatment. Our pumps are in fanny packs that we wear around the house, which allows us to move freely within our home. It's literally like someone has plugged me back into my energy source.

The other symptom of Fabry that affects me a lot is the burning sensation, mostly in my hands, but also in my feet. And the days leading up to treatment, my hands become beet red with white splotches, very hot to the touch, swollen, and it's painful to bend my fingers at the joints. And it's even hard to grip a pen or a cup. I often have to take off my rings these days because the swelling is so severe that the rings leave indentations on my fingers. Although the burning in my hands never fully subsides, it's easier to deal with after treatment. I notice a significant decrease in pain and swelling as well as increased dexterity. On a scale of one to 10, with 10 being the worst, before treatment, I would rate the pain at an eight. Within a few hours of treatment, it would drop to a three or a four. The biggest burden I have with treatment is convenience.

As a patient, but even more so as a mother, I am beyond grateful for the treatment option[s] my family has. However, the reality of spending a full day, every other week, for the rest of our lives, hooked up to an IV is disheartening and overwhelming. So much time and effort are put into making sure everything runs smoothly for home infusion. On top of having a home nurse in our home for nearly five to six hours every other week, having other children in the home not on treatment is a huge burden. While my two non-treated children understand that we have Fabry, and we are well

aware of treatment days, it is difficult for them because our lives are limited—no walks to the park; no swimming in the pool because I'm not there to watch them; no friends over. Constant reminders to watch our tubes and poles. I would consider a future treatment if it were as effective as Fabrazyme, but also if it were more convenient, perhaps a single-dose daily pill or perhaps an injection every so often, rather than an infusion. The most important things to me are: Will the treatment slow the progression of the disease? Is it safe? While life would be easier with a simpler treatment option, I'm unwilling to sacrifice effectiveness.

APPENDIX 5: MEETING POLLING QUESTIONS

APPENDIX 5.1: DEMOGRAPHIC POLLING QUESTIONS

1. I am:

- **a.** An individual living with Fabry disease
- **b.** A caregiver of someone with Fabry disease

2. Where do you or your loved one live?

- **a.** U.S. East Coast (Eastern Time zone)
- **b.** U.S. Midwest (Central Time zone)
- **c.** U.S. West (Mountain Time zone)
- **d.** U.S. West Coast (Pacific Time zone)
- **e.** Canada
- **f.** Mexico, Caribbean Islands
- **g.** Outside of North America (Europe, South America, etc.)
- **h.** What is your or your loved one's age?
- **i.** Birth to 1
- **j.** 2-12
- **k.** 13-17
- **l.** 18-29
- **m.** 30-39
- **n.** 40-49
- **o.** 50-59
- **p.** 60-69
- **q.** 70 or greater
- **r.** Do you or your loved one identify as:
- **s.** Male
- **t.** Female
- **u.** Non-binary or non-gender confirming
- **v.** Prefer not to say.
- **w.** What is the length of time since your Fabry diagnosis?
- **x.** Less than 1 year
- **y.** 1 to 2 years
- **z.** 3 to 5 years
- **aa.** 6 to 10 years
- **ab.** More than 10 years
- **ac.** I'm not sure.

APPENDIX 5.2: TOPIC POLLING QUESTIONS

Topic 1. Living with Fabry Disease: Disease Symptoms and Daily Impacts

1. Have you experienced any of the following Fabry disease-related difficulties? (Select all that apply.)

   a. Pains in feet or hands
   b. Kidney problems (proteinuria, reduced kidney function)
   c. High blood pressure
   d. Heart problems or stroke
   e. Hearing problems
   f. Lung/breathing problems
   g. Heat or cold intolerance
   h. Anxiety or depression
   i. "Brain fog" (forgetfulness, poor concentration)
   j. Fatigue (feeling tired or exhausted)
   k. GI issues (nausea/vomiting, pain, constipation, diarrhea)
   l. Skin issues (such as angiokeratomas)
   m. Swelling (such as in ankles, face)
   n. Other
   o. I do not have symptoms.

2. Which of the following symptoms or conditions most negatively impact your daily life and are NOT addressed by your treatment? (Select top THREE.)

   a. Pains in feet or hands
   b. Kidney problems (proteinuria, reduced kidney function)
   c. High blood pressure
   d. Heart problems or stroke
   e. Hearing problems
   f. Lung/breathing problems
   g. Heat or cold intolerance
   h. Anxiety or depression
   i. "Brain fog" (forgetfulness, poor concentration)
   j. Fatigue (feeling tired or exhausted)
   k. GI issues (nausea/vomiting, pain, constipation, diarrhea)
   l. Skin issues (such as angiokeratomas)
   m. Swelling (ankles, face, etc.)
   n. Other
   o. I do not have symptoms

3. How much does your Fabry disease impact your daily life in general?

   a. Not at all
   b. Minimally
   c. Moderately
   d. Significant amount

4. Which of the following statements is true for you as related to living with Fabry disease? (Select all that apply.)

   a. My general activities in daily life are limited.
   b. I miss work/school more than I'd like or cannot go at all.
   c. I cannot fully participate in sports or other physical activities.
   d. I cannot fully participate in hobbies.
   e. I feel isolated from family and/or friends.
   f. I am not as independent as I would like to be.
   g. Others don't know what it's like to live with Fabry disease.
   h. None of the above; my life is NOT impacted by Fabry disease.

5. What worries you most about your condition in the future? (Select top THREE.)

   a. That my symptoms will get worse
   b. New symptoms will appear
   c. Not being able to live independently
   d. Not being able to attend school, work, or pursue a career
   e. Social and family relationships will suffer
   f. End-stage kidney or heart disease/failure
   g. Transient ischemia attack (TIA) or stroke
   h. Other

Topic 2: Clinical Trials in Fabry Disease

1. Of the following factors related to a test drug in a clinical trial, select UP TO FIVE that you rank as most important to your decision about participating:

   a. Whether I might get placebo ("sugar pill")
   b. Whether I need to stop my current treatment before the trial
   c. Whether I need to stop my current treatment during the trial
   d. Potential side effects from the trial drug
   e. Whether specific benefits have been seen to date in earlier trials
   f. How the drug is taken (by mouth, infusion, injection in muscle)
   g. Frequency of exam appointments

h. Distance to trial site
i. Length of trial
j. Whether a kidney, heart, or skin biopsy is required
k. Whether you may be ineligible to participate in future clinical trials
l. Whether active drug is provided in trial extension phase
m. Whether my physician recommends enrolling in the trial
n. Other

2. Would you be interested in a clinical trial for a drug designed to do one of the following even if it did not slow or stop the overall disease progression (Select ALL that apply.)?

a. Benefit to the kidney alone
b. Benefit to the heart alone
c. Reduce symptoms (eg, pain, GI involvement, fatigue) alone
d. None of the above

Topic 3: Current Challenges to Treating Fabry Disease

1. Select the medications you use or have used for your Fabry disease (Select ALL that apply.):

a. Enzyme replacement treatment, "ERT" (Fabrazyme®, Replagal®)
b. Oral chaperone therapy (Galafold®)
c. ACE, ARB, beta-blocker, or other blood pressure drug
d. Drugs for high cholesterol
e. Drugs for high potassium)
f. Blood thinners (anticoagulants) to prevent blood clots
g. Gabapentin or other anti-seizure drug for pain
h. Hearing aids or drugs for hearing issues
i. Drugs to treat gastrointestinal issues
j. Kidney dialysis or transplant
k. Heart transplant
l. Drugs to treat abnormal heart rhythm
m. Anti-depressants of anti-anxiety drug
n. Anti-inflammatories or immunosuppressants
o. Other (including non-prescription remedies)
p. I have not taken medication or any remedy for Fabry disease.

