

VOICE OF THE PATIENT

Report of Externally-led Patient-Focused Drug Development Meeting on: Complement 3 Glomerulopathy (C3G)

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None of the authors or their organizations have relevant disclosures.

FUNDING

Lead sponsorship was provided by Achillion Pharmaceuticals

Additional support was provided by Novartis Pharmaceuticals

Sponsorship was provided as independent grants that supported meeting logistics, including venue costs, patient transportation, lodging, and meals, medical writer, photographer, and preparation of the meeting transcript.

VERSION DATE

March 26, 2018. This Voice of the Patient report has not been revised or modified since March 26, 2018.

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The Voice of the Patient

Externally-led Patient-Focused Drug Development Meeting

C3 Glomerulopathy (C3G)

Public Meeting: August 4, 2017

Report Date: March 26, 2018

Submitted to: Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA)

This report reflects the National Kidney Foundation's account of the perspectives of patients and caregivers who participated in an Externally-led Patient-Focused Drug Development meeting, an effort to support the FDA's Patient Focused Drug Development Initiative.

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INTRODUCTION

On August 4, 2017, the National Kidney Foundation (NKF) held an Externally-led Patient-Focused Drug Development (EL-PFDD) meeting on C3 glomerulopathy (C3G). The goal of the meeting was to reveal to the U.S. Food and Drug Administration (FDA) the perspectives of patients living with C3G regarding the disease's impact on their daily lives and the currently available therapies. 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 condition and the available therapies to treat it. Recently, the Agency passed the PFDD responsibility to patient advocacy groups to organize and conduct EL-PFDD meetings.

More information on this initiative can be found at:

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm453856.htm>

Overview of C3G

C3G is a rare, chronic kidney disease caused by abnormal activation of the complement system. This leads to deposition of C3 fragments along the glomerular basement membrane (GBM) and in the mesangium, causing glomerular damage and eventual progression to end-stage renal disease (ESRD; kidney failure) for most patients¹. C3G is an etiologically heterogeneous disease, in which complement dysregulation can occur through loss-of-function mutations in pathway inhibitors, gain-of-function mutations in pathway activators, development of antibodies to complement proteins leading to altered function, or combinations of the above². While individuals can be diagnosed at any age, C3G disproportionately affects children and young adults. The prevalence of C3G is estimated to be 2-3 cases per million individuals³.

Diagnosis of C3G is based upon pathology: examination of kidney biopsies by immunofluorescence microscopy reveals dominant C3 glomerular staining without significant staining for immunoglobulins. C3G is further subdivided by electron microscopy into two pathological patterns: dense deposit disease (DDD) and C3G glomerulonephritis (C3GN), based upon the location of complement-associated deposits in the glomerulus.

Dense deposit disease is characterized mainly by dense deposits appearing within the GBM, while C3GN generally shows predominant mesangial and subendothelial patterns of deposits, with mesangial cell proliferation and double contouring of the GBM.

Clinically, these two patterns are treated identically—as C3G. Reflecting the heterogeneity seen in the causes of C3G, the disease itself is variable in terms of progression and symptomology. While the natural history of C3G has not been studied extensively, 10-year renal survival was reported at about 50% for DDD and about 75% for C3GN¹. Moreover, recurrence of C3GN in renal allografts is about 67%, and of those cases, about 50% progress to graft failure⁴. Similar outcomes for renal allografts were reported in DDD⁵.

A 2013 consensus report⁶ provided recommendations for both diagnosis and treatment of C3G. Currently available therapies are largely nonspecific, and first-line treatment is most often steroids and mycophenolate mofetil. “Response” to treatment is limited to slowing disease progression; currently there is no FDA-approved disease-modifying treatment. At the time of this EL-PFDD meeting (August 4, 2017), there were several agents under development targeting different points of the complement pathway; however, there are unresolved questions about how each of these potential treatments may be used (and in what combination) to treat C3G. Because C3G is mediated by the consequences of a dysregulated complement system (i.e., a systemic defect), kidney transplantation does not resolve the underlying disease. Thus, graft survival for C3GN patients was 50% at about six years post-transplantation⁴ and about 50% for DDD patients five years after transplantation⁷.

Meeting Overview

This EL-PFDD meeting provided the FDA the opportunity to hear directly from patients and their caregivers about: (1) their experiences living with C3G and the impact of disease symptoms on their daily lives, as well as (2) their perspectives on available treatments. Discussion focused on the latter. The meeting agenda and discussion questions are shown in [Appendix 1](#).

To address each topic, a panel of patients and caregivers ([Appendix 2](#)) shared their experiences with C3G. These presentations served to open a moderated dialogue with other patients and caregivers in the audience. Participants also joined the meeting via live webcast. Patients and caregivers in the audience were periodically invited to respond to polling questions, which

provided a sense of participant demographics and clinical profiles, as well as the degree to which participants shared a particular perspective on a given topic. Caregivers were instructed to respond for patients under their care.

More than 75 people attended the meeting in person, including 42 C3G patients and caregivers. In addition, the live webcast was joined by 99 attendees, of whom 17 were patients or caregivers.

Responses from demographic polling questions ([Appendix 3](#)) revealed that in-person attendees represented a range of locations in North America ([Appendix 5; Figure 1](#)). In addition, the webinar was joined by people from 11 countries outside of the U.S. ([Appendix 5; Table I](#)). The participants were predominantly young adults ([Appendix 5; Figure 2](#)), with equal numbers of males and females ([Appendix 5; Figure 3](#)). The time since diagnosis was balanced across less than 1 year through greater than 10 years, except between one to two years ([Appendix 5; Figure 4](#)). A small minority of patient participants were on dialysis ([Appendix 5; Figure 5](#)) while about one-third had a kidney transplant ([Appendix 5; Figure 6](#)).

To supplement the patient perspectives gathered at the meeting, patients and caregivers were encouraged to submit comments to NKF until September 1, 2017. Five such comments were submitted (pages 25-27 of this report), each supporting and reinforcing several of the primary insights from the meeting. In addition, NKF executed a post-meeting online survey ([Appendix 7](#)), posing questions related to patient participation in clinical trials for C3G treatments.

Report Overview

This report summarizes the discussion and polling input provided by patients and caregivers at the C3G EL-PFDD meeting. Responses to polling questions ([Appendix 4](#)) posed during the meeting are reported in the text and shown in graphical form in [Appendices 5 and 6](#). Technical difficulties during the webinar broadcast of the meeting may have prevented collection of responses to the polling questions from the webinar audience. Additional polling questions

(Appendix 7) were posed online after the EL-PFDD meeting; the results are reported in Appendix 8. *The graphical (quantitative) representations of polling responses are intended only to summarize participant responses and facilitate portrayal of the results, not to infer or predict from this small sample, the preferences of the broader population of C3G patients.*

To gauge the frequency of specific symptoms experienced by patients and to obtain other information, in certain polling questions patients were asked to rank a list of symptoms or preferences. In these questions, the limited choices introduced bias. However, this bias is partially mitigated, since the options for answers to these questions were chosen through consultation with C3G-expert nephrologists. Moreover, the questions were chosen based on a preliminary survey of C3G patients before the EL-PFDD meeting.

To the extent possible, the terms used in this report to describe specific C3G symptoms, impacts, and treatment experiences reflect the words used by in-person attendees. This report is not meant to represent in any way the views and experiences of any specific group of individuals or entities. There may be symptoms, impacts, treatments, or other aspects of the disease that are not included in the report.

This Voice of the Patient report intends to support the FDA's understanding of the symptom-derived burden of C3G in patients and their families, and their perspectives on treatments currently used to manage the condition. This document also highlights the unmet needs of C3G and the urgency for new treatments. The FDA may consider this input as it fulfills its role in the drug development process, including advising sponsors on their drug development programs, evaluating products for marketing approval, and assessing benefit-risk for products under review (Appendix 9; Table I). This input may also be of value to the drug development process more broadly. For example, the report may guide manufacturers in their discovery and development processes by uncovering previously unappreciated life burdens of C3G. It may also help to describe unmet needs surrounding symptoms that may inform endpoints in clinical trials.

The initial draft of this report was written by a medical writer who was engaged by NKF and attended the EL-PFDD meeting. The draft was further developed solely by NKF staff and the meeting Co-chairs (Drs. Andrew Bomback and Carla Nester).

Key Themes

The input from patients and caregivers attending the meeting emphasized the challenge of living with C3G, its impact on daily life, and the difficulties of treating C3G. Several key themes emerged from this meeting:

- **Symptoms** that were most frequently discussed as negatively affecting daily life included: fatigue, edema, anxiety and depression, weight gain from steroids, joint pain attributed to gout, and immune-related issues.
- Patients described the **uncertainty surrounding their future health** as “crippling” or “paralyzing.” This uncertainty makes it difficult to plan for the future, dims patients’ hopes and aspirations, and leads to depression and anxiety. Because there are no disease-modifying treatments, patients cannot expect their health to improve, which leads to further desperation.
- Patients shared their **experiences with prednisone, eculizumab, dialysis, kidney transplantation, and other therapies**. The majority of patients expressed enthusiasm for participating in clinical trials for new C3G treatments. Some patients willing to participate in such trials expressed frustration about enrollment requirements to stop an effective treatment regimen in order to try new ones.
- Because a **kidney transplant** does not cure C3G, when considering a transplant, patients may feel as though they must “trade in their current condition for another unknown.” Throughout the meeting, participants emphasized the importance of including transplant recipients in C3G clinical trials.

Patients also repeatedly stressed the need for effective, affordable treatments. They expressed frustration at the resistance of insurers to pay for certain medications and the resulting interruptions in treatment.

PERSPECTIVES FROM PATIENTS AND CAREGIVERS

Topic 1: Living With C3G—Disease Symptoms and Daily Impact

The first discussion topic focused on patients' and caregivers' experiences with C3G symptoms and the impact the disease has on their daily lives. Five panelists provided comments to start the dialogue. The panel comprised four patients currently living with C3G and one caregiver speaking on behalf of her young daughter, who is currently living with the disease. Panelists described the physical, emotional, and social impact of C3G and associated symptoms. In the facilitated discussion that followed the panel presentations, patients and caregivers in the audience echoed the sense of anxiety and loss that accompanies a diagnosis of C3G, and the sense of desperation that there are no available disease-modifying treatments. The presentations included descriptions of specific activities that patients could no longer do at all, or as fully as they would like, because of their condition. During the moderated audience discussion, the panelists' and caregivers' accounts were validated by audience participants.

Perspectives on Most Significant Symptoms

A plurality of respondents reported that C3G did not, or minimally interfered with, their daily lives. However, a combined 57% of respondents conveyed that the disease affected their daily lives to a moderate or significant degree ([Appendix 6; Figure 1](#)).

Participants were asked to identify three symptoms that most negatively affect their daily lives. Fatigue, swelling (edema), and anxiety/depression were the three most commonly selected symptoms ([Appendix 6; Figure 2](#)). The facilitated audience discussion explored the impact of these and other symptoms in more detail, and provided insights into the heterogeneity of symptoms and rate of progression in C3G. The symptoms discussed in this session are described in more detail below. One particularly telling comment came from a panelist who shared aspects of her disease that were most apparent when she compared herself to her identical twin sister, who does not have C3G: "Where her endurance increased, mine decreased; when her flexibility increased, mine declined; where she now stands at five feet six inches, I am four inches shorter."

Fatigue

The most frequently cited symptom having a significant, negative impact on patients' lives was fatigue ([Appendix 6; Figure 2](#)). Fatigue can range in severity, but was reported by patients to be worse in periods just prior to kidney transplantation. Several audience members described a gradual increase in symptoms (a “frog in boiling water effect”) before transplantation, and described an improvement in fatigue following transplantation that was “like night and day.”

Notably, some patients at the meeting who had well-preserved renal function reported similar degrees of fatigue as patients who had progressed to dialysis and transplantation.

Participants reported both cognitive impacts of fatigue, such as trouble focusing, as well as physical limitations. Many patients reported being unable to fully participate in sports or an active lifestyle, or in some cases, being unable to help with basic household chores. One audience member described needing to take a break at work and then having his coworkers finding him sleeping in his car.

“Even after a full night of sleep, it looked like she [daughter with C3G] hadn't slept for 24 hours.”

“I had a harder time focusing on my doctoral research, and I couldn't make it through a half-hour basketball game without doubling over with a hacking cough.”

“Everything I did made me tired.”

“The fatigue is overwhelming. Living it, it becomes normal.”

Several audience members on dialysis cited difficulties that they had experienced with “foggy brain” and fatigue from the treatment. One audience member added that fatigue related to dialysis can be debilitating.

Swelling (edema)

The degree to which patients experience swelling, especially in feet, ankles, and around eyes, is variable. While many patients in early stages of C3G do not experience this symptom, some patients with more advanced disease may experience swelling intermittently, or even daily severe swelling that inhibits a patient's ability to walk, and diminishes their capacity for work or physical activity. One patient described experiencing monthly swelling in his

feet and ankles, with occasional episodes that were more severe, making it difficult for him to walk. Another patient described daily swelling that was so severe it required her to pack extra changes of clothes, so she could stay comfortable as her swelling increased during the day. This patient also described several instances where her husband had to carry her into the house from her car because her ankles were so swollen that she couldn't bend them to walk. One audience member added that before his kidney transplant, he was carrying an additional 30 pounds of excess fluid that made it difficult for him to work.

"I have to choose my footwear carefully, because what may fit in the morning may not fit by the time I've been at work for two hours....By the time I get home, my ankles are so swollen I can't bend them..."

"Whereas everyone else seems to have it [swelling] sporadically, I have it every day...I can't walk....can't open my eyes..."

"The excessive swelling....It's hard getting out of a chair....It's crippling. You can't move."

"I had...swelling in my knees, ankles, all the way up. I cut my slippers to put shoes on to try to get to work, and was unable to get them in after cutting them fully off [at] the sides."

Anxiety and Depression

Many participants indicated that they frequently experienced anxiety and depression about their C3G ([Appendix 6; Figures 2, 3](#)). Participants noted that, in addition to the progressive nature of the disease, the uncertainty surrounding the rate of progression, the often sporadic nature of symptoms, and the variable success of kidney transplants are especially difficult to endure. During the discussion, patients expressed that the uncertainty surrounding the disease makes it difficult to plan for the future, and they voiced a need for stability. One panelist described an immense amount of grief surrounding "the loss of a normal life," a feeling that was echoed by audience members throughout the course of the meeting.

