The Voice of the Patient

Externally Led Patient-Focused Drug Development Meeting on:

Primary Focal Segmental Glomerulosclerosis (FSGS)

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

This report reflects the National Kidney Foundation's and NephCure Kidney International's 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.

VOICE OF THE PATIENT

Report on the Externally Led Patient-focused Drug Development meeting on Focal Segmental Glomerulosclerosis

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Dr. Mariani declares the following relationships: Grant funding from NIH NIDDK, Boehringer Ingelheim, Advisory boards: Reata Pharmaceuticals, Inc., Travere Therapeutics, Calliditas Therapeutics

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Mr. Valentine is employed by Hyman, Phelps & McNamara, P.C., a law firm that that represents sponsors developing drugs and patient advocacy organizations.

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This Voice of the Patient report has not been revised or modified since September 10, 2021.

STATEMENT OF USE

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INTRODUCTION

On August 28, 2020, the National Kidney Foundation (NKF) and NephCure Kidney International (NephCure) held an Externally Led Patient-focused Drug Development (EL-PFDD) meeting on primary focal segmental glomerulosclerosis (FSGS). 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 FSGS patients their experiences and perspectives on living with the disease. This meeting was conducted to support the FDA's PFDD initiative, a commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systematically gather patients' perspectives on their conditions and the available therapies to treat their conditions. Recently, the agency passed the PFDD mantle to patient advocacy groups to organize and conduct EL-PFDD meetings.

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 FSGS

Definition of FSGS

Focal segmental glomerulosclerosis (FSGS) is not a disease. Rather, it is a histopathologic pattern of injury to the filters (glomeruli) of the kidneys. The lesions of FSGS result from glomerular injury of diverse origins, the common thread being damage to the cellular barrier against protein spillage into the urine. Consequently, FSGS is frequently the basis for the nephrotic syndrome, which is characterized by massive quantities of protein in the urine, as well as low protein and high cholesterol levels in the blood, high blood pressure, and other complications such as swelling.

The aforementioned glomerular damage progresses to the FSGS lesion: scarring and obliteration of glomerular capillaries in parts (*segmental*) of only some (*focal*) glomeruli seen in a renal biopsy. This scarring reduces kidney function.

Classification and Cause of FSGS

Focal segmental glomerulosclerosis is often classified into three broad categories: primary (idiopathic), in which an unidentified circulating factor is the presumed etiologic agent; secondary, in which a cause can be identified; and genetic. The exact cause of primary FSGS is unknown. In contrast, secondary FSGS is the result of secondary vascular, viral, or chemical damage to glomeruli.

A wide variety of genetic mutations have been linked to the development of FSGS. One mutation that confers risk to African Americans is found in the *APOL1* gene.

Primary FSGS is the most aggressive and debilitating form of FSGS and was the focus of this EL-PFDD Meeting. Hereafter, FSGS refers to primary FSGS unless otherwise specified.

Epidemiology of FSGS

Focal segmental glomerulosclerosis is a rare condition[1], but it is the most common histopathological pattern of glomerular injury in adult idiopathic nephrotic syndrome, explaining 35% of such cases.[2]

The incidence rate of FSGS in the U.S. rose over three-fold between 2000-2011.[3] Similarly, the prevalence of FSGS seems to be increasing world-wide.[4] African Americans are disproportionately affected by FSGS.

The annual rate of incident end stage kidney disease (ESKD; the need for dialysis or kidney transplant) caused by FSGS in the U.S. general population is estimated at 7 per million,[5] making FSGS the most common primary glomerulopathy to cause ESKD in white and African American people.[6] The contribution of FSGS to all new ESKD cases increased by 11-fold from 1980 to 2000 in absolute numbers and in proportion to the ESKD population.[6]

Diagnosis of FSGS

The identification of an FSGS lesion by biopsy is not sufficient to verify a distinctive FSGS diagnosis. Rather, such findings should initiate a search for the cause of the lesion, through exploration of the clinical and family history and laboratory findings.[7] Differentiating between primary, secondary, and genetic causes will determine the course of treatment.

Clinical Course of FSGS

The onset of FSGS is heralded by proteinuria, often sudden (occurring over weeks to months) and in the nephrotic range (>3.5 g/24 h). The nephrotic syndrome is present with variable prevalence.[8] Hypertension may also be present at onset.

Spontaneous remission of primary FSGS occurs in less than 5% of patients.[9] Progression of FSGS to ESKD may occur in 5-10 years in 50% of patients.[10] Recurrence of FSGS after renal transplantation may be seen in 25% of patients.[11]

Treatments for FSGS

There is currently no cure for FSGS: therapy is non-specific, predominantly aimed at managing proteinuria and the nephrotic syndrome. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin-receptor blockers (ARBs) are given to address high blood pressure and proteinuria, and statins are prescribed to control cholesterol, and thus, cardiovascular disease. Diuretics, and a low-sodium diet may also be utilized to combat edema and fluid retention.

For patients with non-genetic FSGS, high dose corticosteroids, namely prednisone or prednisolone, are recommended in an attempt to achieve remission.[12] However, corticosteroids are associated with significant side effects as well as high rates of treatment failure. Other immunosuppressive agents, including cyclosporine and tacrolimus, are used to improve the possibility of long-term remission, but are also accompanied by side effects. The monoclonal antibody rituximab may be considered in patients who are unresponsive or intolerant of conventional treatments.

At the time of this report, there are five U.S. Phase 3 interventional clinical trials[13] in various stages of planning and completion for investigating agents that may benefit patients with FSGS.

MEETING OVERVIEW

This EL-PFDD Meeting on FSGS 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 FSGS and their views on disease-related topics. Specifically, the goals of this meeting were to afford the FDA with an overall understanding of:

- Patients' perspectives on living with FSGS, especially their daily disease burdens
- Factors that influence patients' willingness to enter clinical trials for FSGS, including patients' and care partners' perspectives on enrolling in trials requiring kidney biopsies and clinical trial endpoints that are meaningful to patients
- Perspectives on participating in clinical trials conducted under the Accelerated Approval Program
- Patients' experiences with, and views on, the limitations of current therapies and the desirable characteristics of potential new therapies, and their insights into trade-offs they are willing to make for 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 through dialogue with the virtual audience via email and phone calls. Only patients and care partners were asked to participate in the dialogue.

Discussions during the meeting focused on four key topics: 1) the day-to-day effects of living with FSGS; 2) patients' perspectives on the designs and outcomes of clinical trials executed under the traditional approach; 3) patients' willingness to participate in clinical trials conducted under the Accelerated Approval Program; and 4) current challenges associated with treatment of FSGS. An overview of the meeting is seen in the Meeting Agenda (Appendix 2). The discussion questions used to guide the audience discussions are found in Appendix 3.

Patient Panels and Moderated Discussion

Patient voices were heard through six patient/care partner panels (Appendix 4.1) and moderated audience discussions. These were conducted as follows as described below.

Patient Testimony Panels

Two patient Testimony Panels were heard in which four patients per panel gave five-minute pre-recorded presentations on their experiences regarding symptoms and daily burdens (Topic 1) and current treatment challenges for FSGS (Topic 4). Patient Testimony Panels were not employed for the discussions on clinical trials for FSGS (Topics 2 and 3). Panelists were selected by NKF and NephCure representatives from their organizations' members. Criteria for selecting panelists were set to maximize clinical and demographic diversity on each panel.

Patient Discussion Panels and Moderated Audience Discussion

Each Testimony Panel was followed by a four to six-member Discussion Panel of patients and care partners and a parallel moderated audience discussion. During the moderated audience 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. Although patient Testimony Panels were not used during moderated audience discussions on Topics 2 and 3 (clinical trials), patient input on these topics was gathered by Discussion Panelists, including phoned and written comments on the respective topics.

Polling Questions

Polling Questions (Appendix 5) were posed to the participants, to reveal the demographics of the attendees and to reveal 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 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 NephCure after the meeting. Comments were accepted until September 19, 2020.

Enduring Documentation of Meeting

The archived meeting recording, this meeting report, and the meeting transcript are available on the following websites:

National Kidney Foundation

NephCure Kidney International

Key Themes

The input from the meeting emphasized the challenges of living with FSGS, its impact on day-to-day life, patients' views of clinical trials, and their perspectives on currently available therapies. Several key themes emerged from this meeting:

- Fatigue: Patients described how the fatigue associated with FSGS and treatment significantly affected their daily lives. Patients expressed that this loss of energy, often coupled with "brain fog," which made it difficult to concentrate or focus, affected their ability to function at their jobs and at school, and impeded their abilities to participate in physical or social activities.
- Edema: Patients described the burdens of carrying extra fluid weight from edema, sometimes as much as 75 pounds, and the painful effects on skin stretched to accommodate the fluid accumulation. Edema was

characterized as limbs made of “memory foam,” legs looking like “hot air balloons,” and “barely see[ing] out of my eyes because they are so swollen shut.”

- Psychosocial: Participants described how the invisible nature of FSGS and a lack of understanding of the disease among their friends, coworkers, and peers caused strained relationships and led to social isolation. This often added to the existing anxiety and depression participants described, which was frequently attributed to the many unknowns associated with their disease and treatment.
- Worries/fears: Patients discussed their fears of progressing to dialysis and their concerns about its effects on their quality of life. Patients who had received a kidney transplant frequently noted that this did not end their worries, describing their anxieties about the ever-present risk for recurrence of FSGS.
- Plans/future: Participants described a frustration with the inability to make long-term plans for their or their loved ones’ futures amidst worries about disease recurrence and treatment failure. Female participants also noted that the incompatibility of their treatment options with pregnancy was a significant concern as they considered starting families.
- Clinical trials: Attendees generally voiced their agreement to enroll in clinical trials for FSGS. Outcomes they felt meaningful to them were those showing slowing, stopping, or reversing decline of kidney function. Patients were willing to enroll and stay in a clinical trial conducted under the Accelerated Approval Program, but this was dependent on the patient’s personal outcomes in the initial phase of the trials. Patients considered the opinion of their nephrologist as key in deciding whether to enter a clinical trial. They also sought previous efficacy date in making such a decision to enroll in a trial.
- Treatments: Patients expressed their frustrations with the current “try and see” approach to treatment that they often experienced, as well as the multitude of side effects often associated with these therapies. Many participants noted that the treatment options currently available for FSGS are often worse than the disease itself.
- Ideal treatment(s): Patients’ views on an ideal treatment for FSGS, emphasized the need for drugs specifically targeted to their disease and without effects associated with corticosteroids.

Attendees

A total of 267 people attended the livestreamed meeting, including 112 FSGS patients and care partners.

The demographic composition of the patient and care partner attendees was revealed by demographic polling questions (Appendix 5.1). Based on their responses, most participants (79%) were patients living with FSGS and 21% were care partners of someone with FSGS (Appendix 6; Figure 1). The majority (52%) of attendees resided on the East Coast, followed by 23% in the Midwest, 13% on the West Coast and 4% in the West. Eight percent of attendees were from outside of the U.S. (Appendix 6; Figure 2).

Most respondents were under the age of 18 or between 30-49 years old. Approximately 13% of the participants were between 18-29 years old, while 7%, and 11% of participants were between 50-59 and 60-69 years old, respectively. One person was 70 years old or greater (Appendix 6; Figure 3)

Participants identified predominantly as female (70%) and 30% as male (Appendix 6; Figure 4). The majority of respondents were white (72%), with 19% African American, 5% Hispanic/Latinx, and 5% Asian American (Appendix 6; Figure 5).

Most patients received their diagnosis between 2-5 (19%) or more than ten (43%) years ago and 15% of respondents reported being diagnosed up to two years ago (Appendix 6; Figure 6).

A majority of FSGS patients (58%) were not currently on dialysis and had never received a kidney transplant. Twenty-one percent of respondents had received a kidney transplant and were in remission (Appendix 6; Figure 7).

REPORT OVERVIEW

This report summarizes the perspectives shared by FSGS patients and care partners at the EL-PFDD meeting, 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 FSGS, including symptom burdens, views on clinical trials, and perspectives on current and future treatments, by the FDA, product developers, clinicians, and academic researchers. Through this input, this document also highlights the unmet needs of FSGS patients. Thus, this report is expected to 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 marketing approval, and assessing benefit-risk for products under review.

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

In addition, this report may describe barriers to clinical trial participation by patients with FSGS. Information in this report can also inform endpoints in clinical trials, support the development of patient-reported outcomes measures, and help to design clinical trials to test hypotheses that are inherently meaningful to patients.

In this report, patients and care partners are collectively referred to as “patients and/or care partners,” “participants,” “attendees,” or “respondents.” When responses to polling questions are reported, the

responses are from patients and care partners in the virtual audience. “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.

We note that, while the participants at this meeting represented a clinically and demographically diverse group, the extent to which this group reflected the FSGS patient population at large is unknown, in part due to the lack of quality epidemiology and natural history information on FSGS. 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 FSGS symptoms and impacts, views of participating in clinical trials, and treatment experiences reflect those used by attendees.

Quotes from patients and care partners in this report were taken from patient testimonies, remarks from Discussion Panelists, email comments, and statements transcribed from phone calls.

PERSPECTIVES FROM PATIENTS

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

Quotes have been edited for grammar and punctuation.

The first discussion topic focused on FSGS symptoms and their impacts on the daily lives of patients and their families. The session began with video presentations from four patients currently living with FSGS. The patients described their symptoms and the daily burdens of living with FSGS. Noteworthy excerpts from these presentations are below. Full testimonies are found in Appendix 4.2.

Bernardine (Dine) *(adult patient)*

> *"My nephrologist told me that I would need a transplant or dialysis within a year. I was so anxious and depressed that I began seeing a therapist weekly.*
>
> *"I was told that my new kidney should last for 20 years, but by 2004, just four years later…I was rushed to the emergency room delirious from kidney failure.*
>
> *"**My greatest fear is that the FSGS will recur, and I will lose the second chance at a healthy life**."*

Christopher *(adult patient)*

> *"…it has been a struggle ever since* [my diagnosis] *physically, financially and emotionally.*
>
> *"…planning for the future is almost useless.*
>
> *"…*[I never know] *which days… I* [must] *completely "shut down" and do nothing…*
>
> *"**For eight hours straight, I would experience muscle soreness and tingling, fatigue, and lethargy, and a mental fog that kept me in a zombie-like state**.*
>
> *"I no longer think of life as a journey, but more as a race against the clock."*

Christine *(adult patient)*

> *"**During the most recent relapse, protein spillage went from 97 mg/dl to 880 mg/dl in about 10 days.***
>
> *"When nephrotic syndrome kicks in the edema sets in so fast, there is really no way to prepare for it."*

Jackie (Jacqueline) *(teen patient)*

> *"One of the biggest symptoms that hinders my life the most is swelling.* ***When I'm swollen, it physically hurts to walk, stand, or sit****.*
>
> *"When I go on airplanes, I swell so bad that I can't even walk.*
>
> *"****I don't really get best days.****"*

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 FSGS, followed by a moderated audience discussion structured around the Discussion Questions (Appendix 3.1) which were shared with the audience. This dialogue included a discussion with four Discussion Panelists (Appendix 4.1). During the moderated discussion, patients and care partners in the audience provided verbal (phoned-in) and written comments on their perspectives on the physical, emotional, financial, and social impacts of FSGS on their daily lives. Participants also discussed their worries about FSGS and what it means for their or their loved ones' futures and the social isolation associated with having an "invisible disease."

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

When asked about the daily impact of FSGS (Appendix 5.2; Question 1), over half of participants indicated that FSGS significantly impacts their daily life while 20% each reported that it affects their lives minimally or moderately. Only five percent noted that FSGS does not affect their lives (Appendix 6; Figure 8).

The daily impact of FSGS varied from patient to patient and from day to day. Some patients reported that, on good days, they could accomplish their goals and play with their children like normal. However, many participants noted that, on bad days, even the most basic tasks became too challenging, due to fatigue, swelling, and pain. Daily activities were planned cautiously with consideration to how patients might be affected by the occurrence of symptoms, with many patients and care partners noting that they limited their plans toward minimizing risks and impacts. This affected several aspects of patients' lives, including their jobs and social lives.

Patients were asked to select from a panel of symptoms that they may have experienced (Appendix 5.2; Question 2). The six most frequently cited symptoms were fatigue (13%), anxiety and/or depression (12%), muscle and joint pains, including gout (11%), swelling (edema, 11%), high blood pressure (10%), and brain fog (10%). Gastrointestinal (9%), ophthalmic (8%), bone/teeth problems (6%), and recurrent infections (5%) were also cited (Appendix 6; Figure 9).

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; Question 3), they identified exhaustion or fatigue (24%), anxiety and/or depression (15%), and "brain fog" (15%) as the as the most bothersome symptoms (Appendix 6; Figure 10).

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

Fatigue

Audience members described how fatigue impeded their abilities to not only participate in an active lifestyle, but also to keep up with the physical demands of daily life. While participants indicated their energy levels may have fluctuated throughout the week, most patients indicated that they experienced more "bad" days than "good" days.

> *"On really bad days, it feels like I'm kind of pushing through mud to get everything done. And, I don't often have much energy left by the end of the day."*
>
> ***"I would say it's rare when I have a day that I wake up and realize, 'Oh, this is a good day, I feel good, I have more energy.'*** *Unfortunately, those are rare and far and few between."*
>
> ***"A great day for me is being able to take a two-, three-, four-mile walk with my wife and the dogs. A bad day is having to take everything I have*** **[in me]** ***to go around and just do basic daily cleaning of the house."***
>
> *"I think on the good days, I have more energy to get maybe all the things on my to-do list done, as well as play with my young child, enjoy some activities that I like to do. Where*[as] *on other days, just maybe getting through a workday kind of does me in."*
>
> *"When I'm planning out a day, I need to plan in advance, sometimes two, three days."*

> *"It* [fatigue] *just robs you of everything that you used to do."*
>
> *"**I am tired and exhausted at least half the time**."*
>
> *"But **I would go home at the end of the day and, literally, there were days I crawled into the house to lay on the couch with the fatigue.**"*
>
> *"What I feel corresponds to my labs, and usually I'm right. So, just knowing that they can be lower and that the plasmapheresis helps, that helps me a lot just to feel better, too."*

Care partners of younger patients indicated that while their children are still able to participate in some physical activities, fatigue often limits how much the patients could do at one time.

> *"He's definitely a very active kid, and so I noticed the fatigue much more when he's playing with other kids. He's usually the first one to be tired out…he plays basketball, he does football, he does baseball. So, he's able to lead a very normal kid's life involved in sports, but there definitely is a difference of how long he can last compared to the other kids."*
>
> *"**Most days she sleeps about 14 hours, wakes up very croggy*** [sic] *and, typically, is easily exhausted. She tries to exercise; however, her fatigue gets* [the] *best of her."*

Participants also noted that fatigue had an impact on their ability to participate in both work and school. For school-age children, fatigue reduced school attendance and interfered with social engagement. For adults, several audience members reported that their job performance suffered because of fatigue. Some participants indicated that they left or lost their jobs as a result, creating a significant financial burden for them and their families as well.

> *"When I was diagnosed, I was **so exhausted** that **I could not continue to work and had to take medical leave. I was sleeping 20 hours a day**."*
>
> *"**I was managing a microbiology lab when I was diagnosed.** I was physically unable to keep up with the long hours and sleepless nights that that job demanded. **I was exhausted all the time and eventually made the decision to leave.**"*
>
> *"**I knew as soon as I woke up in the morning that I would be useless,** which would happen **sometimes three days a week**. If I had work, **I would have to push through the meetings, but***

> ***later would be reprimanded for not participating enough*** *in the meeting…**I started to get pulled off of accounts, marginalized**, and I even **anticipated losing my job**."*
>
> *"…due to her fatigue, **she was not able to finish high school**."*

Edema

A significant portion of patients reported experiencing swelling associated with edema, from which many reported significantly negative impacts on their daily lives. Many patients reported that this edema is associated with significant pain, which makes it difficult to do basic activities, such as walking and standing.

> *"**When I'm swollen…No position is comfortable, even laying down**. Even then I'm still in pain."*
>
> *"**On my worst days, I can't even get out of bed due to the pain I'm in**. It hurts to walk and stand, and **I can barely see out of my eyes because there*** [sic, they] ***are so swollen shut**. I have **migraines** because of the pressure I feel on my face from the swelling, it's very unpredictable."*
>
> *"Wardrobe issues are Is a challenge. **Edema might accumulate in your abdomen one day or in your thighs and calves the next** and finding ways to accommodate the swelling can be tough. During that first event, I went from a size 2 to a size 22 in about six weeks. And now **I just keep clothing for every size** in between just in case."*
>
> *"At one point, **I thought my skin was going to bust open**. **I carried 40 pounds of fluid…Carrying so much weight was tiring and exhausting**. It ruined my body as in ways pregnancy never did."*
>
> *"It feels kind of surreal, like waking up in somebody else's body. **Imagine that your limbs are filled with memory foam and that every bit of pressure leaves a lasting indentation in your skin. When I have a relapse, my skin is stretched painfully tight and the simple movement**[s]**, such as walking to the bathroom, are absolutely exhausting under that extra weight**."*

"Brain Fog"

A substantial proportion of participants reported "brain fog" as a symptom which negatively affected their daily lives. Patients indicated that forgetfulness and lack of concentration, along with fatigue, made their work challenging and affected their job performance.

> *"I was so fatigued I didn't want to get out of bed and so unable to concentrate that my work suffered. **Once, I lost my train of thought in the middle of an important work presentation**."*

> *"And it* [brain fog] *really changed over time. I have little sense of what's normal."*

> *"**I can't remember names of kids in my class at times**. I see a kid more than their parents in general, and I see them six months later and I have no idea what their name is."*

> *"**I gave up on teaching because I just couldn't think on*** [my] ***feet and literally be on*** [my] ***feet all day**."*

Additional Symptoms

Although not as extensively discussed or universally experienced, gastrointestinal (GI) problems, cardiac complications, and recurrent infections were noted by audience members as having a significant impact on their daily lives. Participants described the impact of these complications on their home, work/school, and social lives.

