



Patient Reported Outcomes - Pediatric Experience with Olipudase alfa

May 12, 2022






Outline

- Review of the clinical outcomes in ASMD patients taking olipudase alfa
- Highlight the importance of the patient voice and patient reported comes
- Review the qualitative and quantitative data from pediatric patients and families taking olipudase alfa



ARTICLE

One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency

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PURPOSE: To assess olipudase alfa enzyme replacement therapy for non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in children.

METHODS: This phase 1/2, international, multicenter, open-label trial (ASCEND-Peds/NCT02292654) administered intravenous olipudase alfa every 2 weeks with inpatient dose escalation to 3 mg/kg. Primary outcome was safety through week 64. Secondary outcomes included pharmacokinetics, spleen and liver volumes, lung diffusing capacity (DL_{CO}), lipid profiles, and height through week 52.

RESULTS: Twenty patients were enrolled: four adolescents (12–17 years), nine children (6–11 years), and seven infants/early child (1–5 years). Most adverse events were mild or moderate, including infusion-associated reactions (primarily urticaria, pyrexia, and/or vomiting) in 11 patients. Three patients had serious treatment-related events: one with transient asymptomatic alanine aminotransferase increases, another with urticaria and rash (antidrug antibody positive [ADA+]), and a third with an anaphylactic reaction (ADA+) who underwent desensitization and reached the 3 mg/kg maintenance dose. Mean splenomegaly and hepatomegaly improved by >40% ($p < 0.0001$). Mean % predicted DL_{CO} improved by 32.9% ($p = 0.0053$) in patients able to perform the test. Lipid profiles and elevated liver transaminase levels normalized. Mean height Z-scores improved by 0.56 ($p < 0.0001$).

CONCLUSION: In this study in children with chronic ASMD, olipudase alfa was generally well-tolerated with significant, comprehensive improvements in disease pathology across a range of clinically relevant endpoints.

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ASCEND-Peds patient recruitment