"It's horrible all around. You know it's going to get worse."

"You can't plan for the future as well as you want; you don't know where you'll be next year."

"What's most difficult is knowing time is not on my side... without a viable drug treatment, I know that a healthy

diet, exercise, and following doctor's orders will not stop the progression of this disease...This absolutely frightens me...I can only imagine things getting worse and have no expectation other than things getting worse...This expectation leaves me feeling desperate....All I can do is wait and worry about the years to come."

Painful Joints Due to Gout

One panelist and several audience members shared that they had recurrent bouts of gout that made it difficult for them to walk. In combination with edema, gout can be particularly debilitating. One panelist described attending a study abroad program and having to spend all his time outside of class in bed, rather than exploring and learning, because it was so difficult for him to walk. This panelist added that he had been seeing an orthopedist rather than a nephrologist for his gout because he didn't think the two conditions were related. For most patients, gout flare-ups are intermittent, but are incapacitating when they occur. One panelist described grimacing at every step walking from the train station.

"Most of my peers wouldn't know I have this disease if it weren't for the disabling gout I get once a quarter like clockwork, in my feet, wrists, and toes....Several times I have gotten it simultaneously in both big toes."

"The gout can make it painful to wear shoes, walk, or even wear socks."

Treatment-related Symptoms

While many participants indicated that the symptoms of C3G affect them more than the effects of medications ([Appendix 6; Figure 4](#)); others indicated that the side effects of medications are equally difficult to manage. This topic is discussed under Topic 2: Current Challenges to Treating C3G on page 15.

Vision Loss

One of the panelists described his experience with C3G-related drusen deposits, similar to those found in the more common condition of age-related macular degeneration.

Treatments aimed at preventing further loss of his sight include painful and costly injections in the eye on a monthly basis. When describing his symptoms, this panelist indicated that his vision loss is the most difficult of his symptoms, and expressed distress about whether he would “actually see my children grow.”

“My vision struggles have been most difficult and scary to me, because without my vision, I literally lose this part of the world....At the eye doctor for an exam, I was told I had the eyes of an 80-year-old.”

Immune System Concerns

Audience members emphasized that immune system issues do not often receive the attention they deserve. For many patients, the first overt sign of C3G was susceptibility to infection. Several audience members commented that they were first diagnosed with repeated infections as children. The types of infections varied (e.g., urinary tract infections, strep, pneumonia), as did their frequency and severity. By a show of hands, about a third of audience members had experienced repeated infections, and several had endured unnecessary surgeries as a result. In otherwise asymptomatic patients, these immune issues can be significant. Furthermore, one caregiver audience member indicated that he was apprehensive about his daughter’s immunosuppressive treatments because she was already so susceptible to infection.

“I was hospitalized for repeated infections....I had all those red flags for all those years, but nobody put the pieces together...all those unexpected parts of our disease...”

“They [physicians] don’t think it’s related because it’s ‘kidney disease,’ and don’t recognize the immune aspect.”

Overall Impact of C3G on Quality of Life

Because symptoms worsen as the disease progresses, the constellation of symptoms, as well as the degree to which patients experience them, varies. Participants described the physical, social, and emotional impact that living with C3G has had on their lives.

Uncertainty About the Future

Participants shared that the progressive nature of C3G, in combination with the variability of symptom onset and severity, make it difficult to engage in planning for the future.

A significant experience for patients is anxiety and depression from the lack of a disease-modifying treatment and living with the expectation that symptoms will worsen over time. The feelings expressed by audience members and the panel were summarized as:

“We were afraid to travel. We were afraid to make plans.
We were afraid to do much of anything.”

“It could all change any day.”

Isolation

Because C3G is a rare disease, patients often feel as though they are alone in their struggles ([Appendix 6; Figure 3](#)). Many attendees expressed delight at the opportunity to meet in person with other C3G patients. Patients described the hidden struggles of living with C3G. Participants agreed that the general public is unaware of the day-to-day struggles that keep the disease in the front of the patient’s mind. During the meeting, patients shared that adhering to a renal diet makes it difficult to go out to eat with friends. The daily management of C3G can also make it difficult to travel and maintain relationships with geographically distant family members.

Directly related to feelings of isolation was the response by 34% of attendees who they felt others did not understand the experience of living with C3G ([Appendix 6; Figure 5](#)).

“You feel like you’re going through it alone...”

“‘You don’t look sick’ is a common phrase I hear when people learn of my disease.”

Inability to Participate Fully in Physical Activities

Many patients described an inability to participate fully in physical activities ([Appendix 6; Figure 5](#)). For many patients living with advanced disease, failure to partake in activities is rooted in fatigue, edema, fear of disrupting an abdominal dialysis port, or recurrent infections.

“I had physical limits to running, as it caused me immense bone pain. Where I would be involved in multiple sports, I could now only do one activity once in a two-week time frame.”

Impact on Daily Life

Several patients who experienced severe swelling and fatigue indicated that they felt limited in their ability to participate in their home life, such as family activities or performing routine household chores.

“This [swelling] makes it difficult for me to perform simple chores around the house, such as mowing the lawn, and more importantly, being active with my wife and kids...”

“I can’t do dishes because I can’t stand for that long.”

One participant with advanced disease described dehydration and wasting so severe that he “ended up retiring early.” He said, “I was weary, trembling, cold, and shaking....I couldn’t do my job in the condition I was in.”

Because of the dearth of nephrologists who specialize in C3G, many patients must travel significant distances to receive care from specialists. One caregiver panelist drives with her daughter for eight hours to see the child’s physician. Patients noted that such travel is a substantial hardship, requiring time off from work or school, and the need for childcare for other children in the family.

For many asymptomatic patients, the biggest impact on quality of life is the amount of time spent in the hospital as well as “keeping up” with medications. Monitoring C3G can be a particular burden for asymptomatic pediatric patients. One caregiver noted that, “If there is a chance for a real treatment that won’t have her in hospitals all the time, we’ll be all over it, but destroying her quality of life now is not an option for us.”

Impact on Family Life

Participants shared how C3G has affected their family and their relationships.

“You have the patient, or the child, [who] has the disease... but the family also gets all these things that go along with the disease...The anxiety is spread throughout an entire family. Siblings are affected too....Over the long term, it can be pretty important.”

“My husband went from being my partner to my caregiver.”

Young female attendees with C3G reported that planning for having a family represents a significant difficulty and is a source of tremendous heartache for both patients and caregivers.

One participant described traveling regularly to see family prior to a C3G diagnosis, and shared that the needs of the disease had then taken over as a priority, and that developing relationships with family members had suffered.

Topic 2: Current Challenges to Treating C3G

The second discussion topic focused on patients' experiences with therapies used to treat their C3G. Six panelists provided comments to start the dialogue. Five were patients who had been living with C3G, and one was a caregiver of a child living with C3G. Panelists shared their perspectives on different treatments, experiences with clinical trials, challenges they had faced in both obtaining a diagnosis and in finding effective treatments, as well as issues with access to new treatments, such as eculizumab. In the facilitated audience discussion that followed, participants voiced experiences that resembled the comments by the panelists.

Participants identified and described their current treatment regimens, as well as their experiences. They also discussed involvement with a wide range of treatments, including prescription drug therapies, medical procedures, investigational agents, and non-drug therapies. In response to audience polling, almost half of participants indicated that their current treatments reduced their most significant symptoms moderately well, with about one-third reporting very well-addressed symptoms, and fewer patients indicating that current treatments reduced significant symptoms poorly or not at all ([Appendix 6; Figure 6](#)).

During the discussion, participants clarified that the ability of available medications to control symptoms decreases as the disease progresses. Overall, participants expressed frustration that a disease-modifying treatment remains unavailable, and reiterated that currently available treatments do little to slow the progression of the disease or alleviate the most difficult symptoms. Based on audience polling and discussion, the three most significant symptoms of C3G that are not addressed by medication are fatigue, anxiety/depression, and difficulty concentrating and thinking clearly ([Appendix 6; Figure 7](#)).

Participants also provided their perspectives on an ideal therapy for C3G, including the need for better understanding of the genetic determinants of C3G disease heterogeneity and how this information might be used to tailor treatment. The importance of symptom relief and preservation of kidney function was also stressed. As part of this discussion, participants emphasized the need for physician education, because for many of them, their C3G symptoms had been incorrectly treated with medications that were harmful to their kidneys.

Perspectives on Current Treatments

Most participants reported taking drug therapies for the management of their C3G. The two most commonly discussed medications were prednisone and eculizumab. Some patients noted that treatment is a constant balancing act between the benefits and risks of one medication against how it may negatively interact with other medications.

Prescription Drug Therapies

Prednisone

Several participants reported that the anti-inflammatory corticosteroid prednisone was part of their treatment regimen. Patients described the difficulties of tolerating the side effects of prednisone.

Though some patients noticed reductions in proteinuria on high doses of prednisone, the side effects were significant. Prednisone-related side effects most discussed by audience members and panelists are detailed below.

- **Weight gain.** Several audience members commented that the weight gain from prednisone-induced insatiable hunger was difficult to manage. Many patients had gained between 20 and 30 pounds while taking the drug. In addition, fluid retention from prednisone causes “moon face.” Weight gain and “moon face” take a toll on self-image, especially in younger patients.

“My mom and I have spent over \$100 on new clothing for me since I have gained 25 to 30 pounds since being on prednisone. It also caused me to get stretch marks which make me self-conscious....I worry that if other people my age see my stretch marks, they will think that I am pregnant and will judge me. It also gives me a moon face, which I got many comments about...and it is really hurtful to me since I can't help it...” [Teenaged C3G patient]

In some instances, patients who respond well to prednisone may be tapered off the medication. One audience member shared that, on average, he reinitiates prednisone every year or two.

“There is a constant need to balance the need for prednisone and the flare-ups.”

- **Immunosuppression.** Many patients reported susceptibility to frequent infections, a known side effect of prednisone. These can result in hospitalization and can affect patients’ quality of life. One patient noted that, “Being sick damages my kidneys....This past March, I felt like I was sick every week.”
- **Mood swings.** One audience member noted, “The mood swings were hard on me, and everyone around me.”
- **Cognitive effects.** One panelist added that, while taking prednisone, her thoughts are “screaming,” and felt “scrambled.”
- **Insomnia.** For many patients, high doses of prednisone cause severe insomnia. One patient described having to take leave from his job because of sleep deprivation, and the resultant impact on his cognitive abilities.

“That [prednisone] really lit me up....There was a week or so where I could only get 20 minutes of sleep a night. I took vacation time since it was a safety-related job.”

- **Bone problems.** Especially in pediatric patients who are still growing, bone problems were also mentioned. One caregiver for a pediatric patient cited the long-term side effects of prednisone on bone development as a deterrent from using this therapy.

Eculizumab

Eculizumab, a complement (C5) inhibitor, was mentioned by several patients who have participated in clinical trials or have been prescribed the drug, off-label. Several participants indicated that they had taken eculizumab to prevent disease progression and stabilize kidney function.

Overall, patients reported varying degrees of success with eculizumab. For one panelist who took the drug after C3G appeared in his recently transplanted kidney, eculizumab preserved his kidney function for seven years. He is now on dialysis, awaiting a new transplant.

Other panelists shared their experiences with eculizumab:

“...great results throughout the trials, but seeing my kidney function plummet back to pre-trial levels at the end of the trial was difficult.”

“Before this treatment, I had reached stage 4 kidney failure, and my symptoms made it impossible for me to live a normal life. Now I am at stage 2, and no longer steadily declining. My allergies and inflammation have improved. None of the symptoms have been completely addressed, but I can once again enjoy activities like baking and gardening that had become impossible...”

Each patient who had taken eculizumab reported ongoing difficulties with insurance approval and coverage, and voiced that expense and uncertainty surrounding treatment availability and insurance coverage are major sources of anxiety. One panelist shared that “...every six months to a year, my insurance company would dispute my claims, and I would file appeals to have my eculizumab covered. Multiple times I’ve missed treatments because of the back-and-forth with insurance....Nothing compares to the stress I feel when I have to fight for coverage of my drug that gives me a normal life.” He described receiving a phone call from a home infusion nurse to inform him that he may have over 4 million dollars in back balances for treatment because he was “out of network” and how he had to spend hours sorting out the confusion. This incident caused months of missed treatment.

The impact of treatment with eculizumab on daily life can be significant, as the time required for each infusion is approximately four hours. One panelist shared that the need for travel to and from his treatment center had prevented him from taking on professional roles that required him to travel, and had led to him switching his career so that he no longer needed to travel for treatments.

Another participant shared that while she no longer “becomes so swollen I cannot walk,” she misses half a day of work for each infusion (as does her husband who must accompany her to the infusion center) and must travel two and a half hours each way. She further stated that she must sleep 12-14 hours once she returns home due to the combined effects of fatigue associated with C3G, working full-time, and the effects of eculizumab. She shared, “Two weekends of every month are off limits, which is detrimental to my family life, my social life, and my professional life.”

During discussion, audience members reiterated that they feel “frozen,” “stuck,” and afraid to make plans that might compromise their access to the treatments they need.

Other Drug Therapies

- Most C3G patients take several medications such as **lisinopril** or **irbesartan** to control their blood pressure. One panelist added that these drugs keep him from having constant headaches.
- Patients may take **antihistamines** to treat their allergies, which stem from higher-than-normal immune reactions. These antihistamines generally provide little relief.
- Several participants reported taking an **antacid** to alleviate stomach discomfort.
- Patients may also take **immunosuppressive drugs**, such as **azathioprine**, **cyclophosphamide**, or **mycophenolate mofetil**. With these drugs, there are concerns surrounding the increased risk of infection. One panelist described recurrent herpes infections that appear periodically on his nose, and for which he takes **acyclovir**. These infections have more recently begun evolving into staph infections, requiring repeated hospitalizations. The panelist had been hospitalized for infection approximately six times.
- For another patient, **mycophenolate mofetil** is associated with frequent herpes lesions around her mouth. “They are painful, ugly, and bleed. It hurts to eat, brush her teeth, and even smile.”
- Many C3G patients who have had a transplant or are awaiting transplant, take additional **immunosuppressive drugs** to prevent graft rejection.
- To relieve edema, patients take **diuretics**, which patients reported are not very effective and do little to relieve their severe swelling. Participants also reported sleeping in recliners and wearing compression socks to alleviate swelling: “When I wear my compression socks, my knees puff up so bad I can’t bend my legs very well.”
- Many patients who suffer from gout take **allopurinol** to prevent gout attacks. In many cases, this therapy helps to alleviate this symptom and lessens the severity and frequency of attacks.
- To treat anemia and anemia-associated fatigue, patients may use **Procrit or other erythropoiesis-stimulating agents** and/or **iron supplements**.
- Patients may also take several prescribed **supplements** to manage dietary deficiencies.
- One patient added that she wears a **fentanyl patch** to treat pain in her joints and tendons resulting from inflammation.