Gastrointestinal Symptoms

> *"I've been out [from school] for a couple days… with GI issues…I miss out on a lot of things that my friends are able to do."*

Cardiac Complications (arrhythmias, stroke, blood clots, high blood pressure)

> *"…you don't want to miss symptoms of cardiac problems, such as chest pain, fatigue. **The fatigue may not just be from kidney disease; it can be from cardiac issues.**"*

Recurrent Infections

> *"**I'm worried that my kids will bring home germs that will get me sick**, or I'm wondering when I travel to see clients, which germ is waiting for me."*

> *"I transitioned to a remote role with the same company, but the travel that was required was exhausting and exposing me to new illness*[es] *with each trip. Every time I came home, I ended up with a new cold."*

Psychosocial Effects

Patients were asked in a Polling Question which of six psychosocial effects they had experienced while coping with their FSGS (Appendix 5.2, Question 4**)**. Anxiety/worry (22%), depression and/or feelings of hopelessness (20%) (discussed above), and social isolation (17%) were the top three symptoms chosen,

followed by low self-esteem (15%), difficulties with extra-familial (14%) and familial relationships (11%) (Appendix 6; Figure 11).

Anxiety and Depression

Participants commonly reported experiencing anxiety and/or depression while coping with FSGS 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 and the risk for recurrence after transplant. Patients indicated that, even on "good days," they experienced anxiety about when symptoms would appear. They also discussed difficulties in planning for the future and the negative outlook for their quality of life. Although hopelessness was not specifically mentioned frequently during discussions, depression and hopelessness were frequently reported among participants.

> *"And **we've had to have her doctor increase the anti-anxiety meds because it's just an overwhelming amount of anxiety that she's** [daughter] **dealing with.**"*

> *"…it affects my quality of life. Not just biologically, but mentally, **everyday worrying whether or not I'm getting worse**."*

> *"…anxiety and depression [seem] to be linked to the fact that there's really no treatment and there's not…a way to fix the symptoms. And you don't even know what's going to happen **after you get your transplant** with the FSGS. **I have anxiety still, six years out, because I worry about my FSGS coming back.**"*

> *"…even after* [a] *transplant that's supposed to be a very helpful and an awesome experience. And indeed, it was, but the worry and anxiety doesn't* [sic] *go away because FSGS can come back in your transplant and then what do you do?"*

Care partners of patients reported worrying about access to care for their children and what kind of lives their children would be able to lead with FSGS.

> *"…**there's just a lot of unknown**[s] **with this disease. And I think that's where a lot of the anxiety and depression can come in."***

> *"As, he gets older—he's 10 years old now—I think the anxiety and depression is* [sic] *something that is definitely creeping in…I think as he gets older, **as he becomes kind of more aware of***

> ***what his disease is and what it could mean for him, that's definitely where the anxiety comes in.***"
>
> *"Even when I'm feeling fine and I'm excited to do normal activities with my family and friends, I always have anxiety about suddenly not feeling well or getting dizzy, nauseous, or light-headed."*

Effects of edema

In addition to the physical toll of edema, participants indicated that swelling contributes to significant social problems. A substantial proportion of patients reported experiencing low self-esteem while coping with edema. Patients also stated that the extra weight associated with edema negatively affects their appearance. Even for participants who felt their edema was not noticeable to others, they reported social isolation from having "invisible" pain.

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

Finally, patients were queried on which, if any of a set of six experiences they had encountered (Appendix 5.2; Question 5) Respondents most frequently (25%) noted that others do not understand what it is like to live with FSGS. This was followed by not being able to participate in sports or other physical activities (18%); limitations in daily function (17%); missing work or school (16%); family stress (14%); and inability to participate in hobbies (9%) (Appendix 6, Figure 12).

In the audience discussion participants noted that the cumulative effects of having FSGS, experiencing its symptoms and treatment lead to a sense of social isolation, with most respondents indicating that others do not understand what it is like to live with FSGS, which affects their relationships with family and friends and prevents them from participating in normal social activities. Many patients noted that this is particularly challenging when their symptoms are not visible to others and described the challenges of living with an "invisible disease."

Several of participants described how their symptoms affected their ability to work at their job or at school. Fatigue, gastrointestinal symptoms, inability to concentrate, forgetfulness, pain, and fear of infections were all noted as inhibiting participation at work and school.

> *"Definitely— being a teenager and having these symptoms…I miss out on a lot of things that my friends are able to do…that definitely affects my life a lot. And definitely, transitioning into college more…with all of these symptoms, I think it's very hard.*

> *"**I missed a lot of my eighth grade…And then, a lot of my senior year also**, I had to miss for the symptoms."*

Participants reported that social isolation was frequently caused by the "invisible" nature of their disease, which made it difficult for others to understand or empathize with what life with FSGS is like. This caused sometimes unreconcilable strains on friendships and workplace relationships. Many people also noted that they experienced difficulty with relationships outside of the family.

> *"*[Once] *I had to sit in a wheelchair and **people never truly understand because I 'look fine'**. I look like a 'normal kid' with nothing physically wrong with me."*

> *"The hardest part for me was that people around me, **even the doctors, made me feel like I was crazy because they said my symptoms were not related**. And **people around me said that I was just overreacting because I look normal**."*

> *"So, I walk around looking like a pretty normal person. I don't look like I have very many issues, but a lot of **even my closest friends have told me comments like, 'Oh, you're still sick?' because I'll be taking my medicine in front of them**…Trying to explain to them that it's not something that just goes away, is really difficult."*

> *"When I am swelled* [sic], *I have had people say things to me such as "It's so great you don't care about your appearance" or recommend exercise plans to me. People cannot understand the difference between swelling and true weight gain, and when I am swelled* [sic] *they say hurtful things that* [they] *attribute to laziness."*

> *"The friends that I have that don't understand what's going on with this, they have a hard time understanding that sometimes I need to break plans last minute because of the tiredness. But then, at the same time, I have other friends who go the other direction, where if they wake up and they have a cough, they tend to want to stop plans or they just give me a call."*

> *"**This disease stole so much of*** [his] ***childhood from him*** [son]. *He was in the hospital for years."*

Participants also indicated that the social isolation associated with disease can lead to anxiety, revealing a relationship between anxiety, depression, and social isolation.

> *"**I was afraid to leave the house because I had been cooped up so long**. And then I got to the point where I didn't want to be home, because I had been there so much. Anxiety is still an issue."*

One patient pointed to the lack of perceived importance of mental health relative to physical symptoms.

> *"I'm not focusing on how to necessarily fix my anxiety. And it's also really hard to talk to doctors about anxiety and depression when they're trying to fix those other symptoms and it can seem like it's not as important to [address] anxiety and depression, and it can almost feel silly."*

Audience members also described the isolation that comes from friends not understanding the nature of their disease to the extent that they may worry that FSGS is contagious.

> *"…**I have friends that*** [sic] ***are convinced that somehow this is catchy,** and they don't want it. So, I have not been around them at all. **There's a couple that have written me completely out of their lives because of it**."*

> *"**It frightened kids*** [students at school] *at times **when my appearance changed and I couldn't think straight**. Some **parents asked me**, **'What is going on? Are you pregnant? Are you sick? Is this contagious? Are you going to die?**'*

Worry/Planning

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. Patients noted that they frequently worry about future recurrence or progression of the disease. Some worried whether treatment options would be available to them; many expressed frustration and concern about whether they would be able to be available to their families as their disease progressed.

> *"When you are told that you will almost definitely experience renal failure, dialysis, and be in need of a transplant, but nobody knows if it will be five years, 10 years or 20 years, you are left with an **overwhelming feeling of hopelessness**. How can you plan for your retirement? How can you plan for your career? **How can you plan to be around for the important events in your children's lives after such a prognosis?**"*

> *"For me right now, probably the **biggest fear** I have is being on **dialysis** and having **to rely on a machine several times a week to live** and what kind of quality of life that will be for me."*

> *"…**we fear that we're going to run out of different medications to try**. We've had success with some medications, but I feel if things start to flare up here again, 'What else can we try?' because we've tried a lot of different things."*

> *"And the idea of a transplant scares me, not just because of the entire process, but if I'm taking a kidney from a family member, what if it fails immediately?"*

> *"And no one tells you this when you're diagnosed, but **I will never qualify for life insurance for my family**. I have **no way of ensuring that they can survive after I'm gone**."*

> *"**I live alone. So, I fear not having the energy to take care of myself** in the future. I also live hours from my specialist. How will I get to the appointments? Friends can help, but I don't want to be a burden on my friends."*

In addition to interfering with long-term planning, these worries affect short-term planning and may limit the daily activities of patients.

> *"I've always been a very active person, but with the threat of a relapse, it often makes me **hesitate to make plans too far into the future**."*

> *"…**with a toddler…it really affects our decision-making day to day, about what activities he can do**. Like, playing on the playground where there's lots of germs, attending preschool, where there's a lot of germs and something could worsen his nephrotic syndrome and FSGS and cause him to go straight back to the ER. He's been hospitalized so many times that we constantly have this **fear of, 'Will that activity cause him to go back to the hospital?'**"*

> *"*[W]*e feel **uncomfortable traveling**…if something happens and he needs to go to a hospital, **is it a good children's hospital nearby?**"*

Children and Family

Additionally, care partners of young patients with FSGS noted the frustration and hopelessness associated with the unknowns about their child's future quality of life.

> *"Our biggest concern is how will all of this affect her future? **Will she have access left for drug treatments as an adult? Will there be a treatment when her FSGS returns after her second transplant? And when will antibiotics no longer work for her? Will her mental health hold up? Will she live to have a successful future?**"*

Some participants also noted difficulties regarding family planning while living with FSGS and the toll such uncertainty takes on their relationships.

> *"…we want to conceive a child.* ***It's terrifying****…not* [to] *have a treatment for FSGS after 20 years. And then the worry of, '****Do I get off my medication and hope that my disease doesn't progress at the risk of wanting to have a family?****'"*

> *"I'm thinking, in a few years I would want to get married, start thinking about having children. But I have to keep monitoring my labs and* ***praying I don't have to go on a treatment that could risk my fertility.****"*

> *"There's a lot of guilt…****I almost feel guilty because I can't promise*** **[my significant other]** ***a future where I can be healthy.*** *I can't assure*[sic] *that I can give him a potential* [sic] *child down the line—the life that I ideally want to give."*

TOPIC 2. CLINICAL TRIALS IN FSGS USING TRADITIONAL APPROVAL PROGRAM

Following a presentation about the challenges of designing clinical trials for FSGS, polling questions (Appendix 5.2) and audience discussion disclosed patients' experiences with and preferences for participating in clinical trials, their concerns about participation, and what factors were important to them when choosing whether to participate in such studies.

During the audience discussion, patients with experience in clinical trials voiced their support for these studies and many indicated that they would be willing to participate in another trial, citing superior care, a better understanding of their disease, and a closeness with the doctor treating them. Nevertheless, participants expressed caution, noting the importance of the opinion of their nephrologist and seeking evidence for efficacy and safety of the product under investigation. Concerns regarding receiving a placebo and requirements for biopsies were also discussed.

While factors concerning enrolling in a clinical trial were discussed in sessions on Topics 2 and 3 (covering both the traditional and accelerated pathways), many of these issues are consolidated under Topic 2. The concerns expressed in this session apply to Topic 3 as well.

Polling Questions and Audience Discussion

General considerations for enrolling in clinical trials

Responses to the first Polling Question (Appendix 5.2; Question 1) revealed that most participants had not previously participated in a clinical trial because they either were not eligible (35%) or because they were unaware of the opportunity (20%) (Appendix 6; Figure 13). An additional 33%had previously participated in a clinical trial and indicated that they would do so again. No patients reported that they would not enroll or re-enroll in a clinical trial. Nine percent of respondents indicated they were unsure whether they would participate in a clinical trial. Four percent of respondents were aware of and eligible for a trial but did not seek to participate. None were currently participating in a clinical trial.

Experiences with clinical trials

> *"…I had a wonderful experience with* [a clinical trial]…***You get a lot more close attention…So you really get to understand your medical history*** *at a much deeper level than [by] just going to your nephrologist…And while the clinical trial did not work for me, I would definitely consider participating* [again]*."*

> *"…my daughter has been in two drug trials…**the level of care…was superior**…*[due to the frequent visits] *and* [additional] *testing…* ***My understanding of the disease was better*** *because I could see the labs... if there was a third* [trial]*, we would* [re-enroll] *because we* [want] *the absolute best state-of-the-art care that we can get her."*

> *"I would like to help with trying to slow down the progression of kidney disease and also* [address] *the underlying factors, especially within the African American community."*

> *"**I wish I had done this*** **[explored clinical trials]** ***years ago**."*

Major factors influencing a decision to enroll in a clinical trial

When asked in a Polling Question (Appendix 5.2; Question 2) about the top three factors that would affect their decision to participate in a clinical trial, participants most often reported (Appendix 6; Figure 14) their concern regarding potential side effects of a drug being tested (25%, followed by whether they might need to stop their current treatment (14%) and whether they would receive a placebo (13%). Also noted as important factors for patients were: efficacy in previous trials (10%); distance to trial site (9%); whether their nephrologist recommends enrollment (9%); and the need for kidney biopsy (8%).

Nephrologist's opinion is important

Audience members also noted that the opinion of their nephrologist was very important when deciding whether to participate in a clinical trial. Informing patients about clinical trials through nephrologists was emphasized as an important step in facilitating trial participation.

> *"For me,* ***the top motivation would be in the view of my…nephrologist****...the selection of which* [clinical trial] *to participate in is really important.* ***I want to be sure that the one I choose…has the highest probability of positive impact, not only on myself, but on research moving forward****."*

> *"So, my push would be to get the information about clinical trials out to nephrologists…and getting that in the hands of patients and care partners."*

Concern about receiving placebo

The concern about assignment to a placebo arm in a trial was clearly voiced by one patient:

> *"…the fear of taking part in a clinical trial is that I would be placed on a placebo. If you're joining a clinical trial, it's because you are desperate for a new treatment to save your life****. If you are in the placebo group, then you are not receiving any hope of disease control or remission, at least anytime soon. That is terrifying."***

Logistics of a clinical trial

Patients noted the importance of logistical concerns and general expectations for entering a clinical trial. The frequency of 24-hour urine tests was also noted as a factor for consideration regarding participation in trials. This was also discussed at length in Topic 3 (below).

> *"****How far am I going to have to travel to go get this treatment****? Is there going to be more intensive testing for me?* ***There's already a lot of needle sticks with lab work and urine analysis****; how much extra is it going to require…Is it going to prevent protein loss? Is it going to protect the kidney?"*

> *"…****I don't know that people putting together these trials understand what a pain that is to do*** **[24-hour urine tests]** ***if you're working or in and out of the house throughout the day."***

Kidney biopsies

Patients' preferences regarding kidney biopsies were disclosed by polling. Forty-eight percent of respondents indicated their willingness to enter a clinical trial if one biopsy within one year was required (Appendix 6; Figure 15), while 19% and 21% of patients were willing to participate in a trial requiring two

or three biopsies, respectively. Twelve percent of patients reported that they would enroll in a clinical trial only if it did not require any kidney biopsies.

> *"How many biopsies?"*
>
> ***"I didn't have a great experience with my initial biopsy that diagnosed me and I'm not sure that I would be able to handle that multiple times**."*
>
> *"…the pain level was not what they had let me know* [sic] *at the time**. It was supposed to be, 'Oh, you'll feel better in a couple of days.' Weeks later, I was still in pain from that biopsy**."***

Purpose of clinical trial

During the panel and audience discussions, participants voiced a willingness to participate in clinical trials that were designed to:

1) manage the underlying cause of kidney damage in FSGS

2) study if and how well a new drug reduces symptoms or

3) evaluate whether a drug reduces the progression of FSGS**.**

Several patients also focused on the anticipated outcome of the clinical trial.

> *"…what are they expecting the outcome to be at the end of the day?"*
>
> *"I think* [**whether a treatment addresses]** ***the underlying cause would be the most important thing for us** so that we could kind of figure out how it started and then from there, I feel like you find out a lot more information on how to stop it."*

Seeking evidence for efficacy and safety

Participants sought evidence for efficacy and safety in the potential drug being evaluated.

> *"My daughter is six…the biggest thing for us would probably be 'the why.' Like, 'Why is this trial going to work? **What case studies are there to prove what this is going to help?**'"*
>
> ***"I'd also like to know how safe it is and I'd like to be informed along the way of what is happening in the study."***

"[The most important information for considering a trial would be information on] *the side effects of the medication …anything that affects my child neurologically..."*

*"**We mainly looked at how very similar patients responded to different treatments and both the low side effects and success with a few very similar patients…*** **[this]** ***made us willing to give it*** **[clinical trial for daughter]** ***a try.**"*

"And then, the side effects…my symptoms are mostly bone issues and in some of the trials that have been presented to me, some of the side effects could be broken bones or jaw health issues…"

*"**My daughter would not participate in a trial were it to affect her fertility and negatively affect her other organs**."*

"I would like to see case studies using this drug…"

Clinical trials for kidney transplant recipients

Kidney transplant recipients also noted that they are historically ineligible to enroll in clinical trials and that only few clinical trials for FSGS will enroll FSGS patients who have received a kidney transplant. These patients were concerned about participating, even if they might be eligible. Kidney transplant patients also showed instincts to protect their transplanted kidney, being concerned about risks of possible kidney damage during a clinical trial.

*"**I'd love to participate in the clinical trial, but I am not eligible due to transplant**."*

"…this being my second transplant, I'm really unwilling to take a lot of risk, but I'm willing to take the risks that might be able to show that any type of progression could be slowed or the underlying cause of this can be found."

*"**Being a kidney recipient you kind of want to keep what you already have and don't want it damaged**."*

"Obviously, someone needs to start somewhere but being the first person to be the transplant patient within the trial definitely makes me very nervous."

Another patient provided an alternative view:

"…if I start seeing any protein in my urine, it's…most likely that the FSGS is attacking my kidney. ***That's my brother's kidney, and I'm going to do everything I can to protect it****. So consequently, if* [a trial] *was available, I would certainly want to dig into it and I'd want to drive it hard. I'd want to make sure that I was able to do all of the study if I was going to get in."*

TOPIC 3: CLINICAL TRIALS IN FSGS USING ACCELERATED APPROVAL PROGRAM

To prepare the audience for the Polling Questions and discussions on clinical trials executed under the Accelerated Approval Program, a presentation was given on the differences between the traditional and accelerated programs. This talk highlighted the importance of extension phases in clinical trials which result in accelerated approval.

Polling Questions and Audience Discussion

During the Polling Questions (Appendix 5.2), participants were presented with a hypothetical clinical trial in which groups of patients were undergoing a potentially new FSGS treatment or a standard-of-care treatment (Appendix 3.3; Discussion Questions). The trial included an extension phase toward accelerated approval. In this trial, after establishing efficacy for reducing proteinuria, patients would remain in their assigned treatment groups for an extension phase to verify that the product reduced the loss of kidney function. It was noted that during the extension phase, the treatment would be available on the market.

Participants were asked about the factors that would motivate them to participate in the trial, as well as remain in the extension phase. The Audience Discussion confirmed participants' views regarding enrolling in the clinical trial that were expressed in the session for Topic 2. The following summarizes the discussion around remaining in a trial during the extension phase.

Remaining in extension phase of clinical trial

In response to Polling Questions (Appendix 5.2; Question 1), 40% of participants indicated they would remain in their assigned treatment arm for 1 or 2 years during an extension phase, while 16% responded they would remain for three years (Appendix 6; Figure 16). Only 5% of patients responded that they would be unwilling to remain in their treatment arm for any period of time.

In discussions, the majority of participants noted that remaining in their treatment arm would depend on the side effects of treatment, their symptom control, and their disease progression during the trial.

> *"If* [the test agent is] *working for you like any other...you're going to stay on that treatment.* ***But if it's not working, you're going to move on to something else. So, it's scary to be stuck in a treatment for a few years without knowing—'Is this going to really cause GFR to drop or give me side effects that keep me in bed all day?'*** *So I think, really,* ***quality of life and at least stabilizing*** **[kidney function],** ***even if it doesn't help you get better, is key****."*

> *"…if the treatment has a chance to reduce my urine protein levels or edema that, that would motivate me to stay in an extended trial. Because, again, that was my worst symptom I would have up to 30 pounds of edema…and I'd be in extreme pain…So,* ***I would be motivated just for the fact that I could potentially...feel better or improve my quality of life and perhaps even slow the progression of the disease and live a more comfortable life.****"*

> *"…****if her*** **[daughter's]** ***levels were not stable****, I think if it was causing harm to her or her native kidneys, I think if she was not feeling well…If that was still happening while she was on the drug trial,* ***then we would have a serious conversation…about whether or not we would continue****."*

Audience members reported that they were particularly concerned about enrolling in a clinical trial in which they could be assigned to a prednisone treatment group in a standard-of-care arm of the extension phase.

> *"The answer to the question…depends on so many factors and so…prednisone really throws a wrench into it for me personally."*

> *"…it would be something I would discuss with my nephrologist and* ***it would very much depend on how my experience*** **[in the clinical trial]** ***had been to date.*** *Had the clinical trial* ***required that I stay at the same level of other medications…****to give an example,* ***say 10 milligrams of prednisone over the course of the trial…for a couple of years; I think that'd be a deal breaker****. "*

> *"…****I don't know that I could sign on for a year or two of being on prednisone****."*

Logistical issues

Patients felt that logistical issues would affect their thinking around the length of time they would be willing to stay in the extension phase of a trial. Moreover, based on their experiences in traditional (not

accelerated approval) clinical trials, the Discussion Panelists agreed that, while participating in an accelerated approval trial, logistical burdens might assume heightened importance and weigh heavily on a decision to remain in an extension phase, especially when patients could obtain the treatment on the market.