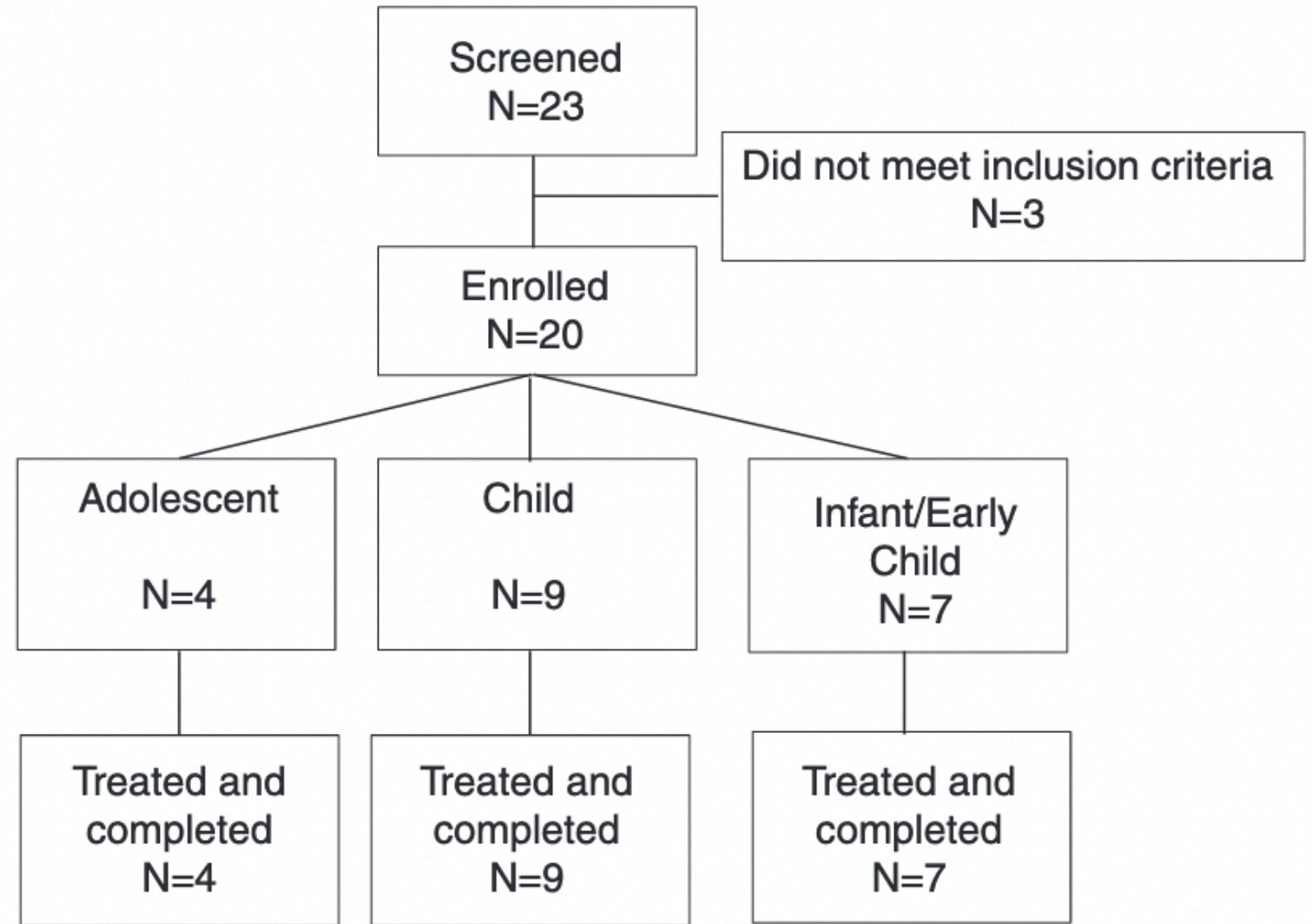
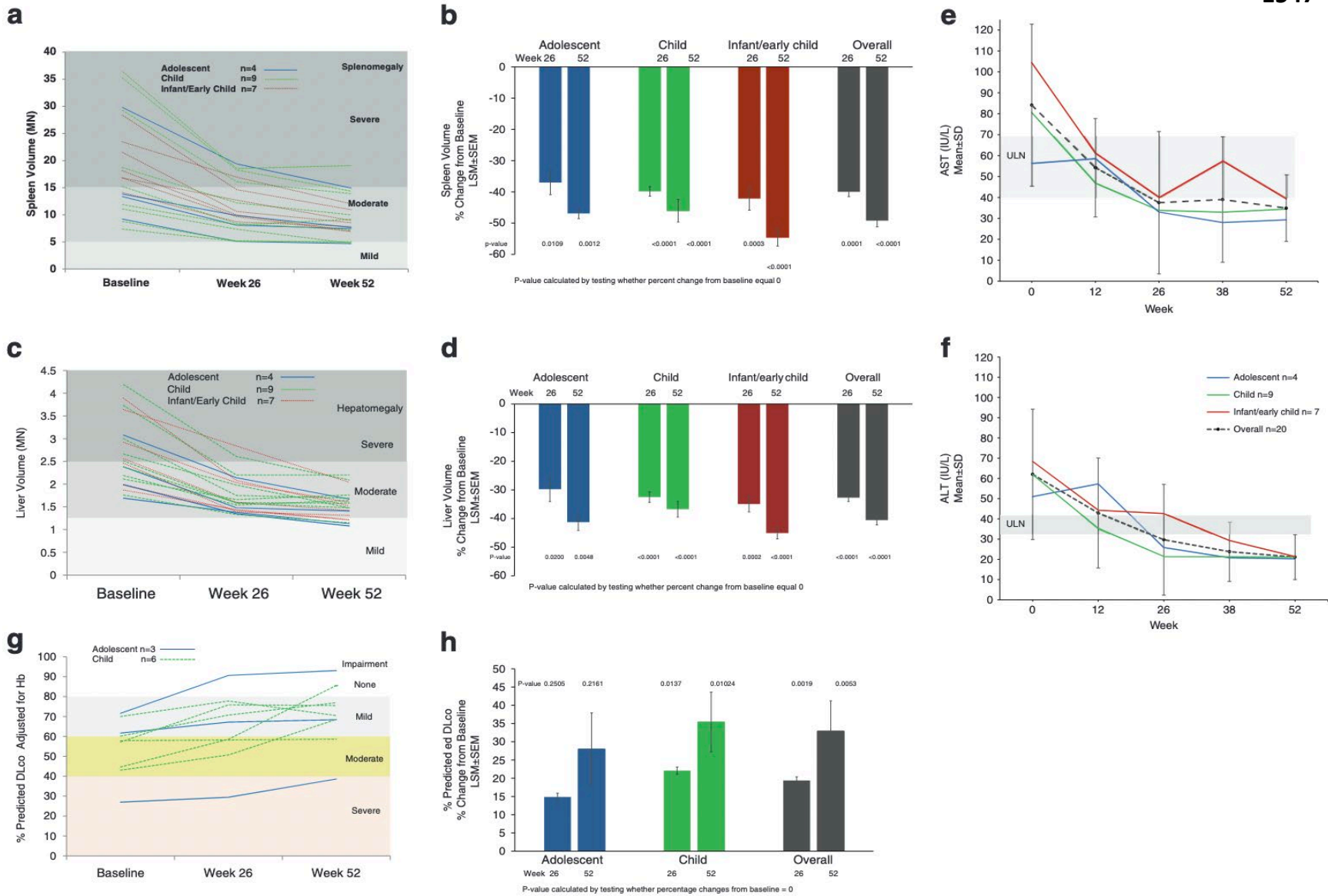
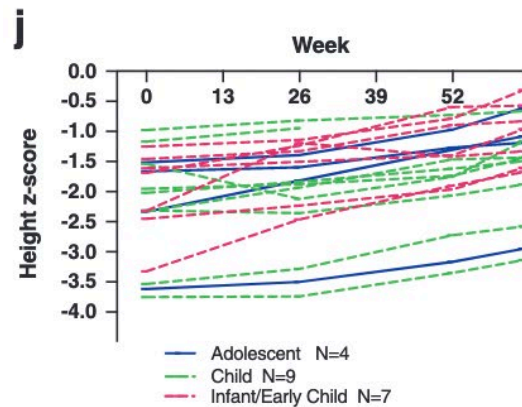
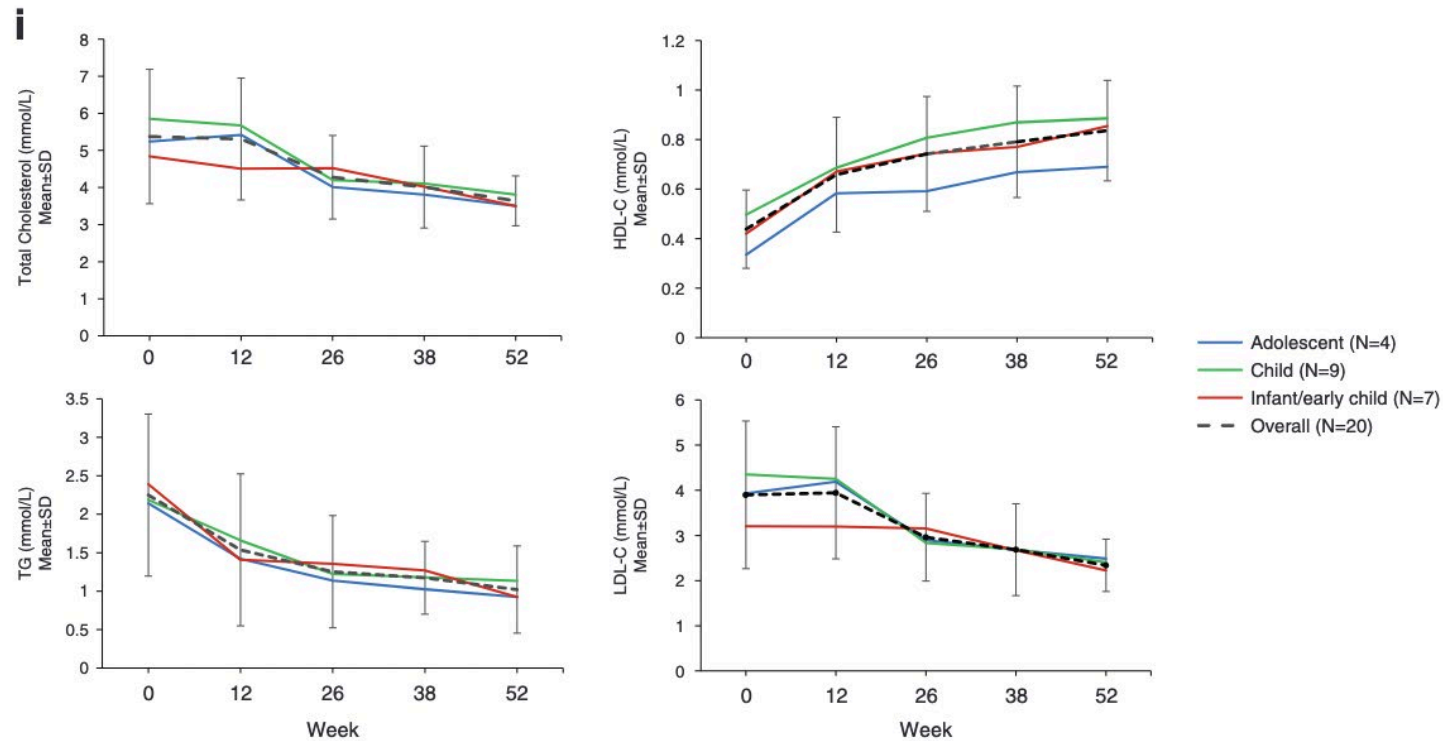


Fig. 1 Patient Disposition in the Trial. Patient disposition.