Plasmapheresis

One participant related her experience with plasmapheresis for one and a half years, which she noted was painful, but that she felt delayed the need for dialysis.

Dialysis

Patients in ESRD who may or may not be awaiting a kidney transplant rely on dialysis to “keep their blood clean from toxins.” Eight percent of patient participants responded to polling that they were currently on dialysis ([Appendix 5; Figure 5](#)). Patients referred to dialysis as a difficult and time-consuming treatment that has a negative impact on quality of life. While many patients reported a significant decrease in energy, and described feeling exhausted “even after a short walk,” one patient recounted a moderate gain in energy by having daily (rather than every other day) dialysis at home, and coupling the daily dialysis with physical activity to build endurance. Patients also noted that dialysis catheters are difficult to manage, and interfere with activities, such as swimming or showering, because of the need to keep the catheter dry. Dialysis patients also spoke of taking medications to bind phosphorous, as well as following a renal diet.

Kidney Transplantation

Kidney transplantation is an option for renal replacement therapy for some patients, and 31% of participants had received a kidney transplant ([Appendix 5; Figure 6](#)). However, kidney transplantation does not cure C3G. Complement dysregulation continues, and transplanted kidneys often suffer damage from accumulated C3, leading to kidney failure. Regardless, patients who received kidney transplants reported enormous benefits.

“Then you go on dialysis...but then transplant; it’s like night and day. You get your energy back; you get color in your face; you’re out; you’re doing stuff; you have a life again...”

Treatments Compatible with Kidney Transplantation

Patients stated that an ideal treatment would prolong the life of transplanted kidneys and be compatible with the medications that kidney transplant recipients must take.

“For patients with transplanted kidneys [taking another immunosuppressive therapy] presents the problem of layering immunosuppressants on top of one another....For patients and their families, the question becomes, would the person’s life be better or worse?”

For patients receiving transplants, a treatment that would prevent C3G progression in the transplanted kidney would, “put that worry at bay after a transplant and ease the anxiety of transplant outcomes...[one could] deal with complications of [a] normal transplant without the C3 element.”

Diet

Patients reinforced that while adhering to a renal diet is important, it does not slow or halt disease progression.

“You can be as healthy as you want, but the disease will still progress....It’s not really a treatment, just what you have to do while you’re declining.”

Participants varied in the degree to which they follow a renal diet from strict adherence to an 800-1000 mg/day intake of sodium, to just paying attention to “what you can and can’t handle.” Following the diet is burdensome (a slice of bread contains 300 mg of sodium). Patients noted that the renal diet limits their ability to go out with friends or travel easily. The further the disease progresses, the more challenging it becomes because of the additional dietary limitations (intake of phosphorous, protein, etc.).

“You reach a point where it doesn’t feel like there’s anything you can eat.”

Most patients at later stages of C3G must strictly adhere to a restrictive renal diet. This includes limiting phosphorous and potassium, as well as fluid intake.

“If the diet is not followed it can lead to swelling and cramping that could last for a few days.”

Perspectives on New Drugs: Selecting New Treatments for C3G

Preserving Kidney Function

Patients discussed new drugs in the context of the importance of slowing progression, symptom control, and the severity of side effects they would accept to control their disease. During discussions, participants stated that the ideal drug would be accessible, disease-modifying, and useful for all patients (asymptomatic, symptomatic, and those who have received a transplant). Participant perspectives on new treatments are provided below.

In responses to polling questions, participants reported that, when deciding on a new treatment, the two most important considerations were whether the drug is covered by insurance and the severity of side effects ([Appendix 6; Figure 8](#)).

In addition, polling of the audience revealed that, overall, the most important outcome from a new drug would be its ability to reverse the decline of kidney function ([Appendix 6; Figure 9](#)).

“We need a way to avoid a lifetime of dependence on a dialysis machine or a series of failed transplants. We need timely and effective treatment to preserve the function of both native and transplanted kidneys.”

“An ideal treatment would slow down disease progression long enough to make the medicine and side effects worthwhile, and would have manageable side effects that don’t cause too much damage to the rest of the patient’s body.”

“I need my kidneys to function. Once they stop functioning, life is never the same again....I will go to pretty great lengths to preserve my kidney function....I can take a lot of things to make that happen.”

“We need a variety of treatment options to fit our diverse patient population.”

“When you have no treatment at all, ideals become negotiable. We need effective treatment that we can obtain.”

For asymptomatic patients, an ideal treatment would prevent progression and potentially allow for reversal of current kidney damage. For these patients, there was an emphasis on securing a treatment that prevents disease progression and allows patients to be, “Well enough to participate in and enjoy life.”

“Every time I look at my little girl, I know that C3 is accumulating in her kidneys....I’d really like to see something that halts the disease, and hopefully that would resolve symptoms for those who do have symptoms.”

Disease Stability

Patients underscored the importance of achieving “disease stability” and used this concept to frame preservation of kidney function (slowing disease progression). For symptomatic patients, stabilizing kidney function was noted as being the most important goal. However, alleviating symptoms, such as edema, high blood pressure, and proteinuria were also priorities.

For transplant recipients, stabilizing the disease would allow for prolonged function of the transplanted kidneys.

“I have a kidney transplant now, and I’d like to keep it as long as possible.”

Patients reiterated the emotional benefits of disease stability. Knowing that their disease is stable and well controlled would allow patients to make plans for the future, and would alleviate the anxiety and depression that accompany an unpredictable and progressive disease such as C3G.

“That’s what I want: just some stability.”

Symptom Relief

Overall, participants focused their discussion on new treatments primarily on preventing disease progression, both pre- and post-transplant. However, participants stated that they also seek relief from “the fatigue and inflammation that are so destructive,” as well as swelling and susceptibility to infection.

“Of course, I want a fix to stop my kidney decline. The next best thing would be a way to tie up unfiltered electrolytes and other elements that cause fluid retention.”

“For now, the best would be improvements in proteinuria, hypertension, and edema. If these symptoms are controlled, it will lead to slowing of progression.”

Side Effects of C3G Treatments

Participants indicated that it is difficult to predict in advance the trade-offs that would be acceptable in terms of side effects vs. preserving kidney function. However, most patients indicated a strong willingness to take a drug they believed would slow the progression of their disease and/or improve their quality of life, even if it showed a side effect profile more severe than their current treatment ([Appendix 6; Figure 10](#)).

One patient added that, “An ideal treatment would not require me to take steroids or have the same bad effects as steroids that makes me gain so much weight or compromise my immune system.”

Female participants also voiced the need for medications that are compatible with pregnancy.

“I would love to be able to have kids someday, but I know that if I am on these medications it could cause harm to the unborn baby.”

Accessibility

Participants stressed that new drugs must be covered by insurance ([Appendix 6; Figure 8](#)).

Participants who have struggled constantly to obtain eculizumab emphasized the negative impact that this uncertainty has on their lives.

“With the current state of insurance, and lack of FDA approval [of eculizumab], I will remain stagnant and unable to take any risks.”

“I feel handcuffed, and unable to make any changes.”

Experience with, or Interest in, Clinical Trials

Patients’ experiences with clinical trials for C3G drugs was limited: only 18% had participated in a trial, but nearly 60% expressed interest in such involvement ([Appendix 6, Figure 11](#)).

Participants voiced the importance of including transplant recipients in clinical trials.

One participant shared an experience in which he improved while taking two experimental drugs as part of a compassionate use program. For him, a clinical trial that required stopping a treatment that was working to try another was “a risk.” He suggested clinical trial designs that allow for patients to continue medications that they are already taking.

Additional Considerations Regarding Living with, and Being Treated for, C3G

Several patients recounted their convoluted paths toward a diagnosis of C3G and shared that, as children, they were misdiagnosed for years, while renal symptoms were not treated.

“I was prescribed a series of drugs to control my misdiagnosed C3G-related symptoms...for inflammation

[I was prescribed] high doses of NSAIDs, immunosuppressants for 'lupus,' anti-depressants for fatigue, and high doses of diuretics."

Participants expressed frustration that, even among specialists, physicians may misdiagnose symptoms or not appreciate the close etiological connection between the dysregulated complement system and C3G, and thus may be uninformed on the ramifications that this connection has for symptoms experienced by C3G patients. Patients suggested educational efforts to bring additional or previously unrecognized C3G symptoms to light.

CONCLUSION

This report describes the patient input at an Externally-led Patient-Focused Drug Development (EL-PFDD) meeting on C3 glomerulopathy held by the National Kidney Foundation. The Food and Drug Administration heard patients' in-depth points of view on challenges of living with C3G, the impact of the disease on their daily lives, patients' experiences with the available treatment options, and their perspectives on new therapies.

Major themes that emerged from patients' contributions to this meeting were:

- The hidden struggles of living with C3G include fighting fatigue, edema, gout-associated arthralgias, anxiety and depression, weight gain from steroids, and vision loss. Patients often have these negative and isolating experiences, while being told "you don't look sick."
- The "crippling" uncertainty surrounding their future health, which makes plans for the future virtually impossible, dimming hopes and aspirations, leading to depression and anxiety.
- The frustration with currently available medications that do little to slow the progression of C3G or to preserve the function of transplanted kidneys. These medicines often come with significant negative side effects.
- The hardship endured by patients and their families when adequate care cannot be obtained close to home. Many patients described traveling great distances to be cared for by a nephrologist who understands C3G.
- Patients expressed willingness to be active participants in clinical trials. Nevertheless, patients have concerns about inclusion criteria since, to participate, they may have to stop taking medications that are effective for them.
- Patients seek accessible drugs that effectively slow disease progression and relieve symptoms. They place high priority on preventing or slowing functional decline in transplanted kidneys.

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

COMMENTS SUBMITTED TO THE NATIONAL KIDNEY FOUNDATION FOLLOWING EL-PFDD MEETING

From the date of the meeting until September 1, 2017, NKF accepted written comments from patients and caregivers. Many of the comments echoed the sentiments expressed at the meeting and are summarized below.

Physician Education

“We briefly touched on the subject of C3G being seen as a kidney disorder. And the kidney certainly is one of our top priorities in our care. However, what we started to discuss, but didn’t get to fully address, is the lack of knowledge and comprehensive care for patients with complement dysfunction. Yes, our kidneys get destroyed by this disease. But the patients have a range from mildly to severely impaired complement function, and the effects on the body can be far reaching. I realize that research of the functions of the complement system is still in its infancy. That is one of the biggest obstacles in comprehensive care. But so long as alternative pathway function is only being addressed by nephrologists, this won’t change. We need research on the non-renal effects of this disease. Even a survey of patient symptoms and experiences would be a start.

“Someone needs to begin to connect the dots, and other specialties need to start becoming educated. We need to speak to drug developers and the FDA—but we also need to include other specialists in the conversation. We need clinical immunologists, allergists, hematologists, rheumatologists, gastroenterologists, obstetricians, ophthalmologists, neurologists...It’s a long list. Even the *patients* don’t understand that many of their health struggles may be related to their complement dysfunction—until they begin meeting other patients who share the same struggles and the pieces begin to fit together. But it is nearly impossible to find physicians who know anything at all about the complement system or how it may impact their specialty. Our doctors do not communicate effectively to share the information that *is* available. We cannot get effective care or drug therapy so long as this continues to be viewed solely as a kidney disease. We need awareness and protocols for

infection prevention and treatment. We need access to specialists who understand that we are *not* the norm. We need drug developers to be looking at *all* of the potential impacts of a drug. And, while I realize that this meeting is focused on therapy for renal failure, I believe your audience for the summary will include not only the drug developers who need this information, but also the physicians who treat us and may be able to help facilitate a broader view of this disease.”

EL-PFDD Meeting Format

“I really liked the set-up of the actual meeting, and that the focus was on the patient’s experience and voice. However, I wish there had been more opportunity for the patients to interact with the drug and FDA reps informally. Perhaps inviting them to the dinner the evening before, having a meal following the meeting, etc. As you saw, many of the patients already know each other and have built a community. We do need to tell our stories without interference—but, as is usually the case with rare disease communities, we are very knowledgeable about our disease and very proactive and motivated. Yet, we do not get many opportunities to interact with professionals who are also knowledgeable about our disease. Most of us know far more about complement pathways, function, and drug mechanisms than the doctors who treat us. We are interested in the people and details involved in drug development and approval. For future PFDDs for other rare diseases, I would really recommend giving the patients the chance to interact with *all* the attendees outside the meeting.

“As we discussed, the C3G community wants to be involved in education, awareness, drug development—anything we can get. We have already formed strong relationships with each other, and we would like to extend those relationships to the organizations who can provide support.”

Personal Vignette

“Had a good time at the meeting. I was happy to tell my story; hopefully it helped. I am writing because I did forget to say something that may have been the most impactful for a new treatment. Many people talked about the hardships of having kidney failure and that’s good. I think I brushed over

that too much and tried to emphasize the stress of it always being a concern, that there was no way to plan because we are at the mercy of C3G. So, I regret not saying more, and what I should have said was, as my second transplant was failing, my aunt decided to give me her kidney. So, when I said I let myself go, it was because of that reason I got to 210 lbs. They still wanted me to go through dialysis, to get me healthy for surgery. A week before the surgery she backed out. My family hated her, but I still went to speak with her, and her reason was that my last two transplants lasted about three and a half years. And she didn't want to give up her kidney if it was only going to last three years. I don't blame her at all. So again, if there was a drug to help stop, heal, or slow the disease, she would have been more willing to do it."

[This submission was edited for grammar and clarity.]

Hopes for New Treatments

"Wish I could've attended the Aug 4th meeting, but wanted to still stress this important request: the FDA needs to develop treatments for people living with C3G that can treat the disease directly where the disease originates from—in the pathway where the dysfunction begins. In addition, treatments need to focus on stopping protein from being leaked into the urine. But most important, the emphasis needs to be on curing this disease, not just treating it. Side effects need be not threatening or create symptoms such as a person's quality of life is affected. The treatments cannot risk a patient's health. With negative side effects, a patient would not be able to continue on with treatment, nor even begin, if threats of side effects were of serious concern, either with short-term or long-term consequences."