> *"I would love to be able to support the science, but at the same time,* ***the design of the study needs to incorporate the fact that we are fully active, engaged people and want to stay that way****."*

> *"…logistics and how far do you have to travel to participate in the trial…****it was…a challenge driving to a larger city than where I live—and traffic jams. It was…stressful at times****…Would I have to fly there or drive there? And* ***how comfortable are you going to be at the location****…? Sometimes I would stay a day and…wasn't compensated for an overnight stay if I chose not to drive all the way home."*

> *"…I was in Manhattan when…I did a year-long trial…I had a great experience. But* ***do you know what it's like schlepping through Manhattan carrying 24 hours-worth of urine?*** *…It meant taking public transportation, holding a bag of my pee."*

> *"…there was no way that I would have been able to* [enroll in] *the study* [without] *great flexibility in my employment and the ability to meet their time schedule…So, these little things really matter. It's the distance driving. It's how we're taken care of overnight, but it's also the frequency* [of visits]. *And you just got to think through, what's it*['s] *like to do a 24-hour* [urine] *test even if you're staying in a hotel."*

> *"…****if it's just been crazy*** **[unmanageable logistics]…*****then why not just go get off*** **[the trial]** ***and get*** **[the medicine]** ***on the market?****"*

Clinical measurements that are relevant to patients

When asked in a Polling Question (Appendix 5.2; Question 2) which measurements for clinical trial outcomes participants felt were most relevant to their FSGS, audience members overwhelmingly (29%) indicated that proteinuria/albuminuria and (25%) kidney function (GFR) were the most relevant parameters, followed closely by delays in time to dialysis or transplant (20%). Several other participants also reported that quality of life (10%), edema (9%), and fatigue (5%) were important (Appendix 6; Figure 17).

TOPIC 4: CURRENT CHALLENGES TO TREATING FSGS

The final discussion topic focused on patients' experiences with FSGS treatments, including pharmaceutical treatments, medical procedures, and non-pharmaceutical strategies. The session began with video presentations from four FSGS patients who described their experiences with treating their FSGS. After the video presentations, five Discussion Panelists provided further insights into the challenges of treating FSGS. This conversation was structured around Discussion Questions (Appendix 3.4) to initiate dialogue. Audience members echoed many of the points made by Testimony and Discussion Panelists and offered additional perspectives on what is needed in the FSGS treatment landscape.

Noteworthy excerpts from the patient testimonies are below.

Nicki *(adult patient)*

> *"I began my fifth treatment, cyclosporine, alongside a three-week burst of prednisone. This time* ***the steroids gave me around-the-clock anxiety, a tight chest, difficulty breathing and panic attacks. But after nearly eight months, I finally saw my ankles again****…and on cyclosporine alone, …*[my] *a daily protein*[uria is] *just above two grams…*

Becky *(adult patient)*

> *"…****prednisone for eight horrible months****. I felt a hundred percent fine until I started the steroid* ***treatment****, and during the eight months* ***I experienced extreme steroid rage****. It was like an out-of-body experience. I felt like I was sitting on my own shoulder, watching myself be completely irrational and telling myself to stop, but I couldn't…*
>
> *"****I gained 30 pounds and got the dreaded steroid "moon face."*** [With] ***Prograf*** **[tacrolimus]** ***…in the shower it felt like my feet were going to burn off****…Like steroids, Prograf had no effect on my protein."*

Taylor *(adult patient)*

> *"****Prednisone alone, caused multiple panic attacks****…I experienced weight gain…*[and loss of] *confidence****. I withdrew from friends****…*
>
> *"****The trial and error of searching for alternatives to prednisone was exhausting****…"*

"The diuretics… caused me to lose potassium, which resulted in me adding a new medication to combat that side effect…

*"I was **diagnosed with osteopenia last year, due to the five and a half years of extensive steroid treatment**."*

Melissa (mother of Alyse, her 14-year-old daughter)

*"**Currently** [**Alyse**] **takes 23 timed daily oral medications with an infusion and an injection every week**.*

"…after transplant [she] *participate*[ed] *in a clinical trial for Liposorber, lipid apheresis…was unsuccessful…*

"[She received] *Acthar injections. Due to the adrenal surges, there were so many days she was so uncomfortable she couldn't walk or go to school because of the swelling…"*

In the discussions that followed the patient testimonies, participants described their journeys through the FSGS treatment landscape by recounting the successes, limitations, and effects of their current treatment regimens. Many patients indicated that they endured multiple drug regimens, ranging from 2 to 23 different daily medications. Polling of the audience revealed that, among the drugs patients were receiving or had taken, ACE inhibitors, ARBs, beta-blockers, diuretics, other blood pressure medications (27% of respondents), and anti-inflammatories and immunosuppressants (24%) were the most commonly reported medications used to treat FSGS (Appendix 5.2; Question 1; Appendix 6; Figure 18). Sixteen percent of participants reported using a statin or other cholesterol-lowering agent and 18% reported that they used some other medication not included in the survey.

In response to another polling question, (Appendix 5.2; Question 2), 29% of respondents indicated that their current treatment regimen reduced their most significant symptoms very well, while 24% considered their symptoms moderately or somewhat controlled. Sixteen percent of respondents indicated "Not at all" for this question. Eight percent of participants reported that they were not currently receiving any treatment to reduce the symptoms of their FSGS. (Appendix 6; Figure 19).

When asked (Appendix 5.2; Question 3) which symptoms of FSGS are not addressed by current treatment, respondents cited fatigue 19%, anxiety and/or depression and "brain fog" (both 15%), and muscle aches and pains (13%) as the top four symptoms (Appendix 6; Figure 20).

Perspectives on Current Treatment

In discussions, patients described the difficulties of finding effective treatments to manage their FSGS symptoms. Participants discussed their experiences with corticosteroids and immunosuppressive agents such as cyclosporine and rituximab. Some noted that they tried over-the-counter supplements such as vitamin D and iron, which they reported did not have a major impact on their disease symptoms.

Participants almost universally voiced frustration with finding effective treatments. They also expressed dissatisfaction and with the "try and see" method of treatment used by their nephrologists.

> *"…my daughter* [is]*…10 now and has been unresponsive to everything we've tried. We've tried prednisone, tacrolimus, CellCept* [mycophenolate mofetil], *rituximab…lisinopril, Anafranil* [clomipramine]*, losartan. We've tried mixing… the ACE inhibitors and the ARBs with the immune* [sic] *suppressants…we tried infusions of rituximab. Her most recent infusion was obinutuzumab…And still, nothing has changed, literally no reduction of her protein… We even tried two different types or two different rounds of apheresis...And then…even a longer …*apheresis [for] *nine months long and* [she] *was still unresponsive."*

> *"We finally gave up on steroids and switched to Prograf* [tacrolimus]. ***This is all part of the normal throwing-spaghetti-against-the-wall-to-see-what-sticks way of treating FSGS****."*

> *"…this disease and the associated medication* [are] *debilitating.* ***It has been difficult to continue taking medication that makes me feel ill without any evidence of improvement with the disease****. The "try-and-see" approach to medicating this illness is frustrating."*

A common theme expressed by participants was that the options for treating FSGS are often as debilitating as the disease, if not more so, especially with prednisone treatment (see below). Dissatisfaction with this aspect of FSGS treatment leads to hopelessness and fear that if current treatments fail, patients are out of options.

> *"…what if it just stops working?* ***It is too scary and painful to comprehend a future that includes dialysis or a kidney transplant.****"*

> *"…a lot of the medications they have right now are affecting my daughter* [neurologically] *as far as a tremor goes, headaches, fatigue."*

Pharmacological treatment

Prednisone and prednisolone

In discussions, audience members most frequently expressed their frustrations with the side effects of prednisone and less frequently, prednisolone. Participants described a wide range of physical, emotional, and psychological side effects, including weight gain, difficulty sleeping, mood swings, heartburn, bruising, vision problems, anemia, joint pains, shakiness, muscle weakness, palpitations, nausea, panic attacks, loss of confidence, social isolation, depression, and suicidal thoughts. The effects of drug treatments on FSGS clinical signs and symptoms varied, with some patients reporting that they responded well clinically to treatment with prednisone, and others reporting that it had no effect on their disease. Collectively though, even when prednisone was an effective treatment, participants felt it was not worth the side effects that they experienced. Reported doses ranged from 5 to 120 mg of prednisone.

> *"I know the medication was meant to help me, but my life was severely restricted by it."*
>
> *"**It was like I woke up one day and, instead of 22, I was now 90**."*
>
> *"I treated it* [FSGS] *aggressively, taking 120 milligrams of **prednisone** straight out…it **did help me go into remission** and I've been in remission since then, **I did have to pay the price of gaining over a hundred pounds of weight.**"*
>
> *"Physical and emotional pain is real from prednisolone. **His** **[son]** **bones hurt**. The swelling causes pain in his skin, where anything that touches him causes extreme sensory pain. **When he is on high dose steroids, his body changes so dramatically that his friends and even his teachers do not even recognize him. This causes such severe depression in him**."*
>
> *"Prednisolone has made me feel **depressed**, have **suicidal** thoughts. Dizzy. **My body is constantly vibrating and shaking**. **Muscle weakness**, especially in the legs. Constantly feel like I'm going to fall over. **Insomnia. Palpitations** after eating. My hip has been affected. "**Brain zaps.**" My **concentration and cognitive abilities have been** affected, and **my hair is falling out**. I feel like prednisolone has affected my quality of life over* [from] *my medication and should not be offered as a first line therapy."*

*"Being on prednisone has resulted in **avascular necrosis, causing pain and bone loss** in my right hip. This has **limited my ability to do some of the things that I love the most**, like running, skydiving, and martial arts."*

"It just breaks my heart that she so desperately wants to live what we would call a typical life, but because of the disease, the side effects of medications, she's not able to do that."

Patients with long-standing disease also noted that taking prednisone was associated with long-term side effects, including atypical hemolytic uremic syndrome, gall bladder failure, and osteopenia. Participants who described these effects also noted that at the start of their treatment they were unaware of the potential for these long-term side effects. Patients voiced concerns that past treatment decisions were creating more consequences now.

"***Unfortunately, the effects of prednisone will follow me for the rest of my life**."*

"Did what I do 15 years ago, to put me in this space, have any effect to what's going on now?"

Immunosuppressants

Anti-inflammatory and immunosuppressive agents were the second most commonly reported treatment currently used by patients (appendix 5.2; Question 1; Appendix 6; Figure 18). In discussions, participants frequently noted using tacrolimus and cyclosporine. Compared with the side effects of prednisone, participants reported milder symptoms associated with the former agents. Audience members noted experiencing burning and tingling sensations in the extremities, including restless leg syndrome, puffy and bleeding gums, and both hair loss and excessive hair growth while taking these drugs.

*"She [daughter] has had **burning in her fingers and toes as a side effect of the tacrolimus**."*

"…side effects [from cyclosporine without prednisone]*…are more manageable, mildly puffy and bleeding gums, a little extra facial and arm hair and tingling in my hands and feet when I touch something too hot or cold…*[but] *I can finally live my life again and feel comfortable in my own skin, but I still live in fear."*

Frequent infections related to immunosuppression caused by prednisone were commonly reported treatment-related events, but other side effects which affected daily activities and quality of life were addressed as well.

> *"Obviously being immunocompromised during a global pandemic is a terrifying thing, but even outside of current events, living* ***with immunosuppression*** *can be daunting.* ***In the past year, I've had bronchitis four times and I seem to catch a cold at least every other month****."*

While most participants noted that immunosuppressants at least somewhat successfully managed their FSGS symptoms, they expressed concerns about the long-term efficacy of these drugs.

> *"And what's going to happen when I have to go off of it* [cyclosporine] *to get pregnant? Or what if it just stops working?"*

> *"I do not believe I can achieve a drug-free remission on* [cyclosporine]*."*

> *"****My biggest fear is having to live the rest of my life on immunosuppressants****."*

Some patients described their experiences with rituximab as well, although this drug was not mentioned as frequently as prednisone or cyclosporine. For those who were able to receive rituximab, most patients reported that treatment either did not have an effect or was effective for only a short time. Some patients noted that they experienced nausea with treatment, as well as fatigue due to the use of antihistamines to prevent an allergic response to the drug. In addition, allergic reactions to rituximab may exclude some patients from receiving treatment and have contributed to a sense of hopelessness. Because rituximab is administered intravenously, treatment is also time consuming.

> *"…****Rituxan*** **[rituximab]** ***sounded like my dream come true…but…it took just 10 minutes into the infusion for me to break out into full body hives with unbearably itchy ears and a throat threatening to close****. I was drowning in tears as the nurses deemed it unsafe to continue the treatment and unhooked me from the IV.* ***I was only 22 and I felt like I was out of options****."*

> *"Because of the Benadryl they give you to combat any allergic reactions you may have, I was also tired during infusion days and had to have someone drive me to and from the appointments. Unfortunately, this poison did not work to reduce my protein either."*

ACE, ARB, beta-blockers, and diuretics

Although ACE, ARB, beta-blockers, and diuretics were the most frequently reported class of drugs patients cited as treatments for their FSGS (Appendix 6; Figure 18), they were not often mentioned in discussions. One patient noted that her blood pressure medication was changed frequently to keep up

with her disease and to balance the risk for hypotension. Another patient described a life divided between sleeping and effects of diuresis.

> *"So basically,* ***I would be sleeping for about 12 to 16 hours a day, and then when I am up, I'm on the toilet for about two or three****."*

Medical procedures

Audience members also described their experiences with the medical procedures used to treat FSGS, including lipid apheresis and plasmapheresis, dialysis, and kidney transplant. Non-pharmacological options for managing FSGS were also discussed, with particular emphasis on strategies for overcoming the psychological and emotional tolls of the disease.

Lipid apheresis and plasmapheresis

Many participants described similar experiences with lipid apheresis and plasmapheresis: participants reported that these treatment options were at least moderately successful but were also time consuming and exhausting. In facilitated discussions, compared with older patients, young patients and care partners of children with FSGS more frequently reported positive experiences with lipid apheresis and plasmapheresis.

> *"…after my transplant, because of…plasmapheresis…my IgG* [immunoglobulin] *levels were low****, I became susceptible to bronchial infections, and now I have acquired a lung disease for the rest of my life****."*

> *"…I've done over 400* [plasmapheresis] *treatments. So, I'm basically living off of a machine, like it's helping me live and that's an hour away from me with no traffic."*

> *"****Acthar Gel and plasmapheresis is*** **[sic]** ***about the only thing*** **[sic]** ***that's given me any kind of lower numbers****..."*

> *"…I had a transplant when I was six. My disease came back and I had to do* ***plasmapheresis every week for over two years, and it kept me in partial remission.****"*

Dialysis

Dialysis is one form of renal replacement therapy available to FSGS patients. Throughout the program, many participants expressed anxiety about the prospect of progressing to dialysis as their disease

progressed and they ran out of pharmacological treatment options. These worries were attributed to the need for machine support to live and the hopelessness of reaching this stage of disease. Some participants had received both hemodialysis and peritoneal dialysis. In discussions, participants expressed that dialysis was painful and time consuming. Additionally, it made day-to-day life difficult, complicating everything from participation in swimming and sports to bathing.

Kidney transplantation

Forty percent of participants had received a transplant (Appendix 5.1; Question 7; Appendix 6; Figure 7), over half of whom were in remission (Appendix 5.1; Question 7; Appendix 6; Figure 7). In discussions, however, participants most frequently described their experiences in the context of disease recurrence and consequent transplant failure. Some patients reported multiple transplant failures. Patients described their optimism leading up to transplant followed by the disappointment with the recurrence of their disease. They emphasized the need to remain positive about the progress science has made and may make before their next transplant but also acknowledged the hopelessness associated with transplant failures.

> *"…when I was going to get my transplant,* ***I never thought that I would have to deal with recurrence****. It didn't even occur to me…and I thought that I had suffered enough, that I was going to get away with it. That obviously didn't help."*

> *"I was told that* ***my new kidney should last for 20 years****, but…****four years later, I began to experience symptoms of FSGS recurrence****…"*

> *"*[I]*t's harder this time around because it's* [sic] *a little bit less hope."*

Non-pharmacological treatment

Coping psychologically and emotionally

Panelists and audience members, particularly those with long-standing disease, emphasized the importance of managing the emotional and psychological effects of FSGS (Appendix 3.1; Topic 1). Although they acknowledged that the disease can feel overwhelming and it can feel like there are no options for some patients, they reiterated the need for hope. Participants offered specific suggestions for remaining positive about their outlook and the progression of science, such as blogging, therapy, anti-anxiety medication, physical activity, and getting involved in causes related to FSGS, including organizations, events, and clinical trials.

"She's [daughter] *been in **therapy**… and now she's on an antianxiety medication. She has so much anxiety from all of the numerous hospitalizations and medical procedures…And that's **the only thing that seems to just kind of help**."*

"It helps me as a patient to go out and breathe...get outside in the woods, on the water, in the water, not just in your neighborhood."

*"**I use yoga and other forms of** exercise to help manage the anxiety, fatigue and joint pain caused by FSGS and the medications I have to take."*

*"**I had a blog**. And that was my place where I just ranted about all the injustices of this disease, how frustrated I was, how crazy I felt, and that didn't change my situation. But I guess, **just having an outlet for it helped.**"*

"It's a terrible rollercoaster ride that you've all been on. But if you can find some solace and some consistency, it gives you a breath before your next big hill."

*"I think **being positive, upbeat, having a sense of humor** with all of this. I think **it's actually key to helping to do something about this disease.**"*

"What helps my 7-year-old is laughter. We stream ""Funny Cats & Dogs"" on YouTube and the house fills with giggles, which lifts our hearts to hear."

Diet

Throughout the program, participants noted that diet change played a key role in managing their FSGS and symptoms, including low-sodium diets and plant-based protein diets. Participants noted that these diet changes can be challenging and socially isolating, particularly for young children.

"[S]*he's six, so as she sees what other children are able to eat, it gets harder* [with age]*."*

Perspectives on an Ideal Treatment for FSGS

Patients emphasized the need for a treatment option specifically for FSGS. They expressed the frustration of needing to piece together a therapeutic strategy from drugs designed to treat other diseases which happened to also control some of their symptoms. Oftentimes these drugs exacerbated other symptoms or created new ones which required additional treatment, complicating the therapy.

When asked to describe their ideal treatment for FSGS, participants emphasized the need to reduce side effects and reduce the number of agents taken. Less than one-third of patients reported (Appendix 6; Figure 21) that they would likely consider a novel drug with severe side effects even if it had clinical evidence that it would slow the progression of disease or improve their quality of life. A majority of patients reported (Appendix 6; Figure 22) that, disregarding side effects, their preference was for an agent that preserves or halts the decline in kidney function. Care partners also emphasized the need to consider the logistical aspects of the drug, such as: frequency of blood draws for monitoring the drug's effects and how the medication is delivered. Parents felt this was particularly of concern for children, for whom they felt the difficulties of FSGS treatment were especially challenging.

> *"**I need a treatment that's going to focus on curing the actual disease, not creating more side effects that make our lives harder than they already are**."*
>
> *"Instead of piecing together multiple medications for other illnesses that just so happened to work for me,* [the drug] *would be for FSGS."*
>
> *"The **ideal treatment would both prevent kidney failure and not force me to sacrifice the quality of my life.** Otherwise, what's the point of a cure?"*
>
> *"What we need in future **treatments** are those **that are novel and developed specifically for FSGS**, designed to stop or lower proteinuria, extending the life of native kidneys, preventing dialysis, while at the same time minimizing side effects and allowing patients a decent quality of life."*
>
> *"My hope is that one day soon a cure will be found for this disease or at least a treatment that doesn't require immunosuppression."*

Female participants also expressed a need for treatment options that are compatible with pregnancy. Patients expressed concerns about the recurrence of symptoms when having to discontinue treatment during pregnancy. A treatment option is needed which is indicated during pregnancy and family planning.

> *"I would like to take one pill—**one pill—once a day. The side effects would not hinder my quality of life and they would not feel worse than the disease itself. It would not ruin my plans of starting a family** one day."*

The meeting ended on a note of hope, similar to that on which it started:

"…after 33 years with the transplant and over 40 years with FSGS, with the fear…that it could return, and being at 70 years old and actually starting to think about end-of-life issues…there's always hope. ***In kidney disease, it's a matter of making sure that you get the right combination of hope and the belief that you can overcome it all***. ***Don't give up hope***."

CONCLUSIONS

This virtual Externally Led Patient-Focused Drug Development meeting held by the National Kidney Foundation and NephCure Kidney International® provided the FDA, product developers, clinicians, and academic researchers an opportunity to hear patients' in-depth views on the challenges of living with FSGS, the impact on their 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:

- The fatigue associated with FSGS and some treatments significantly affects patients' daily lives and their ability to participate in work, school, and social activities.
- The invisible nature of FSGS can cause social isolation and a disconnect between patients and their friends, family, and peers.
- The unknown nature of the disease and the risk for recurrence and treatment failure contributes to depression and anxiety in patients with FSGS. Additionally, this uncertainty can make planning for the future difficult, contributing to a sense of hopelessness and further impeding day-to-day life.
- Currently available treatment strategies are based on a "guess and hope" approach to therapy and are often associated with a host of negative side effects which may be worse than the disease itself. These side effects, particularly for steroid-based treatments, contribute to a lower quality of life, anxiety and depression, and self-esteem issues. Additionally, long-term side effects may occur.
- Patients often expressed a fear of progression to end-stage kidney disease (e.g., requiring dialysis), and voiced concerns about the need for reliance on a machine for survival and the associated poor quality of life. Patients who had received supportive medical procedures, including dialysis, lipid apheresis, and plasmapheresis reported that these procedures improved their physical symptoms but made daily life more challenging as well.
- Most patients were willing to participate in clinical trials but required more information. Their nephrologists were the most trusted source on whether to participate in a clinical trial. The most commonly voiced concerns surrounding clinical trials were potential side effects, the possible need to stop current treatments, being randomized to receive placebo, evidence for efficacy and safety, logistics, and need for multiple biopsies.

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 FSGS

In recent years, the FDA has adopted an enhanced approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics to improve clarity, transparency, and consistency.[1] 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 input provided by patients and care partners through the FSGS EL-PFDD meeting may inform the FDA's understanding of the *Analysis of Condition* and *Current Treatment Options* for this disease.

The information for *Analysis of Condition* and *Current Treatment Options* in the sample Framework table for FSGS below draws from patient contributions at the Voice of the Patient EL-PFDD Meeting on FSGS held on August 28, 2020. This sample Framework table contains the kind of information that may be anticipated to be included in a Framework completed for a drug treatment for FSGS under review.