P-value calculated by testing whether percentage changes from baseline = 0



| Group | Height z-score change from baseline | |
|--------------------------|---------------------------------------|---|
| | Least Square Mean (95% CI) | |
| | P value | |
| | Wk26 | Wk52 |
| Adolescent (n=4) | 0.206 (-0.347, 0.758) 0.2502 | 0.606 (-0.159, 1.370) 0.0763 |
| Child (n=9) | 0.074 (-0.158, 0.306) 0.4761 | 0.371* (0.103, 0.639) 0.0148 |
| Infant/Early Child (n=7) | 0.484 (0.077, 0.890) 0.0298 | 0.736 (0.405, 1.068) 0.0023 |
| Overall (n=20) | 0.231 (0.060, 0.402) 0.0112 | 0.555 (0.377, 0.733) <0.0001 |

P value calculated by testing whether change from baseline=0
* based on eight patients



CLINICAL TRIAL

A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results

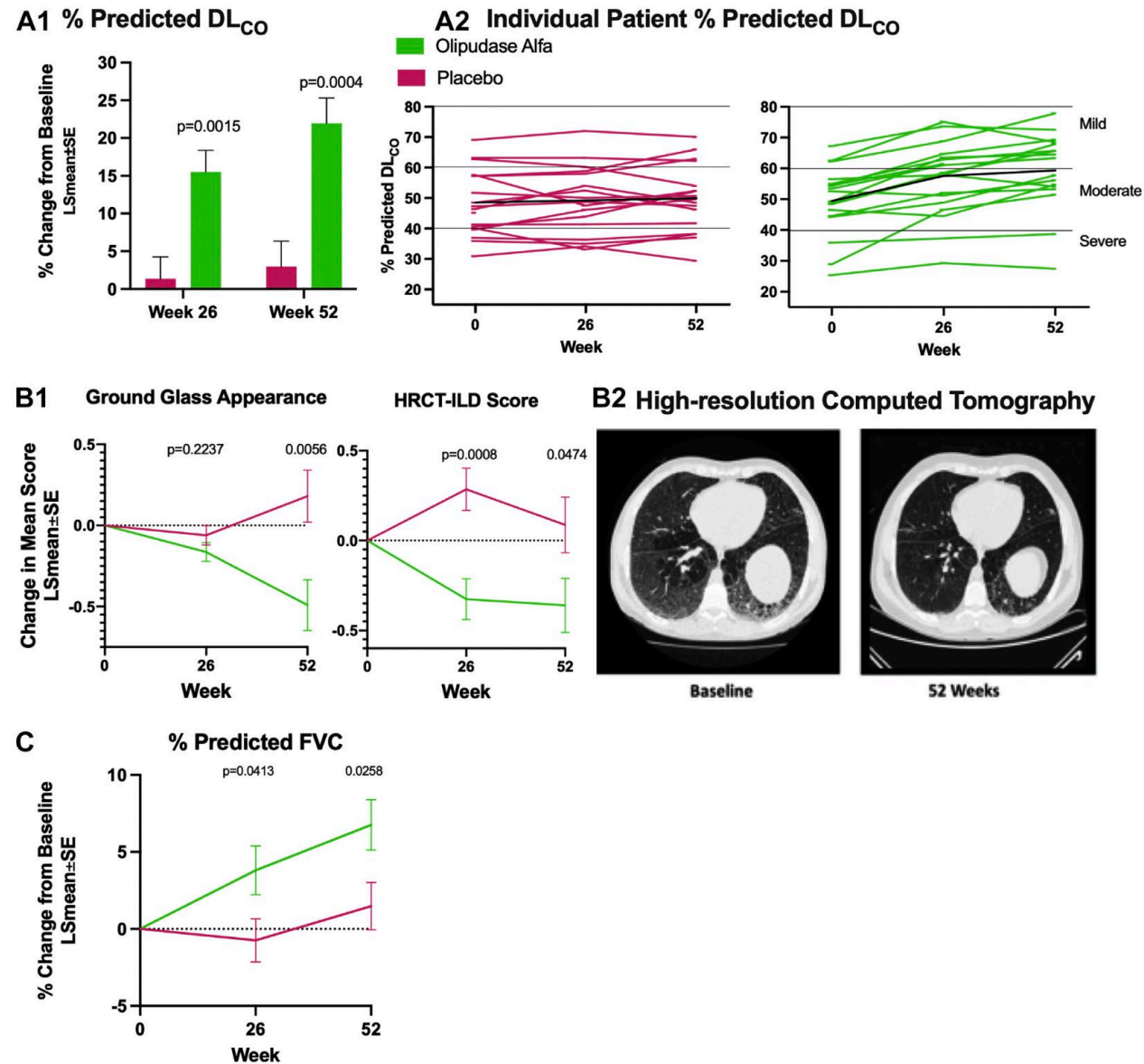
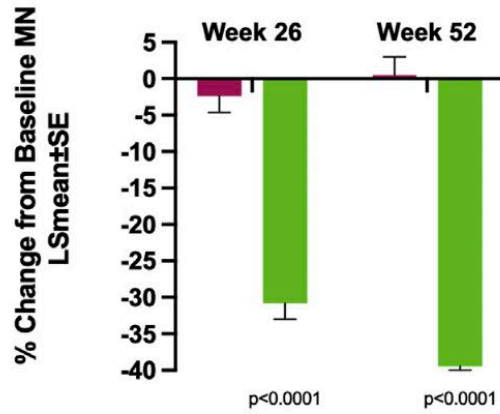
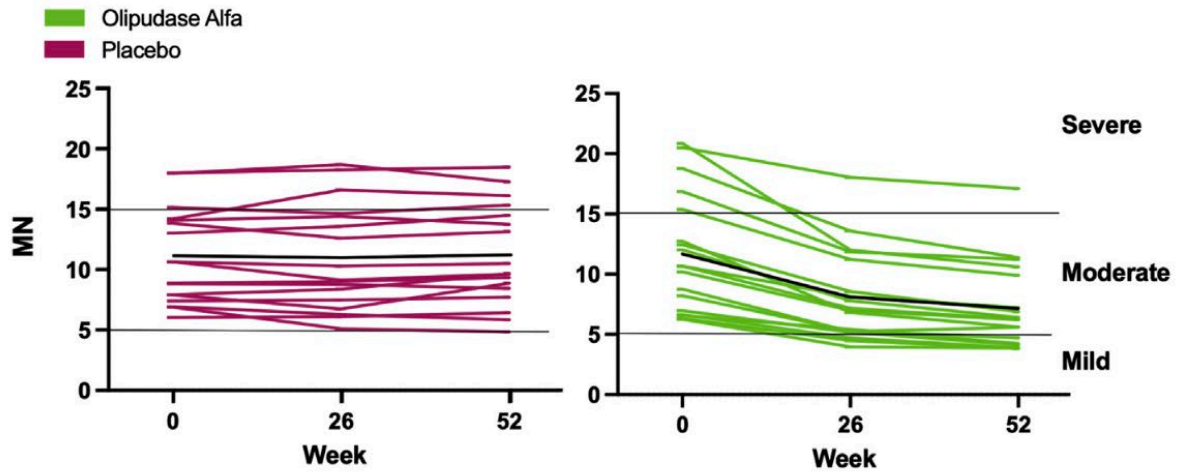


