The Voice of the Patient Report: Pompe Disease

A report on the Externally Led Patient—Focused Drug Development Meeting corresponding to FDA's Patient-Focused Drug Development Initiative

Externally Led Public Meeting: July 13, 2020

Report Date: May 18, 2022

Hosted by:

Muscular Dystrophy Association

Co-hosted by:

Acid Maltase Deficiency Association

United Pompe Foundation

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

MDA® Muscular Dystrophy Association

The Voice of the Patient: Pompe Disease

This document represents a comprehensive summary report composed by patient advocacy organizations as a result of an externally led patient-focused drug development meeting; a parallel effort to FDA's Patient- Focused Drug Development Initiative. This report reflects the organization's account of the perspectives of patients and caregivers who participated in the public meeting.

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

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A Message of Thanks and Hope

On behalf of the Muscular Dystrophy Association (MDA), as well as our partnering organizations, the Acid Maltase Deficiency Association and the United Pompe Foundation, we are pleased to present the Voice of the Patient Report for our Pompe disease Externally-Led Patient-Focused Drug Development (EL-PFDD) meeting held on July 13th, 2020.

PFDD meetings provide key stakeholders, including the U.S. Food and Drug Administration (FDA), patient advocates, researchers, drug developers, healthcare providers, and others with an opportunity to hear the voice of the patient community to better incorporate the patient voice into the drug development and evaluation process. Our EL-PFDD meeting, and this report, focuses on the Pompe community's perspectives on two topic areas: (1) the most significant symptoms of Pompe disease and its impact on daily life; and (2) current and future approaches to treatment.

We would like to thank the panelists for sharing their stories, struggles, hopes, and concerns. We are also grateful to everyone from the Pompe disease community who joined us virtually for this interactive event. As people living with Pompe disease or caring for someone with Pompe disease, you are uniquely positioned to inform the understanding of the therapeutic context for drug development and evaluation – and this is exactly what you did on July 13th.

We also thank the FDA officials, industry professionals, clinicians, and researchers for their collaboration in paving the path for scientific breakthroughs and potential therapies. We were delighted to facilitate this EL-PFDD meeting for Pompe disease, and we look forward to the therapeutic development advancement it hopefully fosters.

Sincerely,

Paul Melmeyer

Vice President, Public Policy & Advocacy

Muscular Dystrophy Association

Tiffany House

President and CEO

Acid Maltase Deficiency Association

David Hamlin

United Pompe Foundation

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Executive Summary

Pompe disease (also called acid maltase deficiency) is a rare, metabolic muscle disorder that is estimated to occur in about 1 in every 22,000 live births in the United States, with an estimated worldwide prevalence of 5,000-10,000 cases.1–3 The disease is comprised of two main subtypes - infantile onset and late onset. Pompe disease causes slow, progressive muscle weakness, especially of the respiratory muscles and those of the hips, upper legs, shoulders and upper arms. Various manifestations of Pompe disease have been described which differ in severity and the age at which the disease becomes clinically noticeable. Without treatment, babies with infantile onset Pompe disease (IOPD) typically die in the first two years of life. The feature which distinguishes infantile from late onset Pompe disease (LOPD) is presence of cardiomyopathy in the first year of life. Overall, Pompe is a continuum of disease severity and many patients with LOPD have severe weakness and respiratory insufficiency, and without treatment, shortened life span.

The Muscular Dystrophy Association (MDA) submitted a Letter of Intent and was granted the opportunity to host an Externally-led Patient-Focused Drug Development (EL-PFDD) meeting, a parallel effort to the Food and Drug Administration's (FDA) PFDD initiative, to more systematically obtain patients' perspectives on the burden of disease and impact of current treatments or lack thereof. The EL-PFDD meeting on Pompe disease was held virtually on July 13, 2020. Through this meeting, patients living with Pompe disease and their families and caregivers were asked to share their unique insights on the impact of Pompe disease on their day-to-day lives. Perspectives on currently available treatment options and strategies for disease management, as well as expectations for future treatments, were also shared.

The objective of the meeting was to increase FDA and other stakeholders' understanding of how patients experience and manage Pompe disease and the factors that are considered when treatments are chosen. This may, in turn, help the FDA understand the severity of the condition, unmet medical needs, and preferences for future treatments, all which can inform an appropriate benefit-risk balance for new treatment options. The voice of patients with Pompe disease was heard through courageous patient and caregiver participants, including from testimonies, polling, open moderated discussions, and solicited written messages. The EL-PFDD meeting was attended virtually by over 100 Pompe community members, a significant gathering for this rare disease. Throughout the course of these activities, the voices of individuals with Pompe disease were heard strongly and consistently, and the following key messages emerged:

Pompe disease is a spectrum disease classified through diverse manifestations, leading to unique presentations in patients. Pompe disease can span multiple generations, appears with diverse symptoms and manifestations, which can progress at different rates even within families, and presents drug development challenges because of disease phenotypic variability.

Patients with Pompe disease deal with very difficult issues in their daily lives, including muscle weakness, loss of mobility, inability to participate in or perform daily activities, difficulty eating, inability to work or go to school, difficulty communicating, and fatigue.

Younger patients with Pompe disease face particular social and emotional challenges, including an inability in keeping up with peers in school, sports, and social activities, difficulty communicating with peers, and fear of the future.

The current state of managing Pompe disease is burdensome for patients. Enzyme replacement therapy (ERT) is time consuming and logistically difficult due to the need for frequent appointments. Management of feeding tubes, infusion ports, and other treatment necessities is difficult for caregivers, and infection is a constant worry. ERT may lose effectiveness in patients over time, leaving them with no therapeutic options. Clear recommendations on when to begin ERT in late-onset disease prior to clinically recognizable symptoms is lacking. Data on the utility of supportive treatments is also lacking.

New treatments should focus on the following unmet needs: Maintaining or improving muscle function, durable effectiveness over time, and preventing loss of respiratory function.

Patients are most likely to use a new medication based on: Benefits shown for symptoms of importance, and on their ability to access the drugs (clinical trial eligibility, drug cost, insurance coverage).

Patients and families are willing to participate in clinical trials in the following cases: They meet eligibility requirements, which are often too stringent to allow participation, possible benefits outweigh the burdens of participating (time/effort required to receive treatments, side effects, etc.), and patients have mixed feelings about gene therapy trials – some are enthusiastic and excited by the possibility of a dramatic improvement, while others worry about potential side effects of the gene therapy approach.

This EL-PFDD meeting was a critical step forward for the Pompe disease community. The insights collected and reported on in this Voice of the Patient Report reflect important perspectives of people living with Pompe disease and will hopefully guide pharmaceutical companies in developing the critical medicines that are desperately needed by this community. These insights may also be used to help develop a benefit-risk framework that the FDA may utilize in their regulatory decision making.

"I believe that in the years ahead, we will have a gene therapy that can be life changing for patients with Pompe disease, and the proceedings of today's meeting, what we hear today from…patients and caregivers will facilitate that development and regulation of new therapies.

At the FDA when we've listened to these meetings, we think about, how are the clinical trials going to be designed? How do we need to design the clinical trials? What you say help us helps us to think about what outcome measures, what clinical endpoints are meaningful, what matters to patients and helps us to think about how to balance risks and benefits when looking at a new treatment."

— Dr. Wilson Bryan, Director of the Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

Pompe Disease Externally-led PFDD Meeting Design

The goal of the meeting was to increase the FDA's understanding of the daily experiences of patients with Pompe disease, including the most troubling symptoms, how patients, families and caregivers manage these symptoms, and the most important factors that are considered when a treatment is chosen. This, in turn, may set the context for FDA when making benefit-risk balance decisions for new treatment options by providing an understanding of the severity of the condition and the unmet medical needs.

"Having this dialogue is extremely valuable for us because hearing what you should care about can help us really lead the way in figuring out how best to facilitate development of new treatments for patients living with Pompe. I study voice of the patient reports all the time in my work with pharmaceutical companies, because while I work with them, I work for you. And so these reports can be a powerful tool in persuading companies to choose broader enrollment criteria so that as many patients as possible have access to new therapies by enrolling in clinical trials."

— Dr. Kathleen Donohue, then-Acting Director of the Division of Rare Diseases and Medical Genetics at the Center for Drug Evaluation and Research, FDA

Due to the COVID-19 pandemic, this meeting was held in an interactive virtual format, with panelists and audience members participating through multiple formats, including prepared statements and live Zoom sessions, real-time polling, web-based messaging, and live telephone calls. Groups of panelists (representing pediatric and adult patients living with either infantile-onset Pompe disease (IOPD) or late-onset Pompe disease (LOPD)) shared testimonies to communicate the real and specific ways by which their lives are impacted by Pompe disease. Each round of panelist statements was followed by a polling session and a period of facilitated discussion with participants over the various remote platforms. Participants attended from across the US and internationally.

"One of the things that I'm most proud of, in regards to the Pompe community, is the way that the entire community works together... patient community, the scientific medical community, regulatory affiliates like the FDA and industry, each one has a unique perspective, but all need to be heard."

— Tiffany House; President and CEO, Acid Maltase Deficiency Association; Chair, International Pompe Association

Pompe Disease Externally-led PFDD Meeting Design

The voice of the patient was supplemented by detailed presentations:

- Scientific and Clinical Overview of Pompe Disease – Priya Kishnani, MD; Chief, Division of Medical Genetics, Duke University
- Regulatory Approach to Pompe Disease Therapies – Kathleen Donohue, MD; Acting Director of the Division of Rare Diseases and Medical Genetics, Center for Drug Evaluation and Research, FDA
- Current and Future Pompe Disease Treatment Options – Barry Byrne, MD, PhD; Director, Powell Gene Therapy Center, University of Florida; Chief Medical Advisor, MDA
- FDA Afternoon Session Remarks – Wilson Bryan, MD; Director of the Office of Tissues and Advanced Therapies, Center for Biologics Evaluation and Research, FDA

Key insights from these presentations have been pulled into the disease background section of this report, and the full presentations and patient community engagement are available on the MDA website at **https://www.youtube.com/watch?v=K12fd5jcP_U&**

Background on Pompe Disease

What is Pompe disease?

Pompe disease is a genetic disorder in which a complex sugar, called glycogen, accumulates in the body's cells, specifically in the lysosomes. The disease is caused by the deficiency of an enzyme, acid alpha-glucosidase (GAA), that breaks downs glycogen in the body. The accumulation of glycogen in muscles impairs their ability to function normally. Pompe disease presents as a disease continuum, with subsets classified by age of onset, organ involvement, severity, and rate of progression.4

What causes Pompe disease?

Genetic factors

Pompe disease is caused by mutations in the GAA gene. To date, 582 variants in the GAA gene have been reported to cause Pompe disease.5,6 Some GAA variants are found with a higher frequency in certain populations, yet many GAA variants are rare and found in a single family or a small number of families.6 In general, patients with the most severe form of Pompe disease have disease-causing variants in both alleles of the GAA gene that completely prevent formation or function of the GAA enzyme.5,7 Conversely, patients with less severe disease have "less severe" variants in at least one allele of the GAA gene that allow for some level of GAA enzyme production and activity.5,7

Pathophysiology of the disease8

GAA enzyme deficiency in patients with Pompe disease causes accumulation of glycogen in lysosomes, resulting in the swelling and rupture of these cellular structures. Since the GAA enzyme is normally found in all tissues, this process can result in cell damage in multiple organs. It is well-accepted that progressive degeneration of cardiac and respiratory muscle, as well as weakening of skeletal muscle, contributes to Pompe disease.8–11

What are the symptoms of Pompe disease?

Infantile-onset Pompe disease (IOPD) encompasses disease presentations with symptom onset before 12 months of life. Classic IOPD presents in the first days of life and has the most severe presentation. If untreated, this form leads to death from hypertrophic cardiomyopathy (HCM) in the first year. Babies with non-classic IOPD also present with cardiomyopathy in the first year of life, but disease progression is less rapid than those with classic IOPD. The muscle weakness in non-classic IOPD typically leads to serious respiratory distress, and most affected children live only into early childhood if left untreated. **Late-onset (Juvenile and Adult) Pompe disease (LOPD)** encompasses disease presentations with symptom onset: (1) before 12 months of life without cardiomyopathy, and (2) after 12 months of life. Presentation can occur as late as the 6th decade of life, is usually milder than IOPD and is less likely to involve the heart. As LOPD progresses, respiratory failure often results in morbidity and mortality. Characteristic features of Pompe disease vary by subtype and can include: poor muscle tone, generalized muscle weakness, thickening of the heart muscle, enlarged liver due to heart failure, failure to gain weight and grow at the expected rate, respiratory distress, feeding difficulties, and hearing loss, among others.

How is Pompe disease diagnosed?

Pompe disease is suspected in individuals with the following clinical and supportive laboratory findings.7

Clinical Findings

IOPD is suspected in infants with: (1) Poor feeding/failure to thrive, (2) Motor delay/muscle weakness, (3) Respiratory infections/difficulty, and (4) Cardiac problems. LOPD is suspected in infants, children, and adults with: (1) Proximal muscular weakness, (2) Respiratory insufficiency, (3) rigid spine, among other signs and symptoms.

Supportive Laboratory Findings

Laboratory findings that support a Pompe disease diagnosis include: (1) Confirmation of GAA deficiency, (2) Elevated serum creatine kinase (CK) levels, and (3) Elevation of urinary glucose tetrasaccharide (Glc4). The U.S. Department of Health and Human Services added Pompe disease to its Recommended Uniform Screening Panel (RUSP) in 2015, making it the first neuromuscular disease recommended for newborn screening (NBS).9 As of February 2021, 28 states include a screen for Pompe in their NBS programs.10

How is Pompe disease currently treated and managed?

Established guidelines

Guidelines for have been published for the initial evaluation of individuals with IOPD11 and LOPD12 to establish the extent of disease and needs of the diagnosed individual. Guidelines for the management of IOPD have also been published by an expert panel from the American College of Medical Genetics.11 Recommended treatments for disease manifestations include: (1) An individualized plan for care of cardiomyopathy, (2) Physical therapy for muscle weakness to maintain range of motion and improve ambulation, (3) Surgery for contractures, as needed, (4) Nutrition/feeding support, and (5) Respiratory support, including inspiratory/expiratory training in affected adults, CPAP, BiPAP, and/or tracheostomy.

Enzyme replacement therapy (ERT) Administration of ERT

To prevent the primary manifestations of disease, enzyme replacement therapy (ERT) with alglucosidase alfa is recommended, though the optimal timing of commencing treatment is still being established. Myozyme® (alglucosidase alfa) was approved by the FDA in 2006 for IOPD.13 Lumizyme® (alglucosidase alfa) was approved by the FDA in 2010 for use in individuals older than age eight years with LOPD.14 Age restrictions on Lumizyme were removed in 2014. Myozyme® and Lumizyme® are administered by slow IV infusion at 20-40 mg/kg/dose every week or every two weeks. A retrospective study has shown that the ERT regimen of 20 mg/kg every other week is insufficient to halt long-term progression of Pompe disease, and it has become increasingly evident that many patients receiving ERT display a diminishing response to therapy.15 As a result, many individuals are now treated with the higher dose.16–18 Although ERT increases patient life expectancy and ventilator free survival, it is not curative.

Complications of ERT

ERT can be accompanied by infusion reactions, and similar to other protein therapeutics, ERT use comes with a risk for anaphylaxis. Infants at high risk for development of antibodies to the introduced alglucosidase alfa enzyme (anti-rhGAA antibodies) will likely need immunomodulation early in the course of treatment.19,20 As of February 2020, the FDA recommends the determination of cross-reactive immunologic material (CRIM) status prior to initiating ERT,21 as individuals who do not produce cross-reactive immunologic material (CRIM-negative) generally develop high titer anti-rhGAA antibodies during ERT and require use of immunomodulatory protocols.

What research is currently being conducted to develop new therapies for Pompe disease?

Current treatments for Pompe disease are life-saving, especially in the case of IOPD. For LOPD, current treatments lessen the rate of decline in patients, and in some instances, lead to functional improvements. Yet, there are still unmet needs for people with Pompe disease. Several groups are working to improve the efficacy of ERT.22 Sanofi Genzyme developed an advanced ERT (avalglucosidase alfa) with a unique strategy of lysosomal targeting, which was shown to have a good safety and efficacy profile and is in phase 3 clinical trials (ClinicalTrials.gov IDs: NCT02032524, NCT03019406, NCT02782741). Amicus Therapeutics has also developed an advanced ERT (ABT200), and is attempting to stabilize the structure of this modified GAA enzyme by co-delivering it into the body with a chaperone protein (ClinicalTrials.gov ID: NCT03911505).

Researchers are also investigating gene therapy to correct the underlying enzyme defect in Pompe disease.22–24 This strategy would require a single, or very few, treatment(s) to achieve long-term benefit, could help overcome mechanistic challenges faced with ERT, and address logistical difficulties that patients face in adhering to weekly appointments. Several groups - Spark Therapeutics (ClinicalTrials.gov ID NCT04093349), AskBio (ClinicalTrials.gov ID NCT03533673), and Regeneron25 - are pursuing gene therapy strategies to replace the GAA gene in the liver. A lentiviral approach being pursued by AvroBio has shown promise in a mouse model of disease.26

One consideration for introducing the GAA gene into patients with IOPD is that these patients produce little to no GAA enzyme of their own and could develop immune reactions to the new enzyme. 27

Finally, emerging research is shedding light on the contribution of additional body sites, beyond skeletal and cardiac muscle, to Pompe disease pathophysiology. The contributions of nervous system dysfunction,27 smooth muscle dysfunction,28 motor neuron pathology and weakness of respiratory muscles29,30 are being explored to understand the contributions of additional cell/tissue types to Pompe disease progression, with the goal of guiding the development of future therapies for the disease.

Information on clinical studies can be found at ClinicalTrials.gov in the US and EU Clinical Trials Register in Europe.

Meeting Participant Demographics

The Pompe disease EL-PFDD meeting was attended virtually by over 250 people. The polling was made available to all members of the Pompe disease community (i.e., patients, family and other direct caregivers), and approximately one-third of eligible attendees engaged in the polling exercises.

The polling revealed that almost all of the participants (91 percent) were U.S.-based. The majority of the participants were patients and caregivers living with Pompe disease. Others in attendance came primarily from the biopharmaceutical industry, advocacy organizations, and the FDA. Gender representation was approximately two-thirds female and one-third male. There was good representation across all age groups.

The poll results indicated that about half of patients displayed symptoms of Pompe disease before the age of five. However, only about one-third of patients were actually diagnosed with Pompe disease before the age of five, while approximately one-half were diagnosed between the ages of 19-50 years. One-third of participants reported receiving a diagnosis by genetic testing, one-third by clinical examination, potentially followed by laboratory testing, and a little less than one-third by enzyme level testing. Only 5% of patients were diagnosed through newborn screening.