[1] Commitments in the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) include further development and implementation of the Framework into the FDA's review process. Section 905 of the FDA Safety and Innovation Act also requires the FDA to implement a structured benefit-risk framework in the new drug approval process. For more information on FDA's benefit-risk efforts, refer to: ***https://www.fda.gov/industry/prescription-drug-user-fee-amendments/enhancing-benefit-risk-assessment-regulatory-decision-making***

Dimension Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• FSGS affects children and adults. • The symptoms that most negatively affect daily life of FSGS patients include: - Fatigue, exhaustion - Brain fog - Muscle, joint pain - Anxiety/depression - Edema • Emotional and social consequences are common and attributed to uncertainties and fears regarding: - Unpredictability of the disease - Prognosis - Future need for dialysis, transplant, recurrence in transplanted kidney - Lack of effective treatments - Long-term efficacy of treatments - Social isolation, poor knowledge of FSGS by others - Limited daily function and ability to participate in life. • Disease symptoms prevent patients with FSGS from engaging in activities: - Physical symptoms, anxiety/depression, and social isolation from FSGS can inhibit patients' abilities to fully participate in work, school, physical activities, and social activities.	• Until the cause(s) of FSGS is(are) clarified, a cure for FSGS will remain elusive. • Currently available treatments for FSGS manage the symptoms and do not address etiology of FSGS: - Off-target effects of many treatments cause additional problems for patients, requiring further treatment. - Prednisone-induced effects cause patients to resist/refuse further/repeated regimens with the drug. • Patients will participate in clinical trials for FSGS if: - They are convinced of a strong rationale and previous evidence of efficacy of the drug being studied. - Their participation in the extended phase of an Accelerated Approval Program study will depend largely on their personal outcomes during the initial phase of the study.
Current Treatment Options	• Curative treatments for are FSGS do not exist. • Treatment is nonspecific and aimed at controlling proteinuria, nephrotic syndrome, edema, and hyperlipidemia: - Patients often receive corticosteroids (e.g., prednisone), immunosuppressants, ACE inhibitors, ARBs, diuretics, and statins. - The efficacy of these treatments is generally unsatisfactory - Treatment for pain, anxiety, and depression may be prescribed. • Prednisone is often associated with severe side effects: behavior changes, weight gain, metabolic changes, bone problems, and potential long-term harm to patients: - Patients often report prednisone-induced side effects are worse than FSGS symptoms. • Plasmapheresis and lipid apheresis have been used, but they present logistical burdens similar to dialysis. • Dialysis and kidney transplant are options for patients in kidney failure, but recurrence of FSGS in the transplant is not unusual. • Safe treatments during pregnancy are needed. • Non-pharmacological treatments include: - Low sodium diets - Psychotherapy - Yoga - Physical activity	• Until the cause(s) of FSGS is(are) clarified, a cure for FSGS will remain elusive. • Currently available treatments for FSGS manage the symptoms and do not address etiology of FSGS: - Off-target effects of many treatments cause additional problems for patients, requiring further treatment. - Prednisone-induced effects cause patients to resist/refuse further/repeated regimens with the drug. • Factors influencing patients' willing to participate in clinical trials for FSGS include: - Being convinced of a strong rationale and previous evidence of efficacy of the drug being studied. - Excessive biopsy requirements. - Potential to receive placebo. - Whether current treatment must be stopped. - Patients' participation in the extended phase of an Accelerated Approval Program study will depend largely on their personal outcomes during the initial phase of the study. Patients are hoping for the development of safe, specific treatments for FSGS, and options which preserve kidney function and thereby slow the progression of disease.

APPENDIX 1: REFERENCES

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APPENDIX 2: RESOURCE MATERIALS

MEETING AGENDA

AGENDA_8-20-20_FNL.pdf

SLIDE PRESENTATIONS

SLIDES_A. Thompson.pptx

SLIDES_L. Mariani.pptx

SLIDES_K.Smith.pptx

SLIDES_S. Udani.pptx

MEETING RECORDING

The meeting recording can be viewed on the:

National Kidney Foundation web site: *here*

NephCure Kidney International web site: *here*

APPENDIX 3: DISCUSSION QUESTIONS

Topic 1: Living With FSGS: Living With FSGS: 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?
3. How do your symptoms and their negative impacts affect your daily life on the best days? On the worst days?
4. How has your condition and its symptoms changed over time?
5. What worries you most about your condition?

Topic 2: Clinical Trials in FSGS Using the Traditional Approval Pathway

1. What information is important for you to understand when considering participation in a clinical trial?
2. In which type of clinical trial would you be more likely to enroll:
    a. A trial that studies how well a new drug manages the underlying cause of kidney damage in FSGS but does not study symptoms or progression
    b. A trial to study if and how well a new drug reduces symptoms of FSGS
    c. A trial to study if and how well a new drug reduces progression of FSGS
3. What would be the most important in deciding whether to participate in a clinical trial (e.g., frequency of 24-hour urine samples, travel to study site, number of biopsies, frequency of clinic visits)?
4. Does the type of medication (e.g., pill, IV infusion, injection) and/or the frequency of taking the medication influence your decision to participate in a clinical trial?

Topic 3: Clinical Trials in FSGS Using the Accelerated Approval Pathway

You are considering whether to enroll in a clinical trial where you have a chance of being given either a potential medication for FSGS or standard-of-care treatment (e.g., prednisone, ACE inhibitor) and you won't know which you are getting.

- The trial will evaluate whether the medication lowers protein in your urine (proteinuria) in the first phase.
- If the trial shows that proteinuria is lowered enough, the medication will be approved under the Accelerated Approval Program.
- To verify that the medication slows the loss of kidney function, patients who enrolled in the trial must remain in the trial in their assigned treatment arm for 1 to 2 more years.

1. What factors would motivate you to participate in an accelerated approval clinical trial?
2. If a medication is approved for reducing proteinuria and has a 50% chance of slowing disease progression or improving how patients feel, how would that impact your decision to use that drug?

Topic 4: Current Challenges to Treating FSGS

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?
2. 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?
3. What are the most significant downsides to your current treatments and how do they affect your daily life?
4. 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 FSGS: Disease Symptoms and Their Daily Impacts

Testimony Panelists

- Bernadine (Dine)—Adult patient
- Christopher—Adult patient
- Christine—Adult patient
- Jackie (Jacqueline)—Teen patient

Discussion Panelists

- Jill—Adult patient
- Karlene—Parent of child patient
- Dan—Adult patient
- Katey—Parent of child patient

Topic 2. Clinical Trials in FSGS Using the Traditional Approval Pathway

Discussion Panelists

- Kayla—Adult patient
- Cheryl—Adult patient
- Curtis—Adult patient
- Eftihia—Parent of child patient
- Gianna—Adult patient

Topic 3. Clinical Trials in FSGS Using the Accelerated Approval Pathway

Discussion Panelists

- Valerie—Adult patient
- Diane—Adult patient
- Kent—Adult patient
- Janice—Adult patient
- Jill – Adult patient

Topic 4. Current Challenges to Treating FSGS

Testimony Panelists

- Becky Oag—Adult patient
- Taylor Faulkner—Adult patient
- Nicki Kaplan—Adult patient
- Melissa Naquin—Parent of teen patient (Alyse)

Discussion Panelists

- Jenn Trunk—Adult patient
- Ely Grau—Adult patient
- Erich Ditschman—Adult patient
- Kimberly Queen—Adult patient
- Fred and Cristina Kuo—Parents of child patient

APPENDIX 4.2: PATIENT TESTIMONIES

Topic 1: Living With FSGS: Disease Symptoms And Their Daily Impacts

Bernadine (Dine)

Hello, my name is Bernadine; most people call me Dine. I'm 69 years old and have lived with FSGS for 36 years. I've had two kidney transplants and spent five years on dialysis. I'm happy to be alive. I was diagnosed with FSGS in 1984 when I was 33 years old, and my doctor found excessive protein in my urine. At the time of my diagnosis, I was a working mom in a failing marriage. I had attributed my exhaustion, intermittent joint pain, and gloomy days to the stress in my life. When my ankle swelled, I assumed that I had eaten too much salty food. For more than 14 years my FSGS symptoms remain mild. My blood pressure and cholesterol readings stayed normal. And my creatinine and proteinuria [sic] levels were stable. I continued to experience fatigue, but lived a healthy, active life. I raised my son and built a successful career.

My nephrologist told me that my prognosis for avoiding kidney failure was good. He was wrong. One day in 1998, my doctor called with my latest lab results. I will never forget his words that day, "Ms. Watson, your creatinine level is ticking up." My nephrologist and I spent the next two years in a fierce battle with FSGS, as my blood pressure, creatinine and proteinuria levels rose, my cholesterol spiked, and the edema in my feet got worse, my nephrologist fought back with the medicines available. On most days of the week, I felt close to normal. However, on one or two days, I was so fatigued I didn't want to get out of bed and so unable to concentrate that my work suffered. Once, I lost my train of thought in the middle of an important work presentation.

By early 1999, I was suffering from acute iron deficiency. My nephrologist told me that I would need a transplant or dialysis within a year. I was so anxious and depressed that I began seeing a therapist weekly. In 2000, I received my first kidney transplant from my older sister. The transplant alleviated some of my FSGS symptoms, such as fatigue and inability to concentrate, and my creatinine level returned to the normal range. However, I continued to experience intermittent joint pain and minimal edema in my ankles, especially after sitting for extended periods. I was told that my new kidney should last for 20 years, but by 2004, just four years later, I began to experience symptoms of FSGS recurrence, including almost daily bouts of fatigue, edema and lack of concentration.

In addition, I began to have symptoms I hadn't experienced before my transplant, such as shakiness and devastating diarrhea. I had just remarried and unfortunately, I was facing in [end-]stage renal disease. My depression and anxiety returned. A week before Christmas, 2004, I was rushed to the emergency room, delirious from kidney failure. I spent the next five years on dialysis until I received a second kidney

transplant in 2009. So far, my new kidney has lasted for almost 11 years. My creatinine readings are excellent. And according to my last labs, there's no protein in my urine. I still have minimal edema and intermittent diarrhea, which my nephrologist attributes to my anti-rejection and blood pressure medications.

I also continued to experience joint pain, which I'm told is probably arthritis. My greatest fear is that the FSGS will recur and I will lose the second chance at a healthy life. I watch my labs closely for an upward trend in creatinine or proteinuria. I'm also watchful for signs of the extreme fatigue, mental confusion, and edema that occurred before my transplants, when FSGS was raging through my body. Thank you for listening.

Christopher

Hello, my name is Christopher and I live in Orange County, California with my wife of 17 years and my 2 sons—Alexander and Christopher, Jr. I'm 47 years old and I work as an Executive Sales Coach. I was diagnosed with primary, idiopathic FSGS 10 years ago and it has been a struggle ever since; physically, financially, and emotionally. In addition to not being able to receive an accurate prognosis for this disease, the therapeutic protocol has not changed for decades, as there have been limited advances in understanding this disease or, more accurately, syndrome, as we call FSGS.

Without an accurate prognosis there is no understanding of how your life is going to change. Of course, planning for the future is almost useless. When you are told that you will most definitely experience renal failure, dialysis and be in need of a transplant, but nobody knows if it will be in five years, 10 years, or 20 years, you are left with an overwhelming feeling of hopelessness. How can you plan for your retirement? How can you plan for your career? How can you plan to be around for the important events in your children's lives after such a prognosis?

With respect to career and financial matters, everything for me had to change. Being in a high visibility sales leadership role, I needed energy on demand wherever I was. That was going to change. I now had to welcome the uncertainty of not knowing which days of the week I would have to completely "shut down" and do nothing but crawl from my bed to the sofa and watch TV. For eight hours straight, I would experience muscle soreness and tingling, fatigue and lethargy and a mental fog that kept me in a zombie-like state. I knew as soon as I woke up in the morning that I would be useless, which would happen sometimes 3 days a week. If I had work, I would have to push through the meetings, but later would be reprimanded for not participating enough and in the meeting. Once a person in sales exhibits low energy and a lack of participation, they are doomed. I started to get pulled off accounts, marginalized, and eventually anticipated losing my job.

As I started to look for another job, I wondered what I would tell prospective employers—"Yes I have 25 years of experience, but on random days I need to completely shut down; at every meeting I will need to get up and walk around for 20 minutes because of swelling and pain, I can't really travel due to my low immune system and risk of stroke, and the commute to the office is too long so I will need to work from home permanently!" This was not going to be easy. But I had to try—I need the health insurance for all of the expensive off-label treatments I would need. And no one tells you this when you are diagnosed, but I will never qualify for life insurance. I have no way of ensuring that my family can survive after I am gone.

My fears of not being the energetic and engaged sales leader I once was, were realized when in early 2020 when I had contracted a fungal infection in my lung. After several stays in the hospital and a painful lung biopsy, I was told that if the infection reached my blood, my chances [sic] of survival was 50/50. This is another fear I live with every day, due to being immunosuppressed. I am worried that my kids will bring home germs that will get me sick or wondering [sic] when I travel or see clients, which germ is waiting for me.

Because of these limitations and potential risks, I have had to change almost everything in my life. I am transitioning from a 25-year career to starting my own business that allows more flexibility. I have now put aside the notion of retirement, and my goal is to build up a nest egg that now becomes my life insurance to support my family. All of the activities I once enjoyed, such as long road trips, coaching my two boys in football, working out, etc. have all become impossible because of the unpredictability of this disease. Now my focus is on how much more time do I have left to function before stroke, infection, or renal failure diminish my capacity even more. I no longer think of life as a journey but more of a race against the clock.

Christine

My name is Christine Gwinn, I am 46 years old and I live in Michigan with my fiancé. I was diagnosed with FSGS in the fall of 2012 at the age of 38. I was on a fly-fishing trip in Denver when I noticed that my pants were getting tighter; I had less energy than normal and my urine looked foamy. When I returned to Michigan a few days later, I found that I was 15 pounds heavier than when I left. Diuretics weren't working and by the time my kidney biopsy results came back six weeks later, I was carrying over 75 pounds of edema. In December, my eGFR was 22 and I was put on dialysis to remove some of the excess water. After about a month, prednisone started to take effect, my kidney function improved and I was taken off dialysis.

I have had a few relapses since then as we tried to find the right treatment. For me, “relapse” has meant the onset of Nephrotic Syndrome. During the most recent relapse, protein spillage jumped from 97 mg/dl to 880 mg/dl in about 10 days, although my eGFR has remained >60 since 2013. When nephrotic syndrome kicks in, the edema sets in so fast that there is really no way to prepare for it. It feels surreal—kind of like waking up in someone else’s body. Imagine your limbs are filled with memory foam—every bit of pressure leaves lasting indentations in your skin. When I have a relapse, my skin is stretched painfully tight and simple movements, such as walking to the bathroom, are exhausting under the added weight. Wardrobe issues are always a challenge; edema might accumulate in your abdomen one day or in your thighs or calves the next. Finding ways to accommodate the swelling can be tough. During that first event, I went from a size two to a size 22 in 6 weeks and now keep clothing for every size in between, just in case.

FSGS has had a dramatic impact on how I live my life. I was managing a microbiology lab when I was diagnosed. I was physically unable to keep up with the long hours and sleepless nights that job demanded. I was exhausted all the time, and I eventually made the decision to leave. I transitioned to a remote position for the same company, but the travel that was required was both exhausting and exposing me to illnesses with every trip; each time I came home I ended up with a new cold. It’s not only my work life that has changed; being on prednisone has resulted in avascular necrosis, causing pain and bone loss in my right hip. This has limited my ability to do some of the things I loved the most, like running, skydiving, and martial arts. I’ve been told that I will need a hip replacement at some point, so for now I’m trying to take care of the one I have.

When it comes to this condition, my biggest worries are the looming threat of a relapse and living life with a suppressed immune system. I have always been a very active person, but the threat of relapse often makes me hesitant to make plans too far into the future—planning something complex like a backpacking or scuba diving trip is difficult when you don’t know if you’ll end up getting sick again and be forced to cancel at the last minute. I have recently been working on getting my private pilot license, and I am concerned with how the progression of this disease might impact my ability to fly in the future.

My biggest fear is having to live the rest of my life on immunosuppressants. Obviously, being immunocompromised during a global pandemic is a terrifying thing. But even outside of current events, living with immunosuppression can be daunting. In the last year, I had bronchitis four times and I seemed to catch a cold at least every other month. Getting sick that often can be a challenge when it comes both family and work. My hope is that one day soon a cure will be found for this disease, or at least a treatment that doesn’t require immunosuppression.

Jackie (Jacqueline)

Hello, my name is Jacqueline.

I am 19 years old and I was diagnosed with Nephrotic syndrome on February 28, 2016. In June 2018, I was diagnosed with FSGS after my second kidney biopsy.

One of the biggest symptoms that hinders my life the most is swelling. When I'm swollen, it physically hurts to walk, stand, and sit. No position is comfortable, except laying down.

Even then, I'm still in pain. Another symptom that impacts my life is all the side effects from my medications. I have been in many drug trials for medications that aren't marketed for FSGS; they are for other illnesses.

FSGS isn't like other diseases. Everyone who has it has a different experience and is affected dramatically different. Lastly, another symptom that affects me is pain. I have a very high pain tolerance with everything I've had to endure thus far from two kidney biopsies to hundreds of IVs and multiple chemotherapy infusions. The pain sometimes is unbearable, even with my extreme tolerance. Sometimes, it gets so bad that I'll faint, have cold sweats, low blood sugar or headaches.

I love to travel. Seeing new places and experiencing all the world has to offer is something I am passionate about. But unfortunately, when I go on planes, I swell so bad that I can't even walk. The amount of pain I feel due to this is indescribable.

I had my "make a wish" trip last summer. I chose to go to Greece. There was no way for me to put my legs up during the plane ride. This negatively affected my experience on the trip because I was so tired. Walking around the cities and enjoying the scenery was difficult. I was so swollen on the plane ride back that I couldn't even walk off the airplane. I had to sit in a wheelchair. People never truly understand my illness because I look fine, I look like a "normal kid" with nothing physically wrong with me.

I don't really get "best days." Every day I experience negative effects from my symptoms. But If I am feeling better than usual, I still worry about being swollen or getting swollen.

Once I start to swell it is downhill from there. Even when I'm feeling fine and I'm excited to do a normal activity with family or friends, I always fear that suddenly I won't feel well. Getting dizzy, nauseous, or lightheaded is an issue that can cause anxiety. On my worst days, I can't get out of bed due to the pain. It hurts to walk and stand.

Sometimes, I can barely see out of my eyes because they are swollen shut and get migraines because of the pressure in my face from the swelling. It is very unpredictable. I can never really plan too far in the future. Having this disease means I won't know how I will be feeling. I have normalized many of the

impacts of FSGS. But that something I shouldn't have to do. I should have the proper treatments that are specific for my disease and that will work for me. I've been fortunate that sometimes my body helps itself and goes into partial remission.

I've never been lucky enough to have a full remission. During my partial remissions, I have been blessed to achieve some of my goals. Unfortunately, that can be ripped away from me at any moment because I never know when partial remission will end. Every day I wake up with anxiety that I'm going to wake up swollen, I'm going to not feel well or that I might need to go to the hospital.

The fear of transplant is always in the back of my mind. People seem to think that a transplant is going to be my saving grace, when in reality it is not. I want to keep my native kidneys healthy for as long as possible. Transplants don't get rid of FSGS. It is very likely that the disease will recur.

Every day, I wake up knowing my kidneys are slowly deteriorating and it scares me beyond belief. The fact that no therapies have worked for me and there are no medications specifically for FSGS is also very scary. One day I may need a transplant, but until that day I'm going to try my hardest to advocate for myself.

Topic 4: Current Challenges To Treating FSGS

Becky

My name is Becky and I'm a 40-year-old mother of an eight-year-old boy and a six-year-old girl. I live 30 minutes outside of Boston. My OB-GYN discovered protein in my urine during the first visit when I was pregnant with my daughter. Four months postpartum, I was diagnosed via biopsy, with FSGS and was spilling around 9 grams of protein.

I started taking a cocktail of prednisone, omeprazole to combat the stomach side effects of steroids, calcium and vitamin D also for steroid side effects, lisinopril, levothyroxine, Lipitor, and folic acid. I was on prednisone for eight horrible months. I felt one hundred percent fine until I started the "steroid treatment." And during the eight months I was on it, I experienced extreme steroid rage. It was like an out of body experience. I felt like I was sitting on my own shoulder watching myself be completely irrational and telling myself to stop, but I couldn't. I had a two-year-old, a newborn, and a husband who all took the brunt of my extreme mood swings and anger. I have also never [been] that hungry in my life. I gained 30 pounds and got the dreaded steroid "moon face."

The steroids also give you so much energy that you cannot sleep. I would wake up at 1am every morning, feeling like I could run a marathon! Just when you think you can't feel any worse after a chronic disease diagnosis, the treatment makes you fat and crazy! Every time I got my lab results, I cried

because the protein numbers were not going down, which meant I was not getting better. It is so defeating to be on this “devil drug” and see zero change in the proteinuria.

We finally gave up on steroids and switched to Prograf. This is all part of the normal “throwing spaghetti against the wall to see if it sticks” way of treating FSGS. We did Prograf for four months and the hardest part about that was in the shower it felt like my feet were going to burn off. I had severe restless leg syndrome and started losing my hair. Like steroids, Prograf had no impact on reducing my protein. After that we decided to try rituximab infusions. I did four rituximab infusions across a one-month period. The first one was the hardest; I felt nauseous and it took about six hours. They got easier after that, but still were about four hours in the cancer treatment clinic. Because of the Benadryl they give you to combat any allergic reactions you might have. I was also very tired on infusion day and had to have someone drive me to and from the appointments. Unfortunately, this “poison” did not work to reduce the protein either.

At this point I was able to qualify for an upcoming clinical trial for abatacept. The clinical trial was one year and required weekly or biweekly visits to Boston for infusions of the drug or placebo. The drug itself caused few side effects. The drug wasn’t effective either.