Figure 2 Pulmonary endpoints (diffusing capacity, lung disease imaging, and forced vital capacity) over time in the placebo and

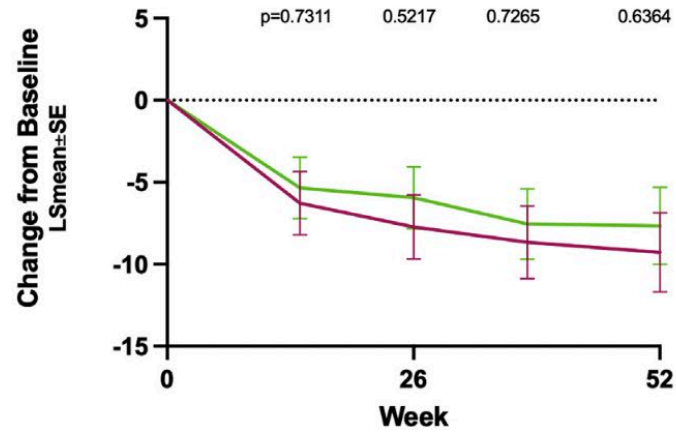
A1 Spleen Volume



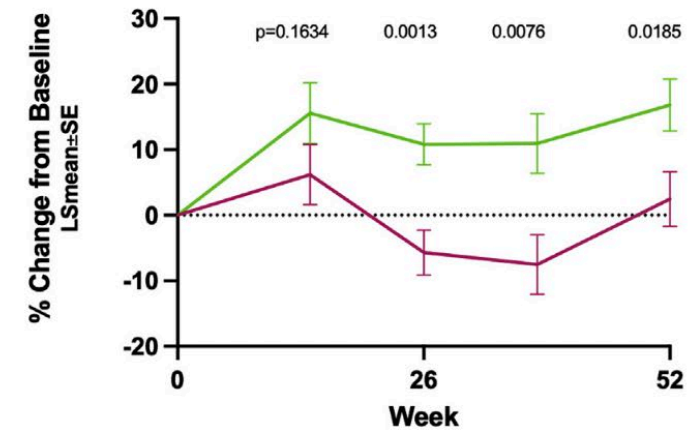
A2 Individual Patient Spleen Volume



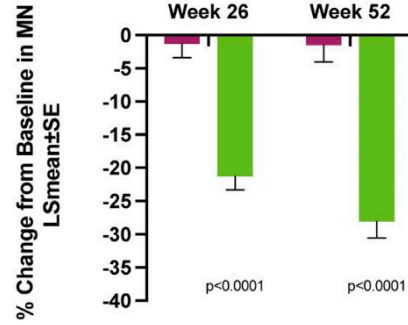
B SRS



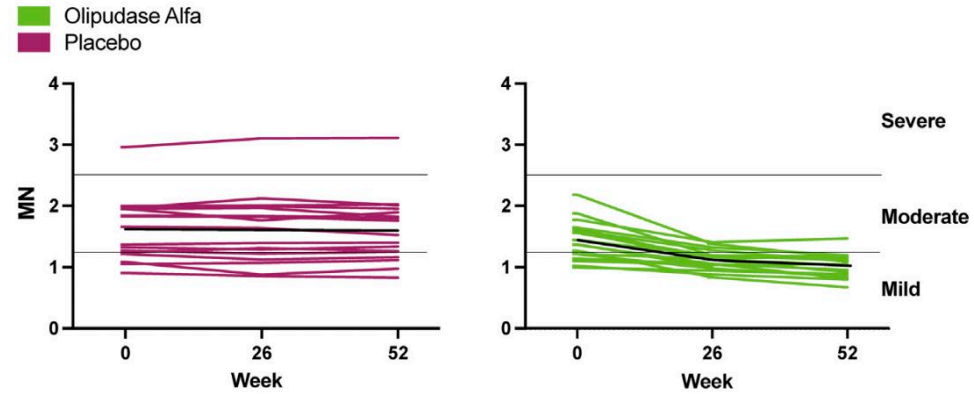
C Platelet Counts



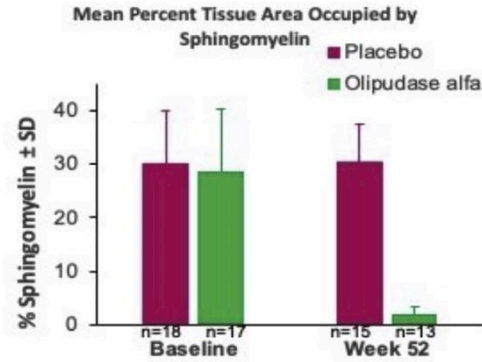
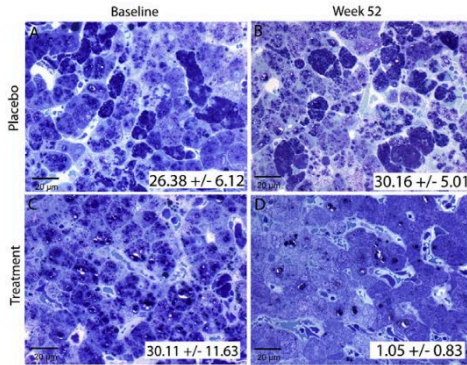
A1 Liver Volume



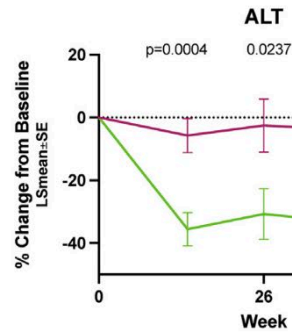
A2 Individual Patient Liver Volume



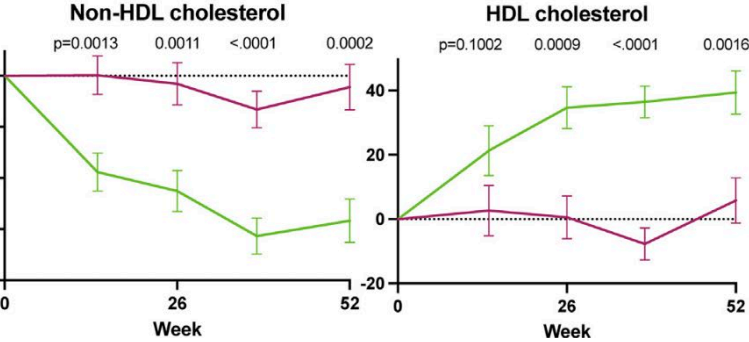
B Liver Spingomyelin Burden



C1 Liver Function




C2 Plasma Lipid Profiles





What can NNPDF/
NPUK/INPDR do
to amplify the
patient voice in
relation to
experience with
olipudase alfa?