The first half of the EL-PFDD meeting was divided into sessions examining the daily experience of patients with IOPD and LOPD. The polling indicated that the majority of participants were patients with LOPD, with only 16% of polling respondents associated with the IOPD population .

Session 1: Daily Experiences with Pompe Disease – Infantile Onset Perspective

The daily experiences of individuals with IOPD were expressed through testimonies from patients and caregivers, by polling the attendees on specific questions, and by in-depth discussion with the audience members. The perspectives described here came from young patients and their caregivers, but are all given from the perspective of what is like to live with IOPD. The objective of the session was to discuss the symptoms and daily challenges that matter most and have the greatest impact on the daily lives of patients living with IOPD, as well as how these may vary over time. The session also sought to uncover what things are the most concerning and worrying to patients with IOPD and their caregivers.

Key Findings from Participant Testimonies and Polling

Muscle weakness and decreased muscle tone

Participants reported muscle weakness and decreased muscle tone as two of the most troublesome symptoms of IOPD (Appendix Figure 9). When asked what symptom of IOPD was experienced most recently, individuals with IOPD and their caregivers also cited muscle weakness and decreased muscle tone as the most recently experienced symptom (Appendix Figure 8).

George – Father of child (Phoenix) living with IOPD

"My son Phoenix is 17 years old and was diagnosed with infantile onset Pompe disease when he was six months …
… Unfortunately in this three month period of searching for a diagnosis, our son lost a tremendous amount of strength. He lost his ability to swallow and eat, crawl, and kick. The use of his arms declined significantly. Most importantly, he was losing his ability to breathe, and also his heart continued to get worse…"

Krystal - Mother of child (Haley) living with IOPD

"The most significant impact, I mean that's definitely changed over the last 14 years. Initially you're just trying to get by those hard winters, keep infections, respiratory infections out, and now just her symptoms are more physical. So low muscle tone, not being able to do your own activities of daily living, being like her peers. Items like that that just are the most significant for her at her time in her teenage life now."

Impact on ambulation and exercise/sports ability

Related to the muscle weakness, participants reported serious effects of the disease on the patient's ability to exercise/participate in sports and take walks, among other activities (Appendix Table C). Lack of ambulation, which likely stems from muscle weakness in the hips and upper legs, was considered by participants to be a particularly difficult impact of the disease.

Krystal - Mother of child (Haley) living with IOPD

"So yeah, going upstairs, things like that, or in school like gym class. So she would just not attend gym class, because it'd be difficult or they'd have to adapt around her abilities…
…About the future, I believe what worries me most right now, we know with Haley, is not being able to walk and using a wheelchair, but that's pretty stable. So, of course, as she gets older, college, higher grades, that's going to become more difficult with driving and being able to go off to college."

Melanie - Mother of child (Ryker) living with IOPD

"We have a lot of fears for our son, or just concerns I would say. Just in the short term, what does school look like for him? He's three. He is unstable when he walks. Do we need a wheelchair? Do we need to make our house ADA accessible?...
...What does the far out future look? Does he need a caregiver? Am I going to be able to carry him up the stairs when he gets 10 years older? There's a lot of concerns about the future and a lot of unknowns that we have right now."

Impact on speech and feeding

One of the most common themes expressed by participants was difficulty with speech and feeding, which often results from facial muscle weakness. Speech and feeding difficulties were reported as a highly troublesome symptom of IOPD (Appendix Figure 9) and a symptom that was experienced recently by patients with IOPD (Appendix Figure 8).

Anxiety due to challenges with speech and feeding was routinely cited as a troublesome symptom, and social difficulties were reported in children with IOPD because of hypernasality or other IOPD impacts on speech that make children with IOPD hard to understand among their peers. Children with IOPD may also be on a feeding tube which may alleviate some growth and low weight challenges, but create social anxieties of fitting in with peers. Solutions to these challenges cited by our participants include hearing aids, augmented communication devices, and sign language to communicate with family members.

Melanie - Mother of child (Ryker) living with IOPD

"My son, Ryker, is three years old. He was diagnosed at three and a half months old, so for infantile that's actually a late diagnosis. ... currently, our most troublesome symptoms at this point is speech, hearing and feeding. It all has to do with the mouth...
...He is unable to speak at all. The only word he says is mama, which is the best word. But he uses a little bit of sign language, and the feeding has also been really difficult. He does not have a G tube, but he is unable to progress in his feeding. So we are still stuck on purees and soft foods, even at three years old...
...Our worst days have to do with feeding.
He's able to do a little bit of sign language for communication. But introducing any type of new food with him is so anxiety producing for him because for the first year of life he was tube fed for a good portion because he was failure to thrive...
... So he just didn't progress like a normal kid does with learning how to eat and progressing in their textures. So introducing any type of new food is just horrible for him. He starts crying. He doesn't want to try it. He throws it off the table. He just wants to get away from it. So we do have him in feeding therapy right now, and that's helping a little bit. Our good days are if he tries one new thing; that's a good day for us."

Sarah - Mother of two children (Bruce and Myra) living with IOPD

"Anxiety was probably a top one, but it is related to the mouth...
... Bruce is nine. He's got the G tube. We're fortunate to have that, but he's going to school. He doesn't want to go because of his G tube feedings. He wants to be with his friends and peers in the cafeteria doing what they're doing...
... And then, like Melanie said, trying new foods is a disaster, so that relates into the growth. He's just not his appropriate weight. He's been on the same steady dose of Lumizyme now for a long time, but just progressing the weights has been our biggest issue, and anxiety...
... Bruce talks with some notable Pompe characteristics, such as hypernasality and articulation difficulties. Myra has severe speech delays, but she definitely gets her point across as a sassy two-year-old. Bruce wears hearing aids, which helped tremendously with his word count

when he received them at four years old. But Myra hears so well."

Paloma - Mother of child (Vaun) living with IOPD

"An augmented communication device has allowed Vaun to communicate with those listeners who have trouble understanding him. It has helped with Vaun's frustration level, and also has started him early in learning how to read. It can be emotional for us to watch other kids struggle to connect or understand Vaun, but he is learning to adapt and handle these interactions more and more each day."

Impact on social interaction

Participants reported effects of the disease on the patient's ability to interact socially, among other activities. This is due to loss or difficulty of ambulation as well as speech barriers. Participant comments reinforced these negative impact of IOPD on social participation making it difficult for children with IOPD to participate in typical childhood social activities.

Krystal - Mother of child (Haley) living with IOPD

"I think mainly just her not being able to walk around, go places with her friends at this time of her life where that's very important, the socialization. We try to do our best to let her have those memories and perform them for her at times. But when there's times she can't go places or do things that her friends are doing, because physically it's not able, that's at this point in time the most difficult."

Haley – Teenager living with IOPD

"I'm not able to get on the boat to go out on the lake as easily…or go somewhere that maybe there's stairs and I'm not able to take my wheelchair inside to…the place that they're going."

Paloma - Mother of child (Vaun) living with IOPD

"…The social interaction and participation…

…it seems to be that his biggest struggle, because of what we've talked about with the speech and things, is his ability to connect with little people his age…

… peers his age have a difficulty, and because it's different and difficult, they just want to shy away and not understand what's going on. So that can be heart wrenching on the playground and stuff. But we've been fortunate. He's done soccer. We've signed him up for your T-ball. He's incredible.

…I really do think it's the inability to understand what he is saying. So his speech therapists have worked a ton on when we meet somebody new, we introduce ourselves; "Hi, my name is Vaun. Hi, what is your name? Do you want to play?"

…He's got these different greetings so he can make those interactions a little easier, whether that's vocal or if use the augmented communication device. But it seems like either way it becomes uncomfortable for that little kid listener, as you can imagine. Little kids, they're used to what's normal, and what's normal for Vaun certainly isn't normal for the masses."

Respiratory concerns

While respiratory issues were not identified via polling as a highly troublesome symptom, a number of participants commented on the susceptibility of individuals with IOPD, to respiratory infections, particularly when they were younger. Parent caregivers also expressed concerns about future respiratory decline.

George – Father of child (Phoenix) living with IOPD

"…At three years old, Phoenix acquired pneumonia and was intubated. After that he was unable to breathe on his own and had to undergo a tracheostomy procedure and was put on a ventilator 24 hours a day. He also had to have a G-tube placed for constant feeding and an Infusaport to administer enzyme replacement therapy into his bloodstream."

Krystal - Mother of child (Haley) living with IOPD

"I know respiratory wise, when she was younger that was a big issue for us and has been very stable recently. But I think as she gets older, and if there is any progression, could her respiratory status get worse is very frightening."

Difficulties with ERT

Participants in the "Daily Experiences with Pompe Disease – Infantile Onset Perspective" session revealed a number of struggles with accessing and receiving ERT. Comments and polling results related to ERT will be highlighted in the below section of this report entitled "Patient Perspectives on Treatments for Pompe Disease."

Additional daily experiences

While participants described common challenges with muscle weakness, ambulation, speech and feeding impediments, respiratory issues, and social concerns, participants also named several other challenges associated with IOPD, including challenges associated with receiving a diagnosis as well as heavy tolls of caring for a child with IOPD.

Issues at diagnosis

George – Father of child (Phoenix) living with IOPD

"My son Phoenix is 17 years old and was diagnosed with infantile-onset Pompe disease when he was six months…"
…at three months old, during a routine pediatric exam, we were informed that Phoenix had a heart murmur and that he needed further investigation. Using ultrasound, Phoenix would be diagnosed with a potentially lethal heart condition called hypertrophic cardiomyopathy. However, hypertrophic cardiomyopathy is a symptom of several different possible conditions…."

Paloma - Mother of child (Vaun) living with IOPD

"…Vaun has trail-blazed a unique and successful path in his journey for this once extremely fatal disease…
…Vaun was born four years ago in Kansas City, Missouri. At six days old we were informed that Vaun's newborn screening had flagged for Pompe's disease…Follow-up assessments at the local children's hospital confirmed our nine-day-old son had Pompe's. The pain and despair of that diagnosis was devastating, but we were fortunate that the news came early, and that made a difference for Vaun…
…We have needed to push doctors, nurses, therapists, even family members, outside their comfort zone to get what is best for Vaun. We don't wait for people to give us answers. We research, become educated and are a part of Vaun's journey."

Sarah - Mother of two children (Bruce and Myra) living with IOPD

"I'm a mom to two of infantile-onset Pompe kids. Bruce is nine and Myra is two."
…Bruce was clinically suspected to have infantile-onset when he was three days old, and his official diagnosis came at 13 days old. He started Myozyme at 20 milligrams per kilo, biweekly at that time…
…After two weeks at home, his PICC line became infected and he landed himself back at Children's for a very long three months battle against Bacterial meningitis. He had a brain abscess and there was a host of doctors and nurses who had never heard of Pompe and were ready to give up on him…
…[Myra] was diagnosed at 20 weeks in utero… At five days of age in the NICU, she had her first dose of Lumizyme and she was discharged home without all the complications that her brother experienced."

Deana – Mother of two children (Mason and Dakota) who have lived with IOPD

"I'm a mother to five beautiful children, two of which have had an infantile Pompe…..My son Mason is the reason I first learned of this horrid disease 19 years ago….
…At seven and a half months old, Mason passed away from cardiac and respiratory complications….

...These doctors in South Carolina had a grim outlook for Dakota and didn't expect him to live long after birth. Right away we had an echo of his heart, which wasn't normally done, but I had been working with the wonderful team at Duke through the pregnancy and the birth and knew to make this special request....
...We've experienced firsthand the incredible change that is possible with newborn screening and treatment before muscle damage occurs, preventing progression of the disease and death."

Difficulties associated with caregiving

Sarah - Mother of two children (Bruce and Myra) living with IOPD

"... Port accessing, it can be good days or bad days. It depends what day it is, but port accessing is really bad too."

George – Father of child (Phoenix) living with IOPD

"...our home is much like a hospital, with Hoyer lifts, oxygen tanks, a ventilator, respiratory equipment, suction machines, a defibrillator, and the list goes on and on...

...I am Phoenix's full-time caregiver, because it has been impossible in this area to find anyone that's capable of caring for a 100 pound 17-year-old on a ventilator 24-hours a day who is 100% dependent upon somebody else for his movement. We also had to learn how to care for G-tubes, tracheostomies, and understand how to operate ventilator proficiently, access his port and help with infusions."

The daily experiences of living with LOPD were expressed through testimonies directly from patients and caregivers, by polling the attendees on specific questions, and by in-depth discussion with audience members. The perspectives described here came from adult patients and their caregivers, but are all given from the perspective of what is like to live with LOPD. The objective of the session was to determine the symptoms and daily challenges that matter most and have the greatest impact on the daily lives of patients living with LOPD, as well as how these may vary over time. The session also sought to uncover what is most concerning and worrying to patients with LOPD.

Session 2: Daily Experiences with Pompe Disease — Late Onset Perspective

Key Findings from Participant Testimonies and Polling

Muscle weakness

Participants reported muscle weakness as the most troublesome symptom of LOPD (Appendix Figure 12) and also as the most recently experienced. (Appendix Figure 11). Participants described the progressive nature of their muscle weakness by describing increasing difficulty in walking up steps, picking things off the floor, walking short distances, and facial muscle weakness causing difficulty in speaking, chewing, and swallowing. Speakers also noted how scary this can be, particularly after long periods of muscle strength stability.

Vanessa – Individual living with LOPD

"I showed some mild symptoms as a child, such as poor posture, gait abnormality, soft speech, and had trouble gaining and maintaining weight...

…The defining awareness of my symptoms came after the birth of my second son in 2003. The above symptoms continued but got progressively worse. I was experiencing trouble standing from a seated position. If on the floor, I couldn't get up without help. My hips felt as if they were totally numb when I tried to use them. My balance and core strength was greatly diminished, and I was having trouble bending over to pick things up…
…The gait abnormality grew worse, which caused trouble when trying to climb stairs. I was having a lot of foot and ankle pain and I became exhausted and wobbly just walking across the parking lot. My poor posture, which would later be defined as scoliosis, made it harder to stand or sit upright completely for an extended period of time. My speech became softer and somewhat slurred, and I began have trouble swallowing and chewing thoroughly. I found that in a reclined position I could not get enough air. These things were very scary…"

Lucas – Individual living with LOPD

"Last summer, for the first time in my life I had started to get weaker. I was diagnosed with Pompe at five months with a muscle biopsy. I've lived in this thing my whole entire life. While I've always known life on a vent as well as use a wheelchair, getting weaker than what I'd already known to be my "normal" was a special new level of hell for me. My legs were getting weaker and my arms were starting to feel more worn out than usual. Doing tasks such as exercises and certain aspects of my work as a musician, guitarist and singer, had gotten harder but not impossible…"

Sean - Individual living with LOPD

"Today, I can relate mobility and strength issues to the disease, and they still continue to progress despite being on enzyme replacement therapy. Picking things up off the floor, cleaning up oneself after the restroom and breathing are just some of the things I continue to notice that are declining, even from the point when I was diagnosed two years ago."

Morgan - Individual living with LOPD

"For me the most [troublesome symptom] is my muscle weakness…fatigue…"

Bryn - Individual living with LOPD

"There are a lot of low-level symptoms I've had for a long time that I never realized were connected to Pompe - fatigue, gastro-intestinal trouble, falling over a lot. These aren't as severe or obvious as the 'headline' symptoms like muscle weakness and gait abnormality, but when you add them up they have a big impact on your life."

Fatigue

Participants reported fatigue as the second most troublesome symptom of LOPD (Appendix Figure 12) and also a symptom that was experienced recently by patients with LOPD (Appendix Figure 11). Participant comments demonstrated a common theme of LOPD affecting energy levels and causing extreme fatigue. Participants described having to carefully budget their energy for the day, consequently substantially limiting what activities could be completed, and what would have to wait or go undone.

Vanessa – Individual living with LOPD

"The worst symptom of my disease revealed itself as I started falling asleep constantly…."

Sean - Individual living with LOPD

"How much effort it takes me to breathe, walk, to talk, run, and that fatigue I deal with every day is a variable that's not really measured beyond self-reflection. Just how affected I am with Pompe is something I still struggle with."

Monique – Individual living with LOPD

"…the biggest obstacle is managing my energy levels. I just don't seem to have enough. So it's just like, well, what am I going to do today? What do I need to accomplish this week? Okay, so do I take a shower tonight and get some rest or take one in

the morning? How many errands do I have to run? How much energy am I going to have? And I really have to kind of ration what I can do with my energy and really time management and plan my days efficiently."

Dave – Caregiver to spouse with LOPD

"In our experience what we've done is say, where do we really want to spend the energy? So we find ourselves spending more time on what's truly important and less time on what's not."

Tiffany – Individual living with LOPD

"I think as you journey through different stages of life, your routine changes. So I've modified my routine to allow me to do the things during the day that I have to do...
...You have to think about what you have to do today, tomorrow, throughout the week. And maybe you rest today so you have the energy for tomorrow."

Respiratory Concerns

Unlike in the IOPD Session, participants in the LOPD Session reported breathing problems/ shortness of breath as a highly troublesome symptom (Appendix Figure 12) and also a symptom that was experienced recently by patients with LOPD (Appendix Figure 11). Similar to caregivers of children with IOPD, anxiety over future respiratory problems and their impacts were expressed by participants.

Lucas - Individual living with LOPD

"....my life is still understandably impacted by Pompe Disease. On any given day, I need assistance for most aspects of daily living, including keeping my airway clear."

Vanessa – Individual living with LOPD

"I am very concerned about not being able to breath as I get older."

Carolyn - Individual living with LOPD

"I want to be able to continue to walk and breath independent of assistance and continue to work with children."

Impact on ambulation and exercise/sports ability

Related to the muscle weakness, participants reported serious effects of the disease on their ability to walk and participate in exercise/sports, among other activities (Appendix Figure 14). Some participants highlighted their history of playing sports and participating in other athletic endeavors but are no longer able to. Others described the impacts on loss of ambulation on daily tasks.

Sean – Individual living with LOPD

"Growing up, I never had any inclination that I was any different from others my age. I enjoyed living like a normal child and excelled at school. Gym class and physical activities, on the other hand, were not something I did very well at..."

Monique - Individual living with LOPD

"...I was a competitive swimmer and a dancer and a gymnast and a golfer. Pretty much all growing up all through high school, I was dancing a lot still and taking private lessons and taking lessons in school. So I was pretty active...
...But today I do need a mobility scooter full-time. I can walk with a walker."

Brian - Individual living with LOPD

"For some of us who are late onset where the symptoms have come on later in life, we've lost the ability to do stuff like...I used to ski, I used to body surf, I used to go hiking, you know, back in my twenties. And those things are long gone."