Four years later and still spilling five grams of protein a day, we felt like the treatments were worse than the disease for me and decided to take a break. In 2018, we did a second biopsy to reconfirm the Stage I was [in] and see if we could uncover any additional information. The Pathologist was able to see what he believes to be a recessive genetic mutation of my kidney filters. They confirmed that the mutation was there in my first biopsy as well; we just missed it. With the genetic form of FSGS, it is rare for any of traditional drugs to work, so everything I went through—steroids, trips to Boston for infusions, a clinical trial, etc., could have been skipped and I would be in the exact same spot that I’m in today. The good news from the biopsy is I’m still Stage 1, which leaves time for us to find a cure.

Today I’m on lisinopril, Lipitor, Inspra, levothyroxine, calcium and vitamin D, and Allegra. My only constant symptom of the disease is foam in my urine and swelling in warm weather or when eating salty foods. I am out of options for treatments and just hoping for some new clinical trial options to bring the protein down. I need a treatment that is going to focus on curing the actual disease and not creating more side effects that make life harder than it already is.

Taylor

Hello! My name is Taylor Faulkner and I live in the sunny state of Florida! I am 24 years old and I work as a personal banker.

A few weeks before my freshman year of college, I noticed swelling in my legs. I went to my primary care doctor who sent me to have a urinalysis and blood drawn. A few days later, she told me she was referring me to a nephrologist. When I asked her why, she told me that the normal amount of protein in one's urine should be about 12 mgs and I was spilling 9,000. A few months later, I was diagnosed with focal segmental glomerulosclerosis.

My ultimate fear was of irreparable kidney damage, but the only tangible evidence of my kidney disease were the symptoms which hindered my everyday life. So, as with most patients, I was prescribed a diuretic to treat my edema and 60 mgs of prednisone in the hopes that my body would stabilize and stop spilling protein. My body reacted positively to the steroid treatment and my nephrologist was able to wean me down to 20 mgs of prednisone. However, we quickly realized that anything below that dose would result in proteinuria and edema again, thus, indicating a relapse. My doctor believed the best course of action to be increasing [sic] my steroid usage back to 60 mgs and start over again.

After several relapses, I began to realize my body could not tolerate this treatment for much longer. I knew the medications were meant to help me, but my life was severely restricted by them. Prednisone alone caused frequent panic attacks that affected my ability to attend my classes. I experienced weight gain of over 30 pounds, which caused me to lose my confidence. I withdrew from friends and eventually had to set everything aside to move home with my parents so that I could focus on my health. I felt hopeless.

The trial and error of searching for alternatives to prednisone was exhausting and limiting. When I would try a new medication, it would cause another issue that needed to be treated with a different medication. For example, I needed to be on a diuretic to keep my edema down. The diuretics I tried caused me to lose potassium, which resulted in me adding a new medication to combat that side effect. At one point, I was taking five different medications at a time totaling 11 pills every day. I have tried fluctuating amounts of prednisone, lisinopril, Prograf, Pravachol, three different diuretics, multiple vitamin supplements, and even dietary changes.

Finding the right "cocktail" of medications took a few years. Eventually, the right mix turned out to be 6 mgs of Prograf, 5 mgs prednisone, 40 mgs lisinopril, 5mgs of amiloride, and 20 mEq of potassium. This mix supplemented my potassium loss, controlled my blood pressure, and limited my proteinuria long enough for me to heal without harsh side effects. After about a year on this regimen and five and a half years of fighting FSGS, I am no longer spilling protein and have no swelling. I am in complete remission.

Unfortunately, the effects of my medications will follow me for the rest of my life. I was diagnosed with osteopenia last year due to the five and a half years of extensive steroid treatment. While I understand that there is no perfect medication for my disease out there, I am hopeful that one will exist soon.

I have thought about what my ideal medication would look like before. My idea is so different from what my actual regimen was. I would like to take one pill. One pill once a day. The side effects would not hinder my quality of life and they would not feel worse than the disease itself. It would not ruin my plans of starting a family one day. It would not cause vitamin deficiencies. It would not be steroids. It would, however, cater specifically to my disease. Instead of piecing together multiple medications for other illnesses that just so happen to work for me, it would be for FSGS.

FSGS makes me feel hopeless. It quickly robbed me of my dreams and aspirations of living a normal life. It might seem like a tall order, but it is my dream to have a medication that lets me regain control of my life and of my future health.

Nicki

Hi, I'm Nicki and I'm 23 years old. I grew up in Chicago and graduated last summer from Northwestern University. I currently reside in the Detroit suburbs and work in product management. I was diagnosed with nephrotic syndrome February of 2019.

My first treatment, a high dose of prednisone, was great for a few weeks. I had a lot of energy, a sense of euphoria and my disease symptoms subsided. I was spilling just above two grams of protein. But soon enough, I chowed Tums like candy to ward off heartburn. I ate like a rabbit and developed large pockets of fat. I gently bumped another person and I bruised black and blue. I was never able to sleep deep enough or long enough. My vision was blurred—but my eyes weren't getting any worse. I never knew when, or for how long, I was getting my period. I snapped at my loved ones constantly when all they did was support me. I shaved my face and my back for my college graduation. 2019 was a year without memories because I hid my "moon face" from photos and spent most days on the couch.

At this point the prednisone side effects were way worse than the disease. So. I tapered off as fast as I could. During [the] tapering, I lost half my hair. I vacuumed my apartment and car daily because it fell out faster than I could keep up with. My knees felt like they were completely busted—I couldn't even bend down two inches without forcing back tears. My joints were in so much pain that I could hardly complete simple tasks like grabbing a water glass from the cupboard. It was like I woke up one day and, instead of 22, I was now 90.

I began my second treatment, tacrolimus, while I was tapering [off] prednisone. It gave me debilitating migraines and brain fog, leaving me in bed every other afternoon for two months. It also did not help my nephrotic syndrome. My protein spillage shot back up to six or seven grams a day. Again, the treatment was worse than the disease.

My third treatment, CellCept, correlated with a bad case of angular cheilitis: a highly visible, itchy and burning rash of the lips. The only thing that cured it was going off the drug. And CellCept also didn't help my disease. My legs were swollen like hot air balloons twenty-four/seven. I attended a wedding and spent the whole event alone at the table. I had my legs hidden beneath the tablecloth and [as I] held a cold glass of water to my burning lips.

My fourth treatment, Rituxan, sounded like my dream come true: a couple infusions, and a drug-free remission with no side effects. But after an eight-month long insurance battle for approval, it took just 10 minutes into the infusion for me to break out into full-body hives, with unbearably itchy ears and a throat threatening to close. I was drowning in tears as the nurses deemed it unsafe to continue the treatment and unhooked me from the IV. I was only 22 and I felt like I was out of options.

I began my fifth treatment, cyclosporine, alongside a three-week burst of prednisone. This time, the steroids gave me around-the-clock anxiety, a tight chest, difficulty breathing, and panic attacks. But, after nearly eight months, I finally saw my ankles again. Fast forward and, on cyclosporine alone, I have been able to maintain a daily protein spillage of just over two grams. In an ideal world there would be no side effects, but they are more manageable: mildly puffy and bleeding gums, a little extra facial and arm

hair, and tingling in my hands and feet when I touch something too hot or cold. Bottom line, I can finally live my life again and feel comfortable in my own skin.

But I still live in fear. If I miss a dose of cyclosporine, I swell up. I do not believe I can achieve a drug-free remission on it. And what's going to happen when I have to go off it to get pregnant...or, what if it just stops working? It is too scary and painful to comprehend a future that includes dialysis or a kidney transplant—I believe those last-resort options are a Band-Aid to a disease that begins with the immune system.

Right now, there are no other "good" treatment options for me to explore. I am relying on new drugs to come to market and allow me another shot at achieving remission. The ideal treatment would both prevent kidney failure and not force me to sacrifice the quality of my life. Otherwise, what's the point of a cure?

Alyse (Melissa, mother of Alyse)

Hello, I am Melissa, mother of 14-year-old Alyse. Alyse's journey began May 2017. While waiting to see our pediatrician for well[ness] checks, I noticed Alyse's legs were edematous. He sent us to the hospital for labs, which revealed protein and blood in her urine. We then saw a pediatric nephrologist in New Orleans, LA, (three hours from home) and Alyse was diagnosed with nephrotic syndrome and immediately started on oral prednisone. She had gained about 35 pounds of fluid, had an appetite out of this world, with terrible mood swings. It was hard as a parent, watching her sit on the couch, not wanting to go outside, and ignoring FaceTime calls from friends.

After only one and a half months of "trying" Prednisone, we sought a second opinion with one of the "top" nephrologists in another state. She was put on more high-dose prednisone, [the] cyclosporines Neoral and Sandimmune, [as well as] Prograf, and CellCept. Without seeing any decrease in protein spillage in the urine and a continual rise in creatinine, Alyse had now progressed to focal segmental glomerulosclerosis (FSGS).

Medical treatment for a chronic kidney [disease] kid is not just limited to medication for the FSGS. With chronic kidney disease also comes Zofran, Pepcid, Prilosec, Miralax, lisinopril, Norvasc, Synthroid, Crestor, vitamin D, magnesium, folate, bicarb, Aranesp injections, as well as the use of long-term immunosuppressants. Currently, Alyse takes 23 timed daily oral medications with [a] weekly injection and an infusion.

Alyse's kidney function still continued to decline despite all the medications, and in March 2018, she began peritoneal dialysis (PD). PD was not easy on Alyse, as it was a rough 10 hours every night with pain. Things like baths, swimming and sports became more difficult each day. After 10 months on dialysis, we began preparing for [a] transplant. It was determined that I was a perfect match, and on December 27, 2018, I donated my kidney to Alyse. It took some immunosuppressive medication adjustments, but after eleven days in the hospital, Alyse was discharged. Unfortunately, Alyse's FSGS reoccurred about a month after transplant, even though her FSGS was genetic and was NOT [supposed] to reoccur. Despite the addition of steroids again, rituximab, plasma, blood, IVIG [intravenous immunoglobulin], Cytoxan, and a total of 62 plasmapheresis treatments, things began taking a toll on her body, [her] psyche, and our family.

Four months after transplant, despite all efforts trying to stop the recurrence of FSGS, Alyse and I moved to Wilmington, DE, to participate in a 12-week clinical trial called Liposorber or lipid apheresis. Although the treatment was easier, as only the lipids were being removed, mentally and physically, living on the East Coast with the rest of our family in South Louisiana, was difficult.

Unfortunately, this treatment too, was unsuccessful at putting FSGS and its side effects into remission and we returned to Children's Hospital in New Orleans to begin Acthar Injections. Alyse had a 50/50 chance of Acthar working; at this point we were willing to take the risk. Due to the major adrenal surge, there were many days she was so uncomfortable she couldn't walk or go to school because of the swelling and soon began albumin-diuretic infusions. But, with rising creatinine levels yet again and a decrease in hemoglobin, Acthar was discontinued after six months. It was determined Alyse was allergic to Prograf and its sister Rapimmune. She was quickly taken off of both and after more medication changes, another kidney biopsy, and a bone marrow aspiration, the diagnosis of thrombotic microangiopathy (TMA) or atypical hemolytic uremic syndrome (aHUS) was confirmed. Yet another "thing" to deal with and both are medication driven! She has since received additional steroid infusions and increased doses of diuretics. Currently, she is on Soliris infusions once a week in an attempt to halt the effects of TMA/aHUS and we are praying the kidney will fix itself and give Alyse many more years of use.

Alyse has had a very rough three years for any child, and despite having to deal with so many multiple comorbidities, we are still struggling to find a treatment that will halt the progression of her FSGS and the need for another kidney transplant—for her and the many kids like her.

Alyse: Although this journey has been a rough one, it has strengthened me mentally and physically, and shaped me into one strong person. I know this journey is not yet done, we will find better treatments for me and others like me!

APPENDIX 5: MEETING POLLING QUESTIONS

APPENDIX 5.1: DEMOGRAPHIC POLLING QUESTIONS

1. I am:
    a. An individual living with FSGS
    b. A caregiver of someone with FSGS

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.)

3. What is your or your loved one's age?
    a. Younger than 18
    b. 18-29
    c. 30-39
    d. 40-49
    e. 50-59
    f. 60-69
    g. 70 or greater

4. Do you or your loved one identify as:
    a. Male
    b. Female
    c. Non-binary or non-gender confirming
    d. Prefer not to say.

5. Is your or your loved one's ethnicity/race:
    a. Caucasian
    b. African American
    c. Native American
    d. Latinx
    e. Asian
    f. Other

6. What is the length of time since your diagnosis of FSGS?
    a. Less than 1 year ago
    b. 1 to 2 years ago
    c. 2 to 5 years ago
    d. 5 to 10 years ago
    e. More than 10 years ago
    f. I'm not sure.

7. I am or your loved one is:
    a. Not currently on dialysis and have never received a kidney transplant.
    b. Currently on dialysis and have never received a kidney transplant.
    c. A kidney transplant recipient in remission.
    d. A kidney transplant recipient with recurrent FSGS.
    e. A kidney transplant recipient and currently on dialysis (e.g., failed transplant).

APPENDIX 5.2: TOPIC POLLING QUESTIONS

Topic 1. Living with FSGS: Disease Symptoms and Their Daily Impacts

1. How much does your FSGS impact your daily life in general?
    a. Not at all
    b. Minimally
    c. Moderately
    d. Significant amount

2. Have you experienced any of the following difficulties? (Select all that apply.)
    a. Muscle and joint aches and pains, including gout
    b. Bones/teeth problems
    c. Issues with eyes
    d. High blood pressure
    e. High blood sugar/diabetes
    f. Anxiety &/or depression
    g. “Brain fog” (forgetfulness, poor concentration, lose track of time)
    h. Being tired or exhausted
    i. Gastrointestinal problems
    j. Recurrent infections
    k. Swelling (ankles, face, etc.)
    l. Other
    m. I do not have symptoms.

3. Which THREE of the following symptoms or conditions most negatively impact your daily life? (Select top 3.)
    a. Muscle and joint aches and pains, including gout
    b. Bones/teeth problems
    c. Issues with eyes
    d. High blood pressure
    e. High blood sugar/diabetes
    f. Anxiety &/or depression
    g. “Brain fog” (forgetfulness, poor concentration, lose track of time)
    h. Being tired or exhausted
    i. Gastrointestinal problems
    j. Recurrent infections
    k. Swelling (ankles, face, etc.)
    l. Other
    m. I do not have symptoms

4. Which have you experienced while coping with your FSGS? (Select all that apply.)
    a. Depression &/or feelings of hopelessness
    b. Anxiety/worry
    c. Low self-esteem
    d. Social isolation
    e. Difficult with family relationships
    f. Difficulty with relationships outside of family
    g. None of the above

5. Which of the following statements is true for you as related to living with FSGS? (Select all that apply.)
    a. My general daily function is limited by FSGS.
    b. I miss work or school more than I am comfortable with.
    c. Family stress is common in my life.
    d. Others don’t know what it’s like to live with FSGS.

e. I cannot participate in sports or other physical activities I enjoy.
f. I cannot participate in other hobbies I enjoy.
g. None of the above.

Topic 2: Clinical Trials Under the Traditional Approach

1. What is your experience in, and perception of, clinical trials for a new drug for FSGS?
    a. I am currently participating in a trial.
    b. I have participated in a trial, and I WOULD do so again.
    c. I have participated in a trial, and I would NOT do so again.
    d. I have not participated in a trial, because I didn't know about the opportunity.
    e. I have not participated in a trial because I was not eligible.
    f. I have not participated in a trial, although I was aware of the opportunity and eligible.
    g. I would never enroll in a clinical trial.
    h. Not sure about participating in a clinical trial.

2. Of the following factors related to a test drug in a clinical trial, select UP TO THREE that you rank as most important to your decision about participating in a clinical trial: (Select top 3.)
    a. Whether I might get placebo ("sugar pill")
    b. Whether I need to stop my current treatment
    c. Potential side effects from a new drug
    d. How the drug is taken (by mouth, IV, injection in muscle)
    e. In earlier trials, whether drug effective for specific benefits most meaningful to me
    f. Knowing if I can make the commitment to participate in a clinical trial
    g. Frequency of exam appointments
    h. Distance to trial site
    i. Length of trial
    j. Whether a kidney biopsy is required
    k. Negative things I have heard about clinical trials
    l. Whether my nephrologist recommends enrolling in the trial
    m. Other

3. Would you enroll in a clinical trial if it required? (Select greatest number of biopsies you would accept.)
    a. No kidney biopsy
    b. 1 kidney biopsy within 1 year
    c. 2 kidney biopsies within 1 year
    d. 3 kidney biopsies within 1 year

Topic 3: Clinical Trials Under the Accelerated Approval Program

1. For the proposed trial, for how long would you be willing to stay in your assigned treatment arm during the post-marketing extension phase?
    a. 1 year
    b. 2 years
    c. 3 years
    d. Not willing to stay in my treatment arm for any time during the extension phase.

2. What TOP THREE measurements (in a traditional or accelerated approval clinical trial) do you consider relevant to your FSGS? (Select top 3.)
    a. Protein leakage in urine (proteinuria, albuminuria)
    b. Kidney function (GFR)
    c. Blood in urine (hematuria)
    d. Swelling (edema)
    e. Fatigue

f. Depression/anxiety
g. Brain fog (forgetfulness, poor concentration, lose track of time, etc.)
h. General quality of life
i. Delaying time to dialysis or transplant
j. Other

Topic 4: Current Challenges to Treating FSGS

1. Select the medications you use for FSGS: (Select all that apply.)
    a. ACE, ARB, beta-blocker, diuretic = "water pill" (or other drug for blood pressure)
    b. Allopurinol (for gout or high uric acid)
    c. Statin (or other drug for cholesterol)
    d. Veltassa® (or other drug for high potassium)
    e. Sevelamer® (or other drug for high phosphate)
    f. Antidepressant or antianxiety drug
    g. Drugs affecting immune system (anti-inflammatories, immunosuppressants, etc.)
    h. Other (including nonprescription remedies)
    i. I do not take medication.

2. How well does your current treatment reduce the most significant symptoms of your disease?
    a. Very well
    b. Moderately well
    c. Somewhat
    d. Not at all
    e. I do not currently take any treatments.

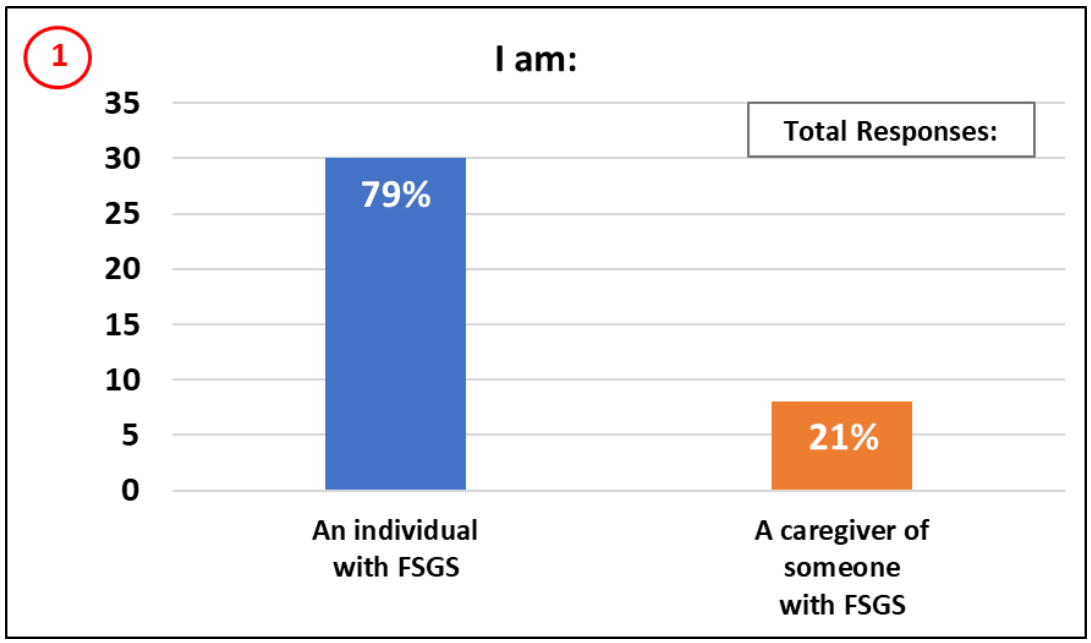
3. Which symptoms or health effects do you have that are NOT addressed fully by your current treatments? (Select all that apply.)
    a. Muscle and joint aches and pains, including gout
    b. Bones/teeth problems
    c. Issues with eyes
    d. High blood pressure
    e. High blood sugar/diabetes
    f. Anxiety &/or depression
    g. "Brain fog" (forgetfulness, poor concentration, lose track of time)
    h. Being tired or exhausted
    i. Gastrointestinal problems
    j. Recurrent infections
    k. Swelling (ankles, face, etc.)
    l. Other
    m. I do not have symptoms.

