amyloidosis research consortium

The Voice of the Patient

June 2016

The Voice of the Patient Report

Summary report resulting from an Externally-led Patient-Focused Drug Development meeting, a parallel effort to the U.S. Food and Drug Administration's (FDA's)

Patient-Focused Drug Development Initiative

Amyloidosis

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Hosted by:

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Center for Drug Evaluation and Research (CDER)
U.S. Food and Drug Administration (FDA)

This report represents the first summary report composed by a patient advocacy organization as a result of an Externally-led Patient-Focused Drug Development meeting, a parallel effort to the FDA's Patient Focused Drug Development Initiative. This report reflects the Amyloidosis Research Consortium's account of the perspectives of patients and caregivers that participated in the public meeting.

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Introduction

On November 16, 2015, at the suggestion Dr. Janet Woodcock, Director, Center for Drug Evaluation and Research (CDER), U.S. Food and Drug Administration (FDA), the Amyloidosis Research Consortium (ARC) hosted an Externally-led Patient-Focused Drug Development meeting to share with the Agency and other stakeholders (e.g., industry) the perspectives of people living with systemic amyloidosis, its impact on their daily lives, and their perspectives on approaches to treating amyloidosis. The meeting was conducted in accordance with a parallel effort to FDA's Patient-Focused Drug Development initiative, an FDA commitment under the fifth authorization of the Prescription Drug User Fee Act (PDUFA V) to more systemically gather patients' perspectives on their condition and available therapies to treat their condition.

More information on the FDA Patient-Focused Drug Development meetings can be found at http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm347317.htm.

Overview of amyloidosis disease and its treatment

Amyloidosis is a disorder caused by proteins that possess abnormal conformational features, leading them to aggregate and deposit in tissues in the form of amyloid fibrils. Systemic amyloidosis is a disease that can damage the heart, kidneys, liver, soft tissue, and nervous system, resulting in multi-organ failure and death. There are several types of systemic amyloidosis. The most prevalent systemic amyloidoses are amyloid light chain (AL) amyloidosis, caused by the deposition of the immunoglobulin light chain, and transthyretin (ATTR) amyloidosis, caused by the accumulation of transthyretin.[1]

AL amyloidosis

The estimated incidence of AL amyloidosis is 8.9 to 14 persons per million per year in the United States. Of these, an estimated 10% to 15% of cases occur in association with multiple myeloma. Clinical presentation of AL amyloidosis can vary widely and depends on the extent and number of organs affected. Symptoms at onset frequently occur in many common diseases and are relatively general (e.g., weight loss, fatigue), and consequently accurate and early diagnosis is challenging. As the disease progresses, symptoms reflect organ dysfunction due to amyloid. The heart and kidneys are most often involved (in ~70% of patients for either or both), but the gastrointestinal and nervous systems and the liver are affected in ~20% of patients. The 1-year mortality rate is approximately 30% and is primarily due to sudden cardiac death.

There are no FDA approved therapies for treating AL amyloidosis. Current treatments involve supportive care for organ dysfunction, and off-label use of multiple myeloma therapies, which target plasma cells to stem the production of abnormal light chain. Due to underlying organ dysfunction, plasma cell–directed treatments can be associated with significant adverse events and impairments in quality of life. Many patients often die before experiencing benefit from these therapies, and notably, these treatments do not directly address existing organ deposits. There is a substantial need for well-tolerated and effective therapies. Current treatments in development include novel plasma cell–directed therapies and agents that can remove light chain amyloid from tissues or inhibit fibril formation.

[1] Only AL and ATTR amyloidosis were covered in this meeting because these are the most prevalent types of systemic amyloidosis and the majority of patients have substantial impairments in quality of life and a paucity of treatment options.

ATTR amyloidosis

ATTR amyloidosis can result from the accumulation of mutant (ATTRmt) or wildtype (ATTRwt) transthyretin (TTR) protein. ATTRmt amyloidosis is an inherited, progressively debilitating, often fatal, disease caused by mutations in the TTR gene. Val30Met is the most common TTR mutation. Additionally, approximately 3.9% of the African American population carry the Val122Ile genetic mutation for ATTRmt amyloidosis, though not all will develop the disease (incomplete penetrance). ATTRwt amyloidosis affects mostly male patients in the sixth and seventh decades of life, and though the risk for ATTRwt amyloidosis increases with age, its true incidence is unknown. The overall survival associated with ATTR amyloidosis is 5 to 11 years, with reduced survival associated with cardiac involvement.

TTR protein is produced primarily in the liver and functions as a carrier for retinol-binding protein, which transports vitamin A around the body. In ATTRmt amyloidosis, TTR aggregation predominantly affects the heart and peripheral nerves, resulting in heart failure and peripheral neuropathy. ATTRwt amyloidosis is associated primarily with heart failure.

There are no FDA-approved drug therapies for treating ATTR amyloidosis. Patients with ATTRmt amyloidosis are sometimes treated with a liver transplant, as this can remove the majority of abnormal TTR protein from the blood. Patients with either ATTRmt or ATTRwt amyloidosis are offered supportive care to attenuate the symptoms of organ dysfunction. Current treatments in development seek to attenuate the production of transthyretin, stabilize a nonaggregation-prone conformation of the protein, or remove ATTR deposits from tissue. The nonsteroidal anti-inflammatory drug diflunisal may have some effect at slowing progression of symptoms.

All patients, caregivers, and health care professionals stressed the compelling need to increase the awareness of systemic amyloidoses through the education of the medical community, which would include providing tools to facilitate early and accurate diagnosis and appropriate treatment.

Meeting overview

Twelve members of the FDA attended the meeting to hear directly from the patients, caretakers, and other patient representatives about patients' experiences with amyloidosis and the available treatments. FDA attendees included Dr. Woodcock together with representatives from the Division of Hematology Products, Division of Cardiovascular and Renal Products, Division Neurology Products, the Rare Diseases Program, and the Office of Orphan Products Development. The meeting also included presentations from clinical experts to provide a wider context on the mechanisms of disease and the experience of patients.

After an initial introduction, the day was divided into a morning session on AL amyloidosis and an afternoon session on ATTR amyloidosis. Both discussion sessions followed a similar program and were facilitated by leading amyloidosis experts. Questions focused on: (a) disease symptoms and daily impact that mattered the most to patients, (b) patient perspectives on current approaches to treatment, and (c) clinical trial participation. After the meeting, attendees were given a set of follow-up questions on these same topics to collect further information on specific areas that they deemed important but that were not fully discussed during the day.

Approximately 69 patients (46 patients with AL amyloidosis and 23 with ATTR amyloidosis) and 56 caregivers or family members (43 AL and 13 ATTR caregivers) attended the meeting; a number of patient advocates

were also present. Using the audience response system (ARS), a total of 88 patients at the meeting answered questions. Patients in attendance represented a broad spectrum of experiences across the disease, as seen in answers to the ARS questions. The majority of patients were between 51 and 70 years, but the age range of patients was from late 20s to older than 70 years. Disease was in remission in 47% of patients and progressing in 37% of patients.

To supplement the input gathered at the meeting, the ARC invited patients and patient representatives, many of whom were unable to attend the meeting to submit their experiences. Thirty-seven patient stories were submitted (see appendix for survey topics and questions and story summaries).

Additional information on the meeting, including the archived webcast, is available on the ARC website: http://www.arci.org/advocacy

Report overview

The report has been divided into 2 sections focusing on AL and ATTR amyloidosis and includes an appendix, as mentioned earlier.

This report summarizes the input provided by the patients, caregivers, and health care professionals during the meeting. To the extent possible, the terms used in this report to describe specific symptoms and treatment experiences reflect the words used by in-person participants and language used in submitted reports. There may be symptoms, impacts, treatments, or other aspects of amyloidosis that are not included in the report. Comments made during the meeting and in submitted reports covered a range of other important topics, which often included the long journey to a correct diagnosis.

AL amyloidosis

Key themes in AL amyloidosis

Patients spoke to a wide variety of experiences that clearly reflect the heterogeneous nature of the disease, varied therapeutic approaches, treatment responses and the impact on their quality of life. A number of key themes emerged throughout the day:

- Patients find it difficult to distinguish between symptoms of the disease and side effects of the treatments. Many patients shared similar experiences, reporting that a number of their most debilitating daily symptoms were primarily a result of treatment rather than the underlying symptoms of their disease.

- Patients described a significant burden of AL amyloidosis, or its treatment, on their day-to-day functioning, including impact on their ability to perform activities at work and at home and on their mental, emotional, and physical health. Many of these ill-effects, or their sequelae (e.g., loss of professional status) persisted long after treatment had been completed.

- Because of the rarity of the condition, patients experience significant burden both in finding qualified and experienced local providers and in dealing with the complex financial and organizational burden of medical bills and insurance claims.

- Current off-label treatments are not well tolerated and some patients are ineligible for these treatments due to multi-organ dysfunction. Even with treatment responses, the majority of patients experience persistent organ dysfunction and treatment-related side effects, and consequently concern about their future.

AL Amyloidosis Topic 1: Most significant symptoms experienced and their impact on daily life

The first discussion topic focused on patients' experiences with their AL amyloidosis symptoms and the impact this has on their daily lives.

The session on AL amyloidosis started with a panel presentation from 2 patients and 1 family member, which included:

- Panelist 1—A 55-year-old female patient who had been through multiple cycles of chemotherapy. She discussed the hardships of both the disease and the chemotherapy treatment.
- Panelist 2—A male patient with young children who had undergone chemotherapy and had an autologous stem cell transplant.
- Panelist 3—A teenage daughter of a patient who is currently receiving dialysis.

The panelists' stories provided a vivid description of living with AL amyloidosis. They explained the hardships and extended delays endured in the process of diagnosis, the adversities resulting from both treatment and symptoms, and the emotional impact of diagnosis, which often included experiences of fear, anxiety, and depression. During a facilitated discussion after the panel, the experience vocalized by numerous patients and caregivers echoed those of the panelists. The most significant AL amyloidosis symptoms, of the substantial array of symptoms experienced by patients, are expanded upon here.