- **Regulators wish to understand the burden of disease, burden of therapy, benefits of therapy, risks, and tolerance of risk**
- While we are fortunate to have multiple publications that outline the experience of the disease, our community lacks data on the impact that olipudase has on patient experience



“The Impacts of olipudase alfa on Paediatric Patients with ASMD and their Families”

- Collaboration of NNPdF, NPUK and INDPR
- Utilizing the strength of national patient organizations and our own registry
- Engaged with a professional third-party research organization (Rare Disease Research Partners) to reduce bias and maintain scientific rigor

STUDY AIMS

The study aims were to:

- increase the understanding of the impacts of ASMD on paediatric patients and their families
- explore the effects of olipudase alfa on paediatric patients and their families
- gain insights from patients and their families into the unmet need for treatment of ASMD

METHODS

The study consisted of an international online survey in English followed by semi-structured interviews.

The survey was open to adults aged 18 years and over (or their parent/caregiver) who:

- were fluent in English (including non-native English speakers) and
- were able to give informed consent and
- had a confirmed diagnosis of ASMD and
- had used the experimental drug olipudase alfa for more than 12 months and
- had commenced treatment with olipudase alfa under the age of 18 years (paediatric age)

Survey

The online survey was designed with input from NNPfD, NPUK & INPDR to cover demographics, first symptoms, treatment with olipudase alfa, symptoms before and after treatment, overall change in symptoms & activities since treatment, current treatment for ASMD, experience with olipudase alfa and satisfaction with olipudase alfa. The survey included multiple choice, matrix and open text questions to provide both quantitative and qualitative data.

The survey was hosted on the on-line Qualtrics^{XM} platform and distributed via a link. The survey was open from 19 January to 15 February 2022.

Interviews

A semi-structured interview guide was developed that covered questions from the survey in more depth and to further understand the impacts of olipudase alfa on patients and their families.

Interviews were conducted via Zoom by Connect Research and by one researcher to ensure a consistent approach. Ten interviews took place between 4th Feb 2022 and 21st Feb 2022 and were audio recorded and transcribed for analysis.

Analysis

A qualitative and quantitative analysis of the survey results was undertaken. Interview transcripts were analysed using an inductive thematic approach using NVivo software.

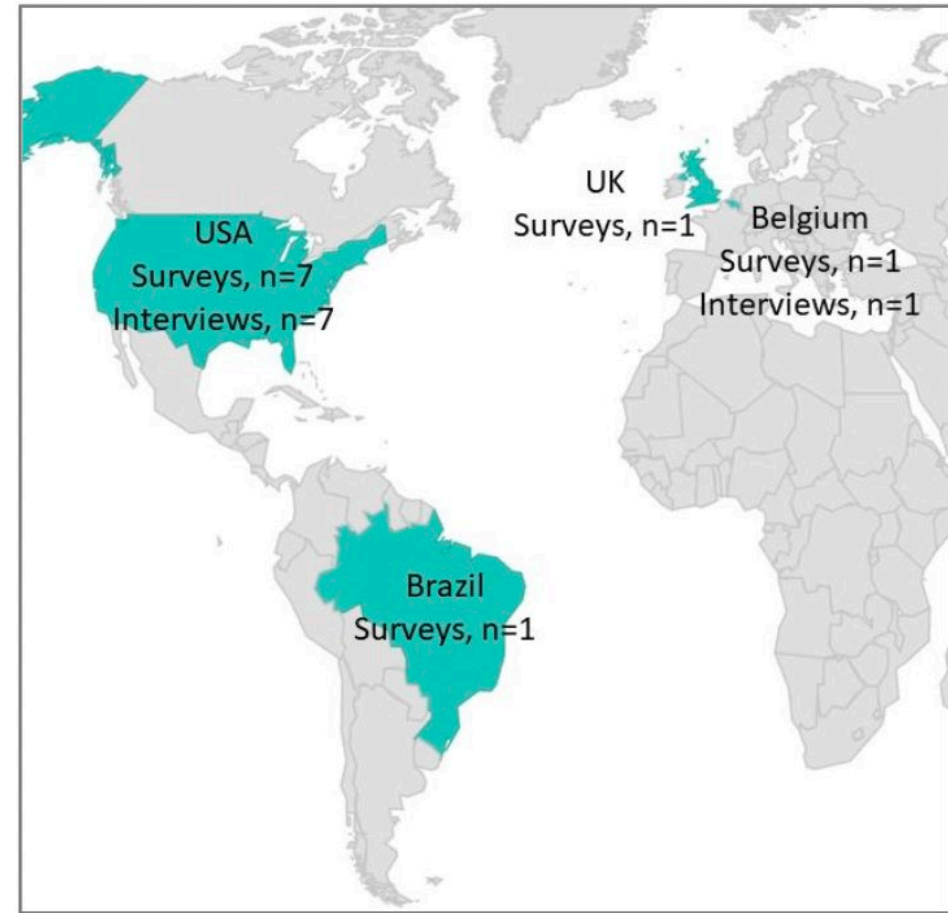
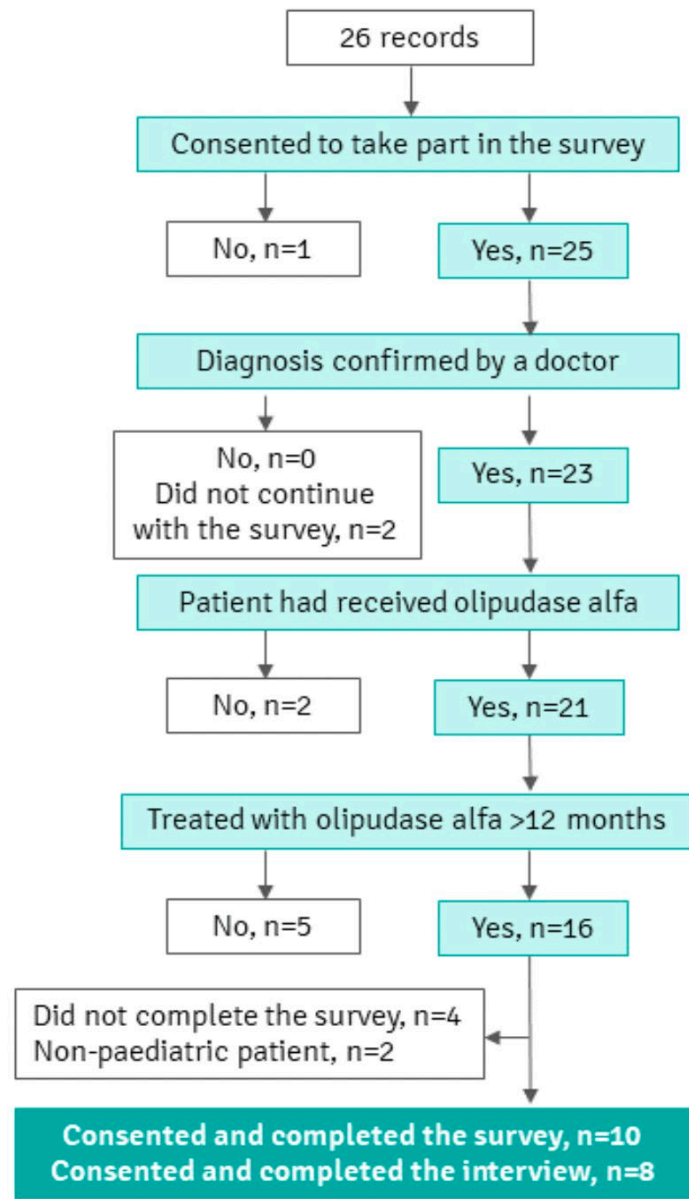
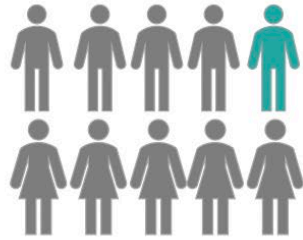