Motivation to Join Clinical Trial

"Regarding my main driver for being on a trial or not, and around [re]moving of a medicine that was slowing the progression of your disease, my main driver would be how effective it still is at slowing [the disease]. Eculizumab is, of course, slowing my disease, but if its ability to slow [progression is reduced] significantly (which non-biopsy labs have potentially suggested a decreased rate), I would be interested to learning more about the trial."

[This submission was edited for grammar and clarity.]

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APPENDIX 1

Meeting Agenda and Discussion Questions

7:30am – 8:30am	Breakfast and Registration
8:30am – 8:35am	Opening Remarks <i>Dr. Joseph Vassalotti, Chief Medical Officer, National Kidney Foundation</i>
8:35am – 8:50am	Background on C3G: Natural History of Disease and Treatment <i>Dr. Andrew Bomback, Columbia University Medical Center</i>
8:50am – 9:05am	Challenges to C3G Clinical Trial Design <i>Dr. Carla Nester, University of Iowa, Carver College of Medicine</i>
9:05am – 9:20am	Welcoming Remarks <i>Dr. Norman Stockbridge, FDA</i>
9:20am – 9:35am	Overview of Discussion Format <i>Mr. James Valentine, Moderator</i>
9:35am – 10:05am	Panel #1 Discussion on Topic 1: Living with C3G: Disease Symptoms and Daily Impact A panel of patients and caregivers will provide comments, followed by a facilitated discussion with participants in the audience. <i>Mr. James Valentine, Moderator</i>
10:05am – 11:05am	Large-Group Facilitated Discussion on Topic 1: Living with C3G: Disease Symptoms and Daily Impact Patients and patient representatives in the audience will be invited to add to the dialogue. <i>James Valentine, Moderator</i>
11:05am – 11:20am	Break
11:20am – 11:50am	Panel #2 Discussion on Topic 2: Current Challenges to Treating C3G A panel of patients and caregivers will provide comments, followed by a facilitated discussion with participants in the audience. <i>Mr. James Valentine, Moderator</i>
11:50am – 12:50pm	Large-Group Facilitated Discussion on Topic 2: Current Challenges to Treating C3G Patients and patient representatives in the audience will be invited to add to the dialogue. <i>Mr. James Valentine, Moderator</i>
12:50pm – 1:05pm	Closing Remarks <i>Drs. Aliza Thompson and Jonathan Goldsmith, FDA</i>
1:05pm – 1:10pm	Next Steps <i>Dr. Joseph Vassalotti, Chief Medical Officer, National Kidney Foundation</i>

Discussion Questions

Topic 1 (Panel 1): Living with C3G: Disease Symptoms and Daily Impact

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

Topic 2 (Panel 2): Current Challenges to Treating C3G

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 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 2

Patient Panel Participants

Patient-Caregiver Panel, Topic 1

- SA: Caregiver on behalf of her 11-year-old daughter/patient
- TA: 22-year-old female patient
- DY: 43-year-old male patient
- JS: 31-year-old female patient
- NM: 33-year-old male patient

Patient-Caregiver Panel, Topic 2

- NM: 27-year-old male patient
- GH: 63-year-old male patient
- AG: 18-year-old female patient
- BN: 28-year-old male patient
- MRF: Caregiver on behalf of her 18-year-old daughter/patient
- LF: 37-year-old female patient

APPENDIX 3

Demographic Polling Questions

1. Where do you live?

- a. East Coast (Eastern time zone)
- b. Midwest (Central time zone)
- c. West (Mountain time zone)
- d. West Coast (Pacific time zone)
- e. Outside of North America

2. What is your age?

- a. Younger than 18
- b. 18-29
- c. 30-39
- d. 40-49
- e. 50-59
- f. 60-69
- g. 70 or greater

3. Do you identify as:

- a. Male
- b. Female

4. What is the length of time since your diagnosis of C3G?

- 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

5. Do you have a kidney transplant?

- a. Yes
- b. No

6. Are you on dialysis?

- a. Yes
- b. No

APPENDIX 4

Topic Polling Questions

Topic 1

Living With C3G: Disease Symptoms and Daily Impact

- 1. How much does your C3G interfere with your day-to-day life in general?**
 - a. Not at all to minimally
 - b. Moderately
 - c. Significant amount

- 2. Which 3 of the following symptoms most negatively impact your daily life?**

a. Swelling (ankles, face, etc.)	f. Gastrointestinal problems
b. Being tired, exhausted, or fatigued	g. Weight gain
c. Anxiety and/or depression	h. Altered appetite
d. Headaches	i. Insomnia
e. Not being able to concentrate or think clearly	j. Other

- 3. In your daily life, what bothers you more:**
 - a. Symptoms from C3G
 - b. Side effects from medicines you take for C3G
 - c. Both: symptoms and side effects are equal
 - d. I can't tell the difference between effects of C3G and side effects from medicines.

- 4. Which have you experienced while coping with your C3G? (Select all that apply.)**
 - a. Depression
 - b. Anxiety
 - c. Low self-esteem
 - d. Social isolation
 - e. Difficulty with relationships outside of family

- 5. Which of the following statements is true? (Select all that apply.)**
 - a. I miss work or school.
 - b. Family stress is common in my life.
 - c. Others don't know what it's like to be affected by C3G.
 - d. I cannot participate in sports or other physical activities I enjoy.

Topic 2

Current Challenges to Treating C3G

- 1. How well does your current treatment reduce the most significant symptoms of your disease?**
 - a. Very well
 - b. Moderately well
 - c. Poorly or not at all
 - d. I do not currently take any treatments.

- 2. Which symptoms do you have that are NOT addressed fully by your current medications? (Select all that apply.)**

<ol style="list-style-type: none">a. Swelling (ankles, face, etc.)b. Being tired, exhausted, or fatiguedc. Anxiety and/or depressiond. Headachese. Not being able to concentrate or think clearlyf. Gastrointestinal problems	<ol style="list-style-type: none">g. Weight gainh. Altered appetitei. Insomniaj. Kidney function (eGFR)k. Albuminuria (= proteinuria = protein in urine)
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- 3. If the side effect profile of a new drug was more severe than you currently experience with your treatments, but you thought the drug would significantly slow the progression of your disease and/or improve your quality of life, how likely would you be to take this drug?**
 - a. I would never take it.
 - b. Not sure; I might take it.
 - c. I would absolutely take it.

- 4. Which 3 factors are the most important to you when deciding to select a course of treatment?**
 - a. Whether treatment is taken by mouth, by IV, by injection in muscle
 - b. How often you have to take the treatment
 - c. Evidence in C3G patients that drug improves specific symptoms most bothersome to you
 - d. Number of side effects known for the drug
 - e. Severity of side effects
 - f. Cost and/or whether covered by insurance
 - g. What your physician recommends

5. Which of the following is true regarding a C3G drug?

- a. I have participated in a clinical trial.
- b. I attempted to participate in a clinical trial, but was unable (e.g., I did not meet eligibility).
- c. I would be interested in participating in a clinical trial, but I have not attempted to participate.
- d. I have not considered participating in a clinical trial.
- e. I have considered participating in a clinical trial, but I chose not to do so.

6. Which ONE of the outcomes below would be most important to you in a new drug?

- a. The drug reverses the decline in kidney function (i.e., halts progression of C3G), but induces moderate-severe side effects.
- b. The drug significantly reduces some signs and symptoms of C3G, but does not affect kidney function or disease progression. Side effects are tolerable.
- c. The drug slows (does not halt) progression of C3G, and has minimal-moderate side effects.
- d. The drug extends time to dialysis or need for transplant, but induces moderate-severe side effects.

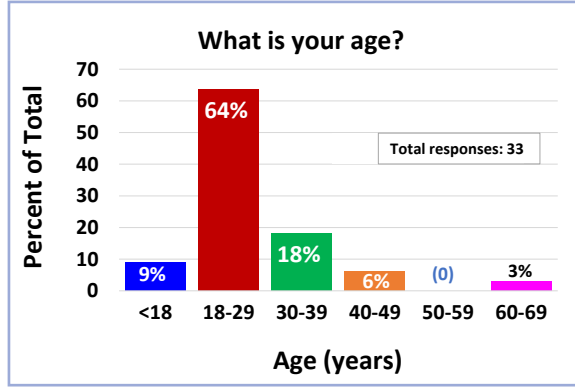
APPENDIX 5

Results from Demographic Polling Questions

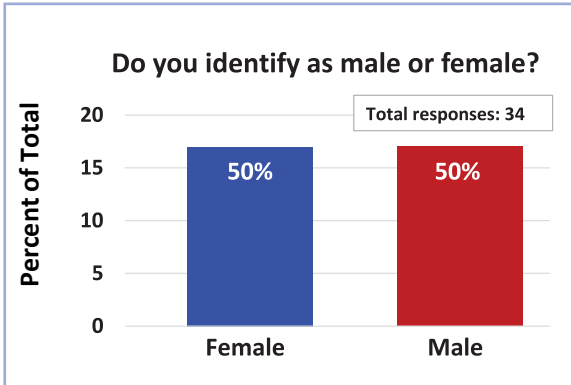
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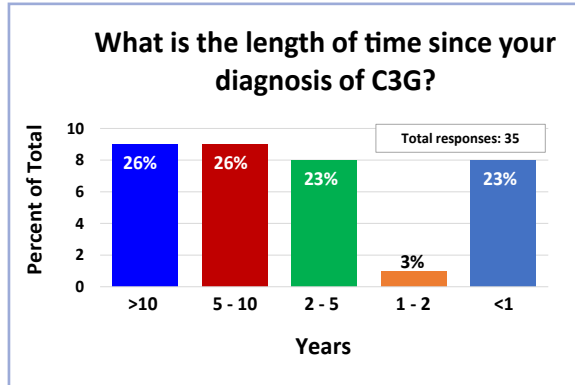
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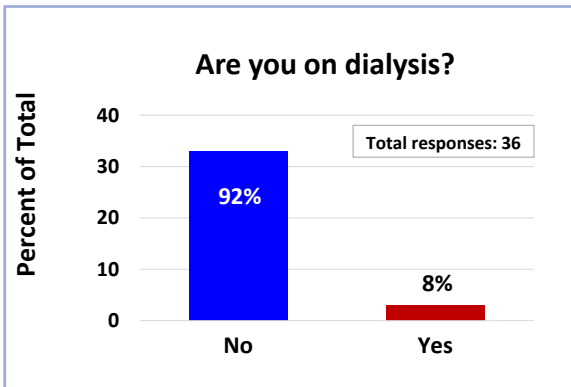
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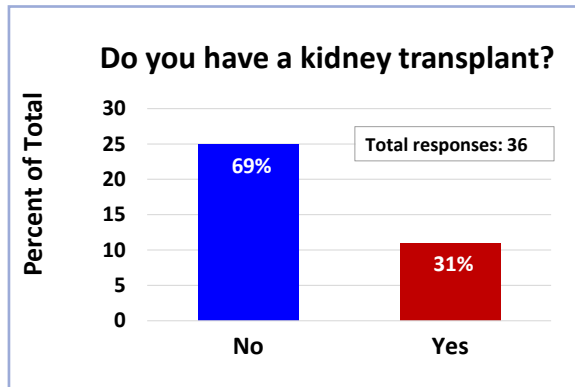


TABLE 1

Countries Represented Online at C3G EL-PFDD Meeting

Australia
Bangladesh
Canada
Denmark
France
Germany
India
Israel
Japan
Switzerland
United Kingdom

APPENDIX 6

Results from Meeting Polling Questions

Results from polling questions are expressed as percent of total responses (total responses = number of patients and caregivers responding to each question, noted on graphs when available). Some polling questions offered multiple answers. For these questions, the software that compiled the responses computed the percent of responses for each answer but did not report the number of responses to each question. Consequently, for [Figures 2, 3, 5,,7, and 8](#), the numbers of total responses to the questions could not be reported on the graphs as they are for [Figures 1, 4, 6, 9, 10, and 11](#). Percentages are rounded off and therefore do not always total 100%.