Most significant symptoms of AL amyloidosis

Patients and caregivers described the substantial array of symptoms experienced by patients with AL amyloidosis.

Weakness and fatigue

"I am shackled by… a disease that leaves me fatigued and unable to do so many of the things that I enjoy."

Patients verbalized the many symptoms that have a significant negative impact on their daily activities. Fatigue was the most prominent symptom on this list. During the meeting many patients described suffering from extreme weakness and fatigue that prevented their participation in daily activities. One patient stated, "I was an athlete before I was diagnosed. Now I can't even walk for exercise." Another patient described how at the age of 32, he was unable to pick up his 1-year-old child. Disease-related fatigue is often exacerbated by treatment-related fatigue. Treatment was noted as an important factor in fatigue and weakness, with one patient stating, "I was so weak that I could not sit up in bed."

Weight loss and muscle wasting

"I left the hospital at 135 pounds, which is about 80 pounds under my healthy weight."

Weight loss and muscle wasting can result from many facets of the disease and its treatment. Patients with AL amyloidosis may experience macroglossia (enlarged tongue) as a result of amyloid deposition in their tongues, which can affect eating. In addition, early satiety is a common symptom experienced by many patients both before and after treatment, potentially influenced by amyloid deposition in the gastrointestinal tract. Furthermore, loss of appetite and nausea are very common side effects of chemotherapy treatment. One patient described his initial experience by stating, "In the first month of feeling sick constantly, I lost about 20 pounds." Many participants echoed this point, with weight loss of as much as 60 pounds in one patient. A participant explained, "I had trouble swallowing and I was full almost as soon as I started eating, and in about another month I had lost another 20 pounds." Another stated, "I have terrible muscle wasting and weakness and weight loss."

Neuropathy

"Each step I take reminds me of this disease because of the pain of neuropathy."

Neuropathy, both peripheral and autonomic, is a significant symptom of amyloidosis. Often a part of patients' initial clinical presentation, neuropathy can manifest in cardiac arrhythmias and orthostatic hypotension, gastrointestinal problems including intractable diarrhea, carpal tunnel syndrome symptoms, and feet/leg neuropathic pain. One patient described, "I have weakness from my neck to my feet along with pain and paresthesia." Another patient stated, "I have neuropathy in my lower feet, my legs, and in my hand." Many patients complained of carpal tunnel syndrome; according to one patient, "I had some pain in my hand that I thought came from being an IT manager; I thought I had carpal tunnel. I was wrong. *[It was from amyloidosis.]*" Neuropathy can be exacerbated by chemotherapy, as described by a patient for whom chemotherapy produced "severe neuropathy with a tremendous amount of pain."

In addition to the debilitating pain associated with peripheral neuropathy, autonomic neuropathy also caused a significant disease burden. As one patient described, "I would get up [from sitting or lying down], feeling lightheaded." Another stated, "I was in the ICU for about a month because of hypotension." Still others highlighted common problems associated with autonomic gastrointestinal issues: "GI problems caused worrisome bouts of occasional constipation and diarrhea." Another explained, "I suffer from constant diarrhea, which is pretty tricky since I'm an elementary school teacher."

Cognitive impairment

"My brain is fuzzy."

Many participants described the negative impact of chemotherapy on their cognition, calling it "chemo brain." One participant said, "Chemo brain is quite debilitating." Another patient said he couldn't quantify his cognitive impairment, but he knew he was not where he used to be. Another stated: "I have definitely lost IQ points since my stem cell transplant." According to another participant, "I play solitaire now, not as a game, but as brain training… and it is impossible to return to work." Another patient analogized that mentally she felt as if she were "sitting in the car and stepping on the gas, and it just doesn't go." A number of patients described their unseen cognitive challenges, with one patient stating, "Physically I look normal, but I am not. It is this impact on the quality of life that is important."

Psychological impact

"I was recently diagnosed with post-traumatic stress syndrome because of all I went through getting diagnosed…"

Patients and family members talked about the psychological impact and "constant emotional stress" resulting from diagnosis. One patient said, regarding the experience after receiving treatment, "I'm physically doing

well 15 months after my transplant… but what's not obvious to people is they think I'm back to normal, and I'm not. I struggle with a lot of the psychological issues**…** like depression and anxiety." A common theme, highlighted by a caregiver, is that for both her and her husband, "the psychological and emotional impact never goes away." Still another patient explained, "My dream of a world cruise has been replaced by a will to survive."

Heart/Cardiac involvement

"I gained 70 pounds of fluid while I was in the hospital. My abdominal girth was 45 inches."

Impaired heart function caused by amyloid deposition can lead to symptoms that include congestive heart failure, severe edema, and shortness of breath. Patients shared the impact cardiac damage has had on their lives: "Sadly, I can't run anymore" and "I can't play any longer because my heart can't handle it." Patients shared how cardiac impairment has further limited treatment options: "Because of my cardiac involvement, it was determined I was not healthy enough to withstand a stem cell transplant." Other participants echoed this situation: "I'm not eligible for a heart transplant or a kidney transplant because of the multiple organ involvement" and "I have heart and kidney damage from the disease. The atrial flutter is likely the cause of my stroke."

Impact of AL amyloidosis on daily life

Patients and caregivers described in vivid detail the disease burden of both AL amyloidosis and its treatment.

Daily activities

"Managing amyloidosis takes a significant amount of time in my daily life."

Patients stated that AL amyloidosis had a negative impact on their day-to-day activities, including their ability to care for themselves and family members. One patient described, "I miss out on a lot of what's going on in my life." Many described ordinary activities in which they could no longer participate. One patient commented on "not being able to shower." During the discussion, a patient explained that for her "physically it's a struggle to do anything, just to pick up something from the floor or just to walk." Others commented "I sleep late now because of the medicine I take [to alleviate] foot pain" and, "I drive only short distances by myself because my hands go to sleep."

For patients with AL amyloidosis who were formerly athletic, their previous mode of exercise has been altered or ended as a result of the disease: "I cannot even walk for exercise" and "I discovered that I physically could no longer run."

Burden to family

"I required around-the-clock care. Someone had to lift me to a sitting position to eat. I had to be lifted out of the bed to use a bedside commode… Getting me to the shower and bathed felt like a marathon."

Several patients shared their challenges with family and social situations as a result of their disease and treatment, as well as daily activities that included their needing help showering and support when walking. One patient explained, "I often miss family gatherings because I'm either just too tired or I'm too sick." Another patient noted, "I can't go on strenuous family hikes or roughhouse with my kids like I used to." Some caregivers commented on the financial burden to family, "My mom is an awesome caretaker. She had to return to a full-time job at a hospital in order to get better health care benefits to pay the medical bills that just keep on coming." Another caretaker commented, "My husband abdicated his health choices to me, a major responsibility."

Doctor's appointments, tests, and treatment

"I have to travel 11,000 miles each 28 days for treatment."

Patients often choose to travel a substantial distance to be treated at one of a limited number of amyloidosis specialty centers and commonly require a multitude of office visits. One patient captured the experience of many when she stated, "In the year since my diagnosis, I have had 122 doctor appointments and numerous tests and procedures." Others highlighted their extensive travel to find treatment, "my physicians in Oregon were unfamiliar with treating amyloidosis…so my husband and I went to Rochester [Minnesota] for treatment at the Mayo Clinic," and from another patient, "I have traveled monthly to Boston for over 1 year now to receive what I consider lifesaving treatment."

Work ability

"I can no longer work."

Physical and psychological impairments can also lead to an inability to work. Some participants described the impact of disease on their livelihood and their self-identification as family providers, "I was forced to retire because of amyloidosis," and "I can no longer work because of immunosuppression… and poor balance and weakness." One participant, who remained in the workforce, tearfully highlighted the pain of professional demotion, "I was an executive for a large company, led a large team, and was accustomed to making executive plans and decisions. The effects of 'chemo brain' from a stem cell transplant have forced me to take a smaller and less-demanding position."

Financial and insurance Issues

"One of the hardest aspects of this disease is constant uncertainly of treatment-related finances and insurance issues. This is so emotionally taxing; it is like having another disease."

Both patient and family members commented on the complex, often-overwhelming nature of their interactions with health care insurers. One patient explained his experience: "We go through multiple [insurance] appeals so that I can be treated at a center of excellence and not by an HMO that has never treated an amyloidosis patient before"; another patient said, "I wonder if the co-payments will be affordable on my teacher's salary." Another pointed out, "I can no longer work…so no work means no insurance… something that we now have to buy at a very dear price. I cashed in some retirement accounts to pay for the treatment."

Living with uncertainty

"It feels like a time bomb…I don't know when it's coming back."

The emotional stress of living with the uncertainty of a life-threatening illness and the fear of recurrence was a common theme. Patients stated, "I'm plagued by constant questions and an uncertainty that I never had before," and "My kids and husband have to live with the knowledge that their mom has a terminal disease. Their mom is going to die, and they know this."

AL Amyloidosis Topic 2: Patient perspective on treatment

The second morning discussion focused on treatment for AL amyloidosis and patients' perspectives on these therapies. There were a wide variety of experiences among patient-attendees. According to the ARS polls during the meeting, participants experienced: organ involvement including the kidney (35/44 participants), heart (32/44) or nervous system (25/44). In response to the polling question, "Have you had any problems tolerating treatment?" more than one-third of patients indicated: "I have reduced dosage for at least 1 medication or treatment." The second-highest–ranked answer was, "I have discontinued at least 1

medication or treatment." The lowest-voted answer was, "I have had no problems." These polling questions echoed what was stated throughout the treatment portion of our meeting.

A panel of 3 patients presented their perspectives, after which there was a discussion with other participants. On the panel were:

- Panelist 1—A 64-year-old female patient who had undergone a stem cell transplant. She had multiple organ involvement and had suffered a disease-related stroke.
- Panelist 2—A female patient who had undergone a stem cell transplant and was currently participating in a clinical trial.
- Panelist 3—A caregiver whose husband had AL amyloidosis. She shared her experience as a caregiver and her husband's experience with numerous treatment protocols and clinical trials.