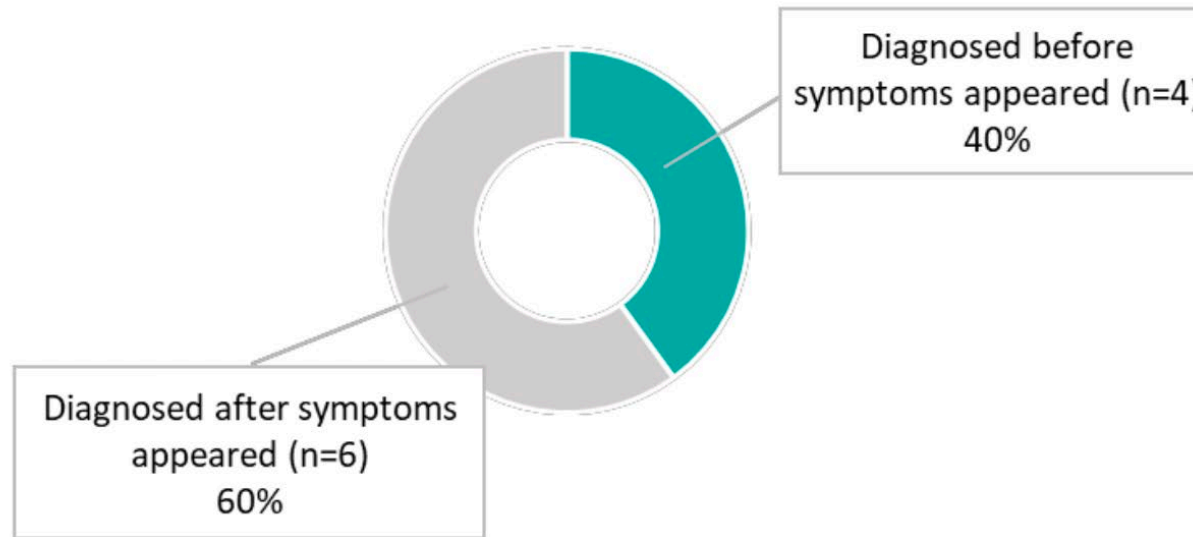
Figure 2. Country of birth and residence of participants in the survey (n=10) and interviews (n=8). All respondents were born in the same country where they resided.

Diagnosis



Only one patient was tested for ASDM because of a previous confirmed diagnosis in a sibling.

None of the ten patients had a diagnosis made before birth. The median age at which diagnosis was confirmed was 1.0 years of age (mean 1.7 ± 1.4 , range 0–5.0). Sixty percent (6/10) of patients were diagnosed after symptoms of ASDM appeared (Figure 5). Only one patient was tested for ASDM because of a previous confirmed diagnosis in a brother, being the only patient with a diagnosis made before the age of one.



First symptoms

Respondents were asked when the first symptoms of ASMD appeared. First symptoms of ASMD were reported to appear between 2 months and less than 2 years of age for sixty percent of patients (6/10) (Figure 4). All patients in the study had experienced symptoms of ASMD before 6 years of age (Table 1).

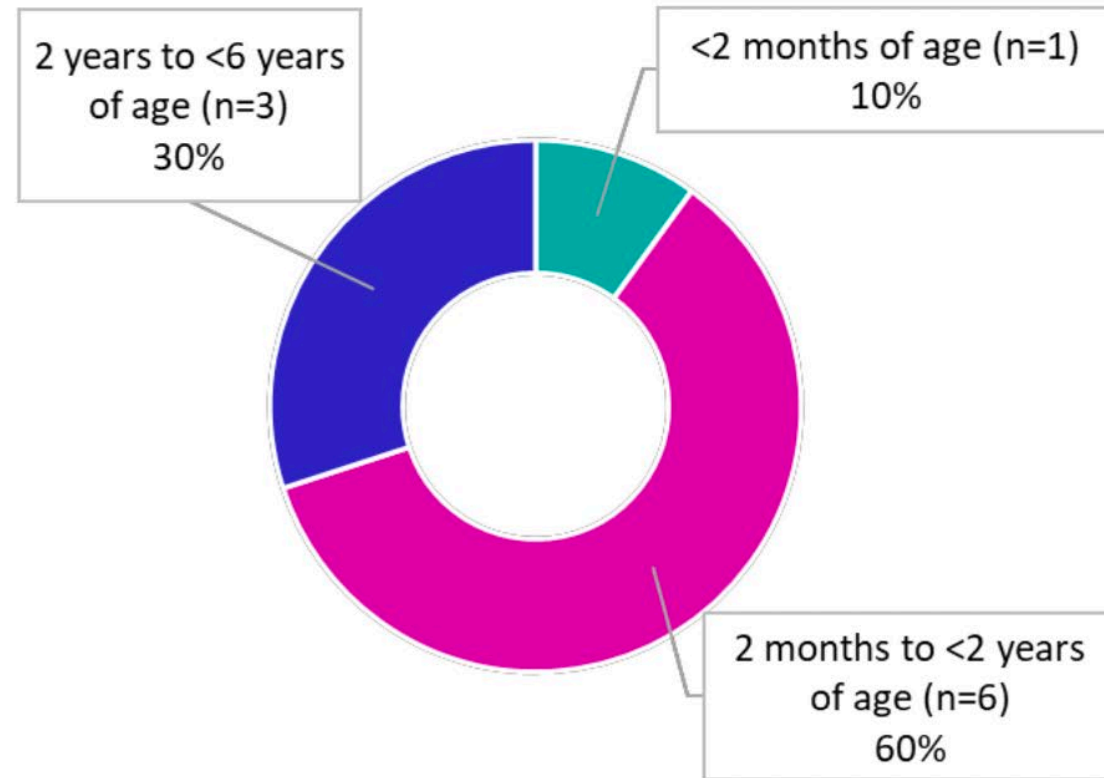


Figure 4. Age of first symptoms of ASMD (n=10)