Sabrina – Mother of child (Zach) with LOPD

"He can walk, he can drive, he can do some basic things like this, but...he's 24. So he wants to... do paint balling with his friends or he wants to go fishing, or he wants to go - things that aren't

necessarily super physically active, but just really typical young adult activities. And he can't without a struggle or without some assistance…
…He can't ride a bicycle because his core balance isn't strong enough. And so our family, we really decide all of our activities and travel and recreational plans around Zach because we never ever want him to feel like we're not getting to do something because of him. And we don't ever want him to feel excluded because life, just in and of itself, excludes people with Pompe from enough things already…we just work really hard to make sure that our travel and our activities are really centered around his capabilities and not his limitations."

John – Individual living with LOPD

"My concern is that I am now 65, in a powerchair, unable to stand or walk, on Bipap and I live alone. My wife died in 2007 I have no family and few friends I can depend on."

Anxiety/depression

Anxiety and depression were identified by some participants as troublesome symptoms of LOPD (Appendix Figure 12) and also symptoms that was experienced recently by patients with LOPD (Appendix Figure 11). Participant comments highlighted the uncertainty of the future, as well as physical and respiratory decline, as sources of anxiety for patients and caregivers dealing with LOPD.

Lucas - Individual living with LOPD

"What impacts me the most, however, is the unknown. Most people deal with the concept of mortality, but this weight is especially heavy on me. The life expectancy for someone in my situation is unknown to the scientific community."

Sean - Individual living with LOPD

" The future is uncertain with Pompe, just because we've seen the progressive nature affects everybody differently. That's perhaps what's really troubling is we don't know individually how we're going to be in 10 years, 20 years, how long we're going to live, how we're going to be affected. That's been something on my mind, and I kind of see living for the present than rather than the future because the future is so unknown.
…I think it really brings importance to the mental health, I know a lot of patients really say that the mental health aspect of Pompe is often unmet, because either we bring it to the forefront or we put it in the back of our mind is what does the future hold, what is 10 or 20 years out…I could be in a wheelchair, am I going to need assisted ventilation? And there's no easy answer."

Impact on social interaction and travel

Some participants reported effects of LOPD on the patient's ability to travel and to interact socially, among other activities. Participant comments reinforced the negative impact of LOPD on the ability to participate in social activities that require these physical skills.

Monique - Individual living with LOPD

"I have to make sure that I have accessible accommodations when I travel, from everything from the hotel to curb cutouts, to the car, to get me from a train station or airport to the hotel. I have to call ahead, even here in the United States, to shops and restaurants and some of the more rural places to make sure they're accessible. My home bathroom has had to be modified."

Brian - Individual living with LOPD

"Now I think it's just hard to go out in society. We used to be able to go out in society at least, because, you know, you have trouble walking, steps are hard, getting out of chairs are hard. So folks may not want to go to the movies. They might not want to go out for dinner as much, just things like that. And going to sporting events where you, you know, got up a row of seats you've got to kind of climb through. All those things are harder to do now and take a toll on you."

Difficulties with ERT

Participants in the "Daily Experiences with Pompe Disease – Late Onset Perspective" Session revealed a number of struggles with accessing and receiving ERT. Comments and polling results related to ERT will be highlighted in the section of this report entitled "Patient Perspectives on Treatments for Pompe Disease."

Additional daily experiences

Several participants described their experiences being diagnosed with Pompe disease, including the diagnostic odyssey many undertook that included various misdiagnoses and many visits with specialists unfamiliar with their disease. Participants also described finally receiving the Pompe diagnosis and the sense of clarity it provided, but also the anxiety and concern.

Other participants described their experience with morning headaches severe enough to cause nausea while others mentioned the scoliosis associated with Pompe.

Issues at diagnosis

Sean – Individual living with LOPD

"At the age of 12, I was diagnosed with type one diabetes. During my stay at the hospital they ran blood labs and determined that my liver enzymes were highly elevated, which quickly drew a lot of curiosity from physicians. They did a biopsy a year later in conjunction, but the results were inconclusive. My liver function remained stellar… yet the elevated liver enzymes suggested some kind of underlying damage….
…Over the years, I'd seen various doctors, seeking answers. One of the specialists I saw in 2012 cut me loose, saying he couldn't further diagnose me, but I probably have some type of glycogen storage disease; so close and yet so far. After a half dozen specialties and a dozen years, in 2018 I was given a blood test for acid maltase deficiency by a new specialist. A few online searches about the test left me curious, confused, and in denial…
…I now have been undergoing treatment for two years. I never thought the diagnosis that I looked and sought for for so many years would be so serious and so severe. A diagnosis of a disease that minimally or severely limit my life enjoyment, and has the high probability of killing me from complications."

Monique - Individual living with LOPD

"I live in central Florida and I'm 45 years old. I was diagnosed with adult onset Pompe disease in January of 2010. It took me 11 years to get my diagnosis. I was diagnosed initially with inflammatory myopathy and it seemed to fit, and I lived with that diagnosis for 10 years….
…It took us another year of a lot of testing, a lot of going to different facilities around the country. Finally, it was the Mayo clinic who diagnosed me with Pompe disease. So three muscle biopsies, countless blood tests, EMGs, all sorts of examinations, and finally, 11 years later I was correctly diagnosed with Pompe disease…."

Lisa – Individual living LOPD

"I am 37 years old and from Fort Collins, Colorado. I am a veterinarian working on a PhD in cancer biology. My journey with Pompe disease began two years ago when I was about four months pregnant with my daughter. My husband and I had genetic testing done to look for another condition and ended up learning that I have two mutations consistent with late onset Pompe disease. Initial follow-up tests came back as possibly consistent with Pompe. Genetic sequencing was done twice just to be sure my first results were correct. The GAA enzyme levels of my white blood cells were a little low. I had some proximal muscle weakness. Was it Pompe or was I just really out of shape? For the first several months after learning about my Pompe mutations, I was in a state of shock and denial. When I finally allowed myself to think about previous life experiences, I realized that I probably did have some subtle signs of Pompe…"

Ryan - Individual living with LOPD

"Five years ago at the age of 31, I was diagnosed with Pompe disease. My diagnosis via targeted sequencing served as the decisive piece of a nearly three decade long puzzle. With it, so many things made sense, and it became clear that Pompe has been with me the whole time...."
...We don't yet have enough of...an understanding of Pompe that leads to a sensitivity to really detect the onset or progression of symptoms. In my case, they were talking for at least 26 years before we heard them..."

Pain and morning headaches

Sandra - Individual living with LOPD

"Lately I've been having a lot of the morning headaches. Before they used to come and go, and now they're getting pretty consistent, like every day...to the point where I feel nauseous. So, [my most troublesome symptoms are] the fatigue, the headache, and...muscle weakness, obviously."

Scoliosis (curved spine)

Sabrina – Mother of child (Zach) with LOPD

"My son was diagnosed when he was 12, showed signs at eight. When he was 15, he had to have scoliosis surgery because his back muscles couldn't support the growth of his spine. And so because of that, he's very limited with his mobility."

To understand the perspectives of patients across the Pompe disease spectrum regarding current and desired future treatments, a panel of patients living with Pompe disease (both IOPD and LOPD) and their caregivers shared their perspectives on the treatment landscape. This was augmented by polling the patient community in attendance, and by in-depth discussion with the audience members. The discussions focused not only on pharmaceutical interventions, but also on the range of physical exercises, occupational therapies, nutritional/dietary tactics, lifestyle modifications, and mental health approaches the community utilizes to help treat or manage the daily impacts of their diseases. The objective of the session was to gain a better understanding of the pros and cons of current treatments, and then to develop patient-focused insights on what the community values most in the development of new therapies.

Session 3: Patient Perspectives on Treatments for Pompe Disease

Current approaches to disease management

Considerations for starting on Enzyme Replacement Therapy (ERT)

During the participant polling, ERT was the most common response to the question of what treatments are used by patients with Pompe disease ¬¬¬- 86 percent of patient and family respondents reported using ERT.

Participants described their experience in choosing to start ERT. For some it was obvious; ERT was clearly the right choice to try to slow the progression of the disease. This was particularly true for individuals with IOPD or more severe LOPD for which their diagnosis occurred before ERT was approved by the FDA. For others it is less obvious, particularly for children diagnosed with LOPD through newborn screening as well as adults recently diagnosed with LOPD and are experiencing few clinically-recognizable

symptoms.

George – Father of child (Phoenix) living with IOPD

"At three months old, during a routine pediatric exam, we were informed that Phoenix had a heart murmur and that he needed further investigation. Using ultrasound, Phoenix would be diagnosed with a potentially lethal heart condition called hypertrophic cardiomyopathy…
…Thankfully, the medicine stopped his heart from getting worse and gradually corrected it to where today he has an otherwise normal heart. However, this new enzyme replacement therapy was unable to correct his weakening muscles and his ability to breathe continued to decline…"

Vanessa – Individual living with LOPD

"…In January 2014 I was diagnosed with Pompe by a blood spot test and gene sequencing….I started enzyme replacement therapy within two weeks of my diagnosis. In February 2019, I enrolled in a double-blinded clinical trial for a new enzyme replacement therapy. I'm now in the open label continuation until it hopefully receives FDA approval."

Dave – Father of child (Caroline) living with LOPD

"Caroline was flagged for Pompe disease through newborn screening in Illinois…After several grueling weeks of waiting for the gene sequencing results, we were informed that she had late onset Pompe disease…
…Unfortunately Caroline's form of the disease proved to be more aggressive than originally expected…As we monitored Caroline's test results and hoped for improvement, we were torn on when to start the only approved drug treatment, Lumizyme…
…On the one hand, we considered the benefits of starting ERT, such as staying ahead of potential damage to her skeletal muscles or even worse, her organs. On the other hand, we were making a lifetime commitment to ERT, and we did not want to put undue strain on Caroline by starting too early. We also had seen research suggesting the effectiveness of ERT diminished over time… Caroline eventually made the decision for us when her biomarkers and physical development reached levels that more clearly demonstrated the need for treatment. We decided to start biweekly infusions of Lumizyme around her first birthday."

Haley – Teenager living with IOPD

"I'm 14 years old and in the ninth grade. I am from Bracey, Virginia. I have been getting treatment since I was six months old, when I was diagnosed with infantile onset Pompe disease."

Lisa – Individual living LOPD

"As a veterinarian, I place a premium on patient quality of life…I'm very grateful to have received the information about my mutations and I can avoid the diagnostic odyssey that so many Pompe patients have had to face. At the same time, it's hard to make a decision about initiating treatment, because I did not present with an obvious problem that needed immediate medical attention. Because my symptoms are relatively mild at this point, I'm not receiving enzyme replacement therapy…"

Morgan – Individual living with LOPD

"I live in Asheville, North Carolina. I am 24 years old. I have late-onset Pompe disease. My story is different from those who were diagnosed with Pompe disease after enzyme replacement therapies became available.
…I was diagnosed at 21 months, when there was still much being learned to best treat Pompe disease. While waiting for treatment, I suffered significant muscle wasting and endured chronic fatigue and muscle pain. Much of my days were spent in bed. Initially, I was able to stand independently and walk for short distances. Eventually, I required a power chair for mobility. Tolerating solid foods became a challenge, I could no longer eat so a feeding tube was inserted. My diaphragm weakened and scoliosis worsened, I became ventilator dependent at the age of four. I was homeschooled, which was very isolating…

...In 2003, at age seven, I was one of the individuals accepted into the extended access clinical drug trial to receive Myozyme...After receiving only approximately seven or eight infusions, my life changed for the better...
...In 2007, at age 11, Myozyme was approved by the FDA for treatment of Pompe disease. My family moved to North Carolina, and I was able to receive infusions at my home."
...My life is a testimonial to how critical timely developments in treatments to people with chronic conditions. If I had received Myozyme a few years later, my life would have gone down a different path. I might not be here today, speaking to you. Getting Myozyme when I did saved me from losing more independence and saved my life."

Paloma - Mother of child (Vaun) living with IOPD

"At 23 days old, Vaun had his first Lumizyme infusion. Knowing others in the IOPD community, getting to ERT as fast as possible makes a huge difference."

Benefits of ERT

Patients with Pompe disease and their caregivers reported that ERT has had a positive impact on their experiences with Pompe disease. Participants cited the slowing of the progression of their Pompe, and the activities they are able to undertake, largely credited to the ERT. Approximately 60% of respondents said that their current treatments have helped a lot or resulted in very significant benefits (Appendix Figure 24).

Lucas – Individual living with LOPD

"I am by far the strongest I've been in years. However, my life is still understandably impacted by Pompe disease...
...Pompe is brutal, debilitating, and it will beat you to your knees if you let it, but it has given me the mental strength to thrive. Despite Pompe's challenges I've graduated magna cum laude with a Bachelor of Science in applied mathematics and use this degree to help to tutor students in various subject matters in science and math. As a musician, I'm playing out regularly. Everything, 20 to 30 shows a year. And I'm currently working on releasing my third album. I've even been asked personally to run for state assembly of all things."

Dave – Father of child (Caroline) living with LOPD

"The progress has been nothing short of amazing. She now walks independently and is meeting milestones we once feared may not even be possible. Her verbal skills also improve significantly to the point where she no longer requires speech therapy and has plenty of opinions to share. While we cannot be more excited about the progress Caroline has made in only a few short months, there remain opportunities for significant improvement in long-term outcomes and quality of life."

Morgan – Individual living with LOPD

"Myozyme had slowed down the progression of my disease, allowing me to live my life the best way that I could. I'm very thankful to those involved in creating this drug that gave me my life back."

George – Father of child (Phoenix) living with IOPD

"...the enzyme replacement therapy...that saved my son's life....

Haley - Teenager living with IOPD

"The treatment that I get every week is Lumizyme infusions and it has some benefits and downsides to it. The benefit of this treatment is that I know during that time it's trying to infuse the bad stuff out, and the good stuff in, and also trying to make me stronger and healthier.

Deana – Mother of two children (Mason and Dakota) who have lived with IOPD

"When Dakota was just 10 days old, we started biweekly road trips for infusions of this new drug Myozyme as a part of the trial at Duke. What a

difference… He was gaining weight and didn't lack in strength. He was strong and not a floppy baby."

Difficulties in administration and frequency/ duration of ERT appointments

While participants were largely positive about their experience with ERT, several indicated that ERT can require weekly, time-intensive infusions that can be both physically and emotionally draining for patients, as well as cost-prohibitive for some.

Haley - Teenager living with IOPD

"The treatment that I get every week is Lumizyme infusions and it has some benefits and downsides to it. The downside of having to get this treatment is that every week I have to get a needle through my port and sometimes I can feel the needle and it hurts. Also, I'm not able to do many things during the infusion time, like going places, and trying to move around in different positions. I do enjoy talking with my home infusion nurse though…"

Lucas – Individual living with LOPD

"As far as the downside…some people complain about how long it takes, but I'd rather be busy and alive, than wide open and dead, as far as my schedule goes."

Dave – Father of child (Caroline) living with LOPD

"… I'm speaking on behalf of my daughter Caroline, who's almost two years old, and for us, the biggest challenge is the frequency and the length of the infusion process. For Caroline and her mom, it's typically an all-day process that begins early in the morning and extends well into the afternoon, and even the next day in the case of Caroline, as she recovered from the infusion. And we're certainly fortunate to be near a great infusion center, but keeping a small child contained in a confined area for an entire day is certainly a challenge…
…The other thing I would highlight is the drug delivery method. Like many people with Pompe disease, Caroline has been characterized as a tough stick when it comes to traditional IVs. That encouraged us to go with the route of having a port installed, which has made the frequency much easier. But still, accessing the port has its own challenges, and it has to be replaced every couple years."

Lisa – Individual living with LOPD

"As a barrier to starting treatment, I do echo the sentiments of several other panelists about the access to infusions, the amount of time that they take, and the drug delivery methods seeming onerous."

Sean – Individual living with LOPD

"I receive weekly ERT infusions and as grateful as I am to receive a treatment and as much as this has become a part of my regular lifestyle the one trade-off I would have to say is making myself available every week for that infusion. That means if I want to take a vacation with my family we cannot go anywhere for too long because of my infusion or just make the decision of missing out on an infusion which is really not much of an option."

Morgan - Individual living with LOPD

"Small changes, such as improving the method of drug administration, would make our enzyme levels more consistent over time, which would have a positive impact on the quality of life."

Adverse events associated with ERT

Comments from some participants highlighted the risks associated with ERT, such as infusion site reactions and the risk of infection at the port site. This was particularly true for children with IOPD when just starting ERT. No one reported that the risk of blood infections, port surgeries, and allergic reactions outweighed the benefits that the ERT provided, but they were nonetheless major concerns for the patient and family.

Sarah - Mother of two children (Bruce and Myra) living with IOPD

"Having an implanted port is a huge risk for blood infections, and unexplained fevers could mean a delay in enzyme replacement therapy for time to resolve that infection."

Krystal – Mother of Haley

"Initially [we began] enzyme replacement [therapy], but found out soon after, that Haley would need to be involved in seeing many specialists and also need many therapies to help her.
...That leads me to the many surgeries that was needed for different reasons. The one that I just mentioned for the G tube, but also many surgeries for ports that would help infuse her lifesaving infusion when an IV was not possible. She had a surgery to loosen tight muscles in her legs from where she was always sitting, not standing, with a recovery period that was extremely rough.
...Surgeries have subsided a bit. However, port surgery is usually necessary every few years.
...Infusions changed somewhat over the years. She went from infusions of Myozyme every two weeks to enrolling in clinical trial for weekly infusion, then increasing that dose... About 11 years after hospital infusions, home infusions became a reality."

Morgan – Individual living with LOPD

"During the switch from Myozyme to Lumizyme, I had a minor allergic reaction at a nearby clinic. My heart started to race, I got dizzy and my blood pressure dropped. My Asheville geneticists ordered Solu-Medrol to stop the reaction. The reactions decreased with each infusion, and eventually they stopped."

Paloma - Mother of child (Vaun) living with IOPD

"Another challenge for Vaun was he was crim negative, meaning he does not produce any of the GAA enzyme. Crim negative patients have always been known to have poor outcome on ERT due to the development of anti rh-GAA antibodies. An immune modulation regimen was recommended by Duke...We now know how vital immune modulation is."

Deana – Mother of two children (Mason and Dakota) who have lived with IOPD

"We had a scare when Dakota started having reactions during infusions, but that was managed quickly by adjusting infusion rates along with IV antihistamines, and he has not had them since."

Enzyme Replacement Therapy Dosing

Some patients experience a decrease in effectiveness of their initial ERT dose over time, as highlighted by participant comments about changes in their ERT dosing. Most participants indicated that a higher dose of ERT, either in frequency, dosing size, or both, resulted in improvements.