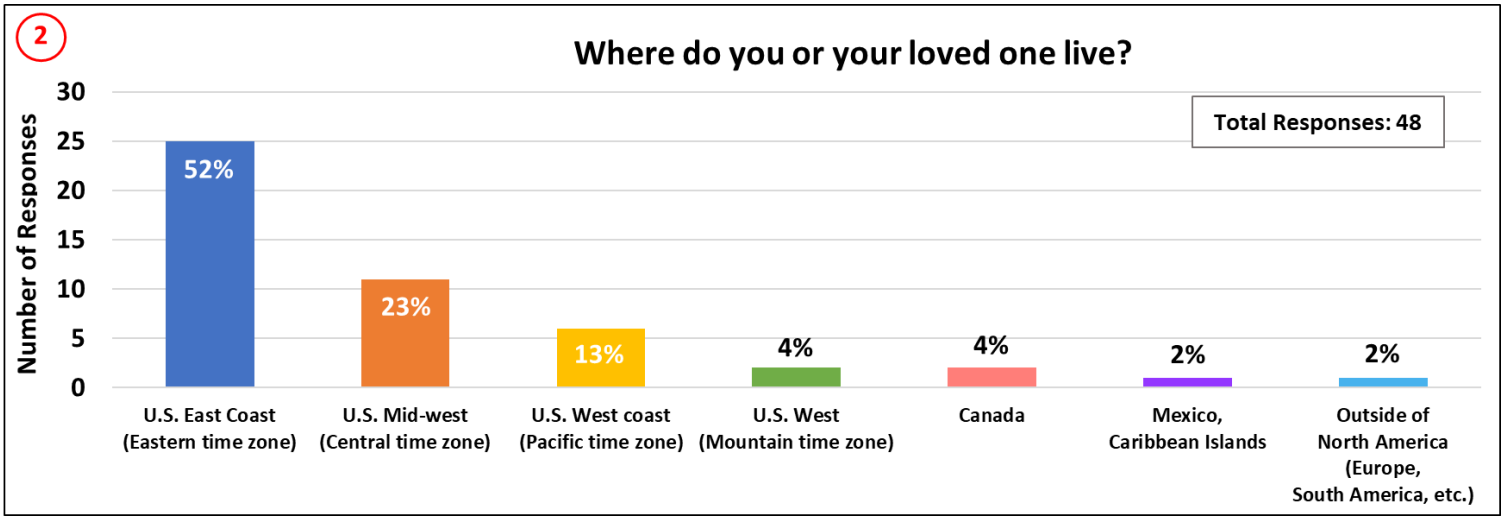
4. If the side effects of a new drug were more severe than your current treatment, but clinical evidence indicated the drug would significantly slow the progression of your disease/improve your quality of life, how likely would you be to take this drug?
    a. High likelihood
    b. Moderate likelihood
    c. Slight likelihood
    d. I would not consider taking it.

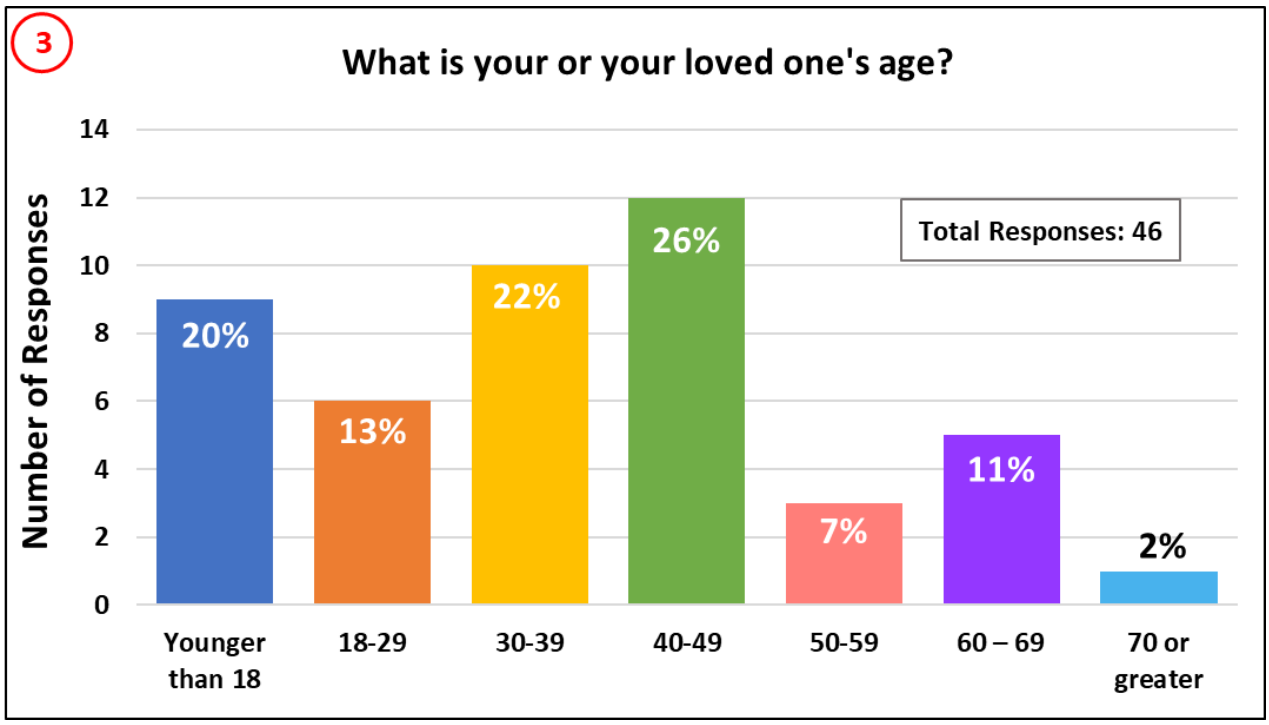
5. Without considering side effects of a drug, which ONE of the following would be the most important to you in a future therapy?
    a. Reverse/halt decline in kidney function (i.e., halt progression of FSGS, delay need for dialysis)
    b. Improve your quality of life/symptoms or prevent future reduction in quality of life symptoms
    c. Prolong your life

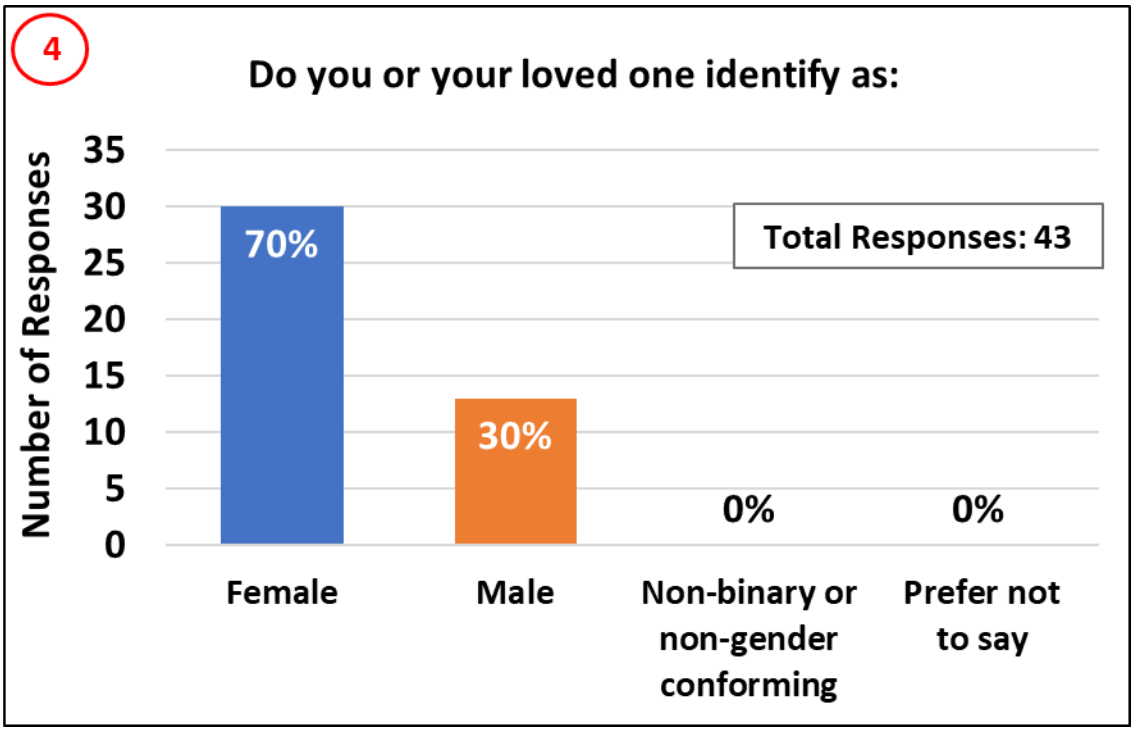
APPENDIX 6: RESULTS FROM POLLING QUESTIONS

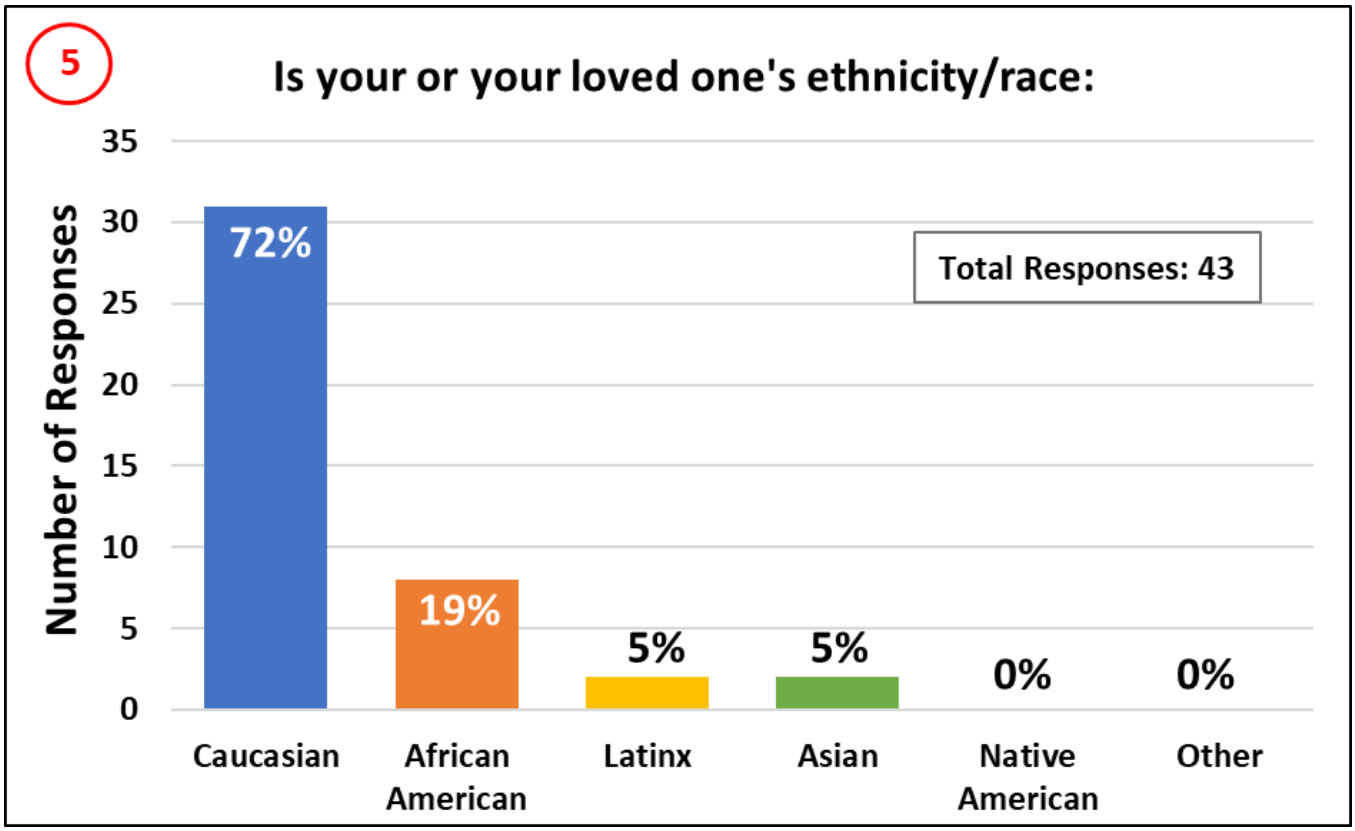
Demographics of attendees

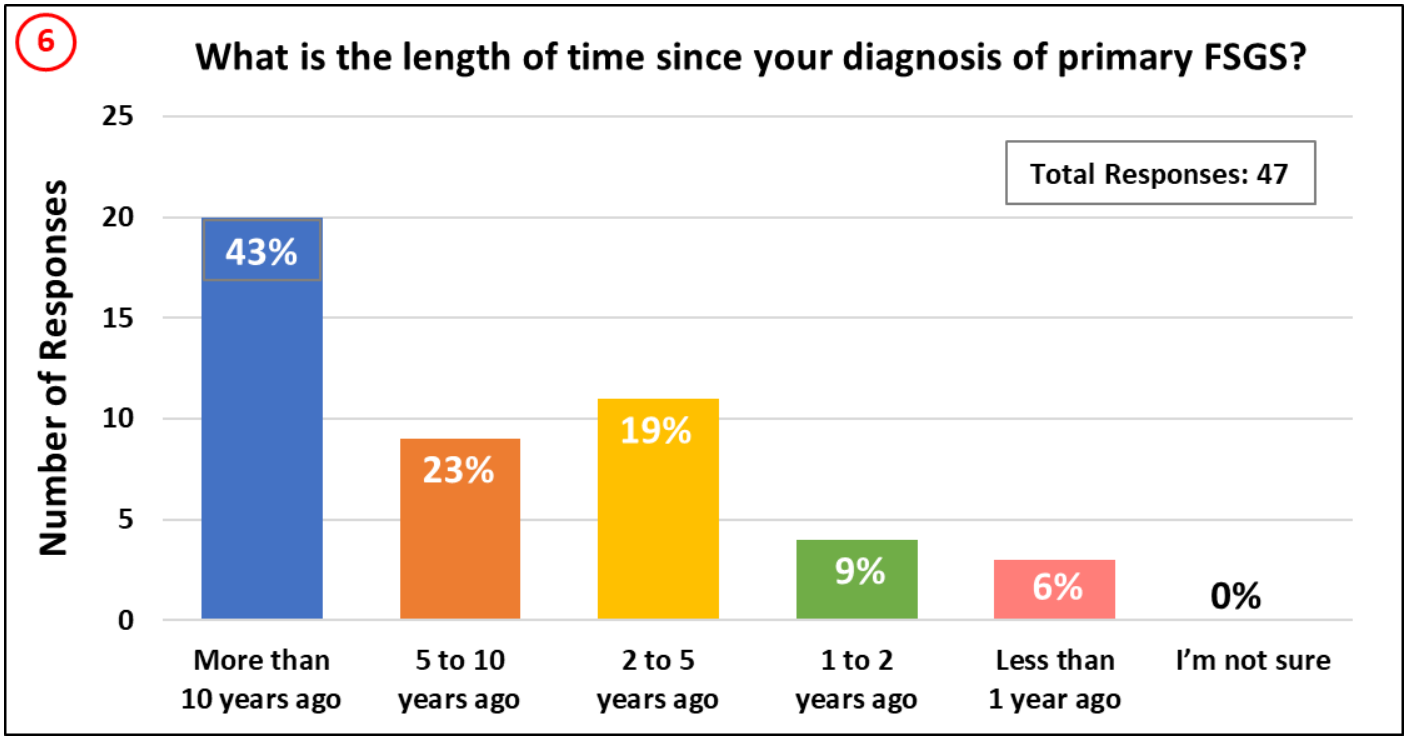


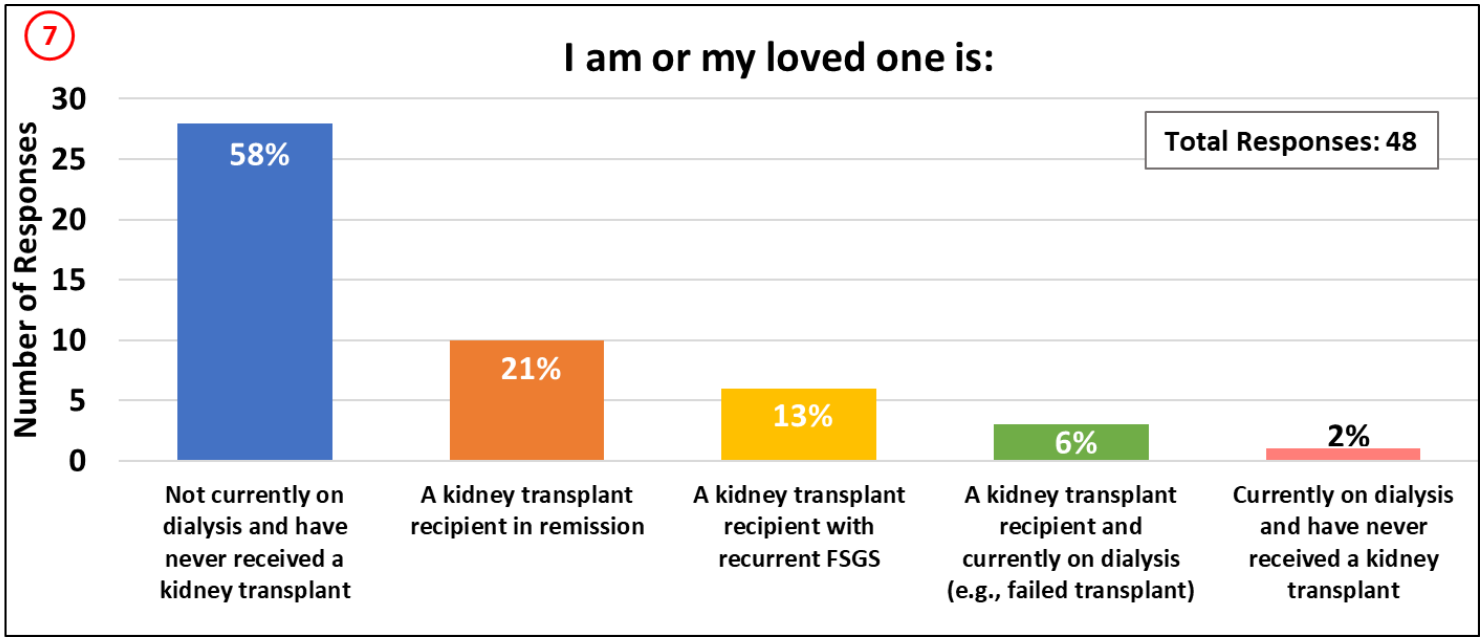



3
What is your or your loved one's age?
Number of Responses
14
12
10
8
6
4
2
0
Total Responses: 46
20%
13%
22%
26%
7%
11%
2%
Younger than 18
18-29
30-39
40-49
50-59
60 – 69
70 or greater


4
Do you or your loved one identify as:
Number of Responses
35
30
25
20
15
10
5
0
Total Responses: 43
70%
30%
0%
0%
Female
Male
Non-binary or non-gender conforming
Prefer not to say

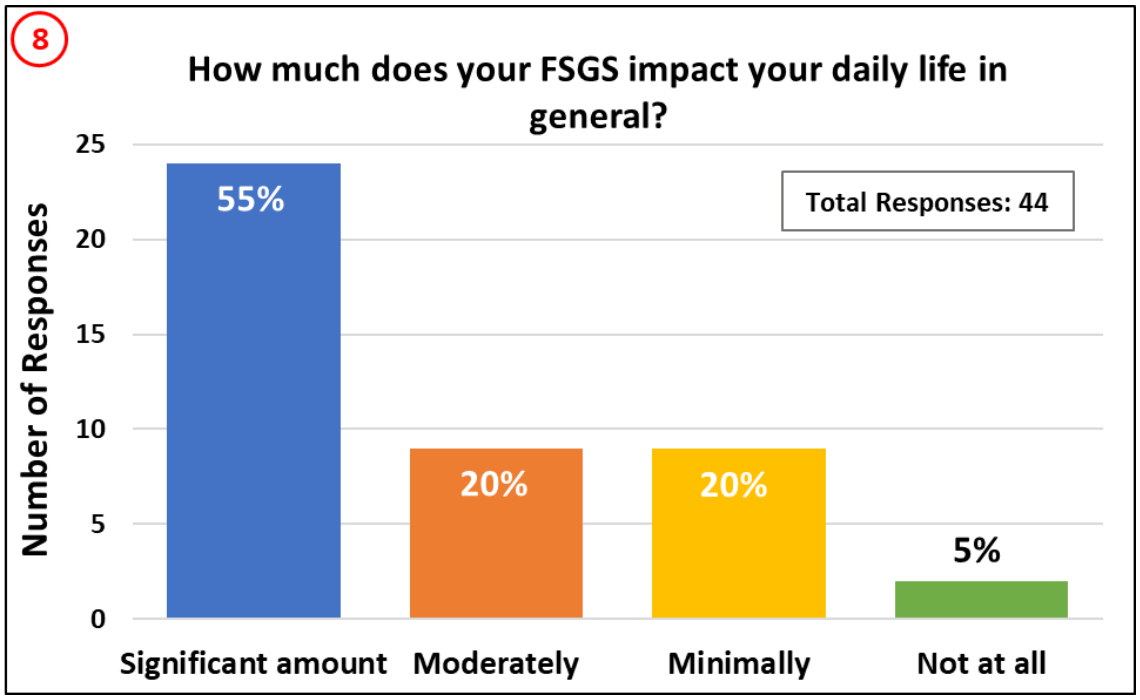

5
Is your or your loved one's ethnicity/race:
Number of Responses
35
30
25
20
15
10
5
0
72%
19%
5%
5%
0%
0%
Total Responses: 43
Caucasian
African American
Latinx
Asian
Native American
Other

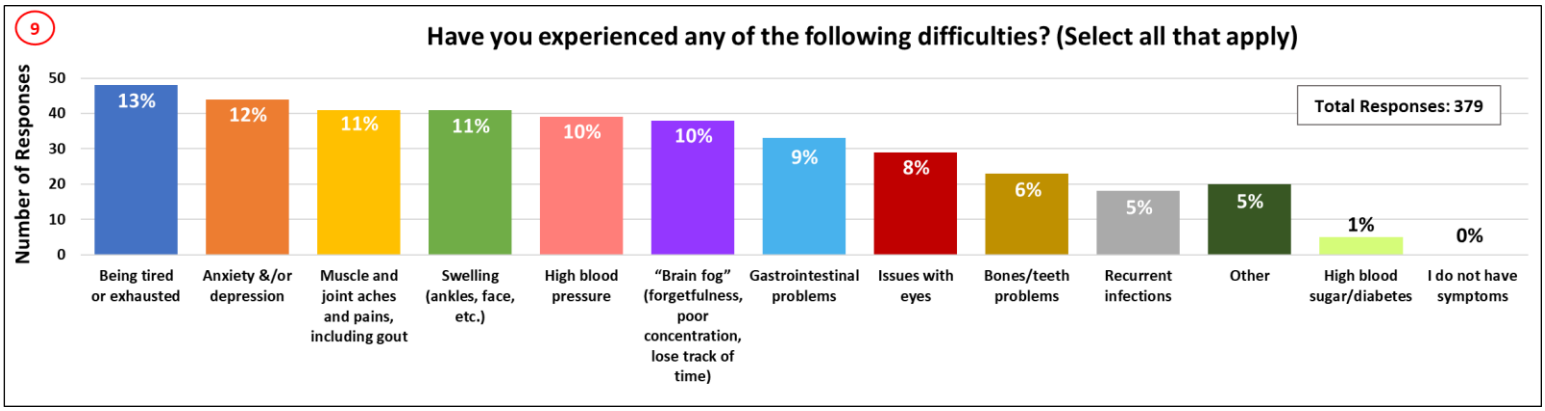

6
What is the length of time since your diagnosis of primary FSGS?
Number of Responses
25
20
15
10
5
0
43%
23%
19%
9%
6%
0%
Total Responses: 47
More than 10 years ago
5 to 10 years ago
2 to 5 years ago
1 to 2 years ago
Less than 1 year ago
I'm not sure