2. How well have your Fabry-specific treatments reduced the most significant symptoms of your disease?

a. Not at all
b. Minimally well
c. Moderately well
d. Extremely well
e. I do not currently take any treatments.

3. What are the biggest drawbacks of your current treatments? (Select top THREE.)

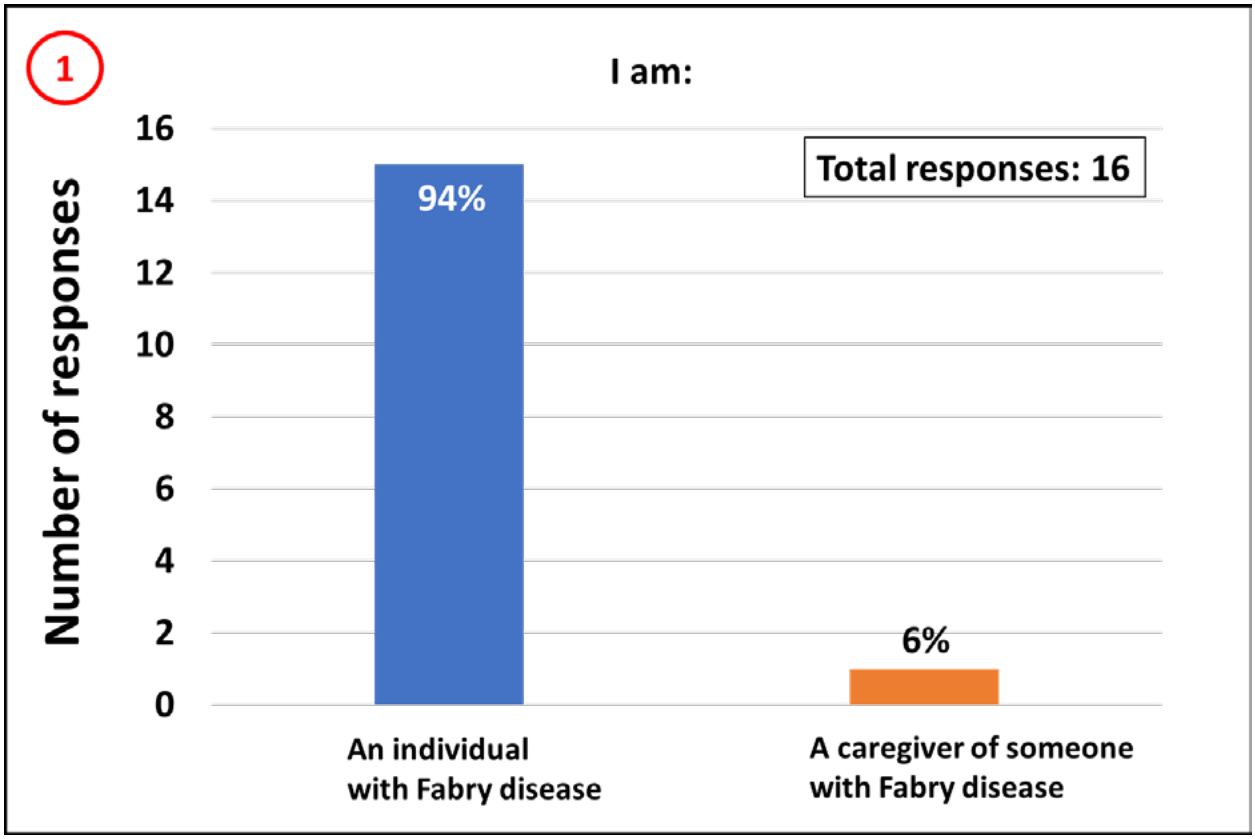
a. Not very effective at treating target symptoms/health issue(s)
b. Only treats some but not all symptoms/health issues
c. High cost or co-pay, not covered by insurance
d. Limited availability of accessibility
e. Side effects
f. Route of administration
g. Requires too much effort and/or time commitment
h. Other
i. I do not currently take any treatments.

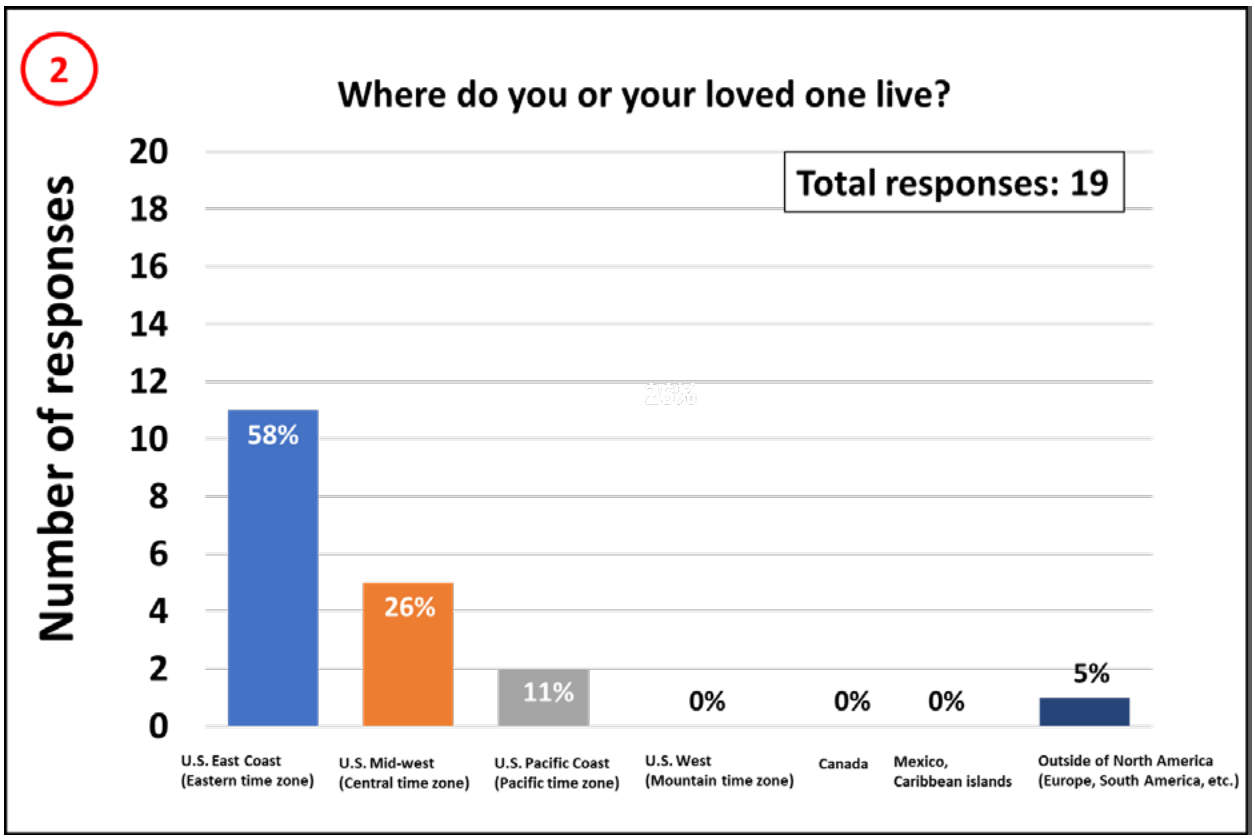
4. Without considering side effects of a drug, which of the following would be most important to you in a future therapy? (Select top TWO.)