Lucas – Individual living with LOPD

"As far as the treatment goes... Myozyme, I've been on that for 16 years on very low doses. I forget how long I've been on 40 mg/kg, but recently I went to every week instead of every other, because it was no longer working that well. But since I've done that, I'm exercising more and I'm exercising harder and doing more things, so I mean for me, I'm very fortunate that it's working well....
...as a musician, it's hard for me to bend the string. And when you're bending a string, you're putting a lot of tension on your wrists, and I'm noticing that I'm doing that without even trying to do it now. Specially in my hands and my shoulders, I notice it being different."

Tiffany – Individual living with LOPD

" I did have to definitely increase my dose. It's now a higher dose. So that was definitely something that I had to do."

Morgan – Individual living with LOPD

" The commercially approved drug regimens seemed to be less effective for me over time. I could no longer lift a cup to my mouth and lost the ability to feed myself. My geneticists at Asheville and at Duke worked together to modify my treatment to suit the rapid progression of my disease by increasing the dose and changing the frequency from biweekly to weekly. For the next year my body had to adjust to the increasing dose, which brought on many challenges, both physically and mentally. Having weekly infusions means that my energy levels are more consistent. But, having weekly infusions is strenuous to say the least."

Insurance coverage and affordability of ERT

Several participants noted the importance of quality, affordable insurance coverage in accessing ERT, including costly copayments necessary for ancillary testing and administration costs.

Jenna – Mother of two children living with LOPD

"My 2 children with LOPD are currently not on treatment, however, are monitored closely due to their unique, never seen genetic mutation combination. The test copays are outrageous leaving us in a very difficult financial situation. 4 Echos (2 each per year) plus weekly PT and feeding therapy alone costs us well over $6,000 a year - again - children NOT on treatment. We must find a way to 1) assist families with these cost burdens and 2) educate families that there IS assistance available. If we are going to (newborn screen) this disease, then we must provide options for assistance to monitor disease progression."

Kathryn – Pompe disease community member

"I'd just like to acknowledge that treatment is integrally linked to funding/insurance options and what that insurance will cover. Without insurance coverage, or limited coverage, the treatment may be available, and even helpful, but cannot be accessed by Pompe patients that desperately need those treatments. It would be wonderful if some research was done to show the benefits of a wider range of treatments, so there is some data that could be used to increase possibility that those treatments would be covered by insurance."

Alternative therapies utilized by participants:

The conversation on current treatment options utilized by the Pompe community also included a variety of additional methods used to treat the disease. Participants discussed physical and occupational therapy, vitamins and supplements, and a high calorie/protein diet as beneficial treatment modalities commonly employed.

Diet and nutrition

Participants routinely cited the importance of a low sugar and carbohydrate, high protein diet in managing the disease.

Dave – Father of child (Caroline) living with LOPD

"We also keep her on a low sugar diet to the best of our ability."

Haley - Teenager living with IOPD

"I also have to eat higher protein and take vitamins everyday. Sometimes it's hard to find food products with high protein in them, and also it being something that you want to eat at the time, and it being something you like as well. When I eat foods with higher protein in them, I feel a lot of difference after a couple of days, mainly healthier and better."

Tiffany – Individual living with LOPD

" When I was diagnosed I was, I think, probably 65 lbs... So diet was something they tried, it never made me feel better, but it got me the weight I needed to gain."

George – Father of child (Phoenix) living with IOPD

"As Pompe folks, especially back before there was a treatment…you tried everything in the book, all the different amino acids and anything. Any holistic thing you would hear, you would try….But then Lumizyme, Myozyme at the time, came around. And we started getting an actual enzyme replacement therapy. But you still wanted to try to add to that or piggyback along with that, because it didn't seem like we were seeing the results that we wanted to."

Kevin – Pompe disease community member

"Low carb diet, stretching, taking Casein protein at night time, Indoor rowing, vibration therapy and walking (swimming before Covid)."

Occupational/physical therapy and exercise

Participants cited occupational and physical therapy (OT and PT) as well as exercise as important facets of their disease management. Others mentioned the importance of a warm bath or pool following an ERT infusion in order to facilitate circulation of the enzymes around the body.

Haley - Teenager living with IOPD

"Throughout my journey with Pompe, I have had to get OT, PT and speech therapy, some of these every few weeks and at sometimes 2-3 times a week… The PT helps me become stronger and helps me loosen my tight muscles. Sometimes I'm a bit sore after exercising."

George – Father of child (Phoenix) living with IOPD

"After his infusion, one of the things that I've always done is I try to either get him in the bath or the pool where it's nice and warm and he can move…"

Brian – Individual living with LOPD

"Pilates have helped strengthen my core and shoulders."

Lisa – Individual living with LOPD

"Well, at this point I haven't experienced too much in the way of Pompe therapy, since I've primarily been focused on diet and exercise. But one of the things that was a surprise downside was I guess realizing the limits of what I could do, with how far my Pompe has actually progressed in the short time since I've had my genetic diagnosis, and learning my limits and learning how to exercise appropriately."

Respiratory support

Participants cited a number of respiratory treatment approaches to manage the adverse breathing symptoms associated with Pompe. Bipap machines, tracheotomies for severely-affected IOPD patients, and respiratory muscle strength training were all mentioned as interventions.

Tiffany – Individual living with LOPD

" When I was diagnosed we found out my breathing was 40% of normal…went on a BiPap right away, and obviously I use it throughout the day to help me breathe, and at night of course. I've tried supplements, I'm in a wheelchair now. There really is a gamut of everything, physiotherapy, massage. I think I checked something like 10 boxes on that list…"

George – Father of child (Phoenix) living with IOPD

"Getting the trache was really one of the best decisions we'd done as far as making him stronger and happier and breathe better. He could gain weight, he could thrive."

Brian – Individual living with LOPD

"My pulmonary function has improved greatly with the respiratory muscle strength training."

Pain management

Tiffany – Individual living with LOPD

"There was a question about pain management.

I've used acupuncture for pain management, in addition to massage, physiotherapy, etc. Medication, and having received benefit from that as well."

Perspectives on future treatment options

Participant hopes for development of new treatments

Both the polling data (Appendix Fiigure 18) and the participant comments indicated that patients and caregivers would like future treatments to slow the progression of the disease and allow patients to maintain or improve their muscle strength. They also indicated a desire for new therapeutics that are more easily administered than current ERT, and for drugs that do not lose effectiveness over time. Finally, the comments highlighted an interest in new treatments, specifically gene therapy, with some participants feeling excited about the possibility of a permanent cure and others expressing apprehension about unknown effects of this clinical strategy.

Maintaining current level of muscle strength and pulmonary function

Comments from some participants highlighted that while improvements in disease experience would be optimal, halting progression of the disease and maintain the current level of muscle function is incredibly important. Participants explained that they have gotten used to their current level of muscle function and would prioritize preserving this level.

Coburn – Caregiver to family member (Morgan) living with LOPD

"Morgan's unique in that our days are characterized by what we can do to help Morgan. So I guess in the future, specifically just assisting her, feeding her, taking care of her, and bringing her places are something that we look forward to spending time with Morgan. I guess looking towards the future, I would like to have that ability to keep doing those things with her."

Haley – Teenager living with IOPD

"For the future, if a treatment kept my muscle strength like it is today, I would be okay with that because that's how I'm used to doing things. The only new treatment that I would like to see happen would include, finding a way to increase my muscle strength and finding a way for me to walk and not having to do therapy anymore…."

Lucas - Individual living with LOPD

"I wanted to say when you have Pompe, you need to be pragmatic and part of that might mean there's just no way, in my opinion, that you're going to get all that back. So, I think you need to be very goal oriented. I've been in the wheelchair my whole life. I don't think I'm going to be walking again or ever…
…If I went and lose my upper body strength, I think that with me the most devastating blow for me because it would completely prevent me from doing anything that I knew work wise. So, I'm doing everything I can to make that not happen."

Lisa - Individual living with LOPD

"I think for me one of the most important things for therapy is preserving pulmonary function, because that is tied in with so many things that one does from talking and being able to sleep comfortably to being able to move and to exercise and to just enjoy everything about life. So for me, that's one of the daunting things about Pompe disease is thinking about the loss of pulmonary function."

Improving muscle strength and pulmonary function

While maintaining current function was highlighted by participants, most participants still hoped for a treatment that could improve muscle strength and pulmonary function. This was particularly true regarding pulmonary function as participants highlighted an improvement (or at the very least

stabilization) in pulmonary function as one of the most important benefits of any new treatment.

Ryan - Individual living with LOPD

"The future is super exciting to me…We have an increasing number of folks diagnosed every year.… … Each of us has a role to play in writing the next chapter of our rare disease story. I look forward to doing that together and have the following thoughts on how we bring that critical sense of urgency to keep this story from dragging on…
…We need to prioritize time and change the way we factor it into our decision making. Symptom progression can be more devastating than any AEs…
…since March when we were supposed to have this meeting, there had been 100 kids born with Pompe disease in the US. There will be 25 next month and 25 the month after. We're recruiting by the day, but our response is in years. We need to find ways to go faster. We need access to treatment while still in a preventive phase of our disease progression, and trial discussion and design that supports this…
…We also need to be more inclusive. Our current approach to trials often excludes folks enthusiastic to participate. This limits properly evaluating efficacy of new approaches across the entire range of Pompe progression.…
…we can rewrite the story of our disease and develop a new understanding that feeds back into helping those of us already living with it."

Tiffany – Individual living with LOPD

"I think the biggest thing for me is something that I think would improve my condition…I'm more or less stable, and I know a lot of people, the routine of the infusions are a problem, but at this point I've been doing it for 20 years, so it's literally just a part of my life. That doesn't concern me as much as something that would be an improvement on where I am today."

Krystal – Mother of child (Haley) living with IOPD

"I can think of several treatment or therapies that could possibly be ideal for those that hear the dreaded words, "You or your child has Pompe disease." Such as an easy cure with no future needs of any treatment or anything. However, in our particular situation, if there was a way to get the already damaged muscles working again, then that would help with many things such as allowing Haley to walk or perform her own daily activities without relying on others. As we look into the future, we ultimately need to keep Haley's respiratory status stable or making sure it doesn't decline…
…Additionally, Haley will be an actual adult in just a few short years. Her being able to attend college, live on her own or any of those things that turning into an adult type things that parents hate and love to see, is what any parent wants for their kids. Ways that Haley cannot lose any independence or ways that she can actually have the ability to do more for herself, would be ideal in regards to upcoming treatment. For her, it would have to involve muscle regeneration or additional equipment that can assist her."

Morgan - Individual living with LOPD

"I am hopeful that the next generation of enzyme replacement therapies will remove more glycogen and allow damaged muscles to rejuvenate.

Tiffany - Individual living with LOPD

"For me, I would love to have an improvement in my pulmonary. That would make a huge difference in my life…
…what we want for the future really depends on the person and the patient and the family and where you are in the disease…
…I think, George, Lucas and I have a different perspective than Lisa and Dave because of when we were diagnosed and where we are in the disease process… Improvement, that's what we want. Stabilization first and then improvement and then an easier way to do it."

Reducing the burden of ERT

Comments from some participants highlighted their hope that future treatments would not involve the same burdens of time, frequency, route of administration, loss of effectiveness, infection risk, etc. as currently available ERTs.

Haley – Teenager living with IOPD

"Another thing is a type of treatment that I wouldn't need to receive as often. As I get older, it will be harder to miss school or work for an all-day infusion each week. Since I've lived with Pompe disease my whole life, many of the things listed above are normal to me. So, I'll be excited for the future and seeing what new things come our way."

Lisa – Individual living with LOPD

"From a patient perspective, an ideal therapy for Pompe would be one that is easily administered and is more effective. There's some very promising gene therapy trials that I'm following with interest.

Sandra - Individual living with LOPD

"I just hope something new will come out to treat Pompe because I am already on weekly Lumizyme treatments and I am already so tired of them after 8yrs."

Gene therapy, and other new therapeutics, to manage/cure Pompe disease.

While many participants were excited about the promise of gene therapy as a long-lasting intervention for Pompe disease, other participants expressed hesitation about use of technology that they viewed to be immature. Participants also acknowledged other interventions under development for which they were hopeful, including orally-administered ERT.

Lucas – Individual living with LOPD

"What I'm concerned about is gene therapy. I really want to make sure they know what they're doing with me, before if I decide to have something put in me like that...
...since gene therapy is in its nascent stages, they don't really know what's going to happen long term, or if it might mean...after effects."

George – Father of child (Phoenix) living with IOPD

"I just wanted to add a little bit to the gene therapy topic. Phoenix actually participated in gene therapy clinical trial, I want to say it was probably six, seven years ago. And I can understand why... people would be apprehensive about gene therapy, because of the science behind it and the sort of the technology, but at the same time, I would say that for me, it's the home run. I've always said it's the holy grail of treatment because the problem lies in our DNA, in our genes....I think that there is so much good science happening right now and in this industry and even outside of the rare disease community, there is tremendous amount of gene therapy clinical trials going on, where there is some good safety data coming out...
...I will echo the same sentiment about being in a gene therapy clinical trial. Because of that one that we were in, we could be omitted from future trials."

Lisa – Individual living with LOPD

"I think George stated beautifully that gene therapy has such tremendous potential for the treatment of Pompe disease, and it's a really exciting field and one that I would like to contribute to as a study participant, if I have the opportunity to do so."

Ryan - Individual living with LOPD

"Just want to get on the record for the meeting that there are folks working on alternate treatment modalities that have not been mentioned yet - such as Oral ERTs, with a hope that even more creative, less "costly" ($, time, invasiveness, etc) and more effective modalities are on the horizon (also recognizing that "gene therapy" isn't just a single thing, that there is a lot of work and iterations before something can work as simply and effectively as discussed.)"

Considerations for clinical trial participation

51% of participants indicated that they had previously enrolled in a clinical trial, while 29% had never even been informed about a clinical trial. Factors that would most influence clinical trial participation include how the treatment might improve the patient's health, the risk of serious side effects, and logistics, such as proximity to the study site (Appendix Figure 17). The promise of receiving the therapy at the end of the trial would also influence the decision for many patients.

Participants also highlighted narrow inclusion criteria as a major impediment to participating in clinical trials for the Pompe community that is non-ambulatory or had a tracheotomy. The clear sense of altruism and service also was evident in motivating those with Pompe to participate in clinical trials.

Krystal – Mother of child (Haley) living with IOPD

"...the last time we were asked to enroll in a clinical trial, we weighed the pros and cons and decided to decline at this time, mainly for fear that we would lose her nurse...
...going forward it's going to be really difficult to determine which trials we would like Haley to be involved in, as well as which ones she would like to participate in. Many of them require lots of testing, appointments and without knowing the expected benefit, how does one take their child that is fairly stable at the moment and try something different...The drug or therapy would have to show great promise or allow for continuing of current treatment for it to be considered or the chance to quickly switch back if necessary. If the benefit outweighed the travel, many appointments and possible side effects, then we would possibly consider a clinical trial...."

Lisa – Individual living with LOPD

"Another point that I wanted to emphasize is that I think it's really important as patients of having a rare disease to really volunteer for opportunities that present themselves because they might advance our health, but then they also advance the field and help other people with Pompe disease and help the scientific community move forward as well."

Ryan - Individual living with LOPD

" When I think about the things that motivate me to consider a trial, one of the things that I think is really prominent is the opportunity to participate in advancing the state of knowledge about our disease and how to treat it. And so I think by having heavy participation and bias towards participation, we learn in those trials, but then we also excite new research into it, because we're showing that there's a fertile audience ready to collaborate with our talented team of researchers and doctors...
...Recognizing that each of these steps immediately in front of us, are part of a bigger picture journey that we're all on together, and that we get there faster by all participating together."

Morgan - Individual living with LOPD

"Unfortunately, I am not eligible to participate in clinical drug trials because I am wheelchair bound and ventilator dependent. The current requirements for new trials allow them to eliminate those who would benefit the most from them. Therefore, I am a strong advocate for the importance of patients like myself with limited mobility and low pulmonary function to have access to new treatments as soon as possible."

Tiffany - Individual living with LOPD

"We also definitely need better inclusion in the clinical trials so that the more severe patients have a chance to participate because...we don't know how treatments work for the entire spectrum right now."

Risk-Benefit Analysis

Evidence and Uncertainties	Conclusions and Reasons
Pompe disease (also called acid maltase deficiency) is a rare, metabolic muscle disorder that is estimated to occur in about 1 in every 22,000 live births in the United States,1 with an estimated worldwide prevalence of 5,000-10,000 cases.2,3 Pompe disease causes slow, progressive weakness, especially of the respiratory muscles and those of the hips, upper legs, shoulders and upper arms. Several types of Pompe disease have been described, which differ in severity and the age at which they appear. • IOPD encompasses disease presentations with symptom onset before 12 months of life with accompanying cardiomyopathy. • Classic IOPD presents in the first days to months of life, and if untreated, leads to death from hypertrophic cardiomyopathy (HCM) in the first year of life. • Non-classic IOPD usually appears by age 1. The muscle weakness in non-classic IOPD typically leads to serious respiratory distress, and most affected children live only into early childhood. • IOPD is suspected in infants with: (1) Poor feeding/ failure to thrive, (2) Motor delay/muscle weakness, (3) Respiratory infections/difficulty, and (4) Cardiac problems. • LOPD typically presents later than IOPD, is milder than IOPD and is less likely to involve the heart. However, LOPD is recognized as a multi-system disease with great variability. Patients with LOPD can survive for decades after a diagnosis, but as the disorder progresses, respiratory failure often results in significant morbidity and mortality. • LOPD is suspected in infants, children, and adults with: (1) Proximal muscular weakness, (2) Respiratory insufficiency, and (3) No clinically apparent cardiac involvement. Pompe disease places a large burden on families and is the cause of great physical and emotional pain. It results in life-long impacts on an individuals' mobility, as well as their ability to eat, communicate, and engage in school or work. In the most severe cases, it leads to a severely shortened life span.	Pompe disease is a rare, life-limiting, and often severe disorder causing profound muscular, respiratory, and cardiac (in IOPD) symptoms that can have devastating impacts on the patients and their families' lives, though it varies in severity from one person to the next. A defining feature of Pompe disease is progressive muscle weakening in the hips, upper legs, shoulder and upper arms as well as the respiratory muscles leading to progressive loss of mobility and various severe complications. In IOPD, severe cardiac and respiratory complications can result in early death if untreated, and extensive loss of muscle function can occur if treatment does not occur early. In both IOPD and LOPD, loss of muscle function results in mobility challenges and fatigue, limiting the number and types of activities that can be undertaken.