ARS respondents reported that all patients had chemotherapy treatment. Additionally, 38/44 respondents had a stem cell transplant; however, this is not representative of the AL amyloidosis patient community as a whole, where less than 20% are eligible for stem cell transplant. Although patients were appreciative that there were a number of off-label therapeutic options, many patients expressed their frustration at the severe side effects that they experienced from these treatments, many of which were long lasting. Problems tolerating treatment, necessitating reduced dosage of 1 medication or treatment, were reported by 25/44 respondents, and 22/44 respondents discontinued at least 1 treatment because of complications.

Experiences with current treatments for AL amyloidosis

Patients and caregivers described their experiences with both the benefits and risks of current treatment options for AL amyloidosis.

Chemotherapy

"My biggest worry is managing the side effects of the disease and the chemo because often I can't tell the difference."

Chemotherapy was the most-mentioned treatment and inspired substantial discussion regarding side effects. Constant diarrhea and difficulty sleeping while taking steroids were mentioned by a number of participants. Many participants described not being able to differentiate AL amyloidosis symptoms from treatment side effects: "My biggest worry is managing the side effects of both the disease and the chemo, because often times I can't tell the difference." A participant who has stopped treatment said, "I needed a physical and emotional break, a self-imposed break. Right now I almost feel like myself. I feel like I am alive again… but I have to start chemotherapy again." Another patient described taking a break from chemo: "As a patient, I thought I was dying from the disease, but when I stopped the chemo I started feeling better." One patient stated, "I don't know if chemo is making me more sick than the disease." Another stated, "My only option is chemotherapy, and I've already blown through 3 different therapies. I'm down to some of the worst ones that I have to start now because that's all I have left."

Stem cell transplant

"The ordeal I went through with a stem cell transplant was a nightmare."

A small percentage of patients are eligible to have an autologous stem cell transplant, but most patients agreed that treatment is extremely difficult to tolerate, describing "massive side effects" and stating that "it left me incredibly weak" and "it was a huge burden on the family."

Other patient comments included:
“As a result of the stem cell transplant my immune system is permanently crappy, so I get sick easily.”
“Two weeks after I finished *[stem cell transplant]* I spent a week in the ICU with septic shock.”
“I had a stem cell transplant as my first treatment... and I didn’t respond well to that.”
”I developed such severe atrophy, I had to go to acute rehab.”
“When the transplant wasn’t effective, I had to deal with the fact that I immediately had to return to weekly chemo.”

Steroids

“I am on steroids, so no sleep for a couple of nights every week.”

Steroids are sometimes administered in conjunction with chemotherapy. However, participants described effects, including uncharacteristic behavior, associated with steroid use: “He's always extremely frugal, but all of a sudden he wanted to spend money.” One caregiver described the harmful effects that steroids had on her husband’s health: "The negative side effects of steroids… resulted in a heart attack.”

Long-term side effects from treatment

Participants also described lasting treatment-related effects: “… I broke 3 bones in 1 year, probably because of steroid use.” A patient who had a partial response noted that the combination of drugs she was treated with gave her “…some organ improvement, but it came at a high cost. I got severe neuropathy with a tremendous amount of pain and weakness.” “Another stated that “the side effects from the treatment mean I can no longer work.”

Treatment responses and continued needs

“I had a partial response and in four months I had some organ improvement but it came at a high cost.”

Participants at the meeting were in different stages of disease treatment and/or remission. One patient stated, “I went through 4 months of chemo and underwent a stem cell transplant and I had a very good response. I was discontinued from all other treatments after that and I regained strength.” Another described, “I had a successful stem cell transplant...and by all measures I’m doing exceptionally well because I’m one of the fortunate ones that didn’t have cardiac involvement.” However, many of the participants described ongoing effects after their disease was in remission. One stated, "I had a great response to the treatment...I still tire quickly.” Another participant stated, “I look physically better by any measure and all my biomarkers are normal, but I’m not.” Remission time is varied for participants, and 1 patient said that even after their response to treatment, they felt as if they were “waiting for the other shoe to drop.” One patient commented that he “participated in [his] first clinical trial… which was prematurely stopped due to neuropathy.”

Supportive care therapies

Participants mentioned a wide range of supportive therapies used to help manage the side effects of their disease and treatment. A number of participants and caregivers described the results of kidney failure. One stated that their family member has “… dialysis treatments because the amyloidosis has gotten to his kidneys. His dialysis takes most of his days.” The effects of the disease in some cases cause complications, “My dad passed out in the dialysis chair.”

Physical therapy

Participants describe the need for support to regain strength after treatment, "...with a lot of in-house physical therapy I was able to sit myself up, and then stand up and then get to a wheel chair." Another

commented, “I was immovable for about a week, I was so deconditioned that I had to go to the rehab hospital for 10 days.”

Support groups
One participant echoed the sentiment of many, stating, “I spend countless time going to amyloidosis support groups… if not for that [group], I wouldn’t know about the other treatments out there.”

Perspectives on future treatments for AL amyloidosis

Patients and caregivers provided input on what they were looking for in future therapies for AL amyloidosis.

Considerations for treatment decisions
There were many factors that patients have to take into account when considering treatment. Discussion focused on gathering insight and understanding the decisions that patients make when considering treatment. These are highly individual and personal decisions.

Prolonging life vs. quality of life
Most participants identified “Whether the treatment could possibly prolong my life by slowing or halting disease progression” as the most important factor in choosing a treatment. Responses also varied by personal situations, including concern for children who “…don’t deserve to be that kid that lost their dad in high school…I need to see Addison and Chet graduate, I need to see them off to college, I need to see Addison walk down the aisle, I need to see them start families of their own and I need to be there for them every step of the way. The idea that I’m going to miss so many of those milestones is just not acceptable to me.” Improving symptoms and quality of life were the second-highest rated factor in treatment choice.

Financial burden
Financial burden substantially impacts treatment decisions for many patients. One patient described the problem as being due to the fact that “the drugs I need are not labeled for amyloidosis.” Fighting with insurance companies for reimbursement, as well as the personal expense owing to the cost of travelling to amyloidosis specialty centers for treatments or to take part in clinical trials were identified as a cause for creating significant financial hardships.

Side effects
The side effects of many of the treatments being used are extreme in patients with amyloidosis. Many patients describe having to weigh the risk of debilitating and potentially severe side effects against possible benefit.

Participants commented on the need for new effective treatments with fewer side effects:
“I sincerely hope that by the time I need treatment again, options will be available to me that don’t require me to choose between organ failure and the progression of this neuropathy.”
“Multiple organ involvement limits my choices. I am the patient that needs the new treatments, needs them faster…I need them very soon.”
“We need these drugs now.”

Participants described uncertainty around making decisions: “Is the upward trend significant enough to change treatment?”

Risk versus benefit
Participants describe relying on their physician to make decisions on their treatment. A theme touched on by participants throughout the day was the risk of significant side effects, but that "there was no other choice." One caretaker stated that, "he didn't want to know the potential risks or side effects." For some participants "the risk of going on dialysis was worse than the risk of stem cell transplant."

Clinical trials
Time was spent discussing the decisions involved in taking part in a clinical trial. Participants commented that taking part in a trial might not directly benefit them; "I don't mind doing that because it might help me and… it will help other people." Others expressed their belief that they would receive better care or treatments: "it gives me a better choice of drugs" and "it was so clear that the clinical trial had benefits. Essentially there was no placebo in the clinical trial I was participating in… it seemed as though, how could I lose?" The importance of having an active therapy was touched on, as one patient stated, "I took part in a clinical trial because there was no placebo."

Summary of comments submitted to the post meeting questionnaire on AL amyloidosis

At the conclusion of the Patient-Focused Drug Development meeting, a set of follow-up questions was sent to the attending participants to further explore areas not fully addressed at the meeting. These are deemed to be important factors to understand the patient experience. A total of 20 AL amyloidosis patients/caregivers responded to the survey. The comments and answers reiterated some key areas and themes touched on during the meeting, but also expressed some novel perspectives, summarized here.

When you think about overall goals of treatment how do you weigh the importance of prolonging life versus preserving quality of life?

There were somewhat more respondents favoring quality of life than those favoring prolonging life. Respondents for whom the most important goal of treatment was prolonging life made the following comments: "Prolonging life is of utmost importance to me. I can tolerate unpleasant treatment." "I am 'pro' prolonging life. After speaking with many AL amyloidosis patients and caregivers… I continually heard the hard road everyone traveled due to treatments, but it was worth it, as they were alive and living life. Sometimes you have to get terribly sick to get feeling better or at least to get to a new normal."

Those respondents who expressed quality of life as their most important goal included the following comments: "Preserving quality of life is most important to me. I am not interested in living with significant disability." "Quality of life is more important to me than quantity. Goals of treatment should be to make each patient more active and able to live a full life." "Quality of life is all that matters to me." "Quality of life is most important."

A number of respondents felt that both prolonging life and preserving life were equally important, and did not distinguish a preference. Their responses included: "Both are equally important." "Those 2 have to come out with some reasonable balance...I do not want a long miserable life that is a burden to me and those around me. I also want very much to keep going for some time here." "Quality of life is as important as prolonging life. What is the point of going through daily pain, if you have nowhere to go?" "My goal has always been to prolong life. This could change if the quality of my life were to reverse."

What are the main factors that you take into account when making decisions about choosing a treatment or clinical trial?

A number of respondents stated that their doctor's recommendations were a key factor when making decisions about treatment or clinical trial participation. One stated, "I have followed the recommendations of my doctor." Another patient explained one of the biggest things that helped in her decision-making was the feedback from her doctors, "I finally have found the best doctors for me and feel their knowledge is a big factor in helping make my decisions."

Several respondents stated that their families were a main factor in their decision-making process. One participant stated that her decisions were based on, "the overall impact it [treatment] will have on myself and my family." One patient discussed her particular situation, wondering, "Since my husband also has a rare cancer, will this affect my ability to help him?" Another patient commented that his main factor was his parental role for his 12-year-old son.