a. Slow/stop progression of condition overall (without improving symptoms)
b. Slow the decline in kidney function (i.e., delay need for dialysis)
c. Slow the decline in heart function
d. Prevent stroke
e. Improve your symptoms
f. Prolong your life
g. Other

APPENDIX 6: RESULTS FROM POLLING QUESTIONS

DEMOGRAPHICS OF ATTENDEES





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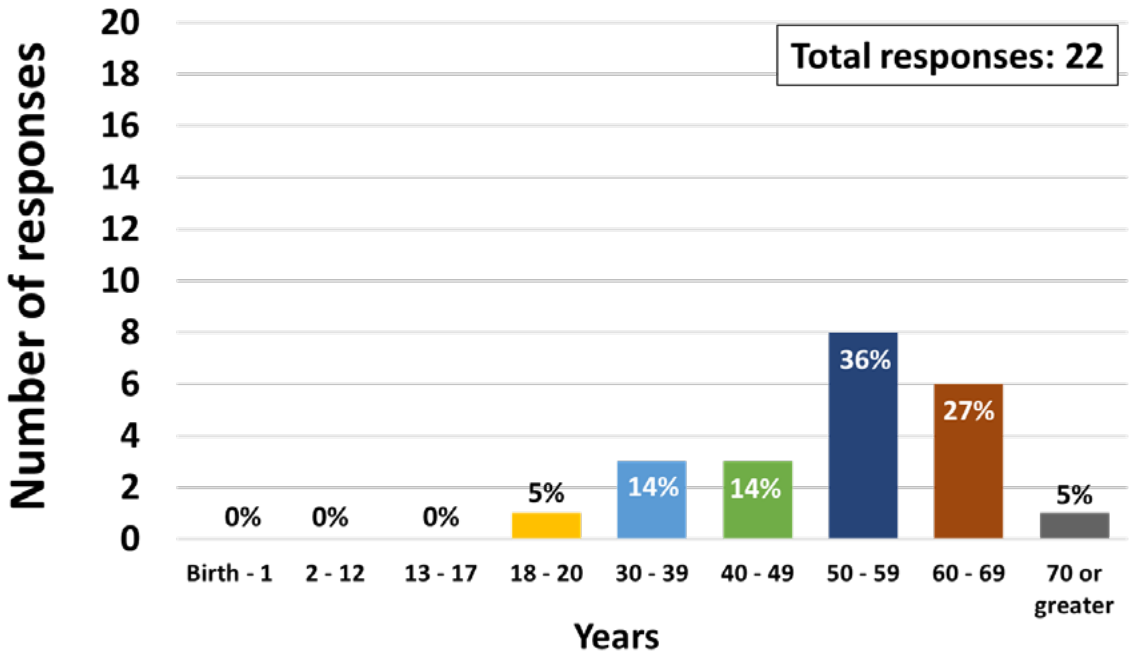
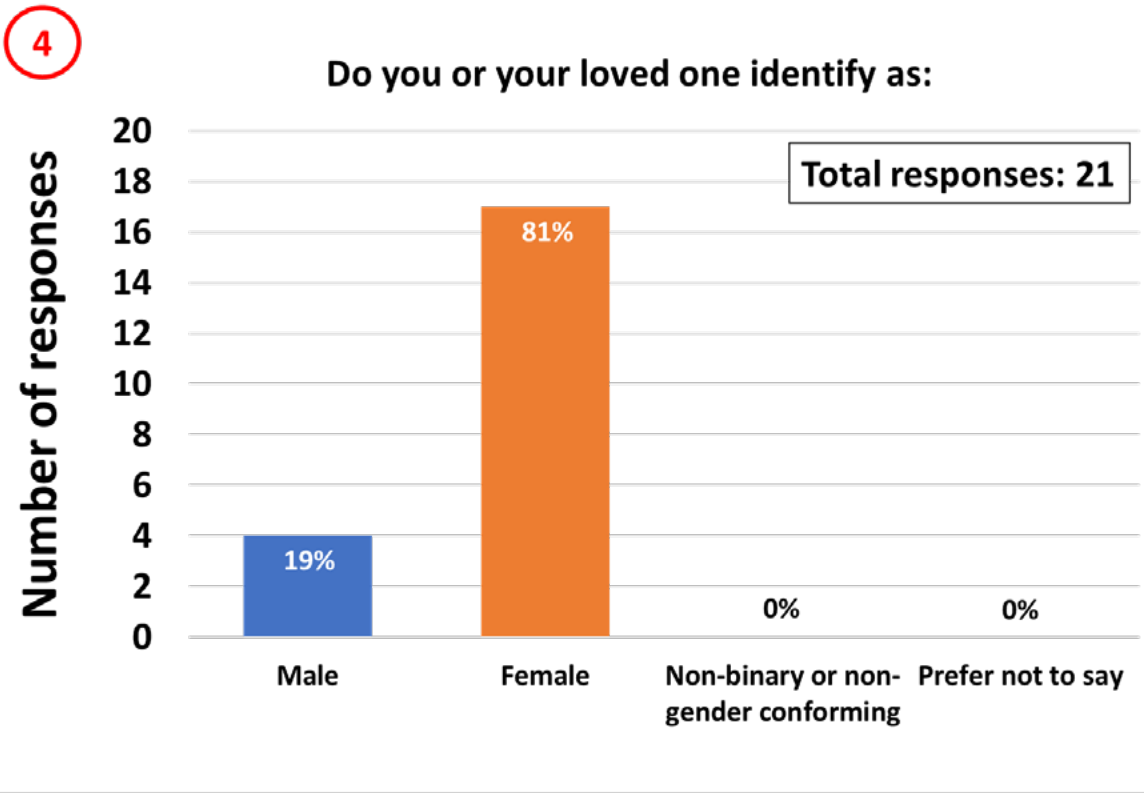
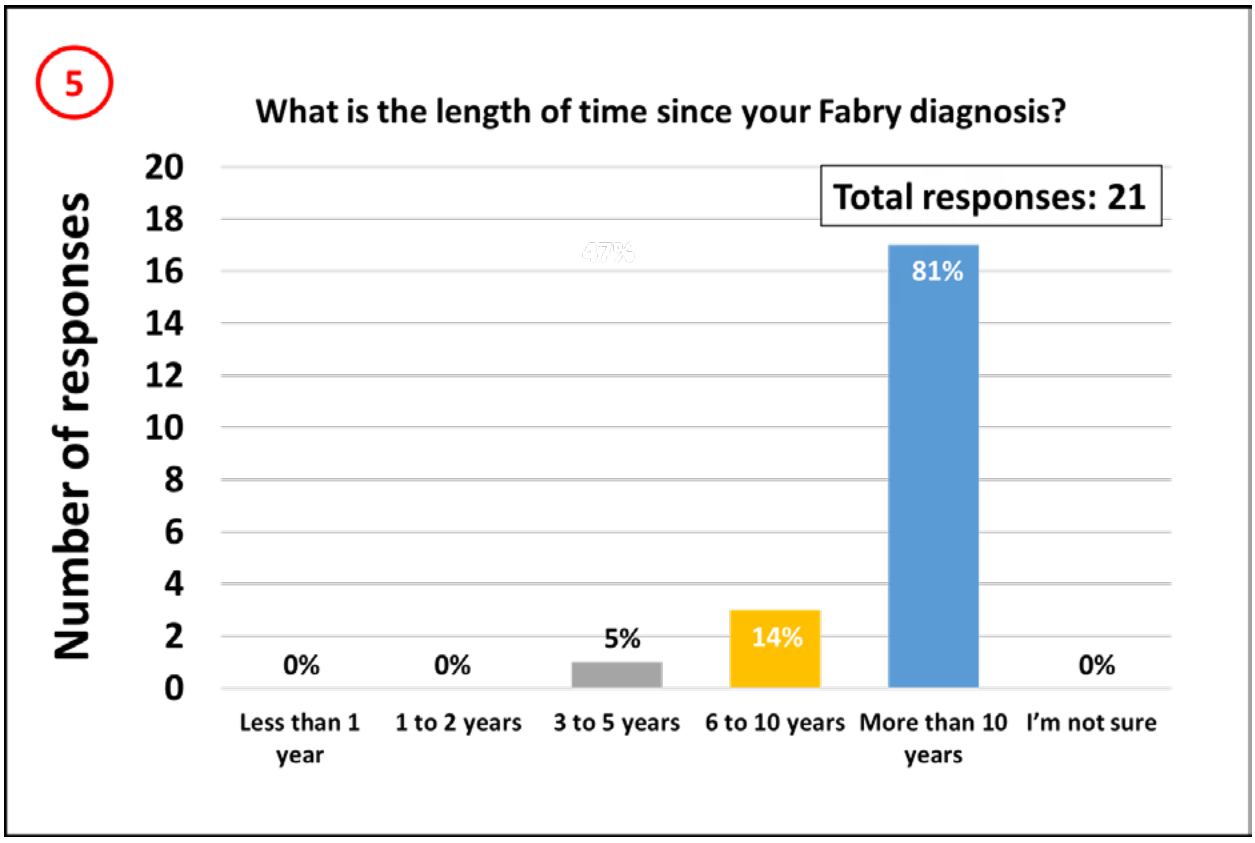
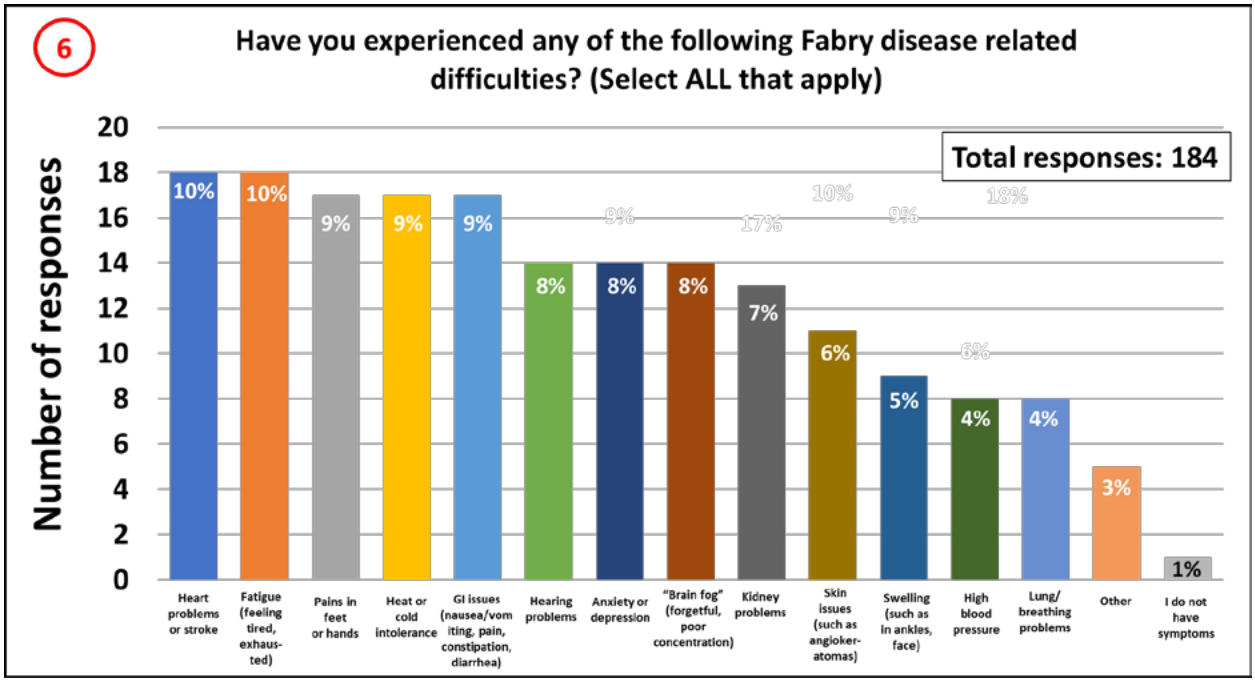