Figure 1

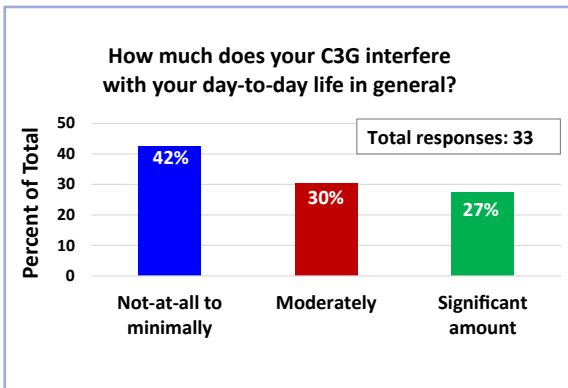


Figure 2

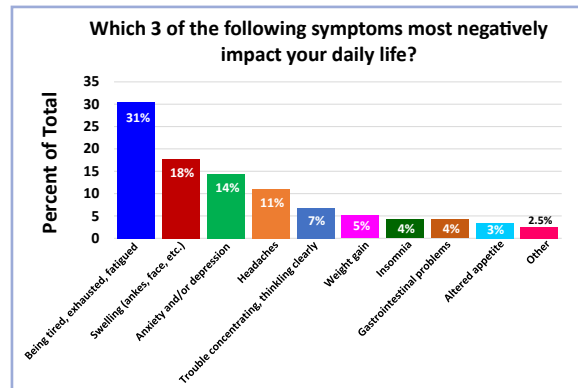


Figure 3

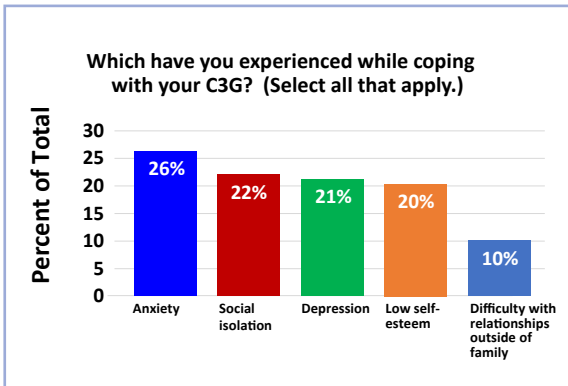


Figure 4

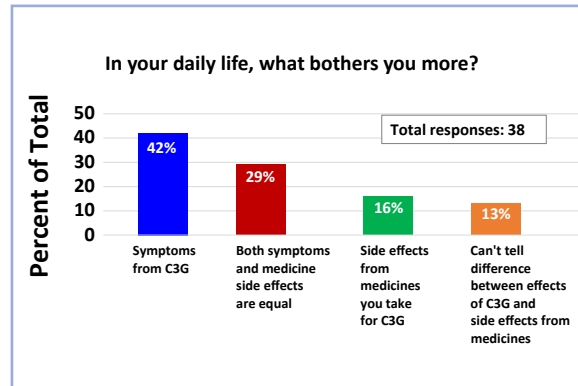


Figure 5

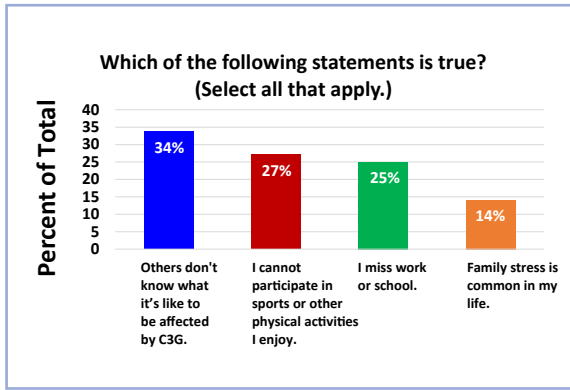


Figure 6

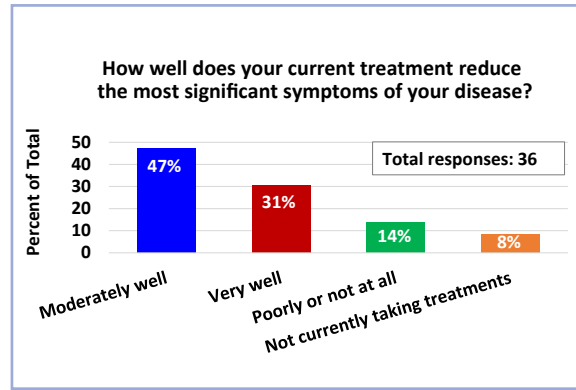


Figure 7

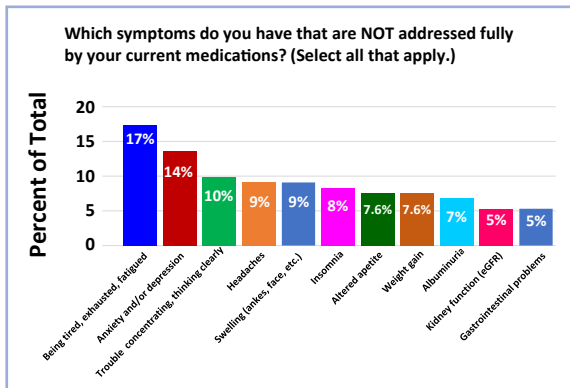


Figure 8

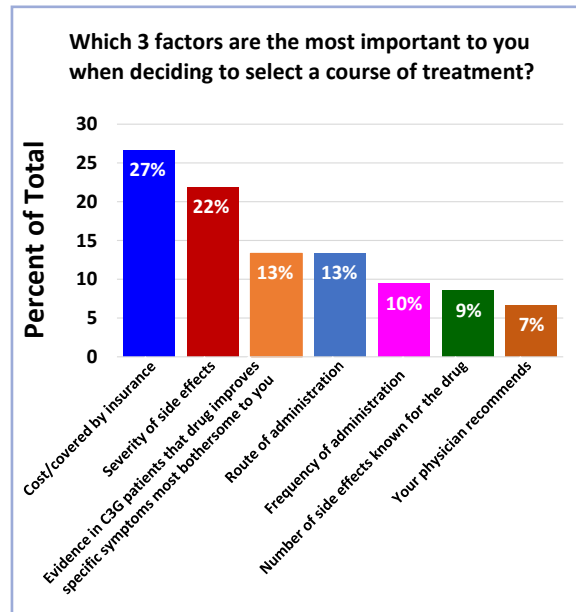


Figure 9

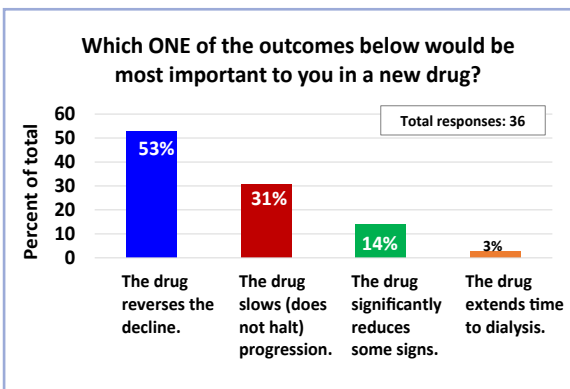


Figure 10

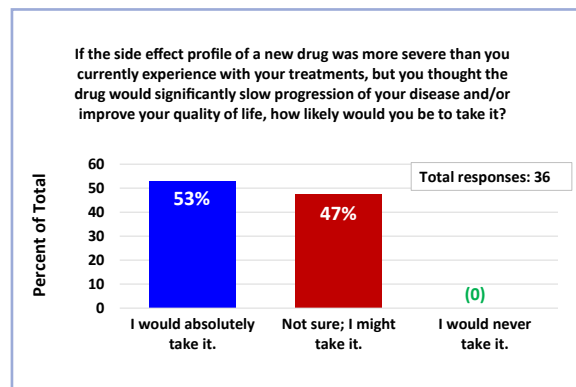
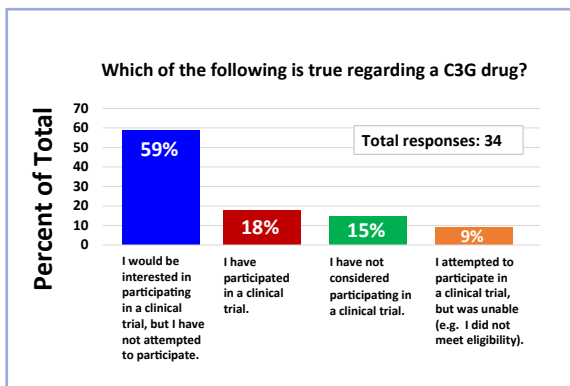


Figure 11



APPENDIX 7

Post-meeting Polling Questions

At the conclusion of the PFDD meeting, the FDA cited topics for further discussion:

- Does the requirement for kidney biopsy affect a patient's decision to enroll in a clinical trial for C3G?
- How willing are parents to enroll their children in a clinical trial for a C3G treatment?

To address these and related questions pertaining to clinical trials, NKF conducted an online survey, posting the questions below.

**PARENTS or LEGALLY RESPONSIBLE FOR A CHILD 18 YEARS OR YOUNGER:
Please answer ONLY questions 7–12.**

The following questions seek to understand factors that are important to you regarding your likelihood to enter a clinical trial for a new C3G drug.

- 1. Would you ever be willing to participate in a clinical trial for a new C3G drug?**
 - a. Yes
 - b. No
 - c. Not sure
- 2. How likely would you be to enter a trial for a new C3G drug if participation required:**
 - a. **NO** kidney biopsy?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
 - b. A **SINGLE** kidney biopsy?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.

- c. **TWO** kidney biopsies within **ONE YEAR** (at month 0 and month 12)?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- d. **THREE** kidney biopsies within **ONE YEAR** (at months 0, 6, and 12)?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- e. A single or repeated biopsy, if you could get a **MEDICINE TO REDUCE YOUR ANXIETY?**
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.

The following question explores your willingness to stop a therapy you are already taking in order to participate in a clinical trial for a new C3G drug.

3. How likely would you be to enroll in a clinical trial:

- a. If you were required to stop a drug that, in your opinion, was satisfactorily improving your **KIDNEY FUNCTION** or **SLOWING** the **PROGRESSION** of your C3G?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- b. If you were required to stop a drug that in your opinion was satisfactorily improving your **SYMPTOMS?**
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.

The following question explores how important anticipated side effects from a new C3G drug would be to you in your decision to enter a clinical trial for the drug.

Listed below are benefits (a. through f.) that you may receive from a new C3G drug, if you participated in a clinical trial. Each question asks what level of severity of side effects you would be willing to accept to obtain these benefits. Assume you would be told about the expected level of side effects and benefits before entering the trial.

Definitions:

Minimal-mild side effects: *For example: mild nausea, headaches, etc.*

Moderate side effects: *For example: frequent infections (upper respiratory, etc.), anemia, increased edema, daily mild side effects, etc.*

Severe side effects: *For example: life-threatening*

4. What level of side effects would you accept in a clinical trial for a new C3G drug to achieve the following benefits:

a. To achieve **MILD** improvement in **KIDNEY FUNCTION**, I would accept:

- Minimal-mild Moderate Severe side effects

b. To achieve **MODERATE** improvement in **KIDNEY FUNCTION** I would accept:

- Minimal-mild Moderate Severe side effects

c. To achieve **GREAT** improvement in **KIDNEY FUNCTION** I would accept:

- Minimal-mild Moderate Severe side effects

d. To achieve **MINIMAL** improvement in **SYMPTOMS** I would accept:

- Minimal-mild Moderate Severe side effects

e. To achieve **MODERATE** improvement in **SYMPTOMS**, I would accept:

- Minimal-mild Moderate Severe side effects

f. To achieve **GREAT** improvement in **SYMPTOMS**, I would accept:

- Minimal-mild Moderate Severe side effects

The following question explores the amount of travel to a trial site (for blood drawing, physical exams, etc.) you would to accept to enroll in a clinical trial for a new C3G drug. Assume: 1) no expense to you for travel, lodging, and meals during the trip to and from the trial site and 2) your choice of travel type (air, train, etc.).

5. How likely would you be to enroll in a clinical trial if travel to the trial site required up to 4 visits the FIRST MONTH, and then ONCE PER MONTH after that and the travel distance was:

- a. Less than 250 miles?
 - i. I would definitely not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- b. 250-500 miles?
 - i. I would definitely not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- c. 500-750 miles?
 - i. I would definitely not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- d. 750-1,000 miles?
 - i. I would definitely not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.

6. How important would it be to your decision to enter a clinical trial if you knew that the drug was believed to treat the underlying BIOLOGY of C3G progression?

- a. Not important to my decision; it would not affect my decision.
- b. Somewhat important; it might affect my decision.
- c. Moderately important; don't know if it would affect my decision.
- d. Very important; it would most likely affect my decision.
- e. Extremely important; it would definitely affect my decision.

QUESTIONS 7–12 ARE FOR PARENTS ONLY

The following questions seek to understand factors that are important to your decision to enter your child in a clinical trial for a new C3G drug.

7. Would you ever agree to your child participating in a clinical trial for a new C3G drug?

- a. Yes
- b. No
- c. Not sure

8. How likely would you be to enroll your child in a trial for a new C3G drug if participating required:

- a. **NO** kidney biopsy?
 - i. I would not enter my child in the trial.
 - ii. I would most likely not enter my child in the trial.
 - iii. I am uncertain if I would enter my child in the trial.
 - iv. I would likely enter my child in the trial.
 - v. I would definitely enter my child in the trial.
- b. A **SINGLE** kidney biopsy?
 - i. I would not enter my child in the trial.
 - ii. I would most likely not enter my child in the trial.
 - iii. I am uncertain if I would enter my child in the trial.
 - iv. I would likely enter my child in the trial.
 - v. I would definitely enter my child in the trial.
- c. **TWO** kidney biopsies **WITHIN 1 YEAR** (at month 0 and month 12)?
 - i. I would not enter my child in the trial.
 - ii. I would most likely not enter my child in the trial.
 - iii. I am uncertain if I would enter my child in the trial.
 - iv. I would likely enter my child in the trial.
 - v. I would definitely enter my child in the trial.
- d. **THREE** kidney biopsies **WITHIN 1 YEAR** (at months 0, 6, and 12)?
 - i. I would not enter my child in the trial.
 - ii. I would most likely not enter my child in the trial.
 - iii. I am uncertain if I would enter my child in the trial.
 - iv. I would likely enter my child in the trial .
 - v. I would definitely enter my child in the trial.

- e. A SINGLE or REPEATED biopsy, if your child could get a MEDICINE TO REDUCE his/her ANXIETY?
 - i. I would not enter my child in the trial.
 - ii. I would most likely not enter my child in the trial.
 - iii. I am uncertain if I would enter my child in the trial.
 - iv. I would likely enter my child in the trial.
 - v. I would definitely enter my child in the trial.

The following question explores your willingness to agree to stop a therapy your child is taking so he/she can participate in a clinical trial for a new C3G drug.

9. How likely would you be to enroll your child in a clinical trial:

- a. If your child was required to stop a drug that in your opinion was satisfactorily improving his/her KIDNEY FUNCTION or SLOWING the PROGRESSION of their C3G?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.
- b. If your child was required to stop a drug that in your opinion was satisfactorily improving his/her SYMPTOMS?
 - i. I would not enter the trial.
 - ii. I would most likely not enter the trial.
 - iii. I am uncertain if I would enter the trial.
 - iv. I would likely enter the trial.
 - v. I would definitely enter the trial.

The following question explores how important anticipated side effects from a new C3G drug would be to you in your decision to enter your child a clinical trial for the drug.

Listed below are benefits (a. through f.) that your child may receive from a new C3G drug if he/she participated in a clinical trial. Each question asks what level of severity of side effects you would agree that your child be exposed to toward obtaining these benefits. Assume you and your child would be told about the expected level of side effects and benefits before entering the trial.

Definitions:

Minimal-mild side effects: *For example: mild nausea, headaches, etc.*

Moderate side effects: *For example: frequent infections (upper respiratory, etc.), anemia, increased edema, daily mild side effects, etc.*

Severe side effects: *For example: life-threatening*

10. What level of side effects would you agree that your child would be exposed to in a clinical trial for a new C3G drug to achieve the following benefits:

- a. To achieve **MILD** improvement in **KIDNEY FUNCTION**, I would agree my child be exposed to:
 Minimal-mild Moderate Severe side effects
- b. To achieve **MODERATE** improvement in **KIDNEY FUNCTION**, I would agree my child be exposed to:
 Minimal-mild Moderate Severe side effects
- c. To achieve **GREAT** improvement in **KIDNEY FUNCTION**, I would agree my child be exposed to:
 Minimal-mild Moderate Severe side effects
- d. To achieve **MINIMAL** improvement in **SYMPTOMS**, I would agree my child be exposed to:
 Minimal-mild Moderate Severe side effects
- e. To achieve **MODERATE** improvement in **SYMPTOMS**, I would agree my child be exposed to:
 Minimal-mild Moderate Severe side effects
- f. To achieve **GREAT** improvement in **SYMPTOMS**, I would agree my child be exposed to:
 Minimal-mild Moderate Severe side effects

The following question explores the amount of travel to a trial site (for blood drawing, physical exams, etc.) you would accept so your child could enroll in a clinical trial for a new C3G drug. Assume: 1) No expense to you for travel, lodging, and meals during the trip to and from the trial site, and 2) Your travel choice (air, train, etc.).