Current Treatment Options

Evidence and Uncertainties	Conclusions and Reasons
There are several interventions employed by the Pompe community to treat the disease. To prevent or slow the progression of the primary manifestations of disease, enzyme replacement therapy (ERT) is recommended. It is important to initiate treatment soon after diagnosis, especially for those with IOPD. While ERT usually prevents or addresses cardiac complications of IOPD, ERT can also slow the progression of respiratory symptom and muscle loss. Still, the frequency of ERT administration (usually every or every-other week), duration of administration (often a full-day endeavor), injection site reactions, port complications, and more make ERT administration burdensome. Other interventions employed by the Pompe community include respiratory interventions such as bipap machines and tracheotomies for the most severely affected, low sugar/carb and high protein diets, pain management for muscle pain, the use of mobility devices. For new treatments, patients and caregivers prioritize the slowing or halting the progression of muscular degeneration as well as preservation of respiratory function. Patients and caregivers also hope for a treatment that is less burdensome to administer compared to currently available ERT options. The community also hopes for innovative treatments, such as gene therapies, that can potentially reverse the effects of the disease on muscle, but understand this may be far off.	There is a high unmet need in the overall management of Pompe disease. The current state of managing Pompe disease is burdensome for patients. ERT is time consuming and logistically difficult. Management of feeding tubes, infusion ports, and other treatment necessities is difficult for caregivers, and infection is a constant worry. Furthermore, ERT loses effectiveness in patients over time, leaving them with no therapeutic options. New treatments should focus on maintaining or improving muscle function, preserving effectiveness of the therapy over time, and preventing loss of respiratory function.

Conclusions

The externally-led PFDD meeting on Pompe disease highlighted a variety of important experiences and perspectives shared by the Pompe community. First, patients and caregivers identified muscle weakness, loss of mobility, inability to participate in or perform daily activities, difficulty eating, inability to work or go to school, difficulty communicating, and fatigue as the major difficulties that they experience in their daily lives.

Patients and caregivers noted that the current state of managing Pompe disease is burdensome. There is a clear need for new treatments that maintain or improve muscle function, retain effectiveness over time, and prevent loss of respiratory function. Patients are most likely to consider a new medication if it shows benefits for symptoms of importance, such as mobility, muscle strength, and ease of breathing. In terms of clinical trials, patients are most willing to participate if they meet the often too stringent eligibility requirements, and if potential benefits outweigh the burdens of participating.

This EL-PFDD meeting was a critical step forward for the Pompe disease community. The insights collected and reported on in this Voice of the Patient Report reflect important perspectives of people living with Pompe disease and will hopefully guide the pharmaceutical industry in developing critical medicines that are needed.

Clinical trials can be structured in ways the community prefers, including limiting burdensome and energy-consuming travel. Respiratory outcomes should be paid particular attention to as the community emphasized the importance of maintaining their current respiratory capabilities. Improvements to the frequency and duration of ERT administration are meaningful to the community and would represent a substantial improvement in patient experience. The community is excited about potential gene therapies, but further education and information is needed on potential long-term effects.

Finally, the meeting conveners believe this is just one of many opportunities for the Pompe community to positively influence therapeutic development efforts. MDA encourages the community to visit MDA's website (mda.org) or the MDA Twitter accounts (@MDAorg for general work or @mda_advocacy for policy and advocacy opportunities) for additional ways to get involved.

This meeting was just the start of the Pompe community's efforts to improve the treatment options available to patients living with Pompe disease.

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About Muscular Dystrophy Association (MDA)

MDA is committed to transforming the lives of people affected by muscular dystrophy, ALS and related neuromuscular diseases. We do this through innovations in science and innovations in care. As the largest source of funding for neuromuscular disease research outside of the federal government, MDA has committed more than $1 billion since our inception to accelerate the discovery of therapies and cures. Research we have supported is directly linked to life-changing therapies across multiple neuromuscular diseases. MDA's MOVR is the first and only data hub that aggregates clinical, genetic and patient reported data for multiple neuromuscular diseases to improve health outcomes and accelerate drug development. MDA supports the largest network of multidisciplinary clinics providing best in class care at more than 150 of the nation's top medical institutions. Our Resource Center serves the community with one-on-one specialized support, and we offer educational conferences, events, and materials for families and healthcare providers. Each year thousands of children and young adults learn vital life skills and gain independence at summer camp and through recreational programs, at no cost to families. For more information visit mda.org.

About the Acid Maltase Deficiency Association (AMDA)

The Acid Maltase Deficiency Association was established in 1995 to assist in funding research and to promote public awareness of Pompe disease. Pompe disease is one of a family of 49 rare genetic disorders known as Lysosomal Storage Diseases or LSDs. Pompe disease is also known as Acid Maltase Deficiency or Glycogen Storage Disease type II. It affects an estimated 5,000 to 10,000 people in the developed world.

About the United Pompe Foundation

The United Pompe Foundation was formed to assist patients and/or their families with medical costs and other expenses that these patients and families face and may not be able to cover, or fully cover, through their insurance.

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Appendix

Figure 1a

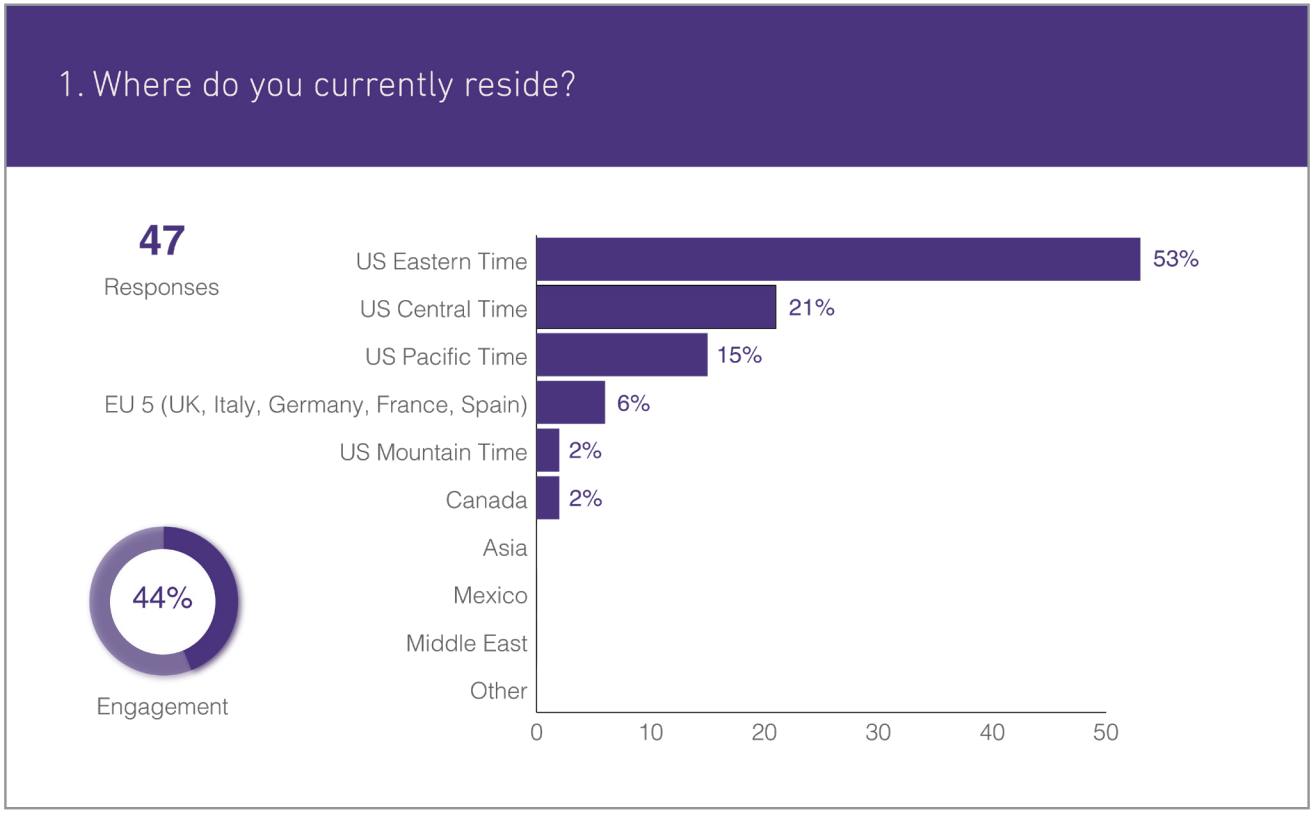
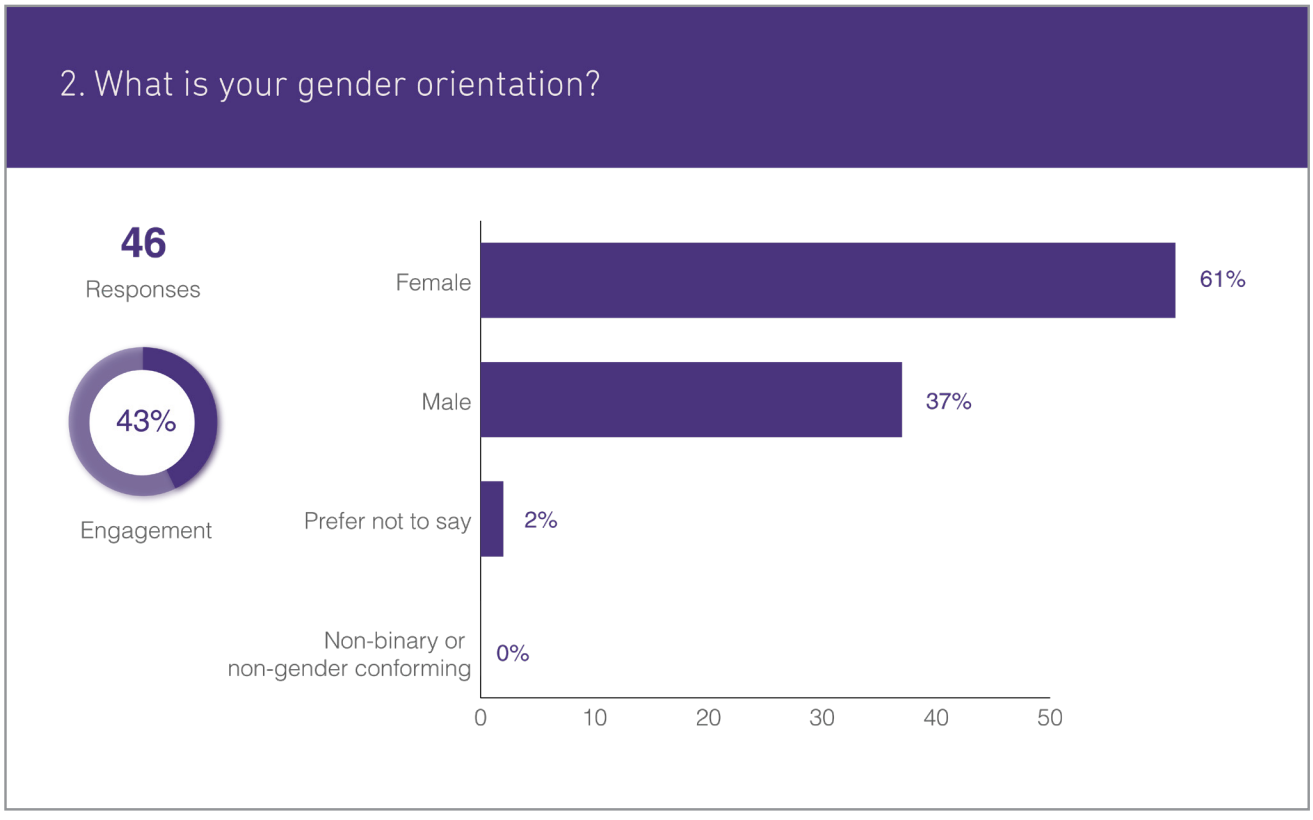


Figure 1b

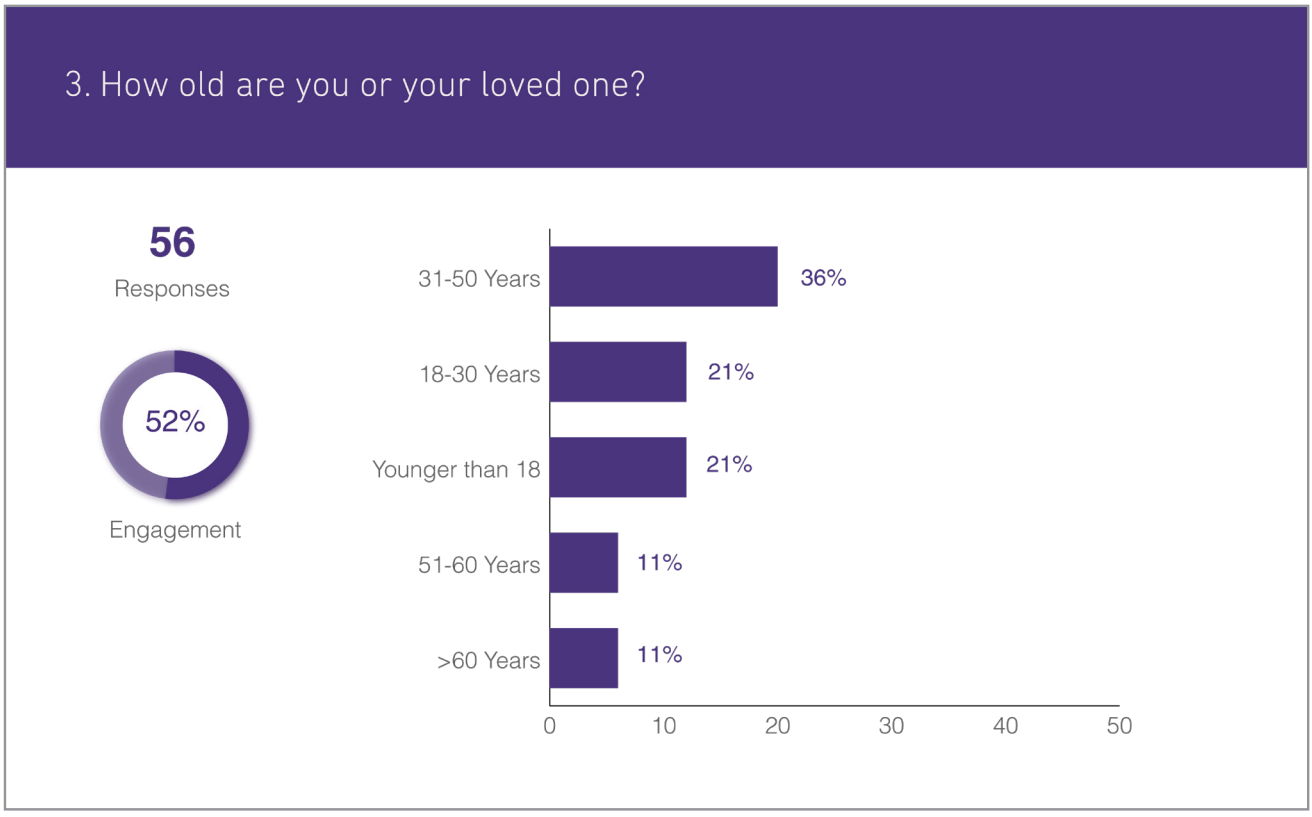
Response Options	Count	Percentage
EU 5 (UK, Italy, Germany, France, Spain)	3	6%
Middle East	0	0%
Asia	0	0%
US Pacific Time	1	2%
US Mountain Time	1	2%
US Central Time	10	21%
US Eastern Time	25	53%
US Alaska Time	0	0%
US Hawaii Time	0	0%
Canada	1	2%
Mexico	0	0%
Other	0	0%

Figure 2



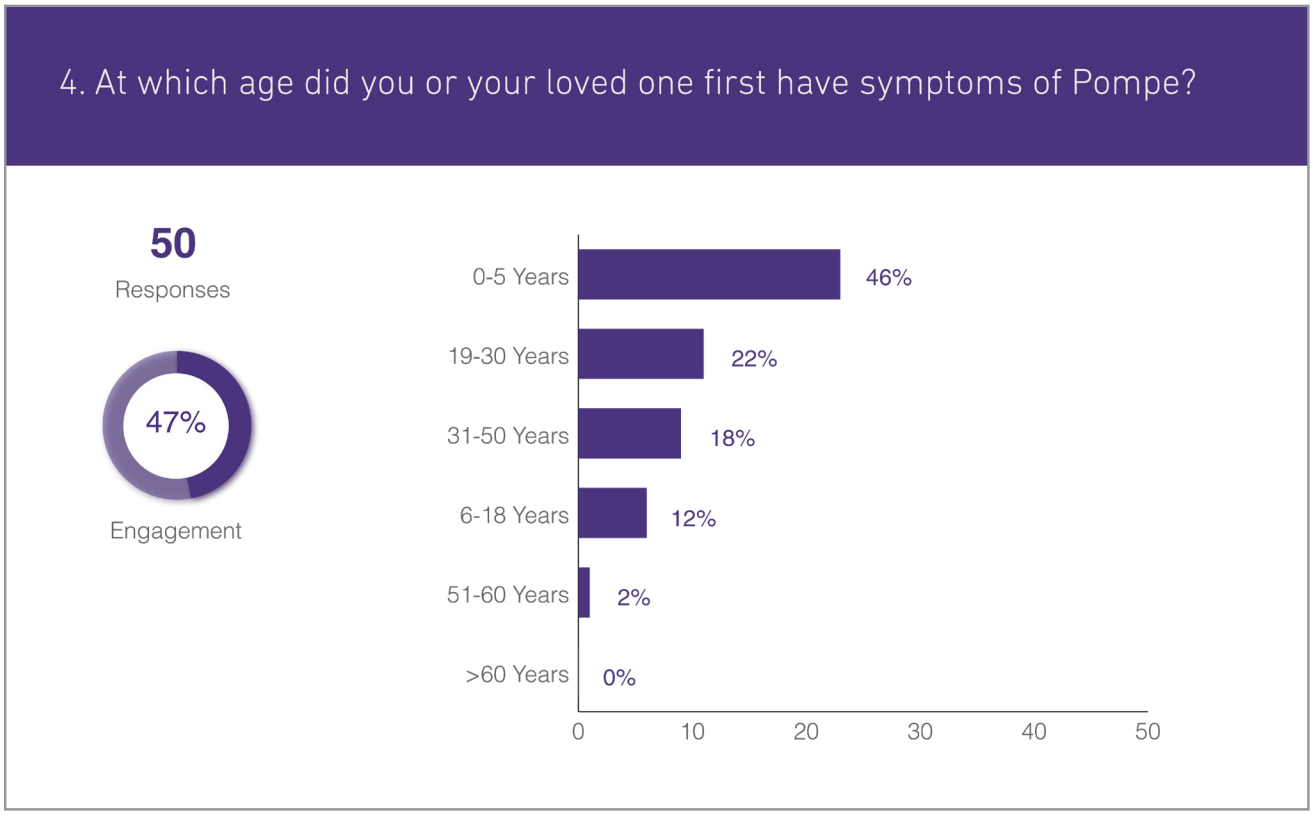
Response Options	Count	Percentage
Male	17	37%
Female	28	61%
Non-binary or non-gender conforming	0	0%
Prefer not to say	1	2%