“We finally got frustrated with that paediatrician and then went and saw another paediatrician and he immediately saw her and her belly stood out to him and he said that that wasn’t normal.” *Interview, diagnosed at 2 years of age*

“There were all sorts of red flags popping up here and there, but the doctors kept telling us she was fine.” *Interview, diagnosed at 5 years of age*

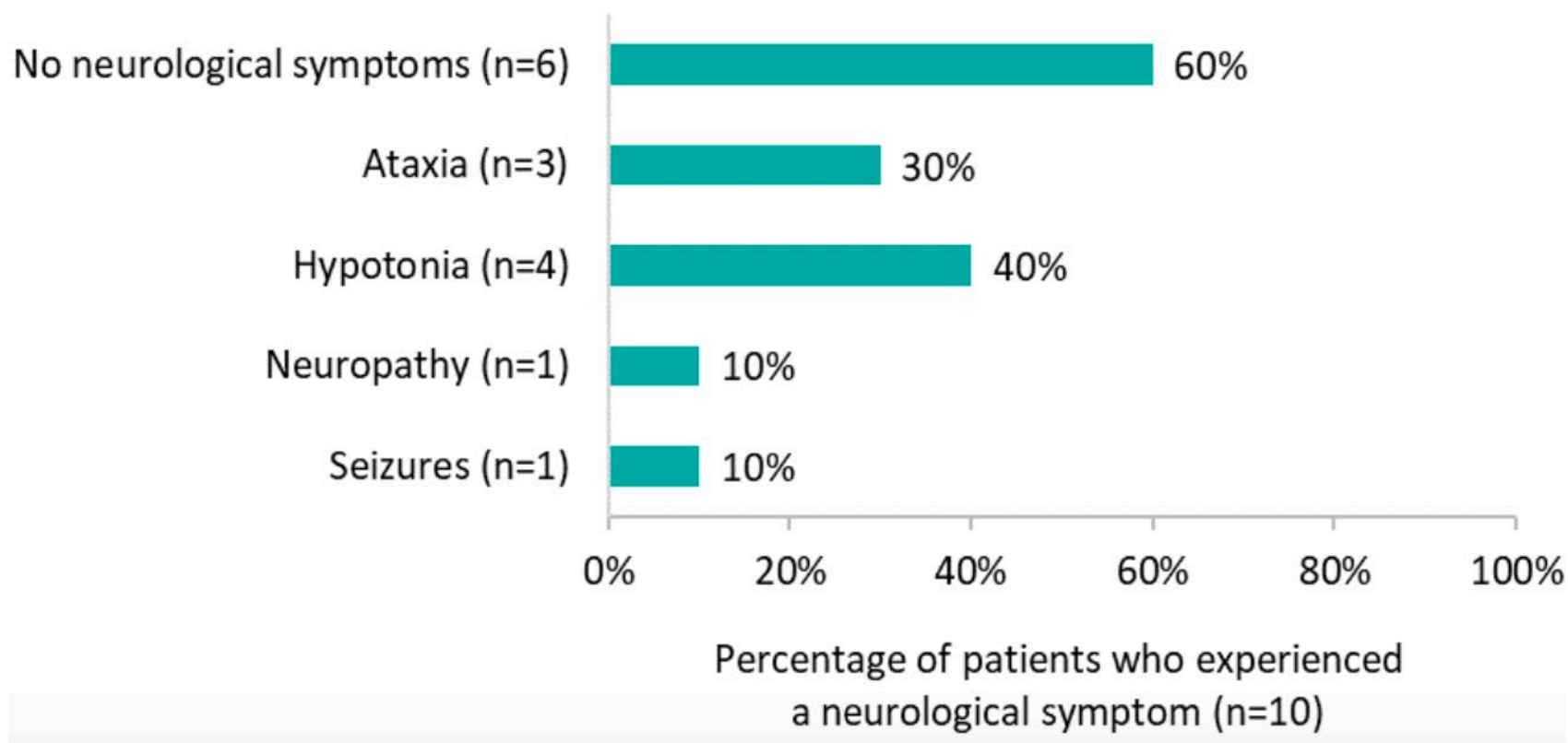
- After many tests on the child, one parent/caregiver did their own research in Google and asked the clinician to test their child for ASMD

“For the next six months, they tested her every week. They took her blood and did tests on her, and they couldn’t figure out what was wrong with her. I, actually, just doing Google research, came across Niemann-Pick and I asked them to test for that because they had tested for everything else.” *Interview, diagnosed at 5 years of age*

- For one child, diagnosis happened very rapidly

“It was about a month, it was a very quick, relatively quick diagnostic journey for us and for him. So it was the initial CT scan that showed the spleen and the liver involvement, and then the initial testing came back for the negative Gaucher. And then the very next panel that the metabolic doctor sent off, found the Niemann-Pick.”
Interview, diagnosed at 1 year of age