11. How likely would you be to enroll your child in a clinical trial if travel to the trial site required up to 4 visits the FIRST MONTH, and then ONCE PER MONTH after that, and the distance to travel was:

- a. Less than 250 miles?
 - i. I would definitely not agree to enroll my child in the trial.

- ii. I would most likely not agree to enroll my child in the trial.
 - iii. I am uncertain if I would agree to enroll my child in the trial.
 - iv. I would likely agree to enroll my child in the trial.
 - v. I would definitely agree to enroll my child in the trial.
- b. 250-500 miles?
- i. I would definitely not agree to enroll my child in the trial.
 - ii. I would most likely not agree to enroll my child in the trial.
 - iii. I am uncertain if I would agree to enroll my child in the trial.
 - iv. I would likely agree to enroll my child in the trial.
 - v. I would definitely agree to enroll my child in the trial.
- c. 500-750 miles?
- i. I would definitely not agree to enroll my child in the trial.
 - ii. I would most likely not agree to enroll my child in the trial.
 - iii. I am uncertain if I would agree to enroll my child in the trial.
 - iv. I would likely agree to enroll my child in the trial.
 - v. I would definitely agree to enroll my child in the trial.
- d. 750-1,000 miles?
- i. I would definitely not agree to enroll my child in the trial.
 - ii. I would most likely not agree to enroll my child in the trial.
 - iii. I am uncertain if I would agree to enroll my child in the trial.
 - iv. I would likely agree to enroll my child in the trial.
 - v. I would definitely agree to enroll my child in the trial.

12. How important would it be in your decision to enroll your child in a clinical trial if you knew that the drug was believed to treat the underlying BIOLOGY of C3G progression?

- a. Not important to my decision; would not affect my decision.
- b. Somewhat important; it might affect my decision.
- c. Moderately important; don't know if it would affect my decision.
- d. Very important; it would most likely affect my decision.
- e. Extremely important; it would definitely affect my decision.

APPENDIX 8

Results from Post-meeting Polling Questions

To address issues that were either not discussed fully, or not addressed at all, during the EL-PFDD meeting, NKF conducted a post-meeting online survey ([Appendix 7](#)) to gather patient and caregiver perspectives on several aspects of clinical trials of C3G treatments. The following topics were explored regarding adults and pediatric patients:

- Willingness to enter a C3G clinical trial that required:
 - Kidney biopsy(-ies)
 - Stopping a currently administered treatment that was providing improvements in kidney function or symptoms
 - Travel to a trial site
- The level of side effects acceptable to achieve a certain degree of improvement in kidney function or symptoms
- The importance of knowing if a drug targets a causative mechanism of C3G in deciding whether to enroll in a clinical trial.

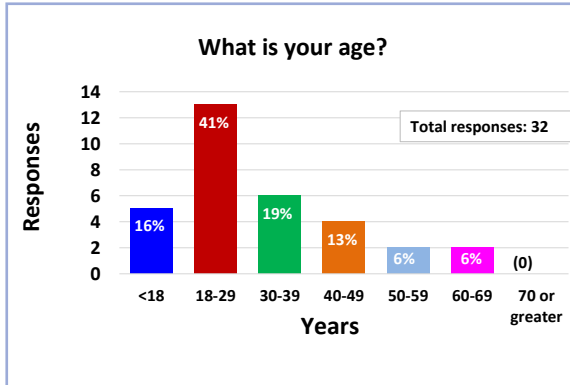
Results from these online polling questions are described below. As with polling questions posed during the EL-PFDD meeting, *the quantitative representation of responses is meant only to summarize participant responses and facilitate portrayal of the results, not to infer or predict from this small sample the preferences of the broader population of C3G patients.*

Results for Figures 1-13 are expressed as the number of responses to each available choice. The percent of respondents selecting a choice is indicated within the bars. Percentages are rounded off and therefore do not always total 100%.

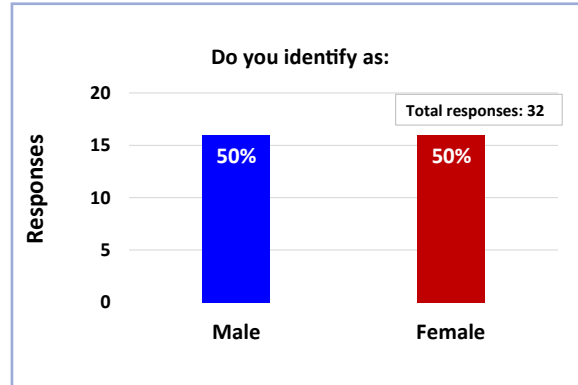
The demographic and clinical profiles of the respondents to this online survey are shown below ([Figure 1 A-F](#)). Thirty-two responses were obtained for each question from 24 patients, 7 parents, and 1 spouse/caregiver.

Figure 1. Demographic Questions

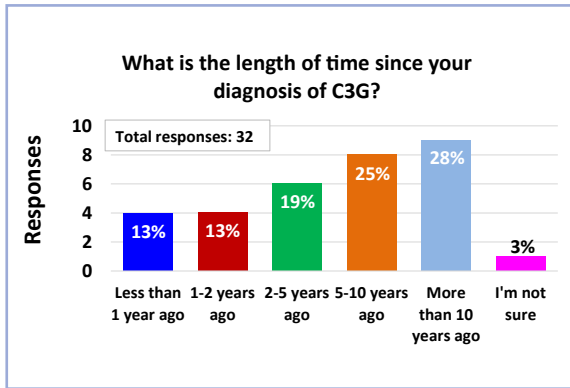
A



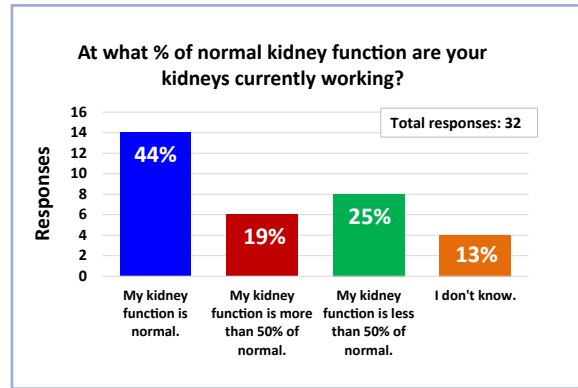
B



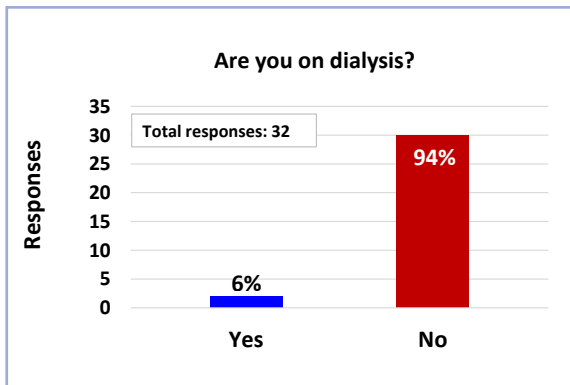
C



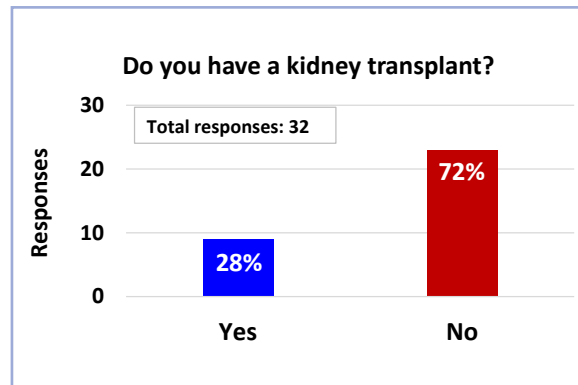
D



E



F



Results depicted in [Figure 2-7](#), are from questions posed to patients; results in [Figures 8-13](#) are from the same questions, but posed to parents for their children.

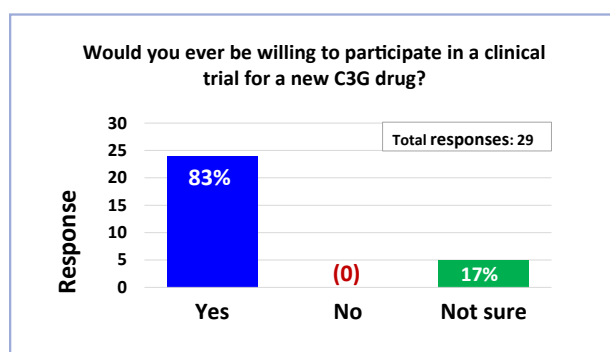
ADULTS IN CLINICAL TRIALS

Likelihood to Enroll in a Clinical Trial for C3G

Appendix 7, Question 1

Most (83%) respondents were open to participating in a clinical trial for a C3G drug; 17% were unsure; and none were not interested ([Figure 2](#)).

Figure 2



Likelihood to Enroll in a Clinical Trial that Requires Single or Multiple Kidney Biopsies, With or Without Anti-anxiety Medication

Appendix 7; Question 2

Patients were queried on the likelihood they would enroll in a C3G clinical trial that required no kidney biopsy, or from one to three biopsies. They were also asked whether the option to take anti-anxiety medication before the biopsy would influence the likelihood they would enter the trial.

Likelihood to enter a clinical trial requiring kidney biopsies

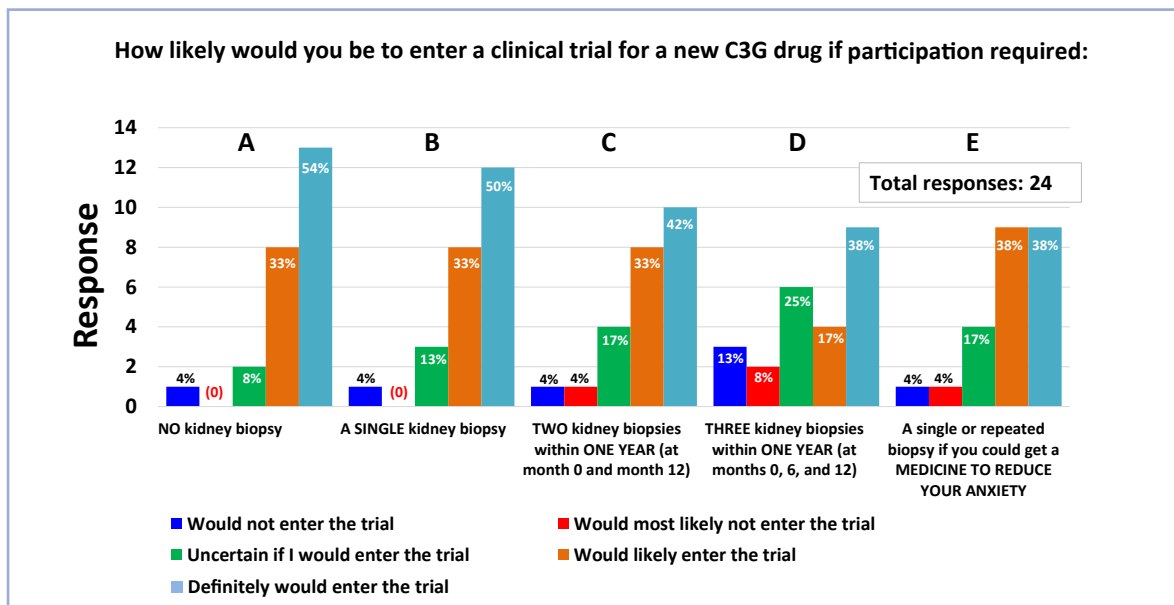
Overall, patients' responses tended toward a reduced enthusiasm to enter a trial as the number of required biopsies increased ([Figure 3-A, B, C, D; light blue bars](#)), whereas uncertainty to enter a trial increased with the number of required biopsies ([Figure 3-A, B, C, D; green bars](#)). At least half of respondents revealed a definite willingness to enter a trial with or without the single biopsy requirement. Overall, this willingness was similar between the two groups ([Figure 3-A, B; light blue bars](#)).

A lack of willingness to enter a trial requiring one or two biopsies (Figure 3-B, C; dark blue, red numeral and bars) was similar for both biopsy requirements and for a trial not requiring a biopsy (Figure 3-A). Nevertheless, within any biopsy requirement, certainty (“definitely would enter the trial”) was the most frequent response (Figure 3-A,B, C, D; light blue bars). Few patients indicated an unwillingness to enroll in a trial requiring one or two biopsies (Figure 3-B, C; dark blue and red bars and red numeral), but this reluctance increased if the trial required three biopsies (Figure 3-D dark blue and red bars).

Likelihood to enter a clinical trial requiring kidney biopsies if anti-anxiety medication was an option

A combined 76% of respondents indicated they would “likely” or “definitely” enter a clinical trial in which taking anti-anxiety medication before the biopsy was an option (Figure 3-E; orange, light blue bars). This response was similar to those for trials requiring a single (combined 83%) or two (combined 75%) biopsies without such medications (Figure 3-B, C; orange, light blue bars). However, fewer patients (17%) would “likely enter” a trial requiring three biopsies if anti-anxiety medication was not offered compared to if it was an option (38%) (Figure 3-D vs. Figure E; orange bars).