Figure 3



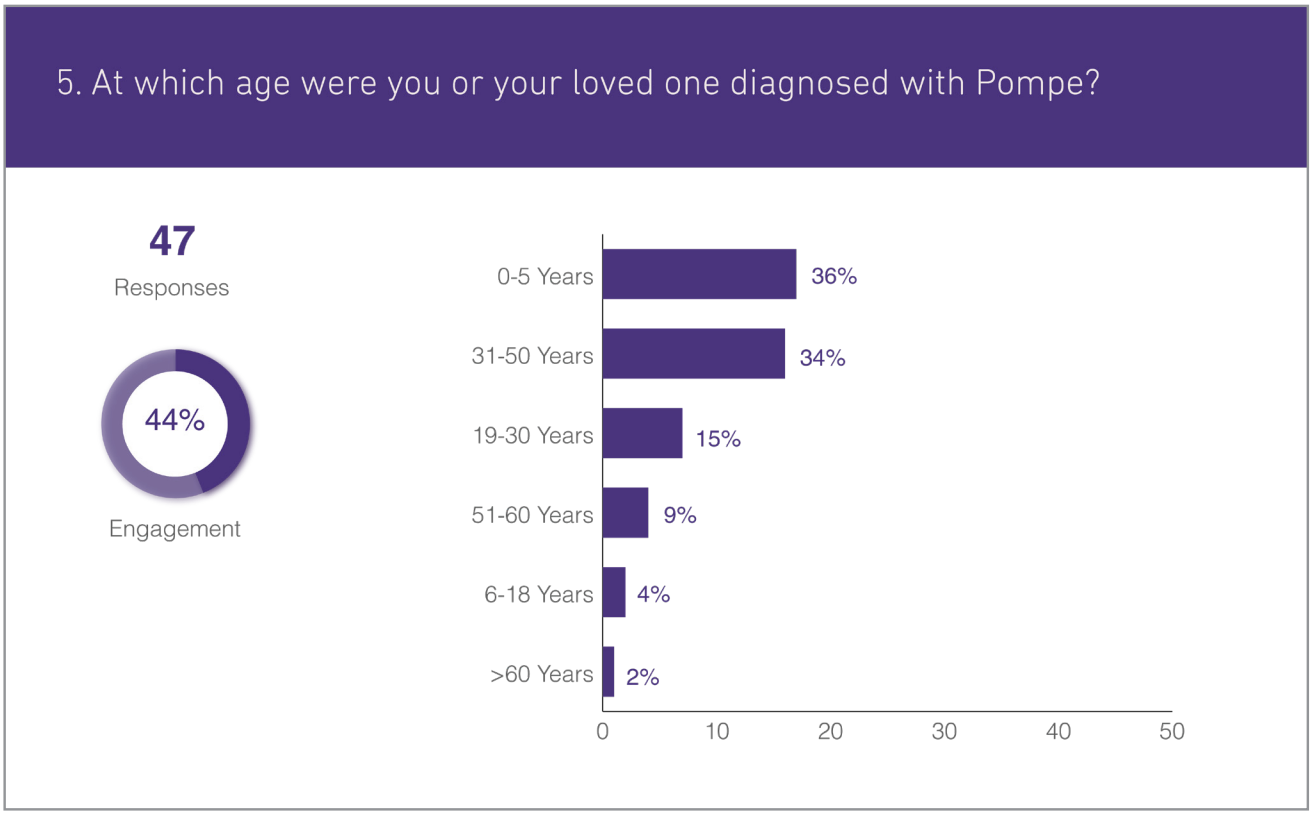
Response Options	Count	Percentage
Younger than 18	12	21%
18-30 years	12	21%
31-50 years	20	36%
51-60 years	6	11%
>60 years	6	11%

Figure 4



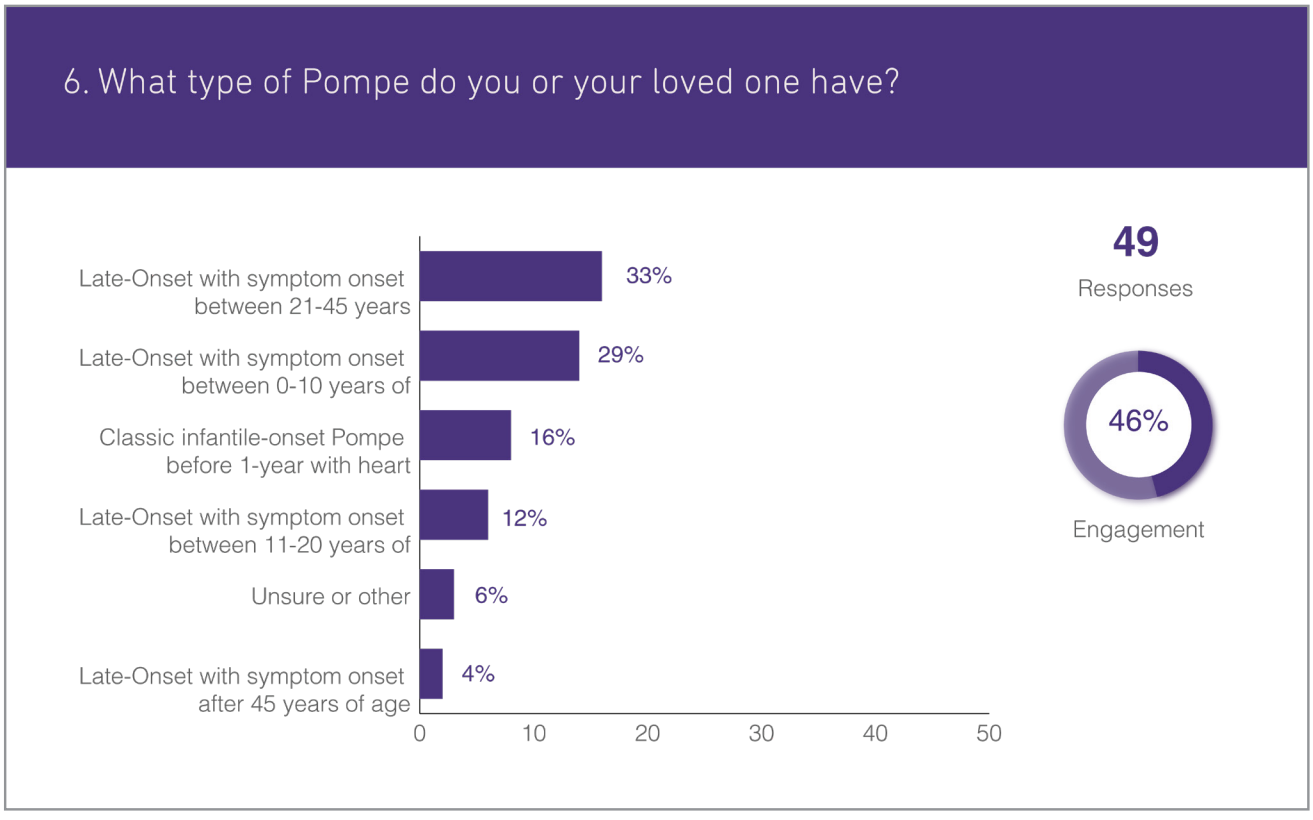
Response Options	Count	Percentage
0-5 years	23	46%
6-18 years	6	12%
19-30 years	11	22%
31-50 years	9	18%
51-60 years	1	2%
>60	0	0%

Figure 5



Response Options	Count	Percentage
0-5 years	17	36%
6-18 years	2	4%
19-30 years	7	15%
31-50 years	16	34%
51-60 years	4	9%
>60	1	2%

Figure 6



Response Options	Count	Percentage
Late-Onset with symptom onset between 21-45 years	16	33%
Late-Onset with symptom onset between 0-10 years	14	29%
Classic infantile-onset Pompe before 1-year with heart	8	16%
Late-Onset with symptom onset between 11-20 years	6	12%
Unsure or other	3	6%
Late-Onset with symptom onset a er 45 years	2	4%

Figure 7

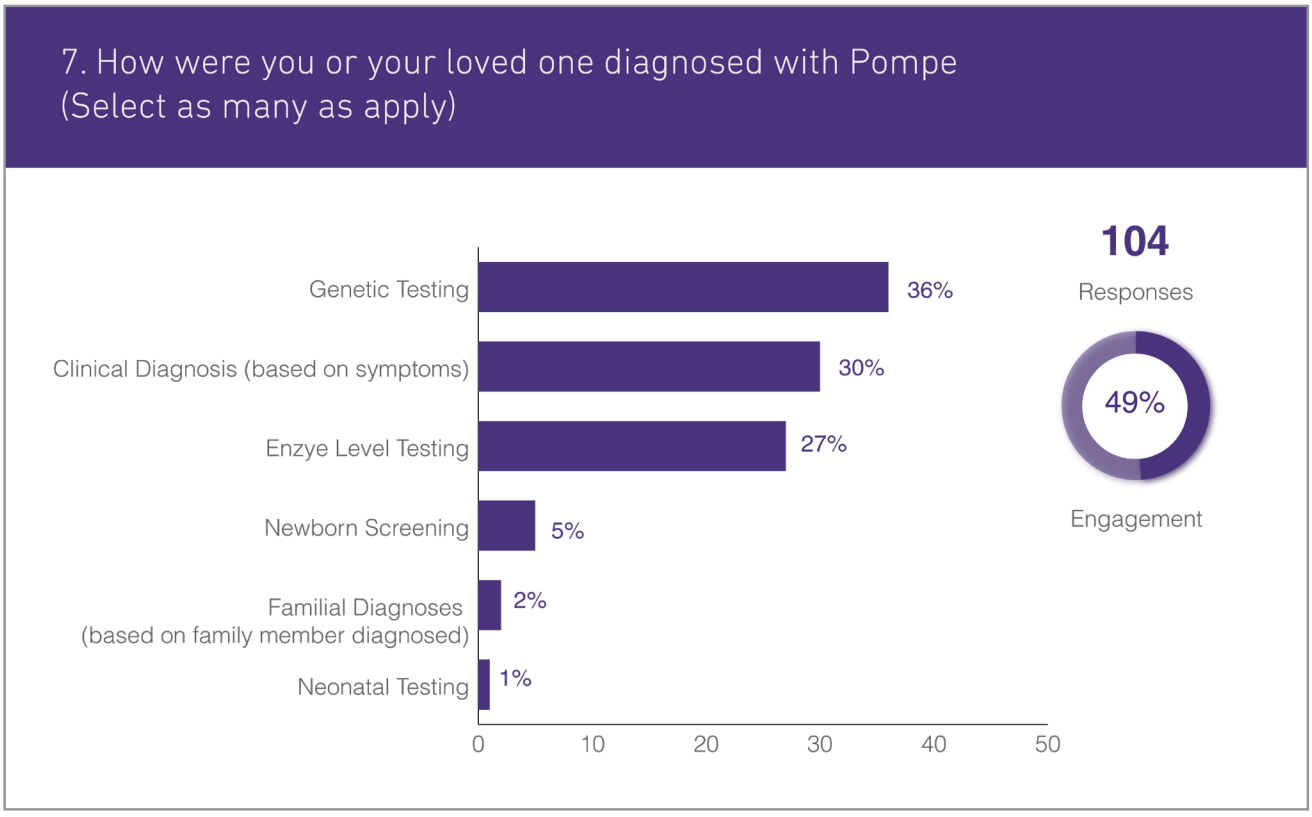


Figure note: Participants were able to choose more than one option.

Response Options	Count	Percentage
Genetic Testing	37	36%
Clinical diagnosis (based on symptoms)	31	30%
Enzyme Level Testing	28	27%
Newborn Screening	5	5%
Familial diagnoses (based on family member diagnosed)	2	2%
Neonatal Testing	1	1%

Figure 8a

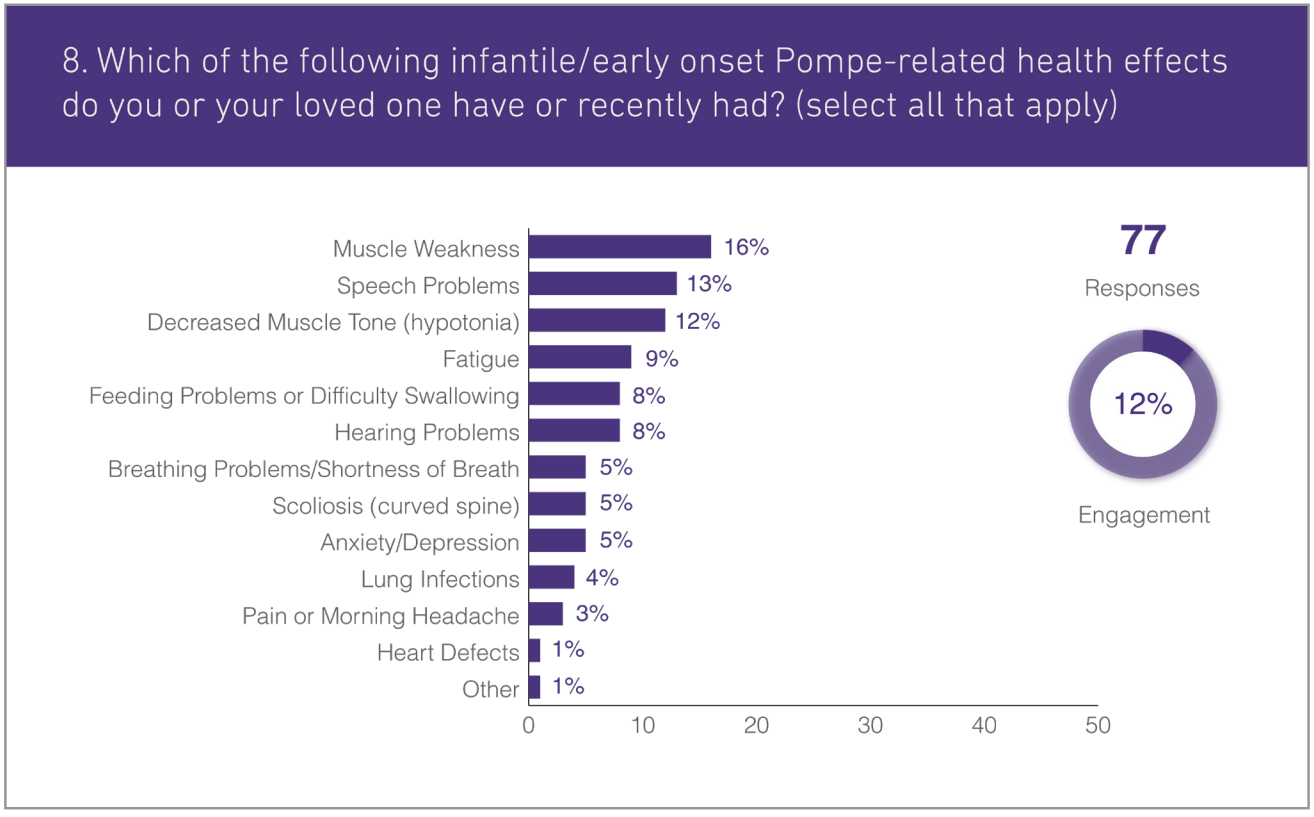


Figure note: Participants were able to choose more than one option in order to capture all health effects experienced by the patient.

Figure 8b

Response Options	Count	Percentage
Muscle weakness	12	16%
Speech problems	10	13%
Decreased muscle tone (hypotonia)	9	12%
Difficulty gaining weight/failure to grow	8	10%
Fatigue	7	9%
Feeding problems or difficulty swallowing	6	8%
Hearingearin problems	6	8%
Anxiety/depression	4	5%
Breathing problems/shortness of breath	4	5%
Scoliosis (curved spine)	4	5%
Lung infections	3	4%
Pain or morning headaches	2	3%
Heart defects	1	1%
Other	1	1%
Enlarged liver	0	0%

Figure 9a

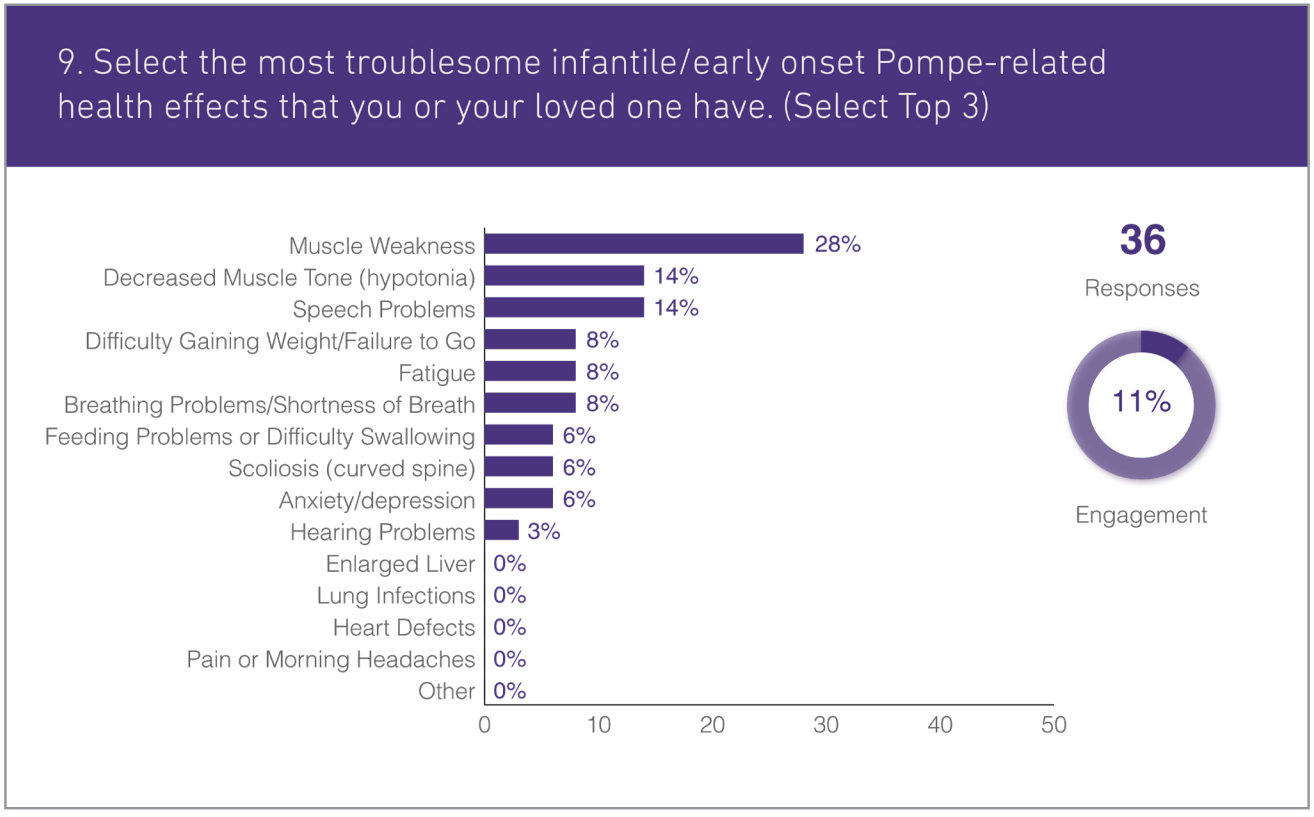


Figure note: Participants were able to choose more than one option in order to capture all health effects experienced by the patient.