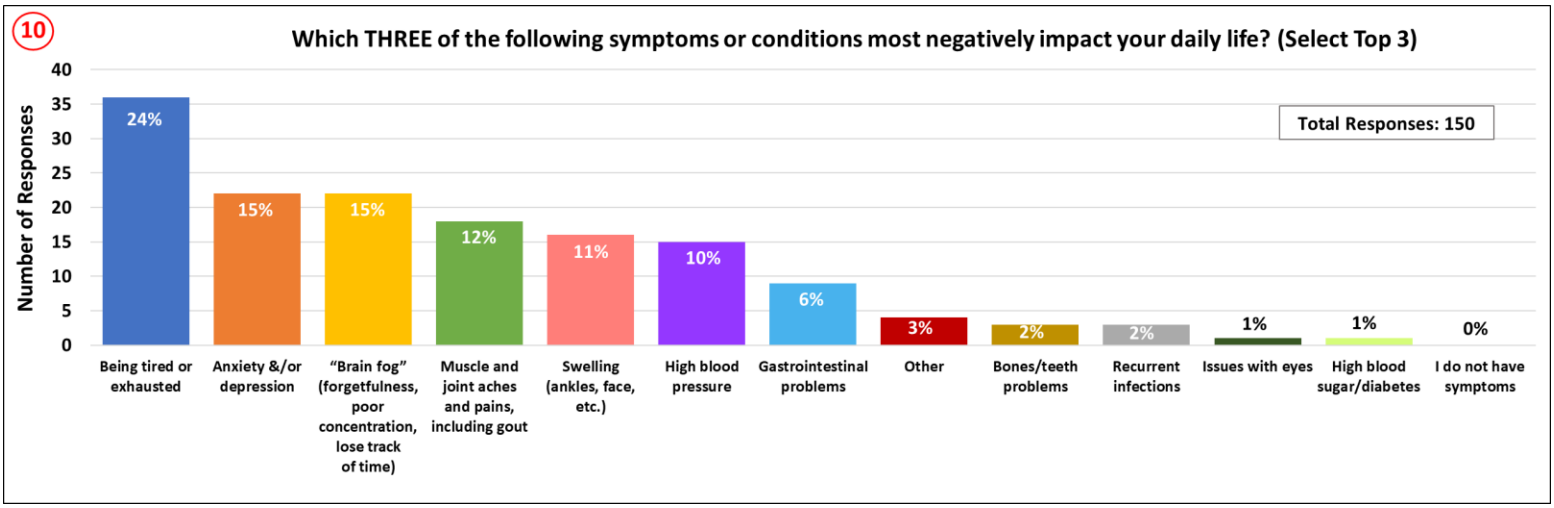

7
I am or my loved one is:
Number of Responses
30
25
20
15
10
5
0
Total Responses: 48
58%
21%
13%
6%
2%
Not currently on dialysis and have never received a kidney transplant
A kidney transplant recipient in remission
A kidney transplant recipient with recurrent FSGS
A kidney transplant recipient and currently on dialysis (e.g., failed transplant)
Currently on dialysis and have never received a kidney transplant

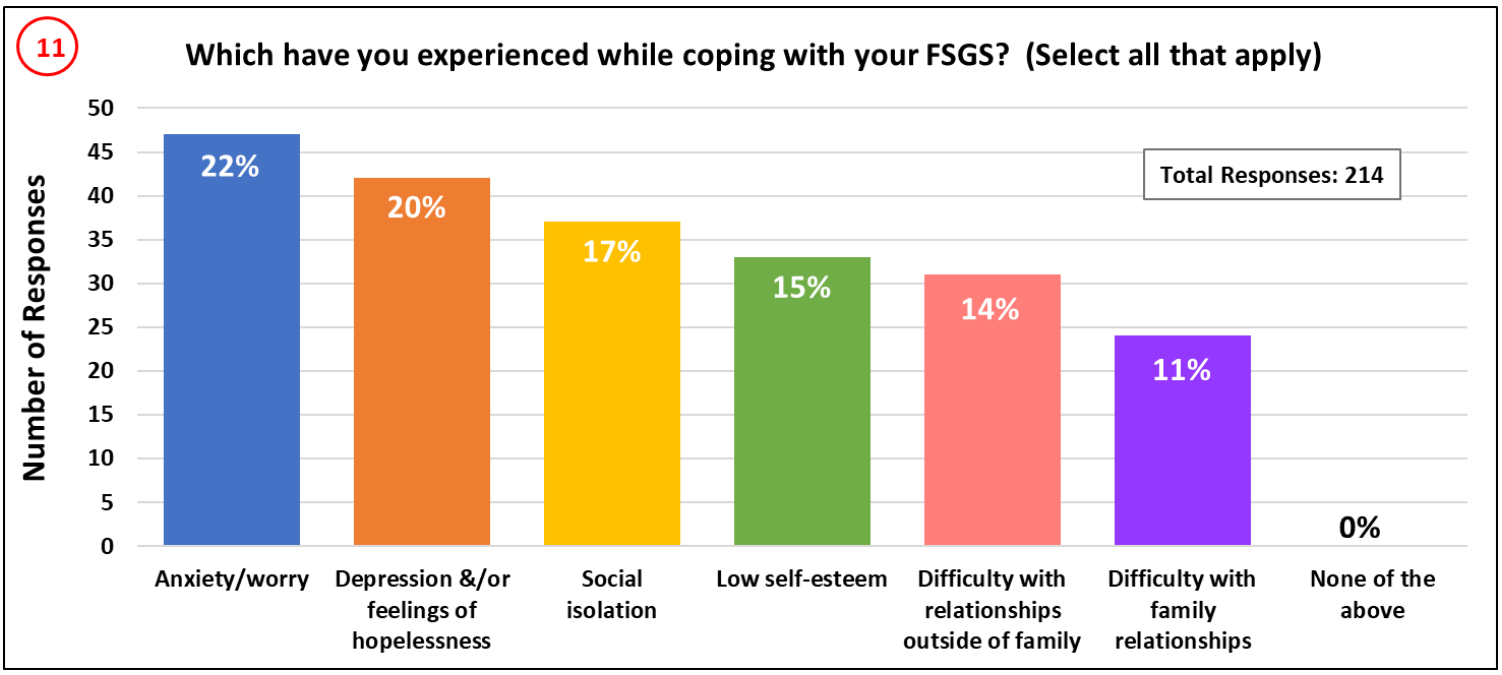
APPENDIX 6: Continued

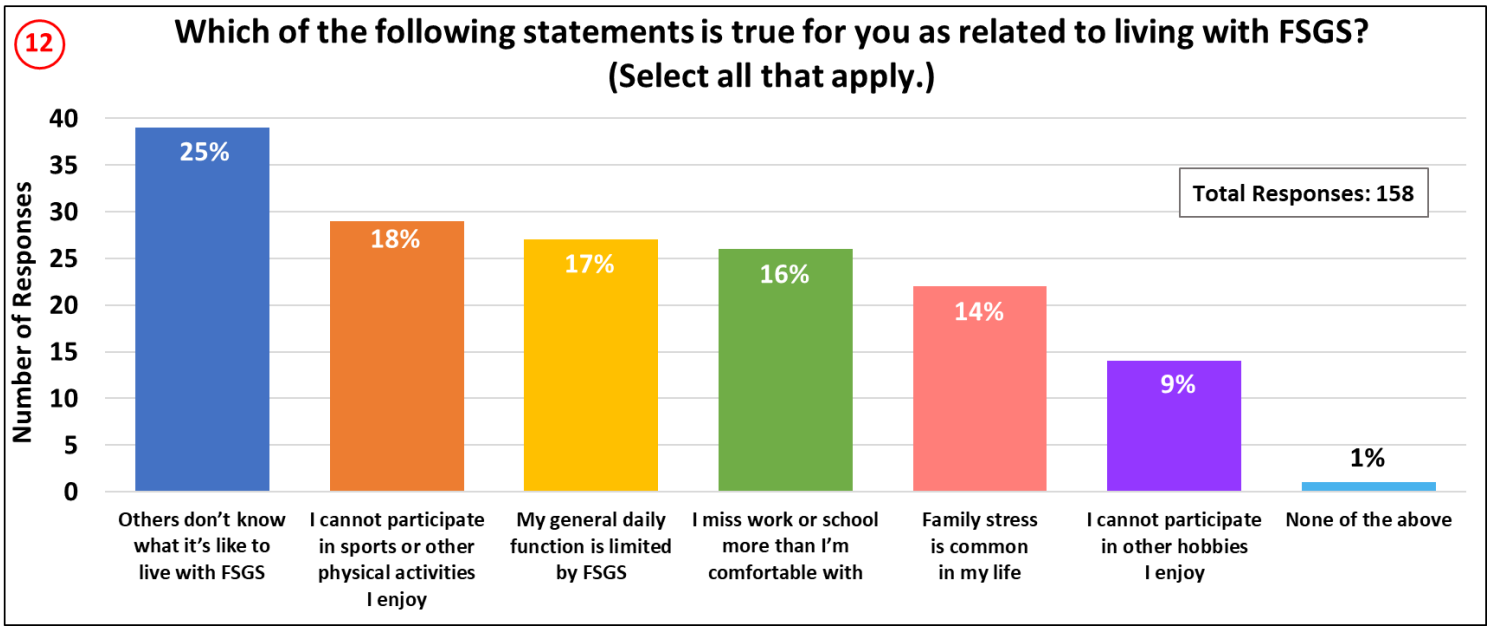
Topic 1: Living With FSGS: Disease Symptoms And Their Daily Impacts





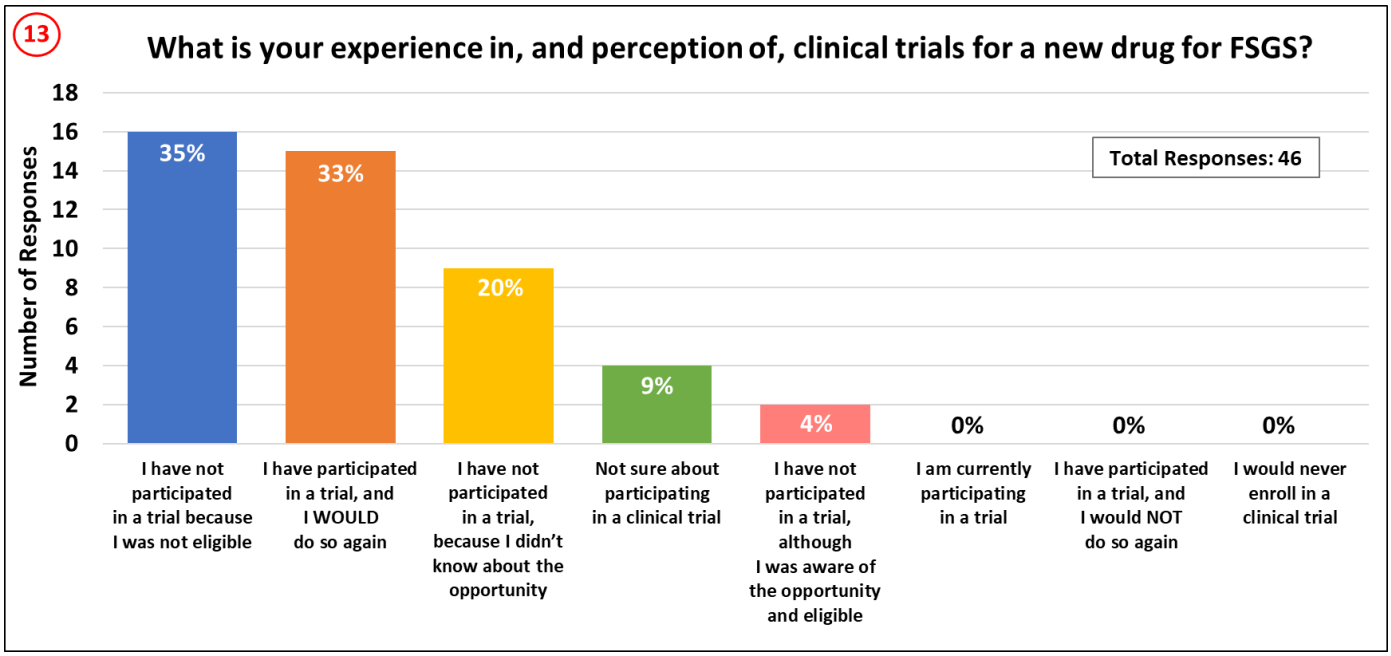

10
Which THREE of the following symptoms or conditions most negatively impact your daily life? (Select Top 3)
Number of Responses
Total Responses: 150
24%
15%
15%
12%
11%
10%
6%
3%
2%
2%
1%
1%
0%
Being tired or exhausted
Anxiety &/or depression
"Brain fog" (forgetfulness, poor concentration, lose track of time)
Muscle and joint aches and pains, including gout
Swelling (ankles, face, etc.)
High blood pressure
Gastrointestinal problems
Other
Bones/teeth problems
Recurrent infections
Issues with eyes
High blood sugar/diabetes
I do not have symptoms

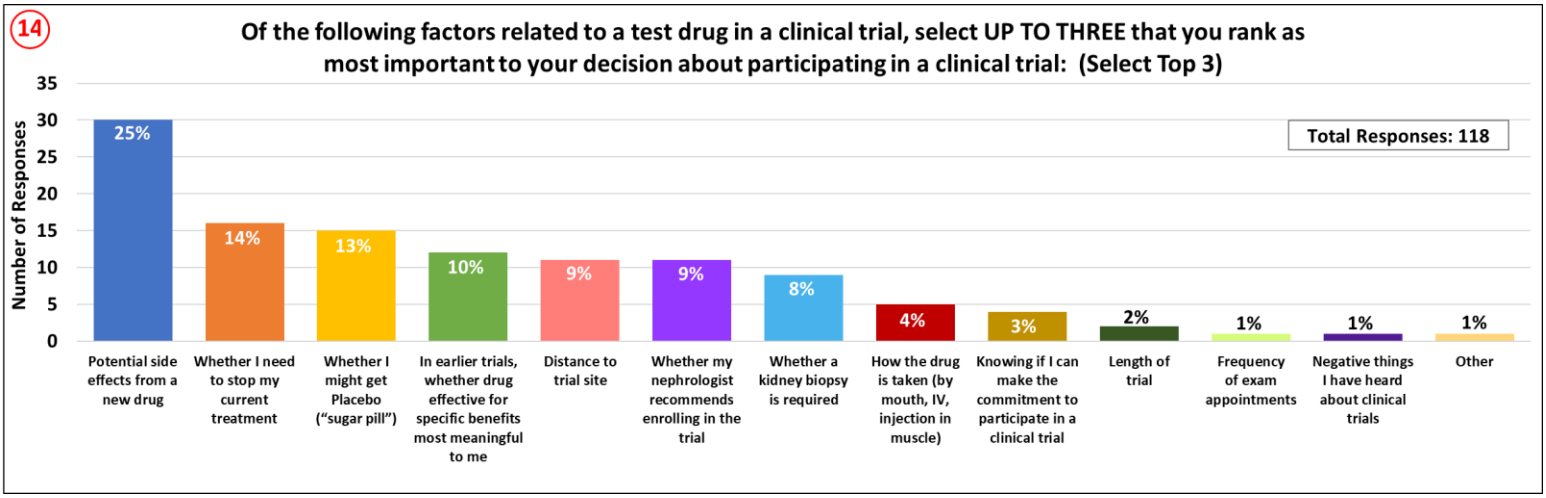

11
Which have you experienced while coping with your FSGS? (Select all that apply)
Number of Responses
Total Responses: 214
22%
20%
17%
15%
14%
11%
0%
Anxiety/worry
Depression &/or feelings of hopelessness
Social isolation
Low self-esteem
Difficulty with relationships outside of family
Difficulty with family relationships
None of the above

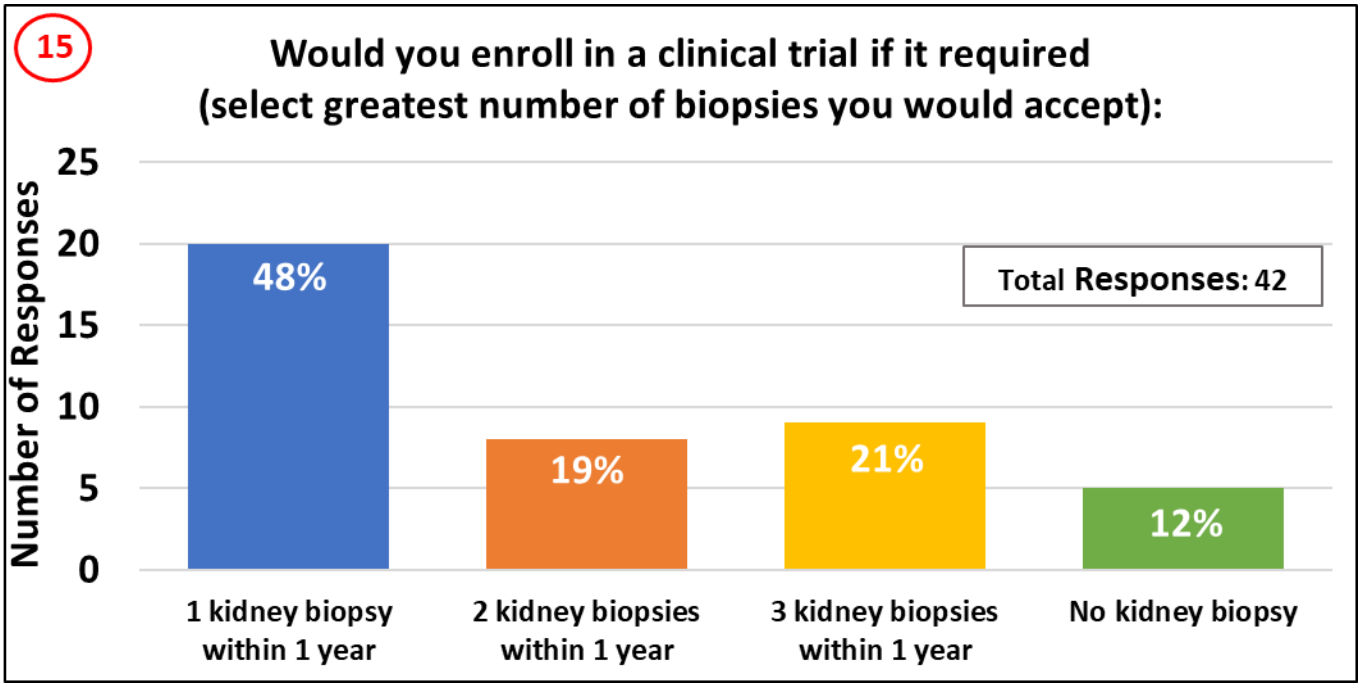

12
Which of the following statements is true for you as related to living with FSGS? (Select all that apply.)
Number of Responses
40
35
30
25
20
15
10
5
0
25%
18%
17%
16%
14%
9%
1%
Total Responses: 158
Others don't know what it's like to live with FSGS
I cannot participate in sports or other physical activities I enjoy
My general daily function is limited by FSGS
I miss work or school more than I'm comfortable with
Family stress is common in my life
I cannot participate in other hobbies I enjoy
None of the above