Figure 3



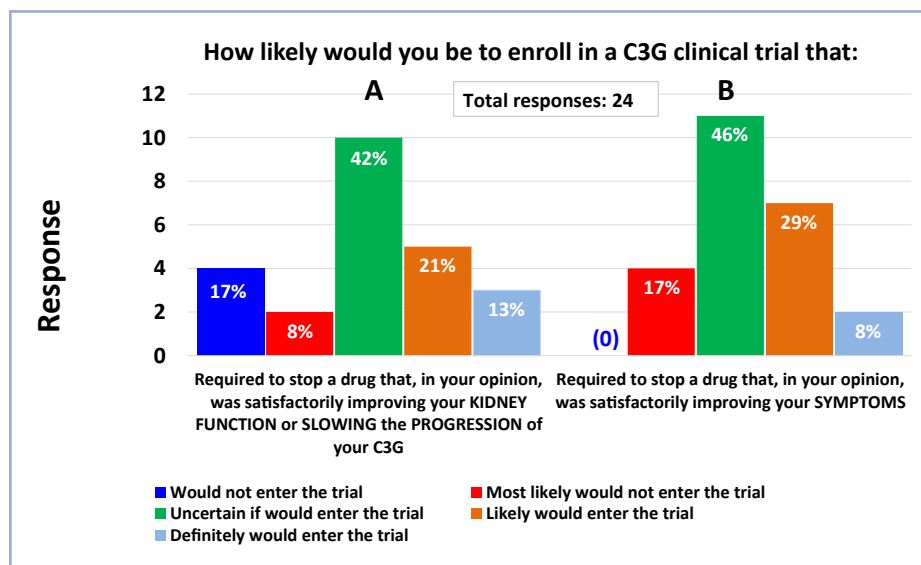
Entering a Clinical Trial that Requires Stopping Treatment that is Improving Kidney Function or C3G Symptoms

Appendix 7; Question 3

Patients were asked about the likelihood of their entering a clinical trial if they were required to stop a treatment that was providing improvement of 1) kidney function/slowing disease progression, or 2) C3G symptoms. Over one-third of responses indicated uncertainty regarding enrolling in a trial under either scenario (Figure 4-A, B; green bars). Few responses indicated certainty for enrolling in either trial (Figure 4-A, B; light blue bars).

More patients (17%) (Figure 4-A; dark blue bar) indicated unwillingness to enter a trial requiring cessation of a treatment beneficial to kidney function or reducing disease progression than did patients in whom C3G symptoms were being improved by their treatment (0%; Figure 4-B; dark blue numeral).

Figure 4



Accepting Side Effects to Achieve Improved Kidney Function or Less Symptoms

Appendix 7; Question 4

Kidney function

Patients were queried about what severity of a drug's side effects they would accept to achieve a certain degree of improvement of kidney function/slowing of disease progression or C3G symptoms. Overall, respondents reported increasing willingness to accept moderate

side effects to achieve increasing levels of improvement in kidney function/slowing of disease progression (Figure 5-A, B, C; red bars), while none-to-few patients indicated they would accept severe side effects for any degree of improvements in kidney function (Figure 5-A, B, C; green numerals/bar). A majority of respondents indicated a willingness to accept minimal to mild side effects to achieve mild or moderate improvement in kidney function (Figure 5-A, B; blue bars). Interestingly, only 39% of respondents would accept such levels of side effects to reach great improvement in kidney function (Figure 5-C; blue bar).

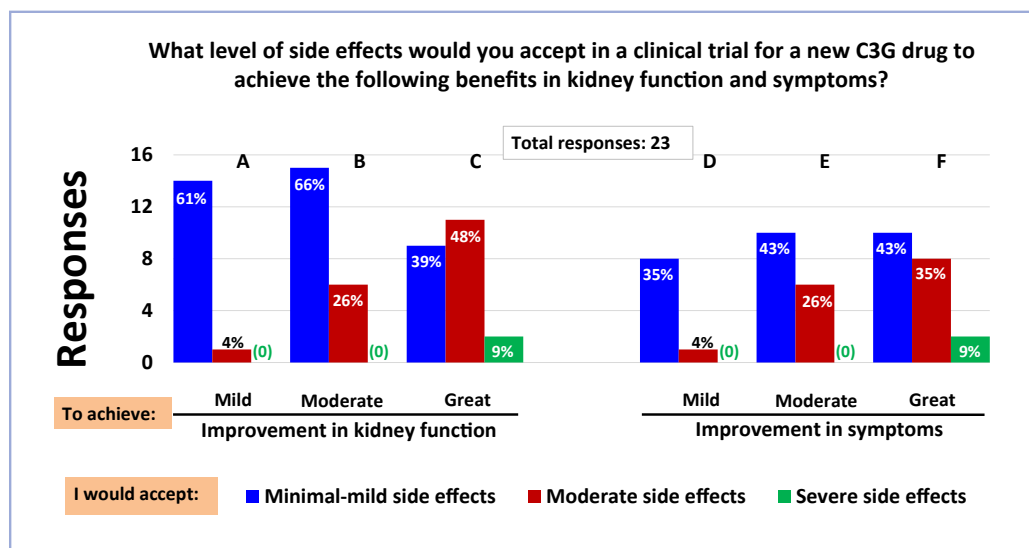
Symptoms

To gain moderate or great symptom improvement, patients indicated willingness to accept a range of severity of side effects (Figure 5-E, F).

Kidney Function vs. Symptoms

Overall, patients in this sample revealed higher acceptance of side effects toward improving kidney function than for improving C3G symptoms. For instance, more respondents reported acceptance of minimal-mild side effects to achieve mild or moderate improvements in kidney function than for comparable increases in symptom relief (Figure 5-A, B, D, E; blue bars). However, patients indicated a general lack of acceptance of severe side effects to achieve even great improvements in kidney function or symptoms (Figure 5-C, F; green bars).

Figure 5.

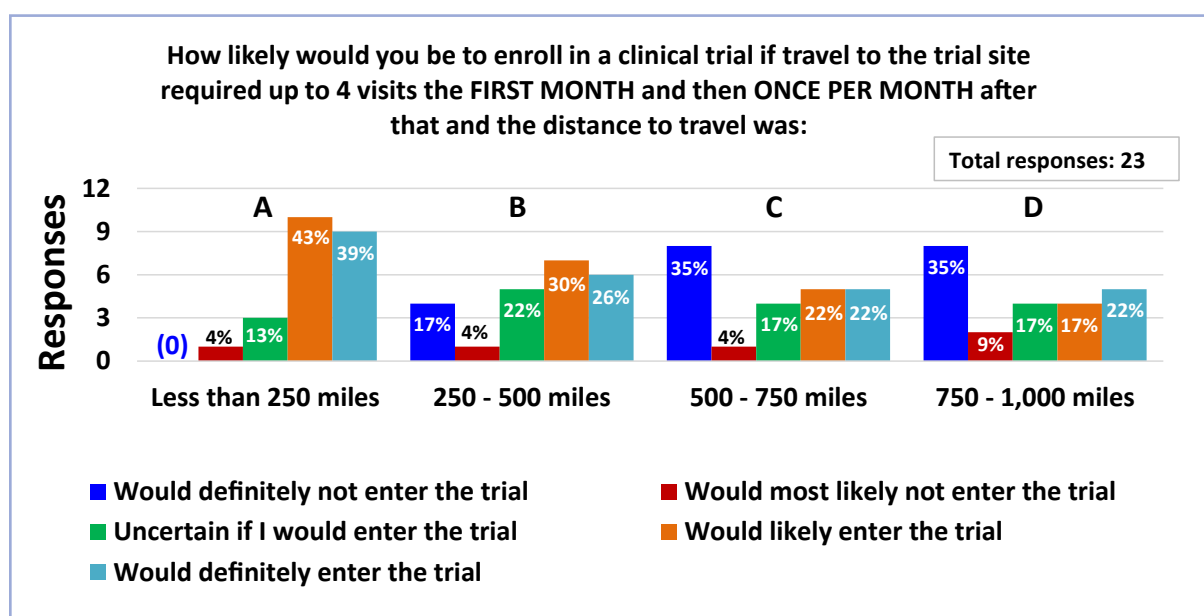


Effect of Distance to Trial Site on Decision to Enroll in Clinical Trial

Appendix 7; Question 5

Patients were queried on how their decision to enter a clinical trial might be influenced by the distance to a clinical trial site, if travel expenses were covered and they had their choice of travel type. Patients indicated a likelihood or certainty (combined: 82%) to enter a trial requiring travel less than 250 miles to a trial site (Figure 6-A; orange, light blue bars). This willingness to travel diminished with increased distance to the trial site (Figure 6-B, C, D).

Figure 6.

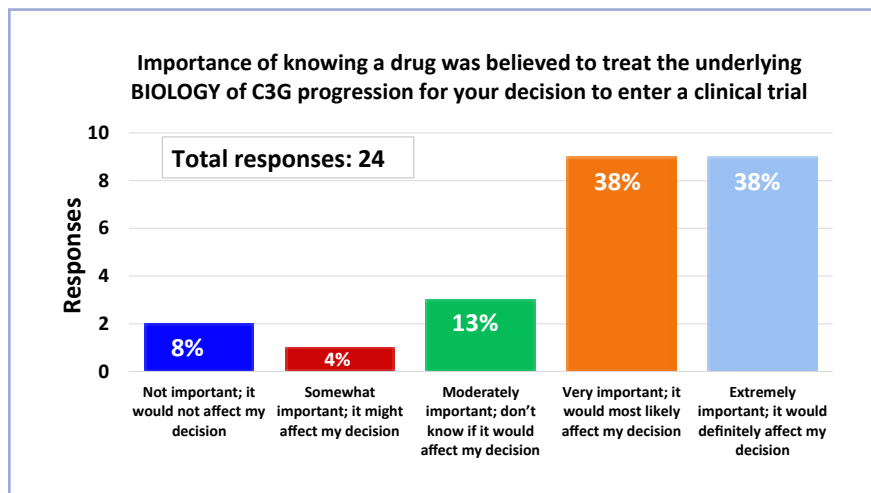


Importance that New Drug was Believed to Treat the Underlying Biology of C3G Progression on Decision to Enter a Clinical Trial

Appendix 7; Question 6

Finally, patients were asked how important it would be in their decision to enter a C3G clinical trial if they knew the test drug was believed to target the underlying biology of the disease progression. A combined 76% of respondents indicated it was very or extremely important to them and it would most likely or definitely affect their decision to enter the trial (Figure 7; orange, light blue bars).

Figure 7



CHILDREN IN CLINICAL TRIALS

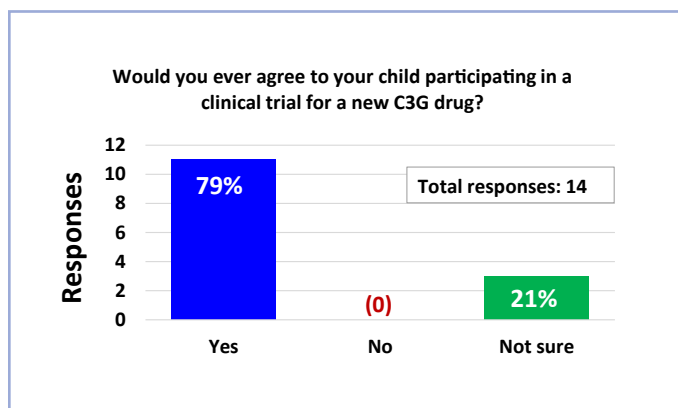
The same six questions as above were posed to parents/caregivers to assess their perspectives on enrolling their child in a clinical trial. Except for Question 7, only seven responses were received for each question, limiting the detection of major trends in responses. Nevertheless, the results may provide a basis for further study.

Agreeing to Your Child Participating in a Clinical Trial for a New C3G Drug

Appendix 7, Question 7

Nearly 80% of respondents showed an openness to enrolling their child in a clinical trial for a new C3G drug. About one-fifth were uncertain, but no respondents were closed to the idea (Figure 8; green bar, red numeral).

Figure 8



Likelihood to Enroll Your Child in a Clinical Trial that Requires Single or Multiple Biopsies, With or Without Anti-anxiety Medication

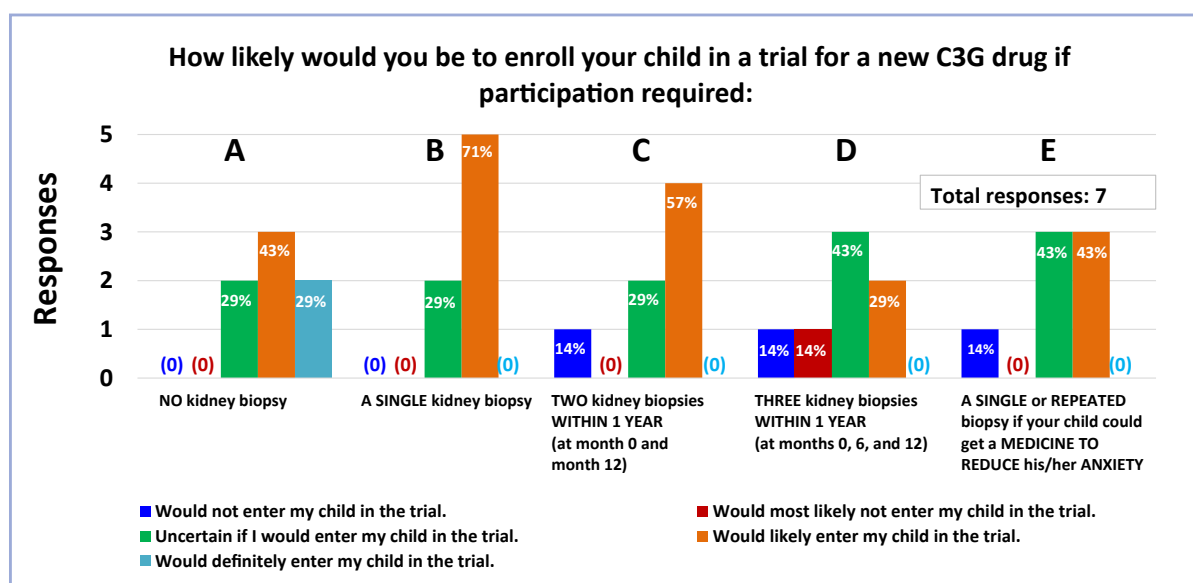
Appendix 7; Question 8

Overall, as the number of required biopsies increased, respondents were less likely to enroll their child in a trial (Figure 9-B, C, D; orange bars). No respondents indicated they would definitely enter their child in a trial requiring one or multiple biopsies (Figure 9-B, C, D; light blue numerals).

In contrast, 2/5 respondents indicated definite willingness to enroll their child in a trial not requiring a biopsy (Figure 9-A; light blue bar).

The option of taking anti-anxiety medication before the biopsy did not seem to appreciably influence parents' willingness to enroll their child in a clinical trial requiring one or multiple biopsies (Figure 9-E vs. B, C, D).