Figure 9b

Response Options	Count	Percentage
Muscle weakness	10	28%
Decreased muscle tone (hypotonia)	5	14%
Speech problems	5	14%
Breathing problems/shortness of breath	3	8%
Difficulty gaining weight/failure to grow	3	8%
Fatigue	3	8%
Anxiety/depression	2	6%
Feeding problems or difficulty swallowing	2	6%
Scoliosis (curved spine)	2	6%
Hearing problems	1	3%
Enlarged liver	0	0%
Heart defects	0	0%
Lung infections	0	0%
Pain or morning headaches	0	0%
Other	0	0%

Figure 10a

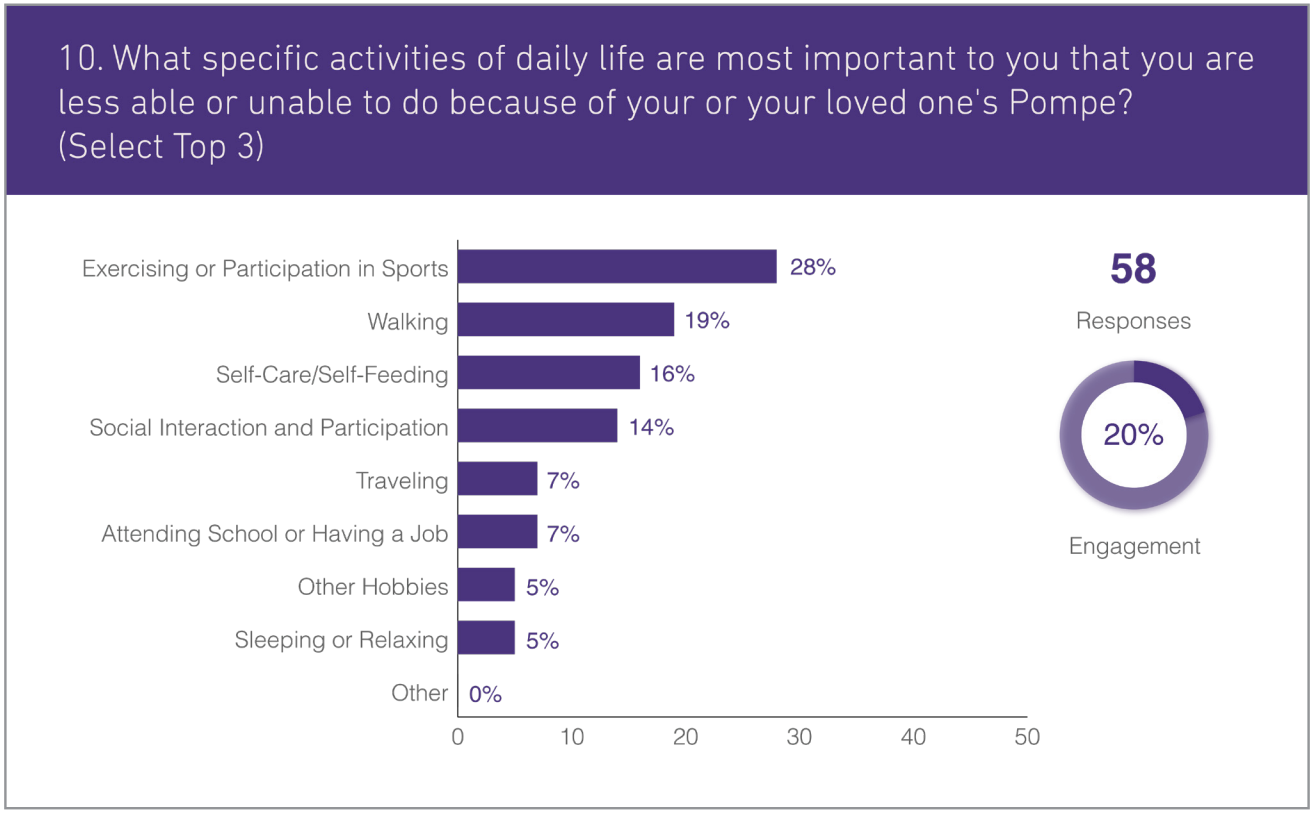


Figure note: Participants were able to choose more than one option.

Figure 10b

Response Options	Count	Percentage
Exercising or participation in sports	17	36%
Walking	11	19%
Self-care/self-feeding	9	16%
Social interaction and participation	8	14%
Attending school or having a job	4	7%
Traveling	4	7%
Other hobbies	3	5%
Sleeping or relaxing	3	5%
Other activities	0	0%

Figure 11a

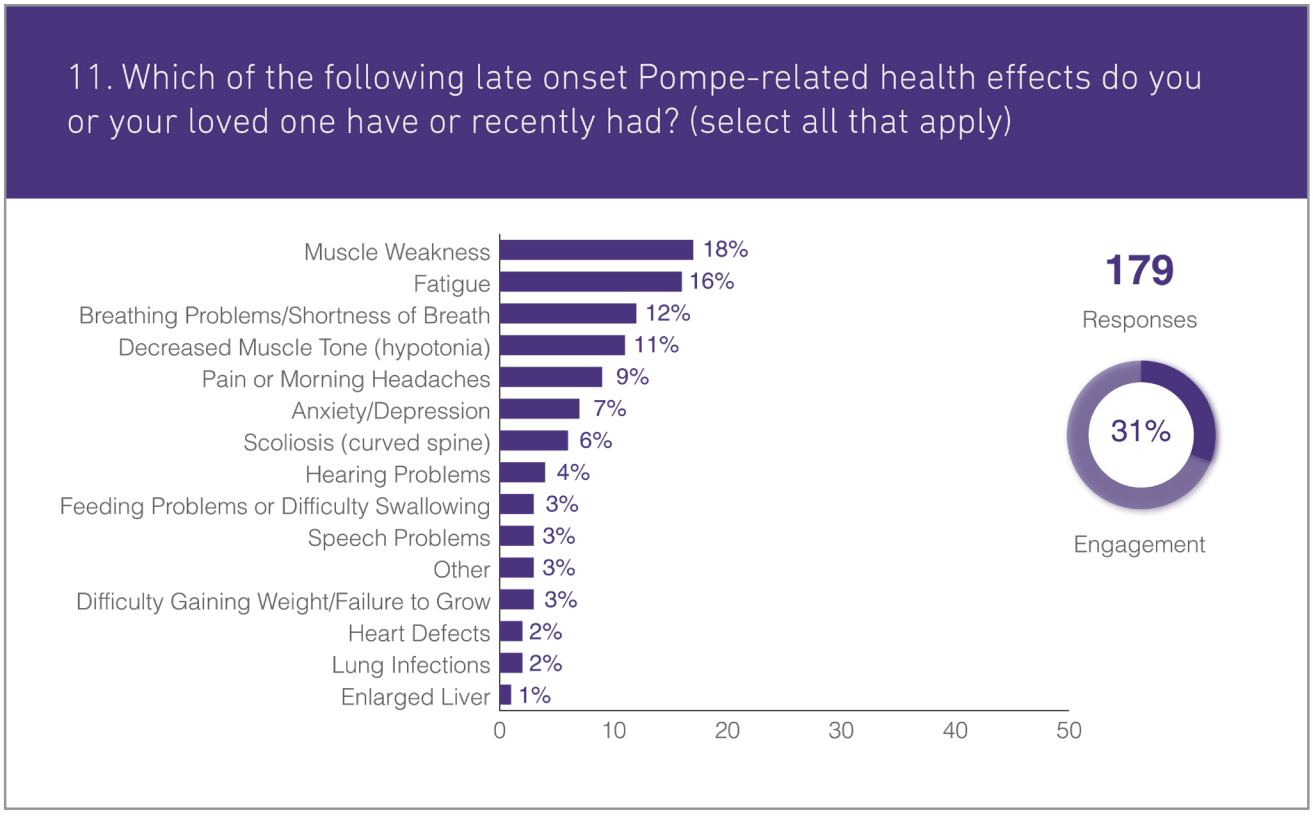


Figure note: Participants were able to choose more than one option in order to capture all health effects experienced by the patient.

Figure 11b

Response Options	Count	Percentage
Muscle weakness	33	18%
Fatigue	28	16%
Breathing problems/shortness of breath	21	12%
Decreased muscle tone (hypotonia)	20	11%
Pain or morning headaches	16	9%
Anxiety/depression	13	7%
Scoliosis (curved spine)	11	6%
Hearing problems	7	4%
Feeding problems or difficulty swallowing	6	3%
Other	6	3%
Difficulty gaining weight/failure to grow	5	3%
Speech problems	5	3%
Lung infections	4	2%
Heart defects	3	2%
Enlarged liver	1	1%

Figure 12a

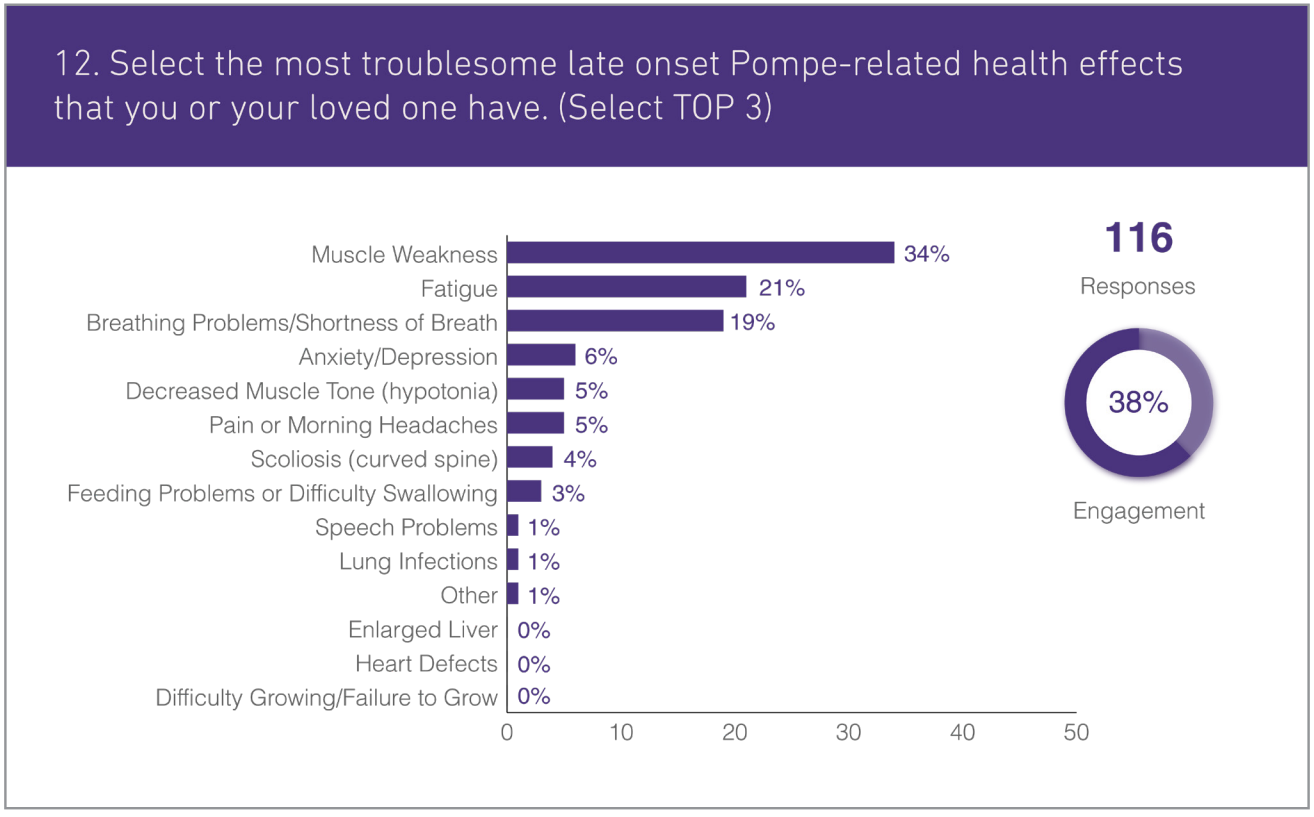


Figure note: Participants were able to choose more than one option in order to capture all health effects experienced by the patient.

Figure 12b

Response Options	Count	Percentage
Muscle weakness	40	34%
Fatigue	24	21%
Breathing problems/shortness of breath	22	19%
Anxiety/depression	7	6%
Decreased muscle tone (hypotonia)	6	5%
Pain or morning headaches	6	5%
Scoliosis (curved spine)	5	4%
Feeding problems or difficulty swallowing	3	3%
Lung infections	1	1%
Other	1	1%
Speech problems	1	1%
Difficulty gaining weight/failure to grow	0	0%
Enlarged liver	0	0%
Hearing problems	0	0%
Heart defects	0	0%

Figure 13a

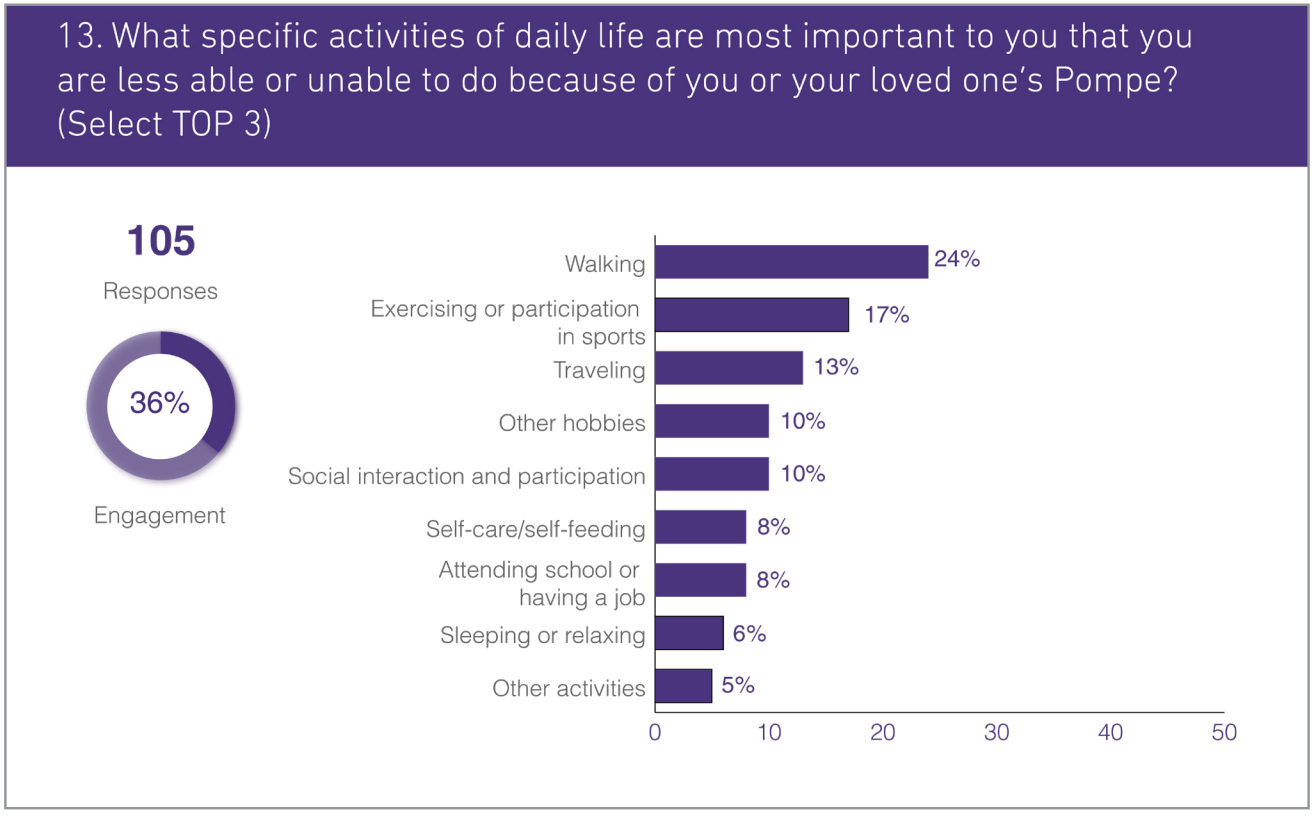


Figure note: Participants were able to choose more than one option in order to capture all effects on activities of daily living that were experienced by the patient. This poll was taken of patients with LOPD and their caregivers.