APPENDIX 6: Continued

Topic 2: Clinical Trials In FSGS Using The Traditional Approach

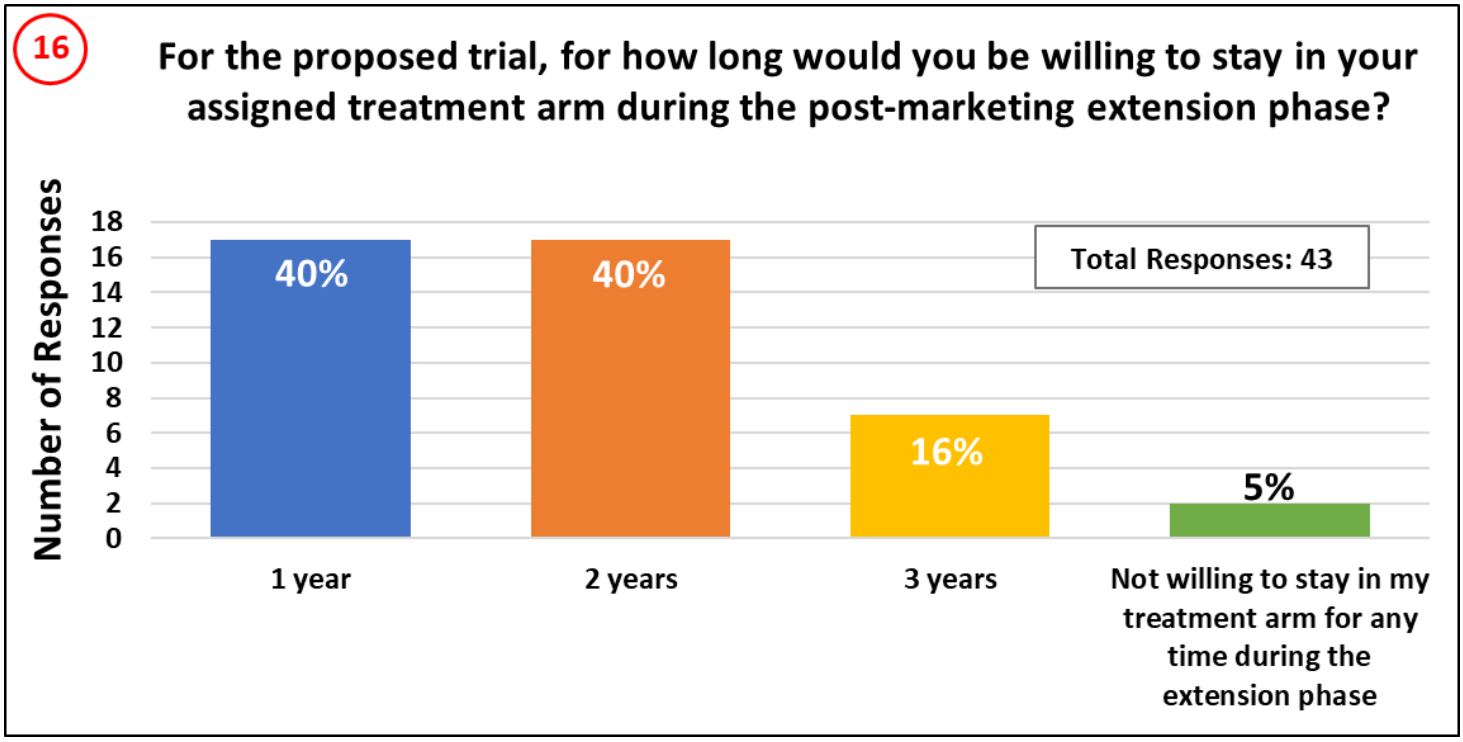


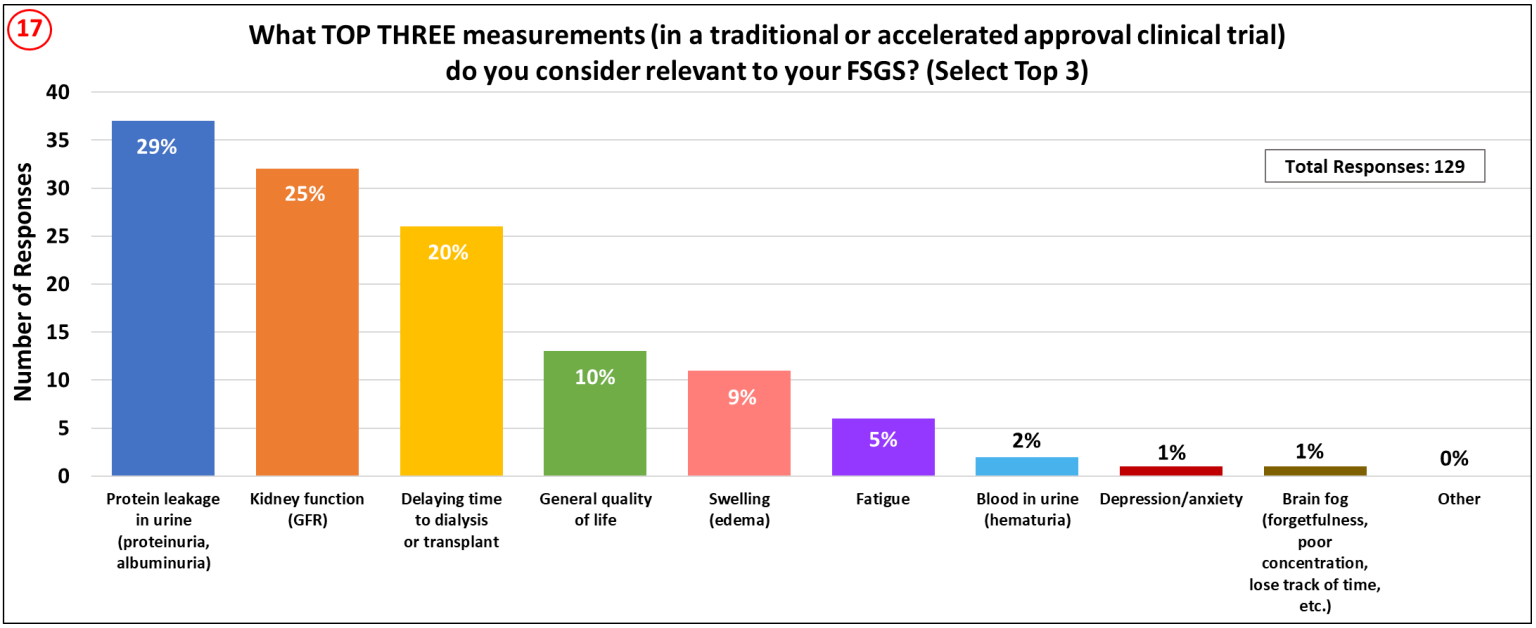



15
Would you enroll in a clinical trial if it required
(select greatest number of biopsies you would accept):
Number of Responses
25
20
15
10
5
0
48%
19%
21%
12%
Total Responses: 42
1 kidney biopsy within 1 year
2 kidney biopsies within 1 year
3 kidney biopsies within 1 year
No kidney biopsy

APPENDIX 6: Continued

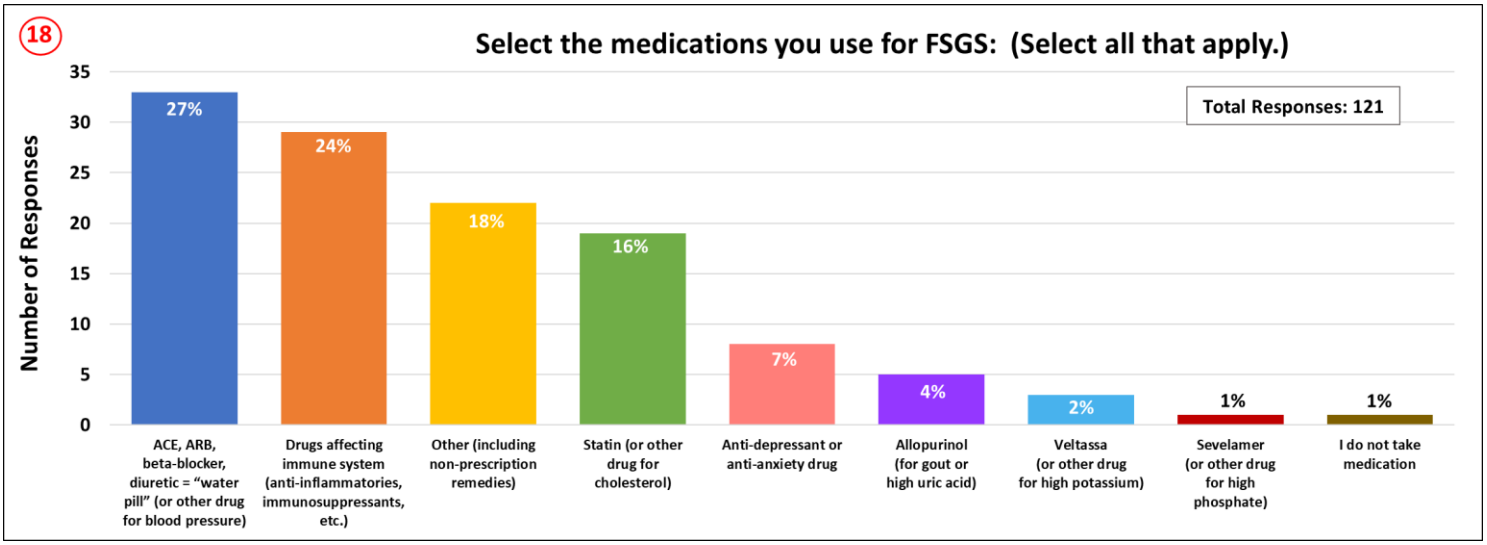
TOPIC 3: Clinical Trials in FSGS Using Accelerated Approval Pathway

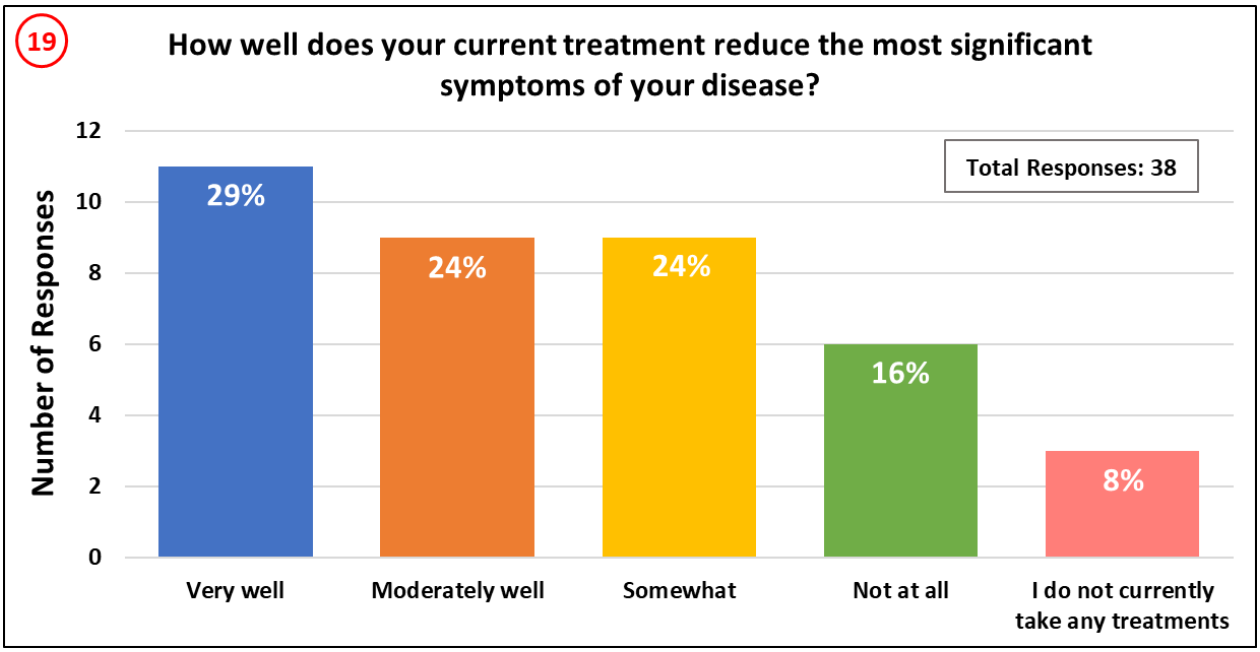


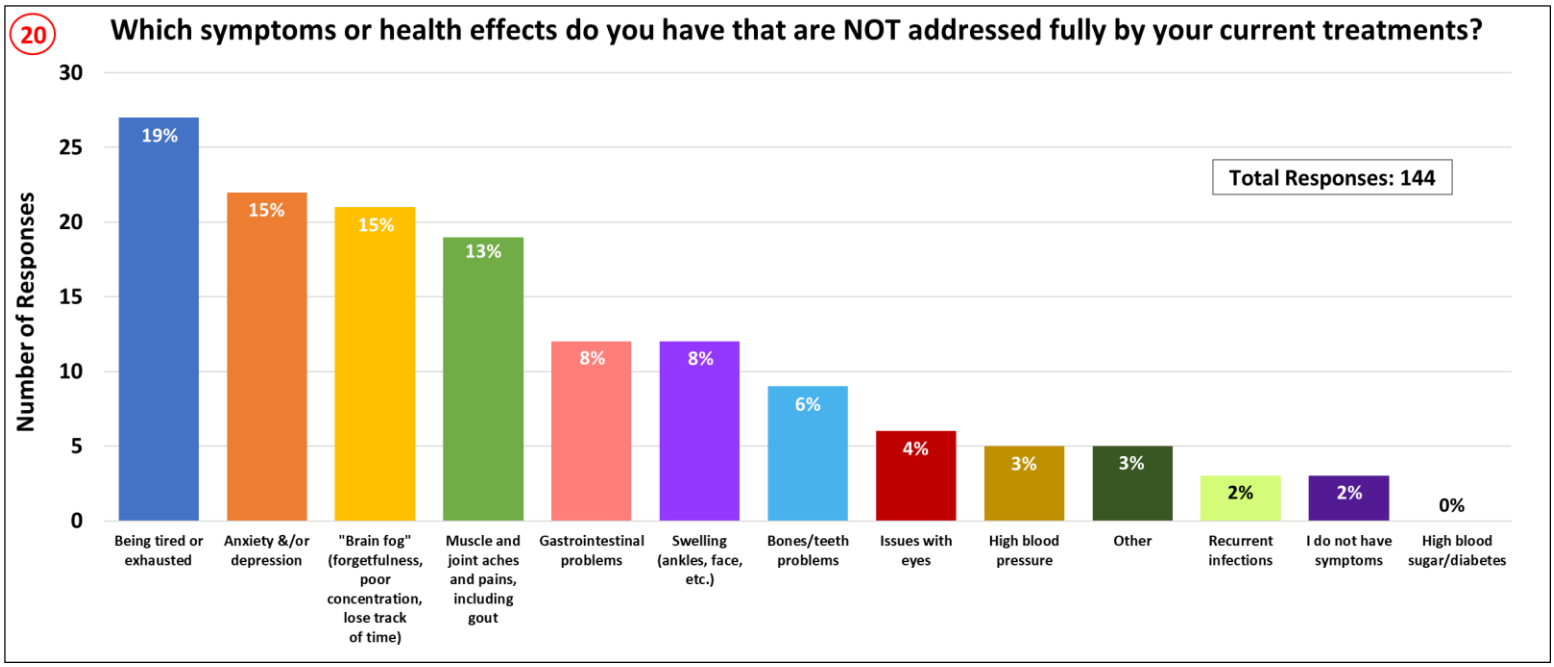


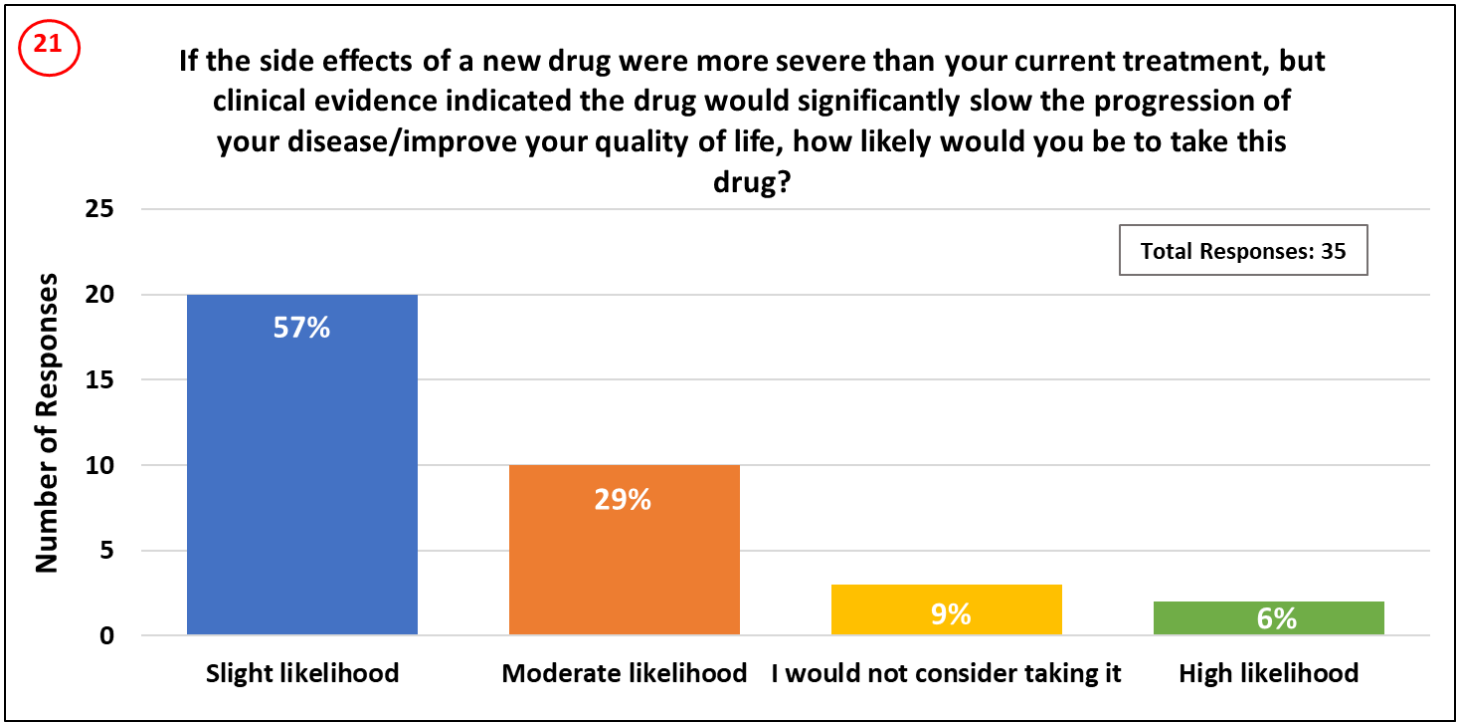
APPENDIX 6: Continued

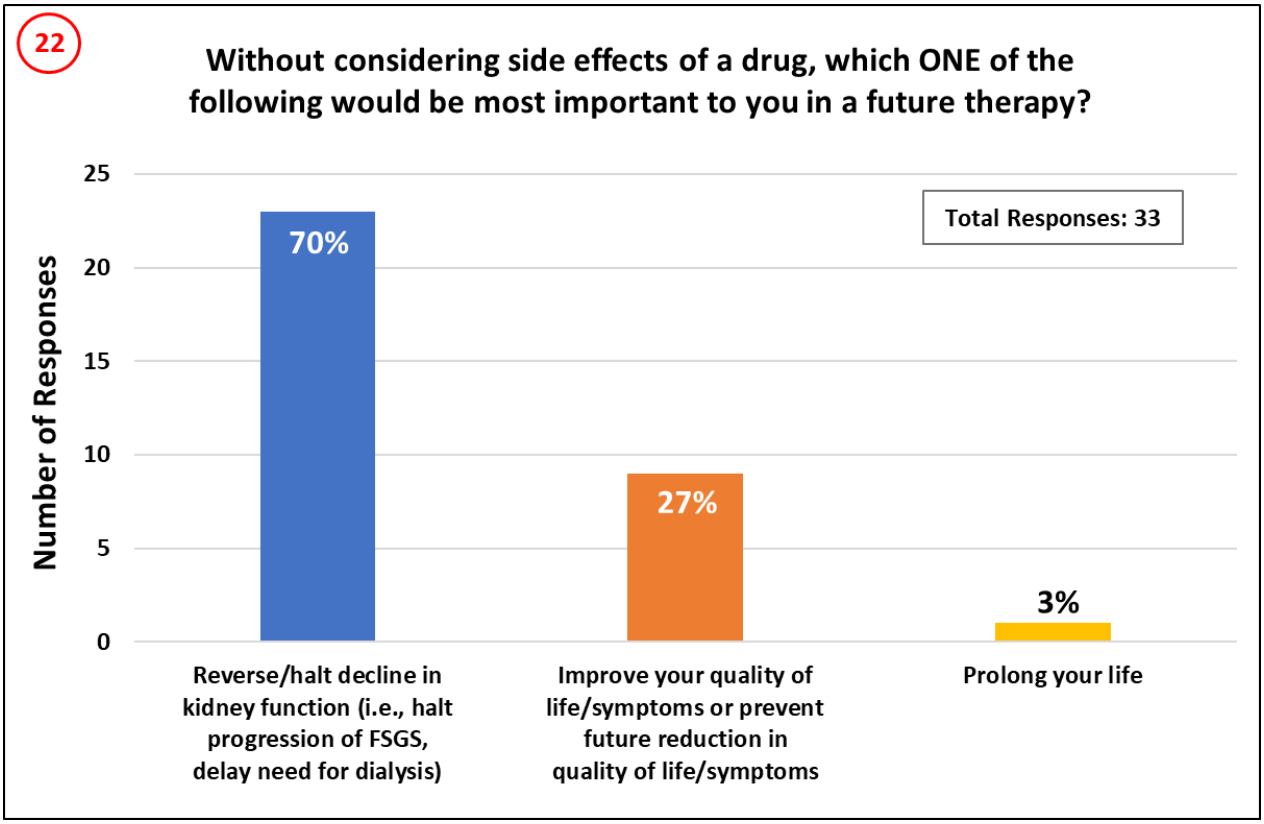
Topic 4: Current Challenges to Treating FSGS






20
Which symptoms or health effects do you have that are NOT addressed fully by your current treatments?
Number of Responses
30
25
20
15
10
5
0
Total Responses: 144
19%
15%
15%
13%
8%
8%
6%
4%
3%
3%
2%
2%
0%
Being tired or exhausted
Anxiety &/or depression
"Brain fog" (forgetfulness, poor concentration, lose track of time)
Muscle and joint aches and pains, including gout
Gastrointestinal problems
Swelling (ankles, face, etc.)
Bones/teeth problems
Issues with eyes
High blood pressure
Other
Recurrent infections
I do not have symptoms
High blood sugar/diabetes


21
If the side effects of a new drug were more severe than your current treatment, but clinical evidence indicated the drug would significantly slow the progression of your disease/improve your quality of life, how likely would you be to take this drug?
Number of Responses
25
20
15
10
5
0
Total Responses: 35
57%
29%
9%
6%
Slight likelihood
Moderate likelihood
I would not consider taking it
High likelihood


22
Without considering side effects of a drug, which ONE of the following would be most important to you in a future therapy?
Number of Responses
25
20
15
10
5
0
Total Responses: 33
70%
27%
3%
Reverse/halt decline in kidney function (i.e., halt progression of FSGS, delay need for dialysis)
Improve your quality of life/symptoms or prevent future reduction in quality of life/symptoms
Prolong your life

APPENDIX 7: ACKNOWLEDGEMENTS

The National Kidney Foundation and NephCure Kidney International® gratefully acknowledge the generous support of this meeting by:

- Boehringer Ingelheim
- Cyclerion Therapeutics
- Mallinckrodt Pharmaceuticals
- Travere Therapeutics Inc.
- Vertex Pharmaceuticals, Inc.