Many patients stated that side effects of the treatment or clinical trial were among the main factors they took into account. One patient explained that she looks for the "most effective treatment with least side effects." Another patient stated their main factors as: "...long-term toxicity of the treatment versus its likely benefits... the treatment's likelihood of success in comparison to the physical/emotional cost of that treatment... the probability that a treatment will induce worse symptoms and conditions that compromise my quality of life."

Are you willing to accept some significant risks and side effects in return for slowing or stabilizing the progression of the disease?

Participants shared varying responses to this question. However, most patients answered "yes" that they were willing to take significant risks and accept side effects in return for slowing or stabilizing the progression of their disease. One patient commented, "I would absolutely be willing to accept some risks and side effects if I knew I would slowly get better."

Some patients who responded are currently in remission. Their current stage of disease brought along a different perspective. One patient in remission shared, "if I had active disease and nothing else worked, I would accept the risks and side effects." Another patient in a similar position explained, "My disease appears to be stabilized at this moment, but if I were to come out of remission, I would be willing to accept some significant risks and side effects to slow or stabilize the progression. I feel like any treatment is risky. Do we really know what the long-term side effects are for the treatment that I'm on today?"

Although most participants indicated that they would accept significant risk to slow or halt their disease, others shared opposing views. One patient commented that they were "…not willing to take significant risks, as I live alone and no one is left in my family to help me."

In order to gain further perspective, participants were asked to consider a hypothetical clinical trial. Patients were asked to provide perspectives and questions based on the proposed trial to better understand their decision-making process. The hypothetical questions included:

Please write the thoughts and questions that come to your mind after reading the following scenario:
• You have been invited to participate in a clinical trial to study an experimental treatment for AL amyloidosis.
• The purpose of this study is to better understand how well this treatment works and its safety.
• The clinical study lasts 2 years, and clinical visits will occur every month, in addition to regular doctors' visits.
• Clinical visits will involve monthly lab tests, scans, and other function tests.
• Treatments will be given in addition to standard of care.

Six participants stated that they would be willing or would strongly consider participating in the hypothetical clinical trial. The following comments include this viewpoint: "I would participate immediately if there are no significant risks and side effects." "Hooray. I will be VERY happy to participate." "I would strongly consider participation in a clinical trial" and "Yes, I would gladly do [the clinical trial]."

Several patients gave insight into their comments and decisions for participating or considering participating in clinical trials. One patient explained, "I truly believe in clinical trials. We need to participate in the trials in order to make amyloidosis either chronic or cured. It may not be for me, but for future diagnosed patients." Other patients shared a similar view, and one participant commented, "I am absolutely willing to participate in a trial, both for myself and for others." Another patient stated, "I hope it helps me, but I would be happy to participate even if it doesn't, if it can help others with this disease."

Contrastingly, several patients indicated that they would not or would be hesitant to participate. The following comments were made by those who rejected the hypothetical clinical trial: "I would not participate in a clinical trial to this extreme unless standard treatments were no longer working for me." "I would have to be tremendously desperate to participate in the clinical trial described in this scenario… This scenario described a situation where I would be living a life around amyloidosis treatment and tests, rather than living my life. That is not acceptable to me at this early stage of my disease." "I would probably not participate unless I was out of remission."

ATTR Amyloidosis

Key themes in ATTR amyloidosis

There were a wide variety of experiences reported by a diverse group of patients and representatives covering the spectrum of disease. Some participants, although diagnosed, were still asymptomatic but had experienced the disease through relatives; others had advanced and debilitating symptoms. A number of key themes emerged throughout the day:

- Patients experienced ATTR amyloidosis symptoms that had a significant impact on their physical, mental, and emotional functioning and quality of life.
- Because of the hereditary nature of ATTRmt amyloidosis, many patients experienced a substantial impact of the disease simultaneously in their lives on personal and familial levels.
- ATTR amyloidosis is associated with significant financial burdens and difficulty professionally.
- Patients expressed frustration with having no treatment options outside of liver transplant for eligible patients and supportive care.

- Participation in clinical trials requires a qualified assessment of potential benefit and risk, but many patients expressed a commitment to participating in the treatment development process as study subjects.

ATTR Amyloidosis Topic 1: Most significant symptoms and their impact on daily life

The first discussion topic focused on patients' experiences with their ATTR amyloidosis symptoms and their impact on their daily lives. The discussion also focused on how the condition and symptoms have changed over time, specific activities patients could no longer perform at all, or as fully as they would like to due to their condition.

The session on ATTR amyloidosis started with a panel presentation from 3 patients, 2 of which were also caregivers of family members with the disease. The patient panel included:

- Panelist 1—A 44-year-old female patient who has lost many family members to this hereditary disease. She was first a caregiver for her now deceased mother and she is a patient. She has a rare variant, ATTR Cys114.
- Panelist 2—A female patient in her forties who shared her massive burden of disease. She described how her disease and symptoms had progressed.
- Panelist 3—A 65-year-old male patient, who has lost many family members to ATTR. He had a heart and liver transplant and no episodes of rejection.

Patient contributions throughout this meeting, along with the responses to the post meeting questionnaire, helped generate a broader understanding of the symptoms and daily burden of ATTR amyloidosis. The panelists' testimony provided vivid descriptions of what it is like to live every day with ATTR amyloidosis. Participants shared their challenging experiences with diagnosis, various treatments, and the day-to-day symptoms that negatively shape their lives. Participants also described the substantial physical, social, and psychological impact their disease has on themselves, their families, and their close friends.

Respondents to the ARS questions shared that loss of balance, GI issues, and fatigue were patients' main symptoms. These symptoms were also reflected by the comments that participants in the meeting shared about their experiences.

Most significant symptoms of ATTR amyloidosis

Patients and caregivers described the substantial array of symptoms experiences by patients with ATTR amyloidosis.

Orthostatic hypotension

"Orthostatic drop in blood pressure resulted in several bouts of loss of consciousness, some resulting in injury."

Throughout the meeting participants described similar circumstances of "lightheadedness upon standing up." Many of these episodes happened during their daily routines, such as when getting out of bed or standing up after going to the bathroom. A few participants also commented on the dangers associated with orthostatic hypotension and how it sometimes results in instances of unconsciousness. One participant described his experience: "I passed out after getting out of bed too fast."

Gastrointestinal symptoms

"My GI system was affected with extreme constipation and diarrhea."

Gastrointestinal problems, often occurring as alternating bouts of constipation and diarrhea, were described by many patients with ATTR amyloidosis. One panelist described, "…experiencing frequent bouts of diarrhea." Weight loss was also common among a number of the participants, one stating "the combination of all the diarrhea and decreased appetite has caused me to lose a lot of weight in the last year, I dropped down a couple of jean sizes." Another participant described the consequence of "… weight loss caused by lack of appetite, nausea, and malabsorption that required hospitalization… and resulted in a feeding tube to restore my nutrition and strength."

Incontinence

"There is no replacement pill one can take for dignity."

Many patients indicated incontinence is a significant symptom. Participants talked about experiencing urinary and fecal incontinence. A young man described, "I had already been experiencing frequent bouts of diarrhea but losing control of [my bowels] at night was so traumatic and continues to be so." He continued to explain "I began wearing extra shorts and underwear as I slept… and ultimately deciding to wear incontinence briefs at night, which was very hard for me." Another participant noted "because of the bladder and GI involvement, I have had issues of bladder and fecal incontinence" and elaborated, saying, "I soil clothing in public often and my children have had to witness such incidents." As a participant's symptoms advanced, "neurogenic bladder caused progressive resistant UTIs that required 4 hospitalizations, resulting in required catheterization."

Peripheral Neuropathy

"My sural nerves are completely dead and placement of my feet is not exact, which often results in trips and falls."

Peripheral neuropathy occurs when those nerves that connect the brain and spinal cord to the body (muscles, skin, and glands) cannot faithfully transmit information to or from the brain. This problem can have debilitating consequences for patients and is considered a significant hardship. One patient who recently started experiencing neuropathy symptoms stated, "within the last month, my hands and feet have begun to tingle with neuropathy," while another whose disease was further progressed described the "peripheral neuropathy which has spread from my feet to legs, to my mid-thigh, arms, hands, below the elbow, torso." A few participants discussed potentially harmful situations resulting because of their neuropathy. One panelist elaborated, "My feet are completely numb; I have no sense of temperature or pain."

Fatigue

"My fatigue is chronic."

Many patients commented on the debilitating effects of fatigue, as well as being ranked highly as a significant symptom in the post meeting questionnaire. One patient said, "My fatigue is chronic," and another said that she felt "far more tired and fatigued than I used to."

Vision problems/floaters

"I was almost blind in my right eye."

Several of the participants described experiencing vision problems such as floaters. One participant identified eye floaters as the one symptom that has the greatest negative impact on her daily life. She stated, "Floaters

in my eye: I've had 2 eye surgeries, one for glaucoma and a vitrectomy." Another participant commented, "amyloid deposits in my eye caused floaters that required a vitrectomy."

Erectile dysfunction

Erectile dysfunction was another symptom that was mentioned. One participant said, "The first major change that occurred a couple years ago was my sudden erectile dysfunction." Another, a young man in his early 30s, said his first sign of erectile dysfunction appeared at age 27 and was followed by very serious issues with incontinence.

Swelling/Edema

A few patients described edema as a significant symptom. Patients describe their experiences: "It does make it difficult for me to walk…." and "Climbing stairs… I would go very, very slowly and it would take me half an hour to go up 7 steps, and then I would have to wait. I would just slowly work my way, grabbing onto the banister."

Psychological impact

"It's that mental health piece, you just are constantly afraid."

Patients emphasized the psychological impact that living with their disease has on their daily lives, including, fear, anxiety, and depression. "I'm very scared of things getting even worse and how it will affect my quality of life." Other patients expressed their fears and anxiety associated with siblings and children who have tested positive for the gene and who may face their illness in the absence of adequate medical treatment options. Several participants who have solid organ transplants expressed these concerns; "I actually live in constant fear of rejection." One participant who had a successful liver transplant explained, "I'm a success story because I beat amyloidosis but the scars will be there forever. I still deal with the uncertainties." The personal impact for many of the participants that often witnessed the course of the disease and loss of a parent, and other close relatives, was expressed by one participant as "the emotional effects and the anxieties that came from being surrounded by this disease as a kid has lived with me until now."