What is your loved one's age?
Total responses: 22
Number of responses
20
18
16
14
12
10
8
6
4
2
0
0%
0%
0%
5%
14%
14%
36%
27%
5%
Birth - 1
2 - 12
13 - 17
18 - 20
30 - 39
40 - 49
50 - 59
60 - 69
70 or greater
Years

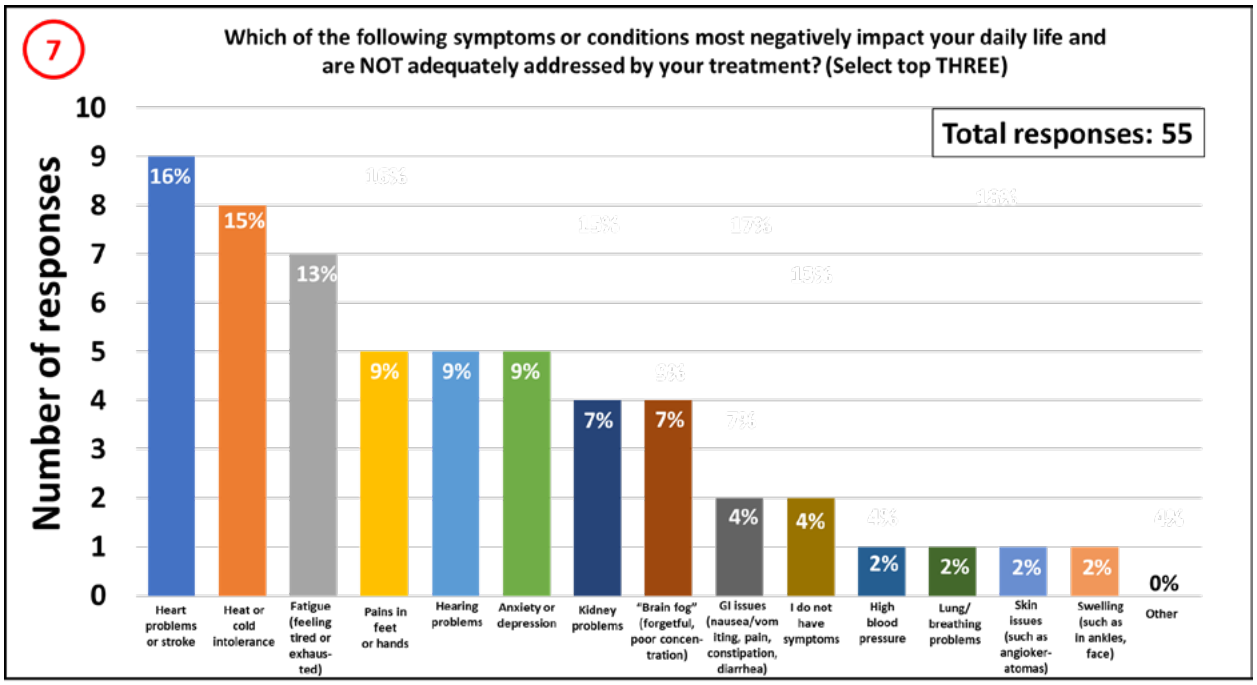
4

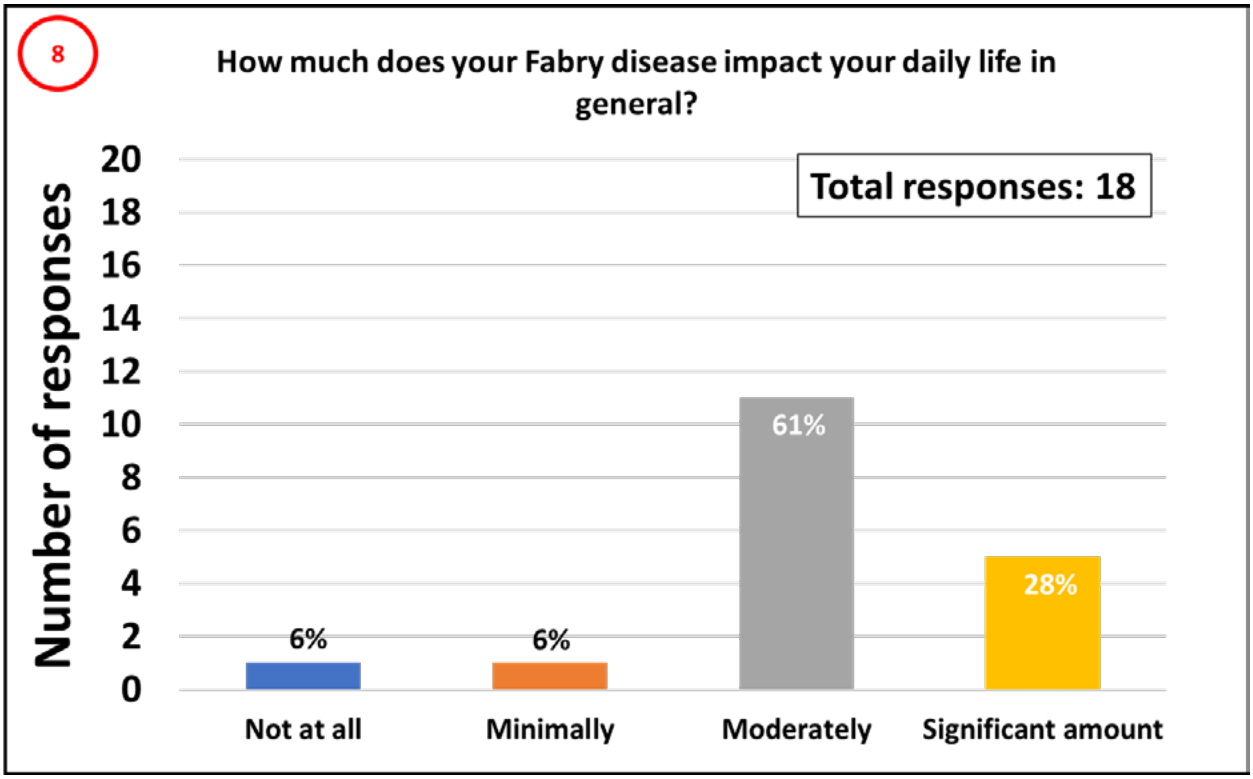

Do you or your loved one identify as:
Total responses: 21
Number of responses
20
18
16
14
12
10
8
6
4
2
0
19%
81%
0%
0%
Male
Female
Non-binary or non-gender conforming
Prefer not to say