Figure 13b

Response Options	Count	Percentage
Walking	25	24%
Exercising or participation in sports	18	17%
Traveling	14	13%
Social interaction and participation	11	10%
Other hobbies	10	10%
Attending school or having a job	8	8%
Self-care/self-feeding	8	8%
Other activities	6	6%
Sleeping or relaxing	5	5%

Figure 14a

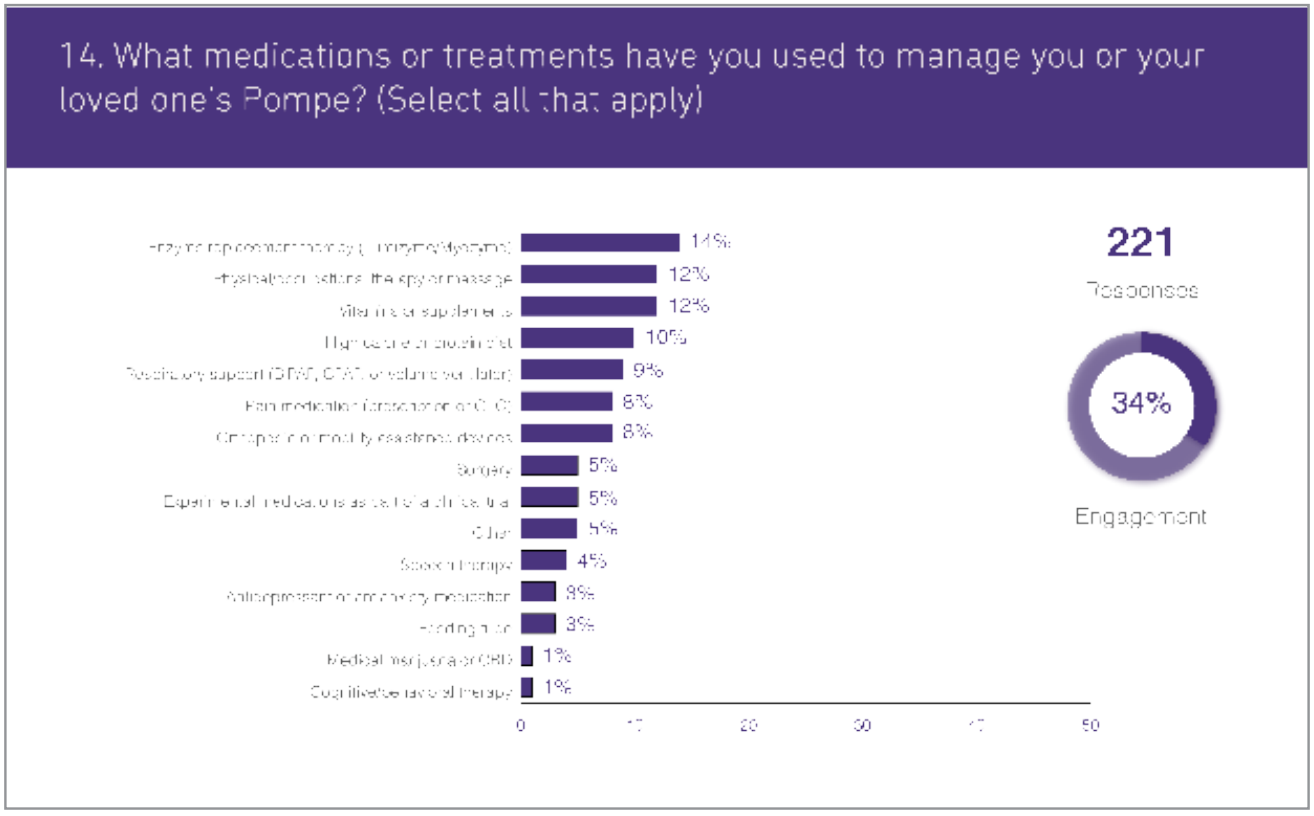
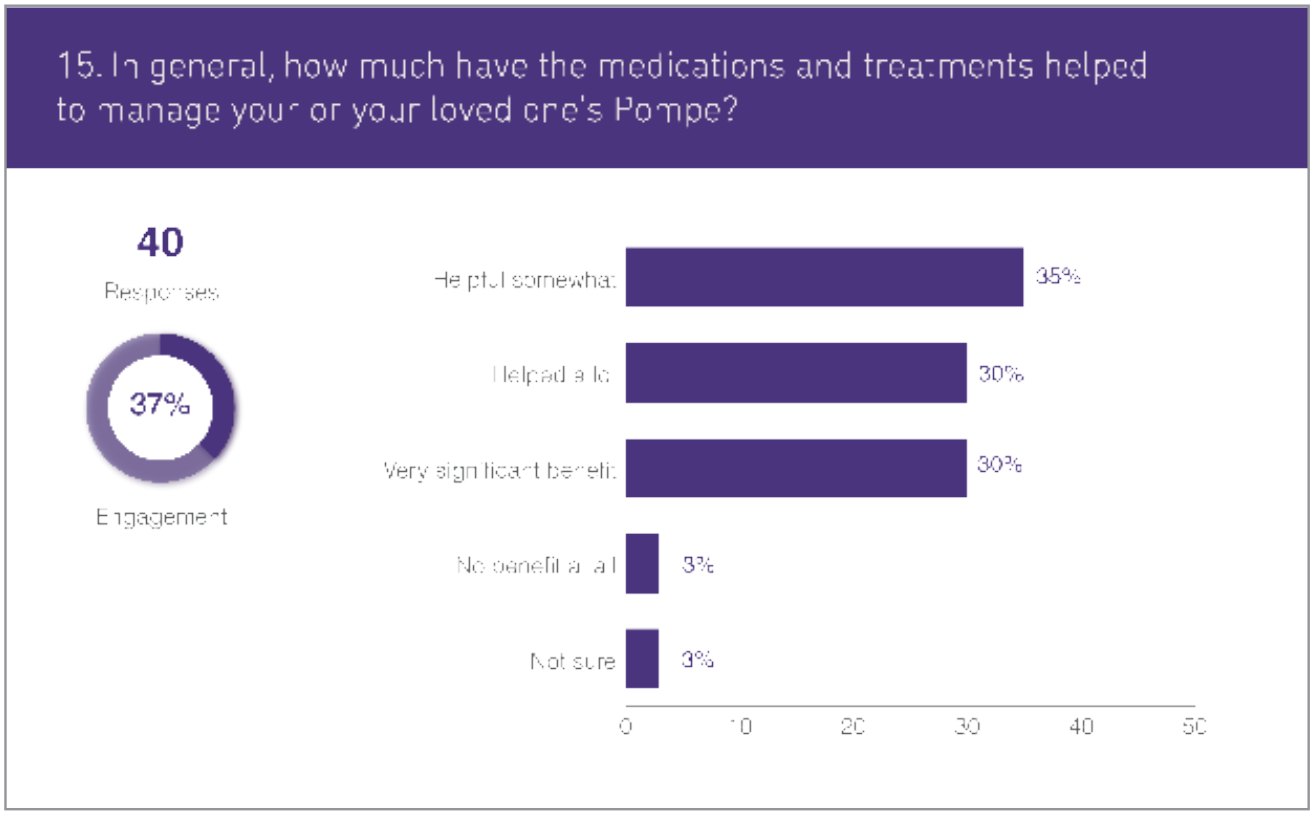


Figure note: Participants were able to choose more than one option in order to capture all treatments used by the patient.

Figure 14b

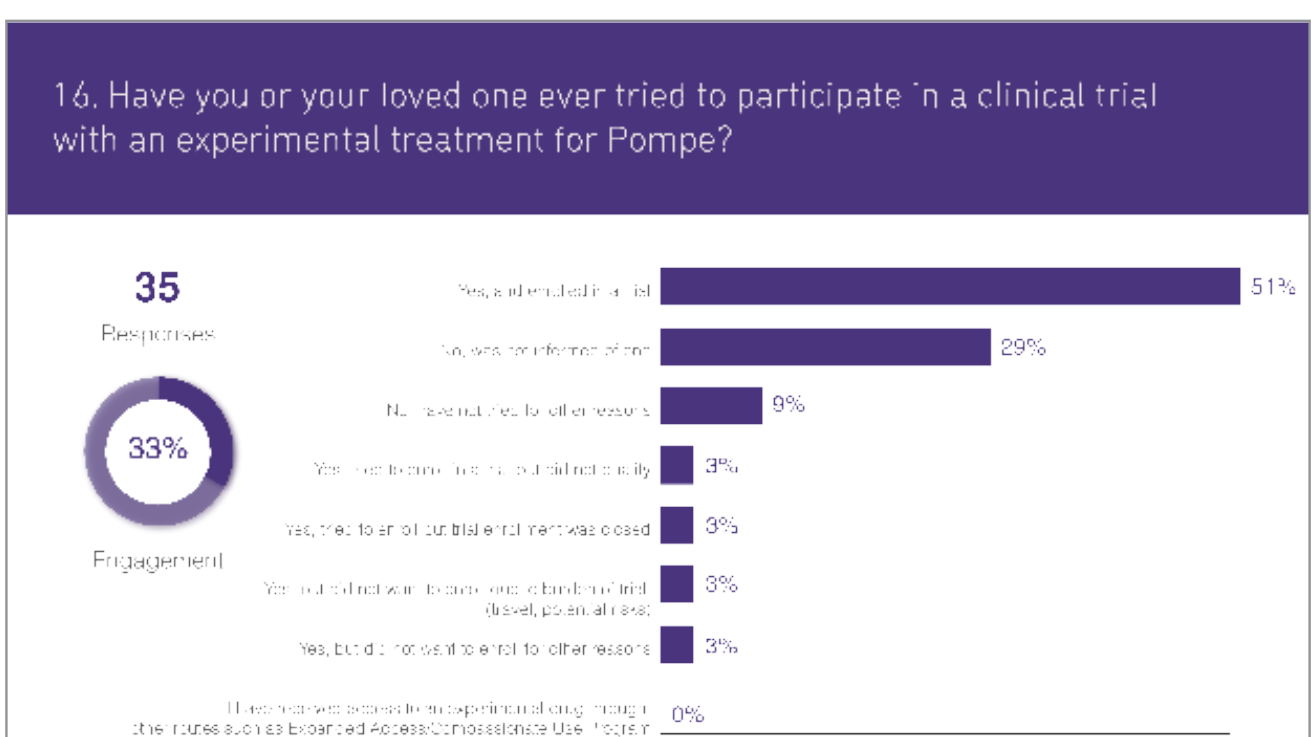
Response Options	Count	Percentage
Enzyme replacement therapy (Lumizyme/Myozyme)	31	14%
Physical/occupational therapy or massage	27	12%
Vitamins or supplements	26	12%
High calorie or protein diet	22	10%
Respiratory support (BiPAP, CPAP, or volume ventilator)	19	9%
Orthopedic or mobility assistance devices	18	8%
Pain medication (prescription or OTC)	17	8%
Experimental medications as part of a clinical trial	11	5%
Other	11	5%
Surgery	11	5%
Speech therapy	8	4%
Antidepressant or antianxiety medication	7	3%
Feeding tube	7	3%
Cognitive/behavioral therapy	3	1%
Medical marijuana or CBD	3	1%

Figure 15



Response Options	Count	Percentage
Helped somewhat	14	35%
Helped a lot	12	30%
Very significant benefit	12	30%
No benefit at all	1	3%
Not sure	1	3%

Figure 16



Response Options		Percentage
Yes, and enrolled in a trial	18	51%
No, was not informed of one	10	29%
No, have not tried for other reasons	3	9%
Yes, tried to enroll in a trial but did not qualify	1	3%
Yes, tried to enroll but trial enrollment was closed	1	3%
Yes, but did not want to enroll due to burden of trial (travel, potential risks)	1	3%
Yes, but did not want to enroll for other reasons	1	3%
I have received access to an experimental drug through other routes such as Expanded Access / Compassionate Use Program	0	0%

Figure 17a

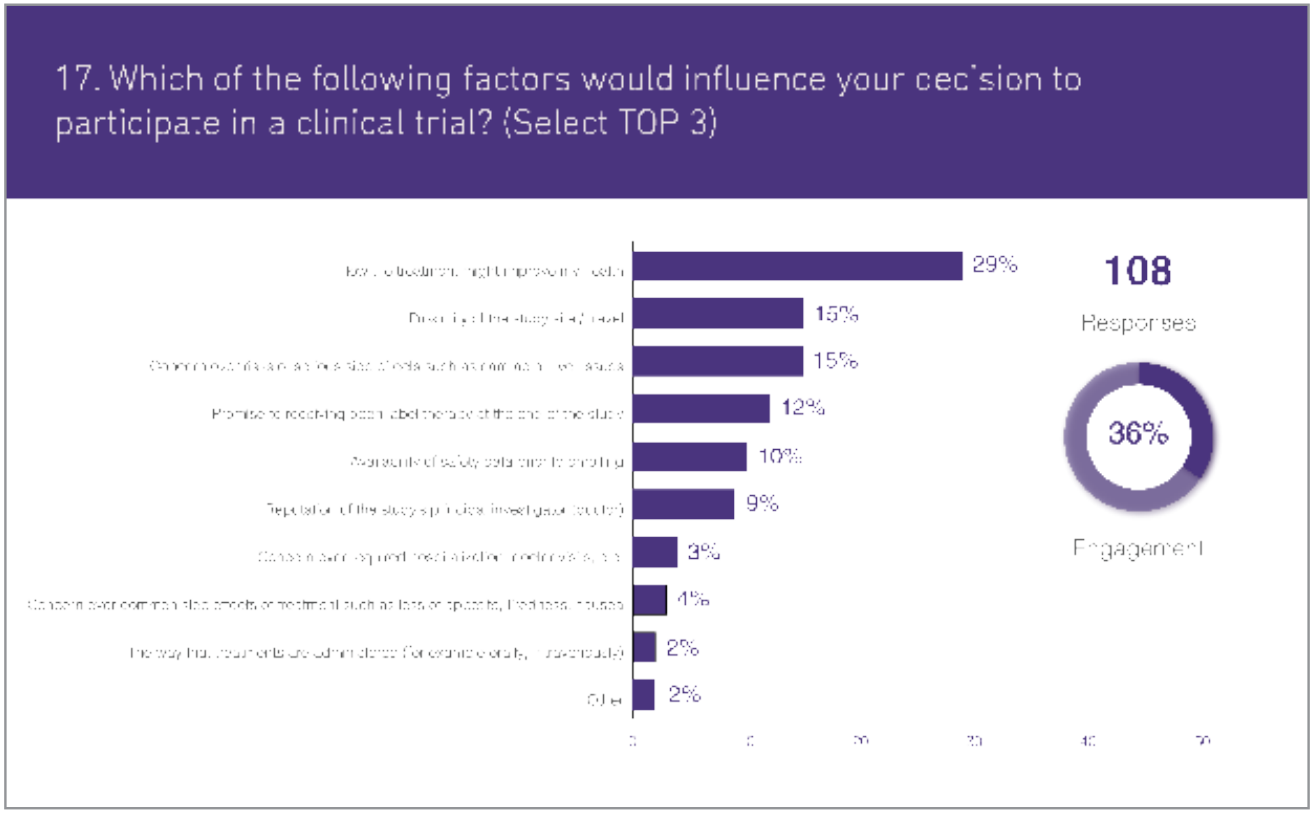


Figure note: Participants were able to choose more than one option in order to capture all factors influencing decisions by the patient.

Figure 17b

Response Options	Count	Percentage
How the treatment might improve my health	31	29%
Concern over risks of serious side effects such as cardiac or liver issues	16	15%
Proximity of the study site / travel	16	15%
Promise to receiving open label therapy at the end of the study	13	12%
Availability of safety data prior to enrolling	11	10%
Reputation of the study's principal investigator (doctor)	10	9%
Concern over required hospitalization, doctor visits, etc.	4	4%
Concern over common side effects of treatment such as loss of appetite, tiredness, nausea	3	3%
The way that treatments are administered (for example orally, intravenously)	2	2%
Other	2	2%

Figure 18a

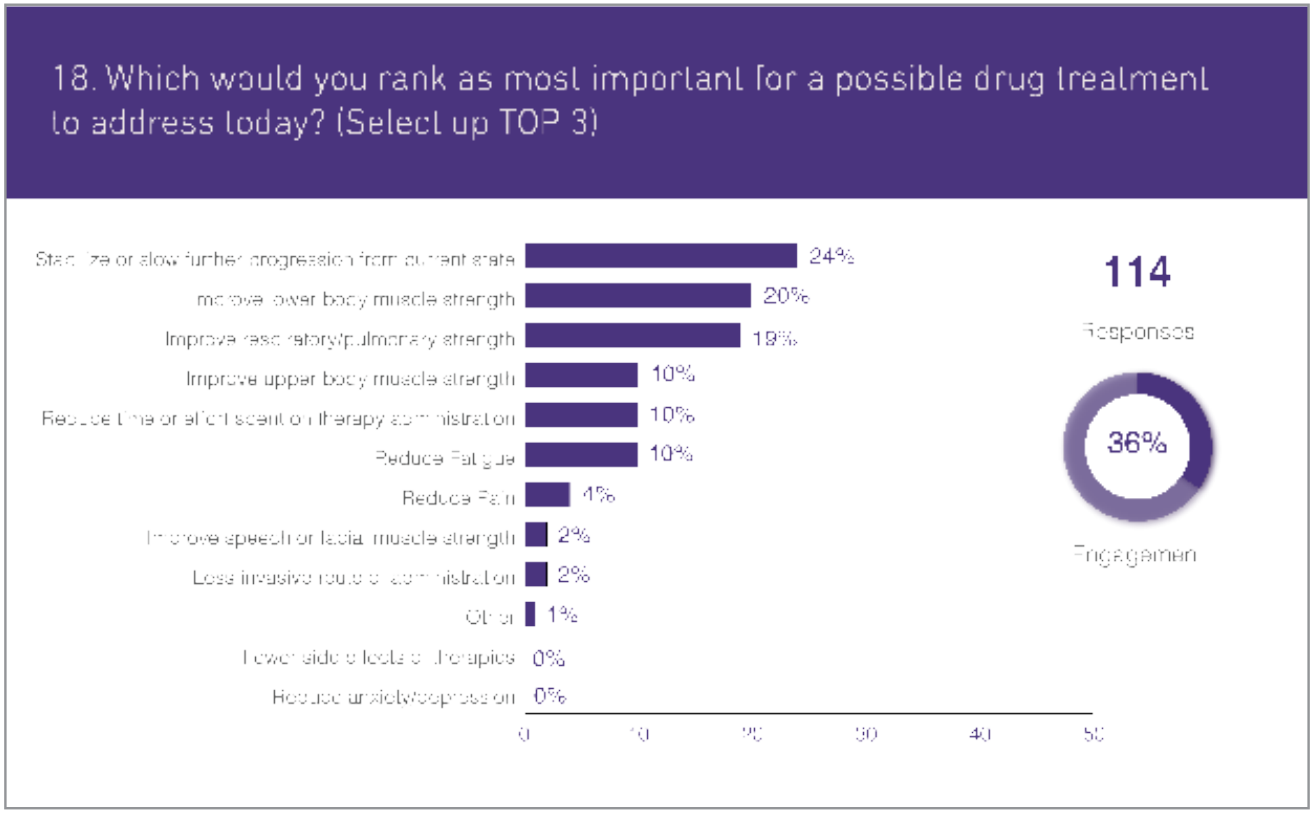


Figure note: Participants were able to choose more than one option in order to capture all potential benefits experienced by the patient.

Figure 18b

Response Options	Count	Percentage
Stabilize or slow further progression from current	27	24%
Improve lower body muscle strength	23	20%
Improve respiratory/pulmonary strength	22	19%
Improve upper body muscle strength	11	10%
Reduce Fatigue	11	10%
Reduce time or effort spent on therapy administration	11	10%
Reduce Pain	4	4%
Improve speech or facial muscle strength	2	2%
Less invasive route of administration	2	2%
Other	1	1%
Fewer side effects of therapies	0	0%
Reduce anxiety/depression	0	0%