Tiredness, fatigue, and shortness of breath were also commonly described symptoms, according to participants:

"I kept losing my breath, wondering if this was just age, with the thought of amyloidosis in the back of my mind."

"I feel more tired and fatigued than I used to."

"I felt this steady decline in my physical being, I felt my strength getting weaker."

"I have suffered chronic fatigue, shortness of breath."

<u>Impact of ATTR amyloidosis on daily life</u>

Throughout the meeting, patients and caregivers described in clear detail their varying experiences regarding the impact that ATTR amyloidosis has had on their daily life, including:

Day-to-day activities

"I struggle to rise every day."

Patients shared the difficulties that ATTR amyloidosis had on their ability to care for themselves, their families, and their household. According to one patient, "[my kids] have watched me deteriorate from a full-time working mom, and an athletic adventurer who was an avid skier, hiker, camper, to a mom who struggles

to be able to rise every day in order to get them up and ready for school." The same patient explained the impact of the disease on her daily life, stating, "It requires ample time in the day for medical interference, to eat, and go to the bathroom." One panelist described how his mother went from being active to "making me my favorite French toast even though she had to do it from her wheelchair, and how she watched my sister's prom grand march not with the other parents at the event but through a tape recorder in her bed." Many patients talked about losing the ability to exercise or continue their hobbies; one stated, "I'm a very active cyclist and within 1 month this has abruptly come to an end."

Many participants described the effects of symptoms, such as peripheral neuropathy affecting their daily lives. A number of patients explained that they could no longer drive. "I have neuropathy in my feet and it has impacted my driving. The other day I was driving and my shoe came off my foot and I didn't feel it."

Effects on work

Many of the participants shared that they could no longer work. A surgeon had cut back on his work, and another said that "not doing my work is killing me." A heart transplant recipient could no longer work in her profession as a nurse practitioner where she is "at risk for infection."

Impact of hereditary condition

"I have watched my maternal grandmother, my uncle, and my mother deteriorate as this disease devastated their bodies and cruelly took away their independence and dignity."

One participant described that "it has affected 7 generations of my father's family." Another participant described the symptoms that occurred in his family, "I was well aware of family members and what they had gone through with this disease; horrible pain, extreme degeneration of limbs to the point where they could no longer walk, they could no longer feed themselves. It is not much to look forward to." Another commented that "we have stock pilings of [medical] equipment in my family." A number of participants talked about the effects on their children. "My children are also positive for V122I, so it's hard. It's really had an impact on our family." Another described letting the "children know that I may have passed something down to them for which there is no cure for and really no treatment." Others were clear that they "are really not willing to consider having children at this point." Many of the participants had taken part in caring for other family members with this disease. "I fear and feel extreme guilt at requiring others' time and attention." A participant with many generations of their family affected described how "rifts within the family arise due to grief and stress of caregiving."

Financial burden

"The financial strain of caring for my mother depleted my parents' retirement savings."

Many participants talked about the disease-related costs: "The financial strain of caring for my mother depleted my parents' retirement savings." The cost of care and treatments for 1 patient was "$10,000 per year. On an income of $3000 a month, this is not sustainable." Another patient expressed concern over being the main provider for his family, wondering "what was the final cost going to be at the end of the road?" One patient said, "I truly had the financial resources that allowed me to be persistent and find the right answer. It was a very expensive endeavor."

ATTR Amyloidosis Topic 2: Patient perspective on treatment

The second main topic of discussion focused on patients' experiences with therapies, surgeries, and additional options used to treat their disease. Four patient panelists shared their experiences. The panelists included:

- Panelist 1—A male surgeon diagnosed with ATTRwt. He commented on his experience with clinical trials.
- Panelist 2—A male diagnosed with ATTRmt. Seven generations of his family have been affected by this disease. He discussed his experiences with clinical trials.
- Panelist 3—A female nurse diagnosed with ATTRmt Val122Ile. She has had a successful heart transplant. Her children have tested positive for the disease.
- Panelist 4—A female diagnosed with ATTRmt Ile85Ser. Many of her family members are symptomatic for or have died of this disease. She described her experience of being denied access to clinical trials.

There are currently a number of ATTR clinical trials for novel therapies. All clinical trials are double-blinded and include a placebo component in which there is no active agent. Liver transplant is the only treatment that is recognized as being effective for some patients in halting progression. However, it is only available to a small percentage of patients with ATTR amyloidosis. Heart transplants are sometimes successful supportive care measures.

Experiences with current treatments for ATTR amyloidosis

Patients and caregivers described their experiences with both the benefits and risks of current treatment options for ATTR amyloidosis.

Solid organ transplants

"I'm terrified of doing nothing and having the transplant."

A patient described his liver transplant experience as being "…very difficult with all the uncertainties and not knowing what was going to happen." Another participant who has seen many members of her family afflicted commented, "the only ones who have survived past 56 years are those who detected the disease early and quickly and received a liver transplant."

Supportive care therapies

A participant described the herbal supplements, vitamins, and diet changes family members took. "I have watched my family go through some very interesting nontraditional treatment, because there has been no [other] treatment." Another commented on "positive thinking, faith and prayer."

Other considerations and issues for treatment

"I had to relocate for 9 months to northern California in order to be transplanted and receive my care."

Participants explained the challenges to travel to amyloidosis centers: "I had to travel 3000 miles to a specialty center."

Perspectives on future treatments for ATTR amyloidosis

Patients and caregivers provided input on what they are looking for in future therapies for ATTR amyloidosis.

Risk/Benefit

"It's so strange conceptually because really it is a terminal illness at this point and nothing feels risky."

Participants discussed the different levels of risk that they were willing to take in trying a new therapy. Patients at different stages of disease had different considerations. One patient stated, “the advantages and the risk far outweigh me just continuing to progress [with the disease].” Another patient, who just recently began showing symptoms, explained how she would be willing to accept the risk associated with clinical trials. Participants commented about the limited options: “My treatment options at Johns Hopkins were very limited, liver transplant or clinical trial. I looked at both.”

Perspective on clinical trials

“Knowing my history, my family history, that was a no-brainer for me; I’ll go on any trial I possibly can.

Participants with hereditary amyloidosis expressed the value they saw in taking part in clinical trials, “I chose a clinical trial, I have 5 children, the only hope I saw was to do it for them.” “My main thought at the time for going into a drug trial was to save my family, not me.” One patient stated, “I know it’s not going to help me. I feel that I am beyond that point; but it will help someone else.” Another patient said, “I’m willing to try any trial that you will let me in.” These examples echoed the sentiments that were heard throughout the presentations.

Enrollment criteria in a clinical trial

“I was denied entrance into a clinical trial because I do not have lower extremity neuropathy.”

Patients expressed their frustration about the need to develop significant peripheral neuropathy in order to qualify for a clinical trial when it is known that they will eventually progress to significant peripheral neuropathy. Concern was also expressed that these were symptoms that would not regress with treatment, thus requiring that patients endure disease progression prior to qualifying for a trial. “I was denied because I didn’t have the neuropathy.”

Placebos

“***I’m convinced I’m on a placebo [now] and my spirits are at an all-time low.”***

A participant described the decision she was faced with in joining a study. “I was reluctant to do so when I was first diagnosed because I didn’t want to take the chance that I would get on a placebo...and I would lose ground instead of gaining it.” Another patient commented, “I am absolutely willing to risk receiving a placebo.”

Diagnosis

“It took about 8 years to get a diagnosis of amyloidosis and I saw about 14 doctors before I got this diagnosis.”

Many patients mentioned the long and challenging journey to an accurate diagnosis. One patient commented, “It took me 5 years to get diagnosed."

Summary of comments submitted to the post meeting questionnaire on ATTR amyloidosis

At the conclusion of the patient-focused drug development meeting, a set of follow-up questions were sent to the attending participants to gain insight into areas that were felt not to have been fully explored in the meeting itself. These are deemed to be important factors to understand the patient experience. Ten responses were submitted. The comments and answers reiterated some key areas and themes touched on during the meeting; new perspectives were also expressed. The follow-up questions and responses are summarized below.

What are your most significant symptoms and how do they affect your daily life?
Participants echoed statements made throughout the meeting. Most patients experience more fatigue, easily tire, and do not have the endurance and stamina that they used to have. Shortness of breath was a significant symptom for many. Half of the responses commented on the effects of neuropathy, "making it difficult to sleep, exercise, and do normal tasks without pain." Another patient commented how neuropathy in her feet "makes it uncomfortable to walk or drive."

Some participants discussed how psychological symptoms such as anxiety significantly affects their quality of life. One patient described how she frequently has "anxiety attacks."

Other health effects cited included erectile dysfunction ("another devastating symptom") and muscle weakness and wasting ("muscle wasting is occurring in my legs as well as causing difficulty with everyday activities"). One patient noted his experience with insomnia. Another patient's comment described how "floaters in my left eye add to not being able to see clearly or drive." These additional responses correlate and reiterate what patients previously stated during the in-person meeting.

When you think about overall goals of treatment how do you weigh the importance of prolonging life versus preserving quality of life?
Participants submitted varied responses to this important question. One participant commented that this was a decision that would need to be made with the patient's doctor. Three of the participants stated that prolonging life was more important. More than half of the submitted answers indicated that preserving quality of life was the most important factor in their overall treatment goals**.** Of the patients who indicated quality of life as a higher priority, many focused on the importance of impact on their family and their ability to enjoy life. The following examples help illustrate this viewpoint: "Preserving one's quality of life is a gift also to one's family members, ensuring that the patient is not a burden to the family." "I would not want to have a treatment that kept me alive at the cost of further enjoying life." "Quality of life is more important to me than prolonging life. If I am no longer able to live without pain and enjoy life, then what is the point in continuing to live. Life is meant to be enjoyed."