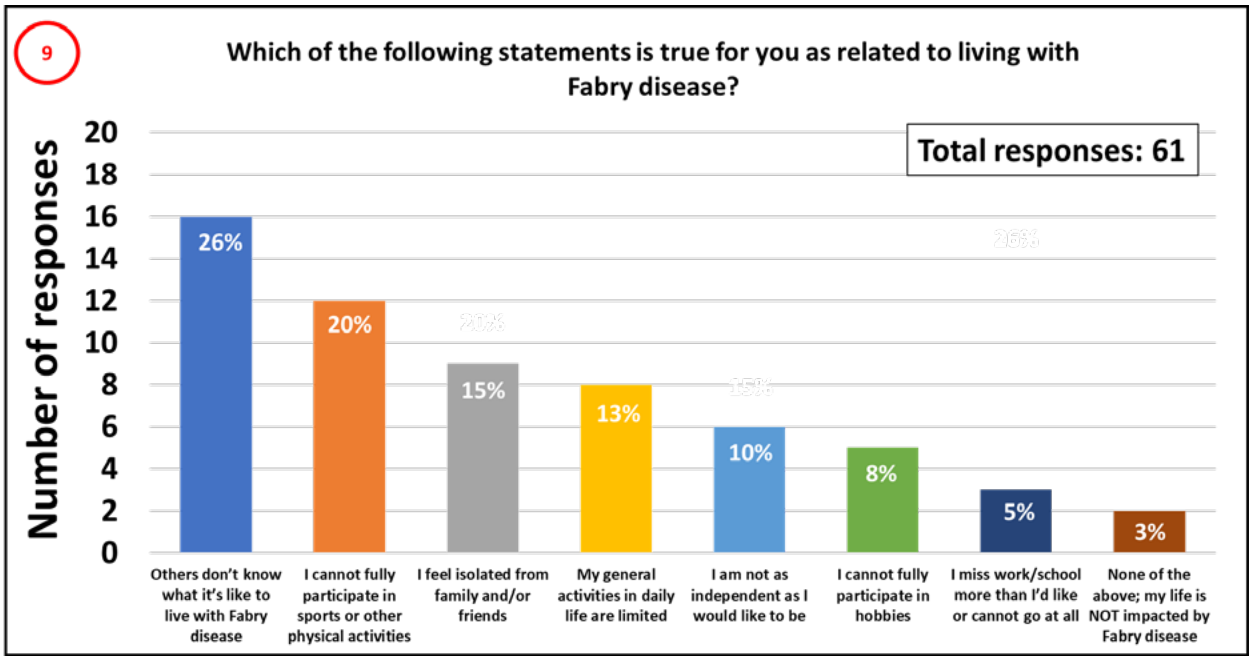


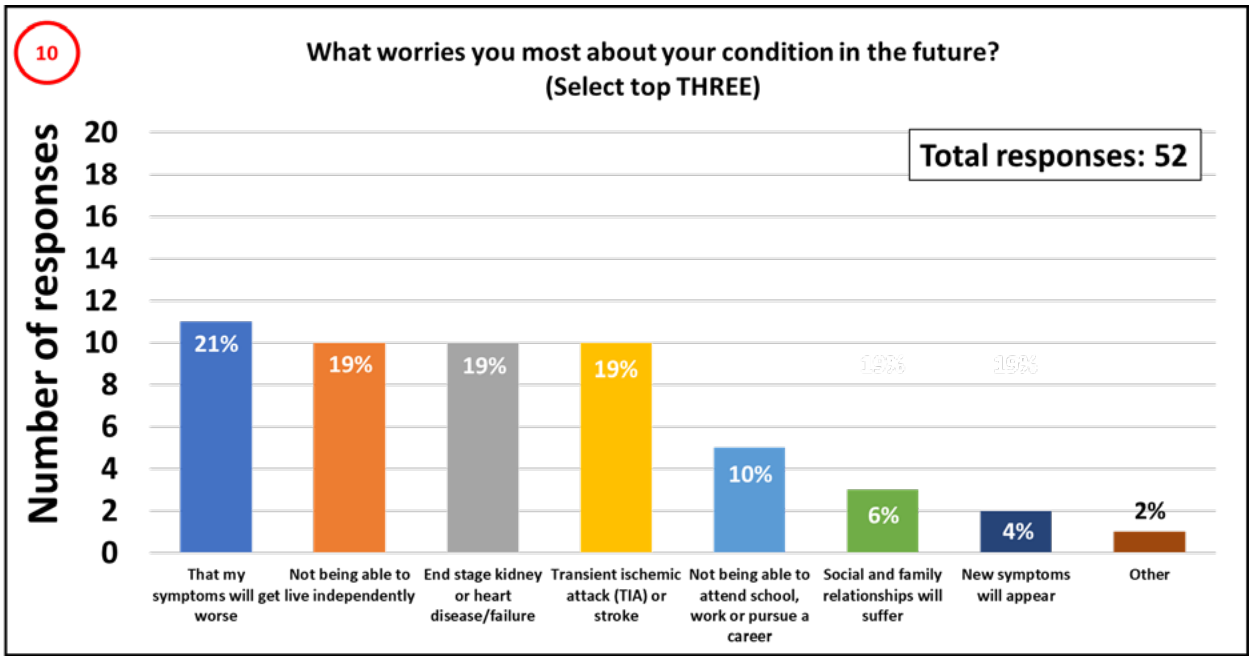
TOPIC 1: LIVING WITH FABRY DISEASE: DISEASE SYMPTOMS AND THEIR DAILY IMPACTS



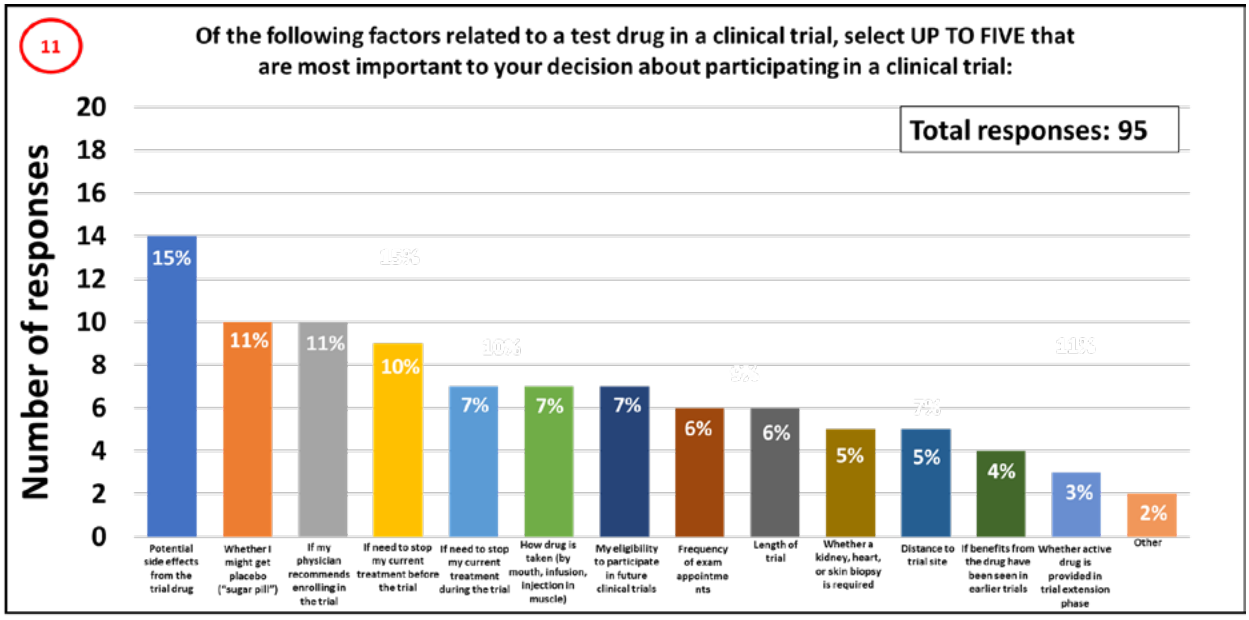

7
Which of the following symptoms or conditions most negatively impact your daily life and are NOT adequately addressed by your treatment? (Select top THREE)
Total responses: 55
Number of responses
0
1
2
3
4
5
6
7
8
9
10
16%
15%
13%
9%
9%
9%
7%
7%
4%
4%
2%
2%
2%
2%
0%
Heart problems or stroke
Heat or cold intolerance
Fatigue (feeling tired or exhaus-ted)
Pains in feet or hands
Hearing problems
Anxiety or depression
Kidney problems
"Brain fog" (forgetful, poor concen-tration)
GI issues (nausea/vom iting, pain, constipation, diarrhea)
I do not have symptoms
High blood pressure
Lung/ breathing problems
Skin issues (such as angioker-atomas)
Swelling (such as in ankles, face)
Other