Figure 9



Entering Your Child in a Clinical Trial that Requires Stopping Treatment that is Improving Kidney Function or C3G Symptoms

Appendix 7; Question 9

Kidney function

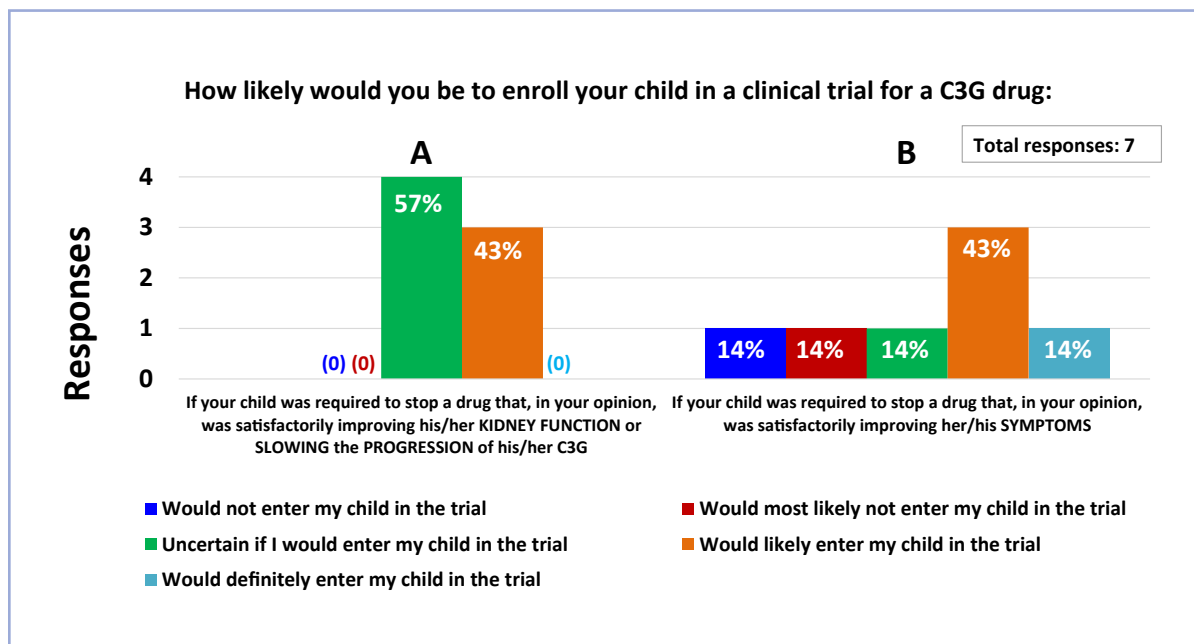
Respondents were either uncertain or likely to enroll their child in a trial that required cessation of a treatment that, in their opinion, was satisfactorily improving kidney function or slowing the progression of the child's C3G (Figure 10-A; green, orange bars). No respondents

indicated a definite unwillingness or willingness to enroll the child in such a trial (Figure 10-A; dark and light blue numerals).

Symptoms

Regarding enrolling in a trial that required stopping a treatment that was improving a child’s C3G symptoms, responses spanned the range of choices. Several (3/7) responses indicated a likelihood to enroll a child in such a trial (Figure 10-B; orange bar).

Figure 10



Accepting Side Effects for Your Child to Achieve Improved Kidney Function or Less Symptoms

Appendix 7; Question 10

Kidney function

Respondents most frequently indicated a willingness to accept minimal-mild side effects for their child from a drug that would improve kidney function to any degree (Figure 11-A, B, C; blue bars) and moderate side effects for a drug that would moderately or greatly improve kidney function (Figure 11-B, C; red bars).

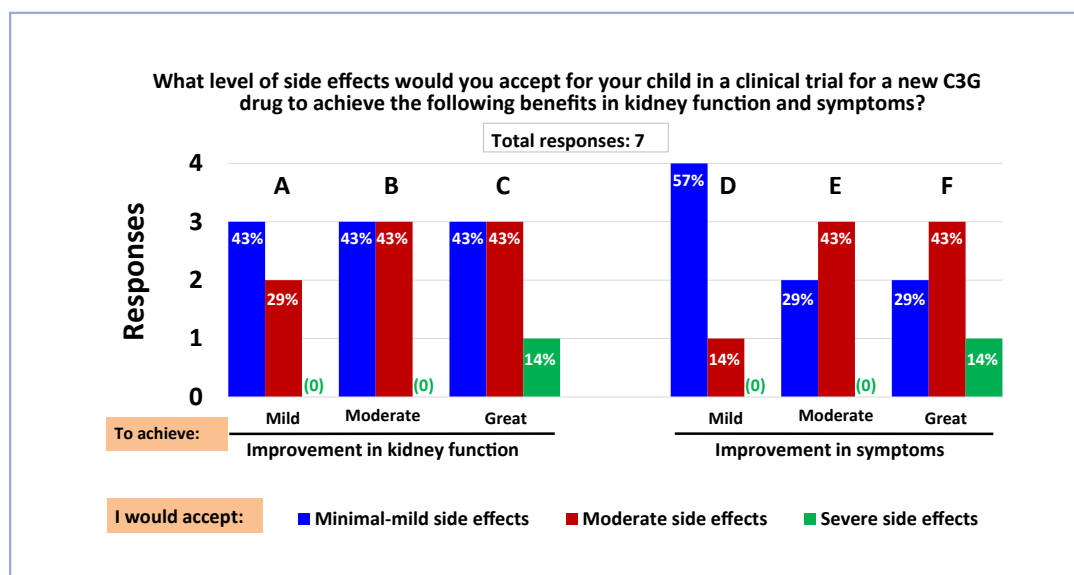
One person indicated acceptance of severe side effects to achieve great improvement in kidney function for the child (Figure 11-C; green bar).

Symptoms

Four out of seven respondents indicated acceptance of mild side effects to achieve mild symptom improvement (Figure 11-D; blue bar). However, no respondents would accept severe side effects for their child to achieve mild or moderate improvements in C3G symptoms (Figure 11-D, E, F; green numeral).

One person indicated acceptance of severe side effects to achieve great improvement in symptom relief for the child (Figure 11-F; green bar).

Figure 11

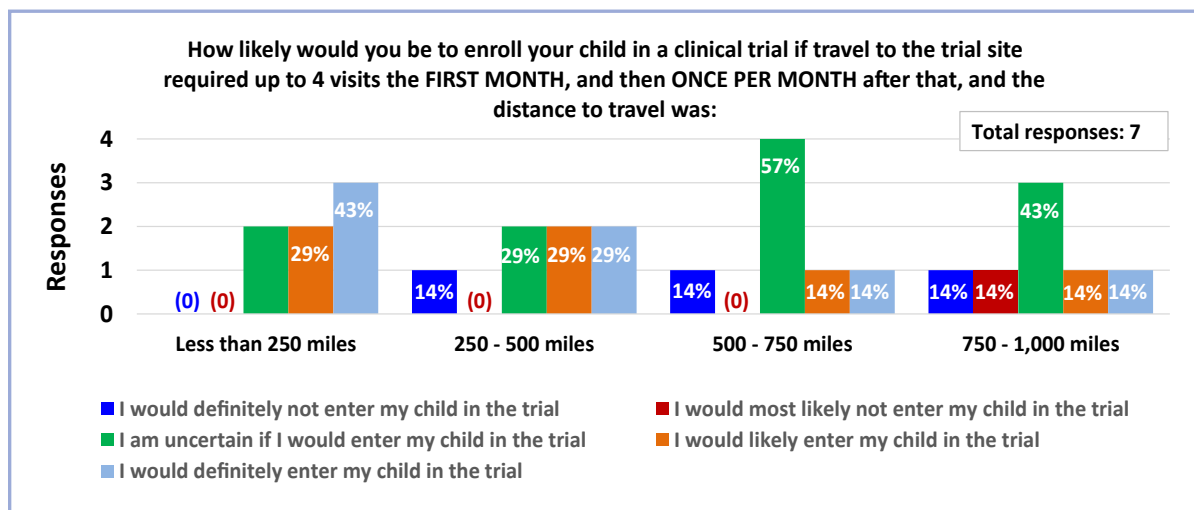


Effect of Travel Distance to Trial Site on Decision to Enroll Your Child in a Clinical Trial

Appendix 7, Question 11

Overall, increased travel distances to a clinical trial seemed to reduce the likelihood of respondents to enroll a child in a C3G trial, even if expenses were covered. Many (3/7) respondents seemed willing to enroll a child in a trial requiring travel less than 250 miles to a trial site. Beyond that distance, likelihood generally diminished (Figure 12).

Figure 12

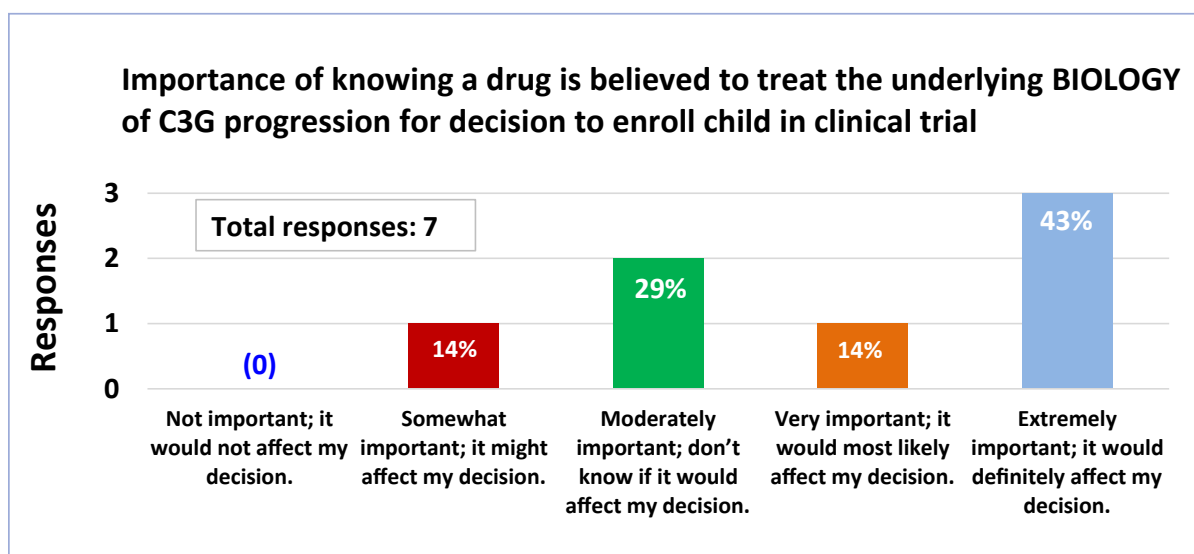


Importance that a New Drug is Believed to Treat the Biological Cause of C3G Progression on Decision to Enroll Your Child in a Clinical Trial

Appendix 7; Question 12

Knowing that a drug is believed to target the underlying biology of C3G progression was very or extremely important to most (3/7) respondents in deciding to enroll their child in a clinical trial for a new C3G drug (Figure 13).

Figure 13



APPENDIX 9

Incorporating Patient Input into a Benefit-Risk Assessment Framework for C3G

Over the past several years, the FDA has developed an enhanced, structured approach to benefit-risk assessment in regulatory decision-making for human drugs and biologics. The Benefit-Risk Assessment Framework ([Appendix 9, Table 1](#)) involves assessing five key decision factors: *Analysis of Condition*, *Current Treatment Options*, *Benefit*, *Risk*, and *Risk Management*. When completed for a particular product, the Framework provides a succinct summary of each decision factor and explains FDA's rationale for its regulatory decision. In the absence of a specific product, this table analyzes the condition and current treatment options.

In the Framework Table ([Appendix 9, Table 1](#)), the *Analysis of Condition* and *Current Treatment Options* rows summarize and assess the severity of the condition and therapies available to treat the condition. The assessment provides an important context for drug regulatory decision making, including valuable 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 patient representatives through the C3G EL-PFDD meeting will 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 C3G ([Appendix 9, Table 1](#)) draws from patient contributions at the C3G EL-PFDD meeting reported herein. This sample Framework table contains the type of information that may be anticipated to be included in a completed Framework for a drug under review for C3G.

Table 9

<p style="writing-mode: vertical-rl; transform: rotate(180deg);">DIMENSION FACTOR</p>		Evidence and Uncertainties	Conclusions and Reasons
		<p style="writing-mode: vertical-rl; transform: rotate(180deg);">Analysis of Condition</p>	<ul style="list-style-type: none"> • C3 glomerulopathy (C3G) is a rare, chronic disease for which curative treatment is not available. C3G is caused by dysregulation of the complement system, leading to amplified production of C3 and its fragments, and their deposition in the glomerulus, causing glomerular damage and eventual progression to end-stage renal disease (ESRD). • C3G may be caused by genetic mutations in, or development of antibodies to, one of a number of complement pathway proteins or regulators, or a combination of the above. The C3G population is also heterogeneous in terms of disease progression and symptoms. • C3G affects people of all ages, and prevalence is estimated at 2-3 per 1,000,000 people. • The timeline of disease progression is variable, but the average time of progression to ESRD is 10 years from the time of diagnosis. • Relapse following kidney transplant is common. • Some patients in early stages of the disease are asymptomatic. However, as the disease progresses, symptoms develop, including susceptibility to infection, fatigue, severe edema, gout, high blood pressure, and severe anxiety and depression. • Through edema and fatigue, C3G can lead to debilitating loss of physical ability, limiting a patient’s capacity to fully participate in physical activities, including work and basic family life.
<p style="writing-mode: vertical-rl; transform: rotate(180deg);">Current Treatment Options</p>	<ul style="list-style-type: none"> • For patients in the U.S. living with C3G, there are no FDA-approved treatments . • Treatments are nonspecific and may include blood pressure medications, prednisone, immunosuppressive therapy, mycophenolate mofetil, or eculizumab (to which patients have limited access). • To manage symptoms, patients may take medications such as allopurinol for gout or diuretics to manage edema, as well as additional drugs to manage nutritional deficiencies, side effects of medications, and susceptibility to infection. • Though many patients follow a strict renal diet, this does not slow progression. • Though kidney transplantation may prolong survival and improve quality of life, C3G has a high rate of recurrence. • Many patients with ESRD rely on dialysis. 	<ul style="list-style-type: none"> • Few of the available treatments effectively slow disease progression, and efficacy varies from patient to patient, as does the ability of medicines to treat significant side effects, especially edema and fatigue. Each medication has side effects. • Thus, there is a continued need for effective and available treatment options for patients to maintain function of both native and transplanted kidneys, as well as to control symptoms so that daily functioning and quality of life can be maintained. 	