However, because of the complexity of this issue, some participants offered alternative opinions and views on this question. Additionally, although some agreed strongly with one side, they drew from their experiences and shared their considered opinions. The following examples illustrate these complexities: "Don't think that the 2 goals are incompatible. We want to have as comfortable a life as possible, but the extension of life to help the family and to tie up loose ends that ensures a better life for the children is just as important." "I know that I would accept some decrease in my quality of life if the treatment was able to prolong life." "Treatment goals should focus on improving the quality of life while trying to prolong life through improvement of quality." "Prolonging life IS the goal but I saw my sister decline to the point of not having any quality of life. It's a difficult thought." "I feel both are important."

What is the biggest downside to any treatment you have had? Include comments for drug treatments and/or organ transplant?
Patients described in detail the side effects of current drug treatments, issues with clinical trials and the stresses associated with solid organ transplants.

Four shared their experience with taking the drug diflunisal, commenting on both the efficacy and side effects. "I am taking diflunisal and battle headaches, tiredness, and lightheadedness that wasn't previously

present in my day-to-day life." Another patient whose only current treatment is diflunisal described the frustration: "For me the biggest downfall of this drug is knowing it is not a cure but rather a stabilizer to help slow down the disease until further drugs can be discovered." The single asymptomatic patient explained how she preemptively started taking a regimen of diflunisal and the downside of this approach: "My kidneys didn't tolerate the NSAID and I developed nephrotic syndrome." Meanwhile, another patient stated, "I am on diflunisal and have not had any side effects."

One responder described how the arduous experience of "doctor visits and scheduling my life around the injections and medicine" was the biggest downside to treatment.

One patient who received both a heart and liver transplant described the long experience, "Before transplant my symptoms were being managed with drugs with some success but my health continued to fail. Organ transplantation can cause a lot of anxiety for you and your entire family." However, despite living with the anxiety, the patient also explained how they got through this trying time using alternative methods, "the only way I got through it was trusting the good Lord for his will for me. This took the fear out of the equation."

What are the main factors that you take into account when making decisions about choosing a treatment or clinical trial?

For most patients with ATTR amyloidosis, ongoing clinical trials provide the only possibility for treatments that may potentially arrest the disease. One patient explained, "I had no other option. I either participate in a clinical study and possibly get treatment, or choose not to participate and receive no treatment."

Placebo-control groups are a key topic discussed throughout the responses**.** Many patients described the anxiety and hardship of possibly being assigned to receive a placebo. One participant explained: "[I] do not know if I am on drug or placebo and I won't know until I finish the trial in 23 months. The unknowing aspect of the future is a big obstacle to planning any long range activity." Another participant noted the biggest factor that deterred them from a clinical trial was "obtaining the placebo and not the real drug, especially because they want to take me off diflunisal." One participant was interested in learning about the "safety nets available for those that receive a placebo." The asymptomatic patient commented, "If eligible, I'd look at… the percentage of people in the placebo category." Although the concern about receiving a placebo is a main factor patients take into account, on weighing up the factors many seem to be willing to take this risk for the potential benefit of being in the active arm of the trial.

Respondents offered many important considerations for choosing a treatment or clinical trial. Two responses indicated the importance of quality of life as a factor in their decision process, posing, "Main factors when partaking in a trial or therapy would be how will this help my quality of life?" Another patient shared a similar view, stating that, "what considerations the trial has for quality of life" is important to them.

Several patients commented on the importance of drug effectiveness in making treatment decisions. One patient explained factors they would take into account: "The published research established with the treatment, the effectiveness of the treatment, the cost." Another patient emphasized the "…effectiveness slowing or halting the disease."

A few other considerations were mentioned by participants. One patient described how the "length of the trial" and "ease of traveling to the facility conducting the trial and frequency of needing to physically be there," were important factors in making treatment decisions. Additionally, a few participants commented on

the "availability of the drug at the end of the trial." One patient expressing both: "I believe a clinical trial is acceptable for a short term but has to have extension benefits as a reward to taking the risk of participating."

"I am not just doing this for me. I have children, nieces and nephews, and family that could (we hope not) have this. This is a genetic disease and I have an opportunity to do my part." This statement echoed the responses we heard throughout the meeting. Because of the hereditary nature of this disease many patients expressed their willingness to take part in clinical trials and accept a high risk to advance research, in the hopes of someday helping future generations of their family affected by this disease. One patient shared their opinion: "I am so thankful that there is a trial for me that I can put up with ANY downside if it saves my life and gives hope to my family."

Are you willing to accept some significant risks and side effects in return for slowing or stabilizing the progression of the disease?

Many participants grew up seeing family members afflicted and, through genetic testing, learned that they too are at risk of developing the disease prior to becoming symptomatic. As the disease progresses, decisions and priorities regarding benefit versus risk may change.

The responses of the symptomatic patients were unanimous in being willing to accept risk for potential benefit in treatment. "Yes," "Absolutely!" The one asymptomatic responder had a different opinion and response to the question, stating, "At this point in my life, no, as I am relatively healthy… However, once my condition worsens I would probably be willing to take bigger risks. It's an awful consideration to account for taking on bigger risks that I would not previously take if I were a healthier person."

Please write the thoughts and questions that come to your mind after reading the following scenario.

- *You have been invited to participate in a clinical trial to study an experimental treatment for ATTR amyloidosis.*
- *The purpose of this study is to better understand how well this treatment works and its safety.*
- *The clinical study lasts 2 years, and clinical visits will occur every month, in addition to regular doctor's visits.*
- *Visits will involve monthly lab tests, scans, and other function tests.*
- *One-third of patients will be given a placebo.*

Participants agreed that this scenario generally aligned with the perspectives they shared throughout the questionnaire. Many responders had concerns and questioned the need for a placebo group. One participant commented on a view felt by many, "I think anyone in the trial people would want the actual drug not the placebo." Another patient, who is currently enrolled in a clinical trial, addressed concerns about the length of the trial and repercussions of receiving a placebo, saying, "My concern though, is the 30-month length of the study, especially if I am in the 40 percent placebo group. If that is the case, my disease continues to get worse and I am getting no medication for it, even if it is not FDA approved."

Some responders provided alternative solutions to having a placebo arm: "Patients can tell if their progression is ongoing, slowing down or halted." Another patient agreed, saying, "All should get the drug… It should be enough to track the effectiveness of the drug without doing the placebo for a comparison." Some responders said they would be hesitant of taking the risk and giving up effective treatments: "I do not want to give up diflunisal since it appears to be working for me in slowing down the progression of disease." Another

responder questioned, “Can you participate in another trial if it is deemed a completely different mechanism of action in treating the disease?”

Participants raised a number of other concerns with the hypothetical situation. One mentioned apprehension about the travel distance, commenting, “depending on where a person lives and which amyloid center is hosting the trial, travel can be a real nightmare… Having the ability to get labs, samples, etc., locally (thereby minimizing travel) would be a huge factor.” The issues of access to treatment and center experienced in treating amyloidosis were also highlighted during the meeting.

Participants raised a number of questions and other thoughts regarding the posed question**:** “The risks do not matter as there are currently no alternatives for a cure.” One patient addressed evaluating the risk in relation to placebos, stating, “The risk of having the placebo is unfortunate, but if there is no other trial option it is worth taking.” Several participants described their reasoning for taking part in a trial to advance treatment options and help future generations. One participant explained, “As a mother of 4, and already one child is positive for the genotype, I would do whatever it takes to help the advancement of pharmaceuticals that will become available for my children. Most of us don’t care about the side effects of these drugs, we just want hope. Hope for ourselves, and for the future generations who will have to deal with this horrible disease.”

CONCLUSION

This meeting emphasized the urgent need for increased awareness, early diagnosis, and available treatments for AL and ATTR amyloidoses. Furthermore, the FDA was provided with a unique opportunity to hear directly from patients at this Patient-Focused Drug Development meeting and to better appreciate their physical and emotional burdens related to living with systemic amyloidosis. Presentations by world-renowned amyloidosis researchers provided a unique insight into the complex issues faced by clinicians and scientists in developing better treatments for this disease. We are grateful to the patients and their representatives and to the physicians and scientific experts who participated.

Appendix 1: Meeting agenda

Enhancing the Amyloidosis Drug Development Pathway:
Guidance for More Efficient and Successful Programs

9:00 AM	**Introduction: Integrating the voice of patients into drug development and the regulatory process** I. Lousada
9:15 AM	**Overview of AL and ATTR amyloidosis: Including the challenges of diagnosis** M. Gertz, MD
9:25 AM	**Patient presentation: 3 faces of amyloidosis**
9:40 AM	**Why now? A pivotal moment in amyloidosis** G. Merlini, MD
9:55 AM	**FDA's commitment to sound drug development: The case of amyloidosis** J. Woodcock, MD - FDA
AL amyloidosis First Session	**Burden of disease in AL amyloidosis** Facilitator: R. Comenzo, MD
10:15 AM	**Patient perspective: Living with AL amyloidosis** Panel
10:30 AM	**Understanding burden of illness and quality of life in AL amyloidosis** V. Sanchorawala, MD / M. White, PhD
10:45 AM	**Moderated discussion**
AL amyloidosis Second Session	**Current approaches to treatment & clinical trials in AL amyloidosis** Facilitator: M. Gertz, MD
11:15 AM	**Novel therapies & clinical trials** A. Dispenzieri, MD
11:20 AM	**Patient perspective: Current approaches to treatment** Panel
11:40 AM	**Moderated discussion**
12:05 PM	Lunch
12:45 PM	**Short film:** **'Amyloidosis: The Voice Of The Patient'**