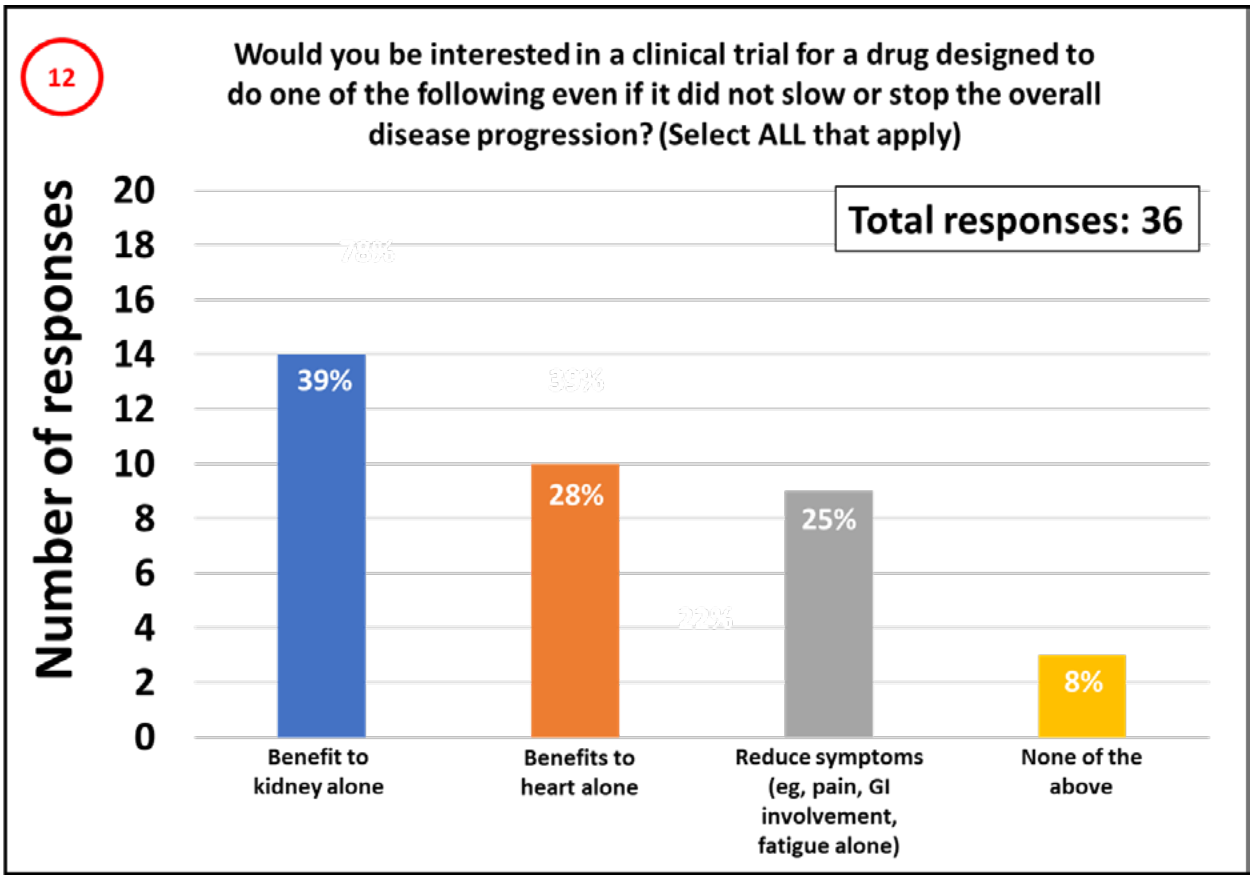

8
How much does your Fabry disease impact your daily life in general?
Total responses: 18
Number of responses
0
2
4
6
8
10
12
14
16
18
20
6%
6%
61%
28%
Not at all
Minimally
Moderately
Significant amount


9
Which of the following statements is true for you as related to living with Fabry disease?
Total responses: 61
Number of responses
0
2
4
6
8
10
12
14
16
18
20
26%
20%
15%
13%
10%
8%
5%
3%
Others don't know what it's like to live with Fabry disease
I cannot fully participate in sports or other physical activities
I feel isolated from family and/or friends
My general activities in daily life are limited
I am not as independent as I would like to be
I cannot fully participate in hobbies
I miss work/school more than I'd like or cannot go at all
None of the above; my life is NOT impacted by Fabry disease

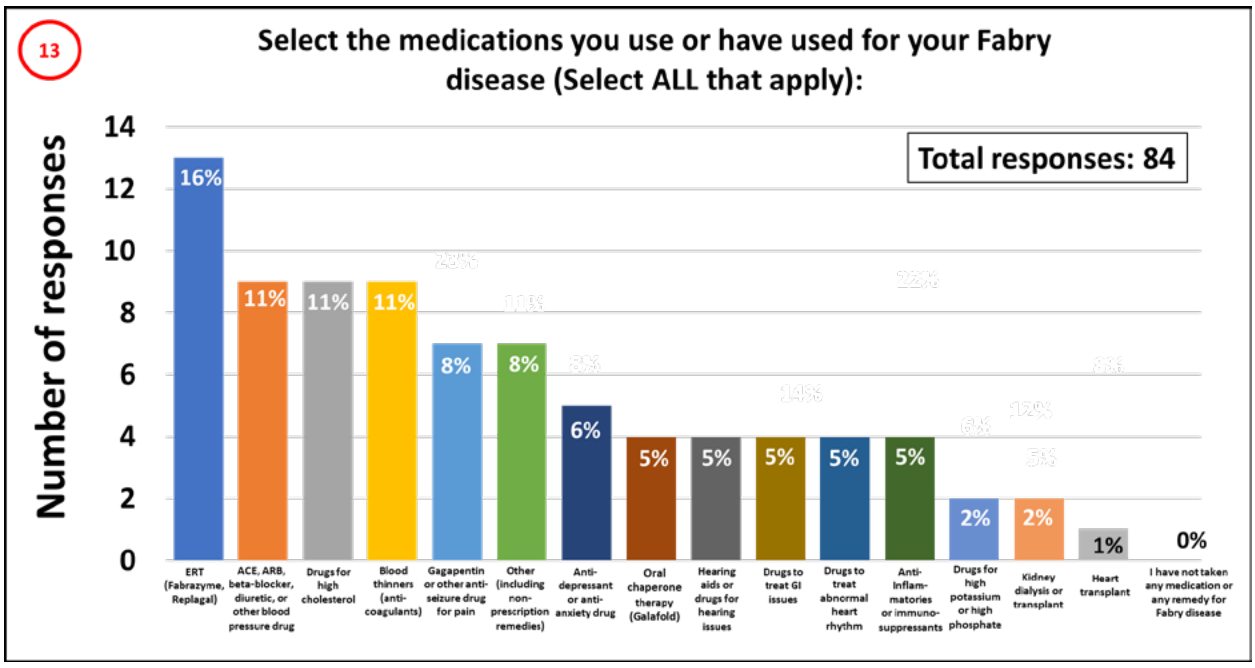

10
What worries you most about your condition in the future? (Select top THREE)
Total responses: 52
Number of responses
0
2
4
6
8
10
12
14
16
18
20
21%
19%
19%
19%
10%
6%
4%
2%
That my symptoms will get worse
Not being able to live independently
End stage kidney or heart disease/failure
Transient ischemic attack (TIA) or stroke
Not being able to attend school, work or pursue a career
Social and family relationships will suffer
New symptoms will appear
Other

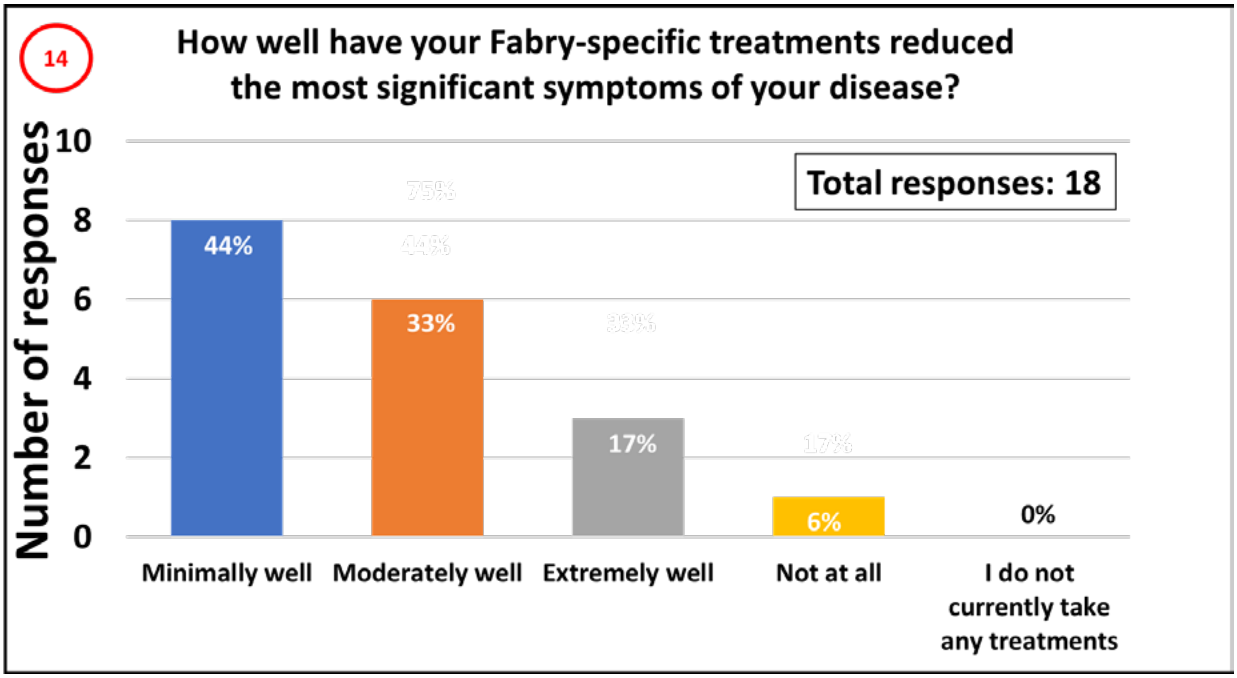
TOPIC 2: CLINICAL TRIALS IN FABRY DISEASE

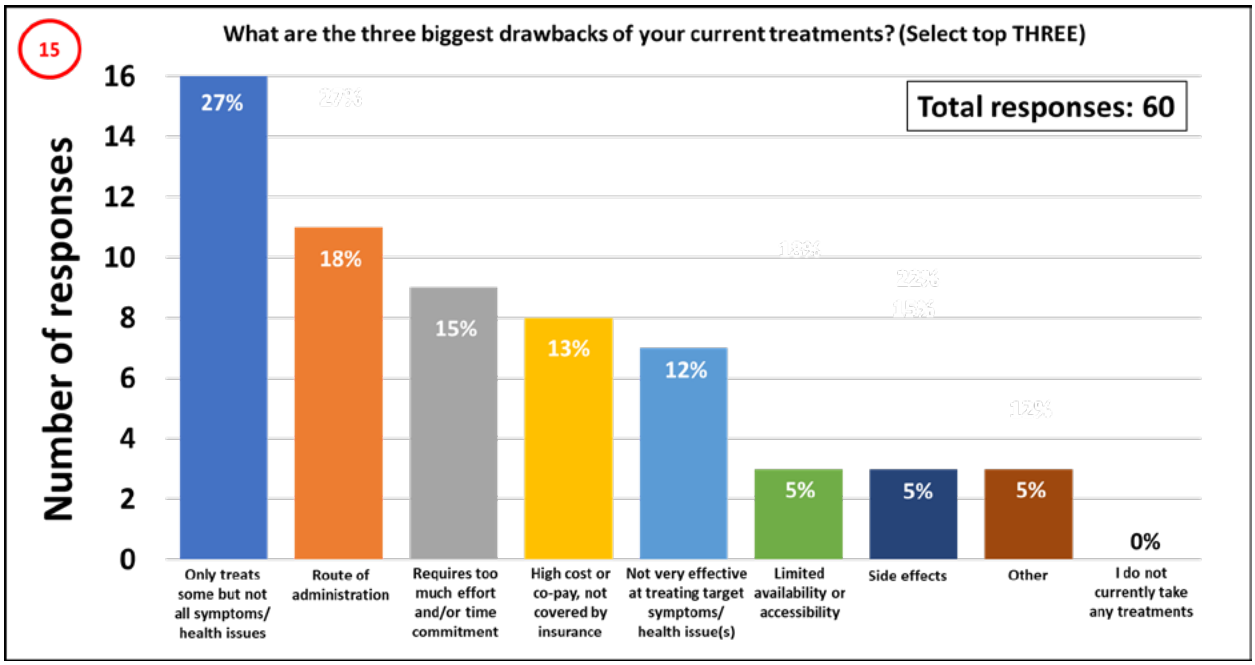


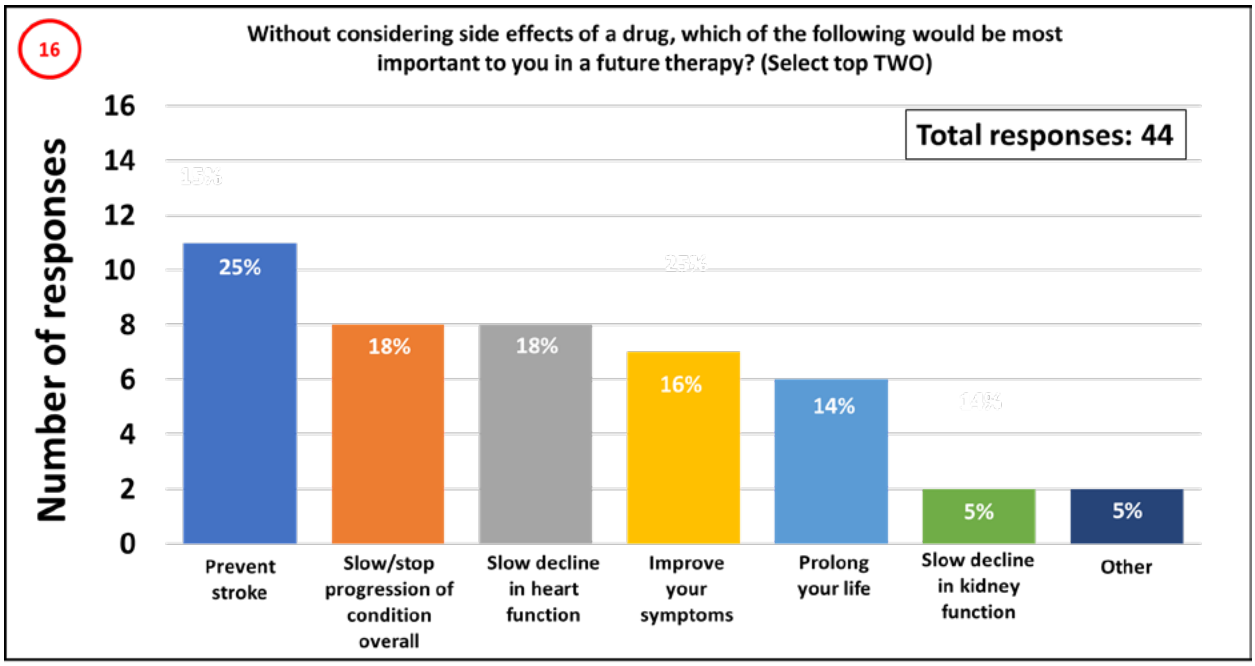


TOPIC 3: CURRENT CHALLENGES TO LIVING WITH FABRY DISEASE: EFFECTS OF TREATMENT REGIMENS AND CLINICAL TRIAL CONSIDERATIONS






15
What are the three biggest drawbacks of your current treatments? (Select top THREE)
Number of responses
Total responses: 60
27%
18%
15%
13%
12%
5%
5%
5%
0%
Only treats some but not all symptoms/ health issues
Route of administration
Requires too much effort and/or time commitment
High cost or co-pay, not covered by insurance
Not very effective at treating target symptoms/ health issue(s)
Limited availability or accessibility
Side effects
Other
I do not currently take any treatments


16
Without considering side effects of a drug, which of the following would be most important to you in a future therapy? (Select top TWO)
Number of responses
Total responses: 44
25%
18%
18%
16%
14%
5%
5%
Prevent stroke
Slow/stop progression of condition overall
Slow decline in heart function
Improve your symptoms
Prolong your life
Slow decline in kidney function
Other

APPENDIX 7: ACKNOWLEDGEMENTS

The National Kidney Foundation and Fabry Support & Information Group gratefully acknowledge the generous support of this meeting by:

- Chiesi Pharmaceuticals
- Sangamo Therapeutics

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