ATTR amyloidosis First Session	**Burden of disease in ATTR amyloidosis** Facilitator: R. Comenzo, MD
12:50 PM	**A physician's experience: ATTR amyloidosis** F. Ruberg, MD
12:55 PM	**Patient perspective: Living with ATTR amyloidosis** Panel
1:10 PM	**Understanding burden of illness and quality of life in ATTR amyloidosis** W. Lenderking, PhD
1:25 PM	**Moderated discussion**
ATTR amyloidosis Second Session	**Current approaches to treatment & clinical trials in ATTR amyloidosis** Facilitator: M. Gertz, MD
1:55 PM	**ATTR treatment approaches** G. Merlini, MD
2:05 PM	**Patient perspective: Current approaches to treatment** Panel
2:20 PM	**Moderated discussion**
2:45 PM	**Acknowledging the unmet need in ATTR amyloidosis** J. Berk MD
	The Pathway Forward: **Guidance for More Efficient and Successful Programs**
2:55 PM	**FDA Summary** J. Goldsmith, MD - FDA
3:05 PM	**Concluding remarks: Charting the path ahead with ARC** I. Lousada

Appendix 2: FDA, expert, and meeting panel participants

AL Panel—Patient Presentation: Three Faces of AL Amyloidosis: Burden of Disease

Panel	Experts	FDA
Karen, patient Sydney, family member Josh, patient	Dr. Michelle White, Optum Dr. Vaishali Sanchorawala, Boston University	Dr. Jonathan Goldsmith

AL Panel—Patient Presentation: Current Approaches to Treatment and Clinical Trials

Panel	Experts	FDA
Margret, patient Carolyn, patient Jayne, caregiver	Dr. Angela Dispenzieri, Mayo Clinic	Dr. Jonathan Goldsmith

ATTR Panel—Patient Presentation: Three Faces of ATTR Amyloidosis: Burden of Disease

Panel	Experts	FDA
Dawn, caregiver and patient	Dr. Frederick L. Ruberg, Boston University	Dr. Ronald Farkas
Amy, patient David, patient	Dr. William R. Lenderking, Evidera	Dr. Devanand Jillapalli

ATTR Panel—Patient Presentation: Current Approaches to Treatment and Clinical Trials

Panel	Experts	FDA
Barry, patient Gary, patient Cecelia, patient Jennifer, caregiver and patient	Dr. Giampaolo Merlini, University of Pavia, Pavia, Italy Dr. John Berk, Boston University	

Appendix 3: Discussion questions

Disease symptoms and daily impacts that matter most to patients

- Context—how long ago was the diagnosis made?
- What are your most significant symptoms?
- Of all the ways amyloidosis affects your life, which 1 to 3 symptoms have the most significant impact on your life?
- What specific activities that are important to you are you not able to do?
    - daily chores
    - social life
    - work
    - financial
    - sleep
- How does your disease affect an average day?
- Has this gotten worse over time?
- What worries you most about amyloidosis?

Patient perspective on current approaches to treatment

- Are you currently undergoing any treatment to halt the progression of the amyloidosis?
- What do you consider the most significant down side of these treatments, may include side effects, going to hospital?
- Are you taking anything else to improve or manage your symptoms?
- What specific symptoms do these treatments address?
- How well do these work?
- Are there symptoms that are not treated?
- When thinking about the overall goals for treatment, how do you weigh the importance of prolonging life versus improving the symptoms that you experience because of your amyloidosis?
- What factors do you take into account when making decisions about using treatments?
    - What information on the potential benefits of these treatments factors most into your decision (i.e., the potential benefits from treatments may include slowing down the deposition, regression of symptoms)?
    - How do you weigh the potential benefits of these treatments versus the common side effects of the treatments (e.g., neutropenia, fatigue, loss of appetite)?
    - How do you weigh the potential benefits of these treatments versus the less common but serious risks associated with the treatments (e.g., not re-engrafting, serious infection)?

Appendix 4: Meeting polling questions, clinical trial scenario, and post meeting questionnaire

Meeting polling questions and clinical trial scenario

The following questions were posed to in-person participants at various points throughout the November 16, 2015, Patient-Focused Drug Development meeting. Similar to the meeting structure, the AL and ATTR polling questions were divided throughout the day and contained different questions. Participation in the polling questions was voluntary. The results were used as a discussion aid and to help gain a better understanding of the full impact of the disease and should not be considered scientific data.

Asked of all patients

Demographic Questions

1.) Where do you live?

a. Washington DC area
b. Outside Washington DC area

2.) What [Amyloidosis] type?

a. AL amyloidosis
b. ATTR amyloidosis
c. Other

3.) How old are you?

a. Younger than 30
b. 31-40
c. 41-50
d. 51-60
e. 61-70
f. Over 70

4.) Are you?

a. Female
b. Male

5.) What is your current status?

a. Newly diagnosed (less than 6 months ago)
b. In remission
c. Disease is progressing
d. Not sure

We asked that questions 6 to 11 only be answered by people with AL amyloidosis and their representatives.

Question for Topic 1:

6.) Which of the following organs are affected by your disease? Check all that apply

a. Heart
b. Kidney
c. Nerves
d. GI
e. Liver
f. Soft tissue
g. Other

7.) Check ALL of the below symptoms which have had a significant negative impact on your daily life

a. Fatigue
b. Shortness of breath
c. Edema
d. Orthostatic hypotension (dizziness upon standing)
e. Sleep problems
f. GI problems such as constipation or diarrhea
g. Neuropathy
h. Other

Question for Topic 2:

8.) Have you undergone any of the following treatments? Check all that apply

a. Stem cell transplant
b. Chemotherapy
c. Complementary/alternative therapies
d. Other

9.) Have you had any problems tolerating treatment?

a. I have discontinued at least one medication or treatment
b. I have reduced dosage for at least one medication or treatment
c. I have had problems tolerating at least one medication or treatment but it did not result in a change to my treatment
d. I have had no problems

10.) Of the following factors, which two would you rank as most important for your decision about using treatment?

a. Whether the treatment is expected to help relieve the symptoms I experience, improving my quality of life

b. The small but significant risk of serious side effects, such as cardiac issues or kidney damage
c. Whether the treatment could possibly prolong my life by slowing or halting disease progression
d. The expected side effects of the treatment, such as nausea, loss of appetite, etc.
e. How the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.

Scenario Question:
For Discussion

11.) AL amyloidosis Clinical Trial Scenario

• You have been invited to participate in a clinical trial to study an experimental treatment for AL amyloidosis.
• The purpose of this study is to better understand how well this treatment works and its safety.
• The clinical study lasts 2 years, and clinical visits will occur every month, in addition to regular doctor's visits.
• Clinical visits will involve monthly lab tests, scans, and other function tests.
• Treatments will be given in addition to standard of care.

We asked that questions 12 to 16 only be answered by people with ATTR amyloidosis and their representatives.

Question for Topic 1:

12.) Which of the following organs are affected by your ATTR amyloidosis? Check all that apply

a. Nerves
b. Heart
c. Nerves and heart
d. Kidney
e. Other

13.) Check ALL of the below symptoms which have had a significant negative impact on your daily life

a. Nerve pain
b. Lack of mobility/physical limitations
c. Loss of balance
d. Orthostatic hypotension (dizziness upon standing)
e. Eye or vision problems
f. GI problems such as constipation or diarrhea
g. Fatigue
h. Sleep problems
i. Cardiac issues

Question for Topic 2:

14.) Have you undergone any of the following treatments? Check all that apply

a. Liver transplant
b. Heart transplant
c. Diflunisal
d. Clinical trial for amyloidosis targeted therapy
e. Other

15.) Of the following factors, which two would you rank as most important to your decisions about using treatments?

Please select up to two responses
a. Whether the treatment is expected to help relieve the symptoms I experience, improving my quality of life
b. The small but significant risk of serious side effects, such as cardiac issues or severe neuropathy
c. Whether the treatment could *possibly* prolong my life by slowing disease progression
d. The expected side effects of the treatment, such as nausea, loss of appetite, etc.
e. How the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.

Scenario Question:
For Discussion

16.) ATTR amyloidosis Clinical Trial Scenario

- *You have been invited to participate in a clinical trial to study an experimental treatment for ATTR amyloidosis.*
- *The purpose of this study is to better understand how well this treatment works and its safety.*
- *The clinical study lasts 2 years, and clinical visits will occur every month, in addition to regular doctor's visits.*
- *Visits will involve monthly lab tests, scans, and other function tests.*
- *One-third of patients will be given a placebo.*

<u>Post meeting Questionnaire</u>

Current disease status:
a. Disease is active
b. Disease is in remission

Treatment:
a. On a therapy for symptoms
b. On a therapy for disease
c. Had a stem cell transplant
d. No treatment
e. On a clinical trial

What are your most significant symptoms and how do they impact your daily life?

When you think about overall goals of treatment, how do you weigh the importance of prolonging life versus preserving quality of life?

What is the biggest downside to any treatment you have had? Include comments for both drug therapy and/or organ transplant?

What are the main factors that you take into account when making decisions about choosing a treatment or clinical trial?

Are you willing to accept some significant risks and side effects in return for slowing or stabilizing the progression of the disease?

Please write the thoughts and questions that come to your mind after reading the below scenario:

- You have been invited to participate in a clinical trial to study an experimental treatment for AL amyloidosis.
- The purpose of this study is to better understand how well this treatment works and its safety.
- The clinical study lasts 2 years, and clinical visits will occur every month, in addition to regular doctors' visits.
- Clinical visits will involve monthly lab tests, scans, and other function tests.
- Treatments will be given in addition to standard of care.

Appendix 5: Results of meeting polling questions

The following questions were posed to in-person participants at various points throughout the November 16, 2015, enhancing the Amyloidosis Drug Development Pathway: Guidance for More Efficient and Successful Programs meeting. Similar to the meeting structure, the AL and ATTR polling questions were divided throughout the day and contained different questions. Participation in the polling questions was voluntary. The results were used as a discussion aid and to help gain a better understanding of the full impact of the disease and should not be considered scientific data.

Demographic Results:

Active Participants: 88

1.) Where do you live?

Category	Count	Percent
Washington DC area	10	15.38%
Outside Washington DC area	55	84.62%
Totals	65	100%

2.) What [Amyloidosis] type?

Category	Count	Percent
AL amyloidosis	42	73.68%
ATTR amyloidosis	15	26.32%
Totals	57	100%

3.) How old are you?

Category	Count	Percent
Younger than 30	2	2.86%
31-40	5	7.14%
41-50	5	7.14%
51-60	22	31.43%
61-70	26	37.14%
Over 70	10	14.29%
Totals	70	100%

4.) Are you?

Category	Count	Percent
Female	36	52.94%
Male	32	47.06%
Totals	68	100%

5.) What is your current status?

Category	Count	Percent
Recently diagnosed (less than 6 months ago)	3	4.92%
In remission	29	47.54%
Disease is progressing	23	37.70%
Not sure	6	9.84%
Totals	61	100%

We asked that questions 6 to 10 only be answered by people with AL Amyloidosis and their representatives.

Question for Topic 1:

6.) Which of the following organs are affected by your disease? Check all that apply

Category	Count	Percent
Heart	32	76.19%
Kidney	35	83.33%
Nerves	25	59.52%
GI	17	40.48%
Liver	6	14.29%
Soft tissue	6	14.29%
Other	2	4.76%
Totals	123	292.9%*

*Respondents (n=42) could indicate multiple organs

7.) Check ALL of the below symptoms which have had a significant negative impact on your daily life

Category	Count	Percent
Fatigue	30	71.43%
Shortness of breath	21	50.00%
Edema	21	50.00%
Orthostatic hypotension (dizziness upon standing)	20	47.62%
Sleep problems	26	61.90%
GI problems such as constipation or diarrhea	20	47.62%
Neuropathy	21	50.00%
Other	4	9.52%
Totals	163	388.1%*

*Respondents (n=42) could indicate multiple symptoms

Question for Topic 2:

8.) Have you undergone any of the following treatments? Check all that apply

Category	Count	Percent
Stem cell transplant	38	90.48%
Chemotherapy	44	100.00%
Complementary/alternative therapies	8	19.05%
Other	6	14.29%
Totals	96	228.6%*

*Respondents (n=42) could indicate multiple treatments

9.) Have you had any problems tolerating treatment?

Category	Count	Percent
I have discontinued at least one medication or treatment	22	33.33%
I have reduced dosage for at least one medication or treatment	25	37.88%
I have had problems tolerating at least one medication or treatment but it did not result in a change to my treatment	11	16.67%
I have had no problems	8	12.12%
Totals	66	100%

10.) Of the following factors, which two would you rank as most important for your decision about using treatment?

Category	Count	Percent
Whether the treatment is expected to help relieve the symptoms I experience, improving my quality of life	25	25.51%
The small but significant risk of serious side effects, such as cardiac issues or kidney damage	15	15.31%
Whether the treatment could possibly prolong my life by slowing or halting disease progression	39	39.80%
The expected side effects of the treatment, such as nausea, loss of appetite, etc.	11	11.22%
How the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.	8	8.16%
Totals	98	100%

We asked that questions 12 to 15 only be answered by people with ATTR amyloidosis and their representatives.

Question for Topic 1:

12.) Which of the following organs are affected by your ATTR amyloidosis? Check all that apply

Category	Count	Percent
Nerves	9	60.00%
Heart	11	73.33%
Nerves and heart	11	73.33%
Kidney	1	6.67%
Other	2	13.33%
Totals	34	116.7%*

*Respondents (n=15) could indicate multiple organs

13.) Check ALL of the symptoms which have had a significant negative impact on your daily life?

Category	Count	Percent
Nerve pain	5	33.33%
Lack of mobility/physical limitations	5	33.33%
Loss of balance	9	60.00%
Orthostatic hypotension (dizziness upon standing)	6	40.00%
Eye or vision problems	4	26.67%
GI problems such as constipation or diarrhea	6	40.00%
Fatigue	7	46.67%
Sleep issues	3	20.00%
Totals	45	300%*

*Respondents (n=15) could indicate multiple symptoms

Question for Topic 2:

14.) Have you undergone any of the following treatments? Check all that apply

Category	Count	Percent
Liver transplant	5	33.33%
Heart transplant	3	20.00%
Diflunisal	7	46.67%
Clinical trial for amyloidosis targeted therapy	8	53.33%
Other	0	0.00%
Totals	23	153.3%*

*Respondents (n=15) could indicate multiple treatments

15.) Of the following factors, which two would you rank as most important to your decisions about using treatments? Please select up to two responses

Category	Count	Percent
Whether the treatment is expected to help relieve the symptoms I experience, improving my quality of life	10	37.04%
The small but significant risk of serious side effects, such as cardiac issues or severe neuropathy	1	3.70%
Whether the treatment could *possibly* prolong my life by slowing disease progression	13	48.15%
The expected side effects of the treatment, such as nausea, loss of	1	3.70%

appetite, etc.		
How the treatment is administered, such as how long the treatment takes, whether it requires hospitalization, required doctor visits, etc.	2	7.41%
Total	27	100%

Appendix 6: Incorporating patient input into a benefit-risk assessment framework for AL amyloidosis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• In the US ~4500 patients/year are diagnosed with AL amyloidosis. • AL amyloidosis is a progressive and fatal disorder caused by a small clonal plasma cell population that produces excess monoclonal immunoglobulin free light chains that misfold, aggregate, and deposit (amyloid) in organs and tissues. Progressive organ damage results from both extracellular deposition of amyloid and direct cytotoxicity. • Without treatment, median survival is ~12 months; 1/3 of newly diagnosed patients die <12 months despite treatment. • Patients are frequently misdiagnosed due to variable symptoms that overlap with many other common conditions, which leads to advanced organ involvement and damage by the time treatment is initiated. Approximately 1/3 of patients present with more than 2 organ systems involved. • Symptoms are often severe, though varied organ involvement and commonly include fatigue, shortness of breath, edema, orthostatic hypotension, diarrhea, constipation, and neuropathy. • AL amyloidosis and its treatments can have a significant physical, emotional, and social impact on patients' quality of life, as well as on their ability to manage work and family life. Many patients live with fear, anxiety, and depression. The burden of illness and morbidity of the disease is significant. See the *Voice of the Patient* report for a more detailed narrative.	AL amyloidosis is a serious, life-threatening condition. It is a rapidly fatal disease, and the prognosis is poor. While symptoms vary dependent on organs involved, the disease and its treatment have a significant debilitating impact on patients and their quality of life. Patients with AL amyloidosis have complex treatment needs.
Current Treatment Options	• There are no FDA-approved therapies for AL amyloidosis. • Plasma cell–directed agents commonly approved to treat multiple myeloma (MM): alkylating agents, proteasome inhibitors, corticosteroids, and/or immunomodulatory drugs (IMiDs), either as single agents or in combinations are being used off-label with insufficient data to indicate an optimal use. • Patients require therapeutic interventions that stop their production of amyloid-forming light chains, provide supportive care for organ dysfunction, and remove existing amyloid deposits to potentially limit and reverse organ dysfunction. • These therapies are typically more poorly tolerated than in MM patients, have significant risk, and substantially impact quality of life. Side effects include pain, nausea and vomiting, neuropathy, fatigue, hair loss, myelosuppression, and cognitive impairments. • Stem cell transplant after myeloablative conditioning is effective in a small percentage of eligible patients but is associated with significant treatment-related adverse events and mortality. • Supportive care manages organ dysfunction (e.g., heart failure) and may include dialysis for renal failure. For patients with lasting damage, solid organ transplants may be an option. • Many patients use multiple medical or nondrug supportive care therapies to manage pain and other side effects of treatment and symptom relief. See the *Voice of the Patient* report for a more detailed narrative.	There is a need for FDA-approved therapies to treat AL amyloidosis. Current treatments are toxic and their side effects can have a significant impact on patients' daily lives. Patients have to make difficult treatment decisions between quality of life and the chance to prolong life. Additional effective and tolerable treatment options are needed to slow the progression of disease and reduce the impact of symptoms for patients. These treatments are required to improve quality of life and overall survival of patients with AL amyloidosis.

Appendix 7: Incorporating patient input into a benefit-risk assessment framework for ATTR amyloidosis

Decision Factor	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• ATTR amyloidosis is a rare and progressive disorder caused by the aggregation and deposition of either wildtype or mutant TTR (inherited mutations) • A proportion of the elderly population have wildtype ATTR, which predominantly features cardiac involvement, among experts there is a consensus that it is massively underdiagnosed. • The destabilization of TTR favors fibril formation and deposition in the extracellular space to predominantly cause peripheral and autonomic neuropathy, cardiomyopathy and vitreous opacities; these conditions substantially diminish patients' quality of life. • Symptoms of neuropathy include diarrhea, constipation, nerve pain, incontinence, fainting, loss of mobility. • Symptoms of cardiomyopathy include fatigue shortness of breath and edema. • The hereditary nature of mutant TTR places a large burden on families and has a significant social and emotional impact. • Patients die of organ dysfunction and failure; cardiac involvement hastens death (mean life expectancy is reduced from 9 to 11 years to 5 to 6 years with cardiac involvement) See the *Voice of the Patient* report for a more detailed narrative.	ATTR amyloidosis is a rare, progressive, and life-threatening condition with a considerable disease burden. Hereditary variants that affect many generations have a devastating emotional impact on patients and families.
Current Treatment Options	• There are currently no FDA-approved drugs for treating patients with ATTR amyloidosis. • Patients with inherited ATTR amyloidosis may benefit from liver transplant, which can remove the source of ~95% of mutant TTR. • Cardiac transplant may benefit patients with inherited ATTR or patients with wildtype ATTR amyloidosis. • In recent years diflunisal has started being used off-label, even though it can have significant side effects including GI bleeding and worsening of kidney and heart function. • Other care focuses on managing symptoms such as nerve pain, GI problems, and heart failure. See the *Voice of the Patient* report for a more detailed narrative.	There is a substantial unmet need for safe and effective FDA-approved therapies for patients with ATTR amyloidosis. Patients' survival and quality of life will benefit from treatments that stabilize the TTR tetramer, inhibit deposition and remove existing deposits. Therapies are needed that can delay the onset and progression of symptoms. Emerging targeted therapies are aimed at disrupting production of the protein. Patients with a family history of the disease are willing to take significant risk to improve quality of life or overall survival.

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