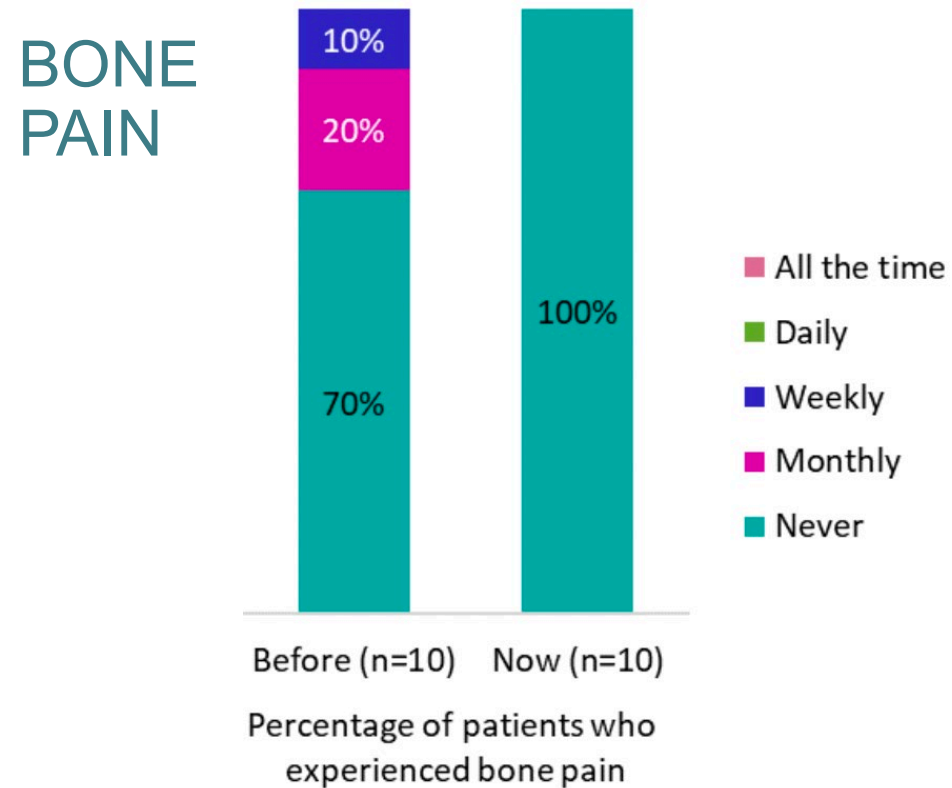
Patient reporting neurologic symptoms of ASMD



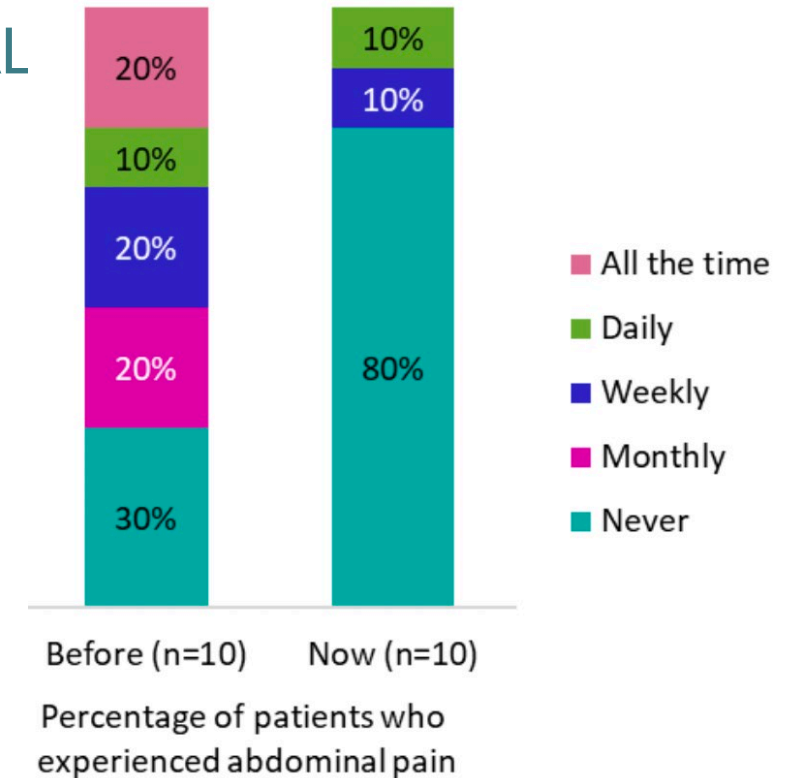
Olipudase initiation and duration of exposure

- Children started receiving olipudase at a median age of 3.5 years
 - mean 5.0 ± 3.8 , range 1.5–14.0, n=10
- All patients were still on olipudase at the time of the survey
 - mean 4.6 ± 1.5 , range 1.3–6.1. n=10

Olipudase exposure and impact on pain



ABDOMINAL PAIN



Qualitative reporting in addition to quantitative data



Before treatment:

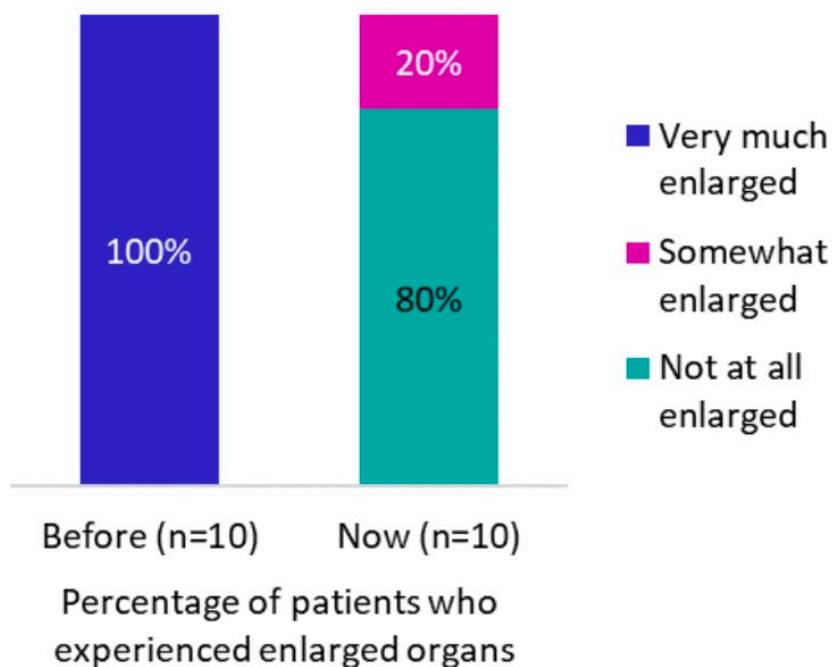
“...she complained about pain in the belly. So, that’s very difficult for us to exactly understand what it is that she feels, but I remember that every day she said, yes, my belly hurts, I have pain. Maybe it was the organs that were very dense. I don’t know. It was also difficult for her to exactly indicate where it was, but every day she told us that she was having pain in the belly.”

After treatment:

“Also, the pain in the belly is completely gone, I think it’s due to the organs that went to normal size again, and that is also supported by what the doctors tell us.”

Interview, diagnosed at 2 years of age, started treatment at 4 years of age, 3 years and 6 months on treatment

Hepatomegaly and splenomegaly



“But his organs, his belly was becoming increasingly more distended before the ERT [...]. He was hooked up to feeding pumps, because the pressure that was being put on his stomach, he was only able to tolerate small volumes at a time. He was on continuous feed, so he had a feeding pump hooked up to him all the time, and oxygen hooked up to him. It’s just a lot of stuff for a little kid to deal with.”

Interview, before treatment, started treatment at 2 years of age

“Before treatment:

“She fell a lot. So, due to the bigger belly, she had some stability problems and she really fell a lot.[...] The only times when she missed school was when she fell. That happened I think two times or something, yes, and she got an impact, a trauma on her head.”

After treatment:

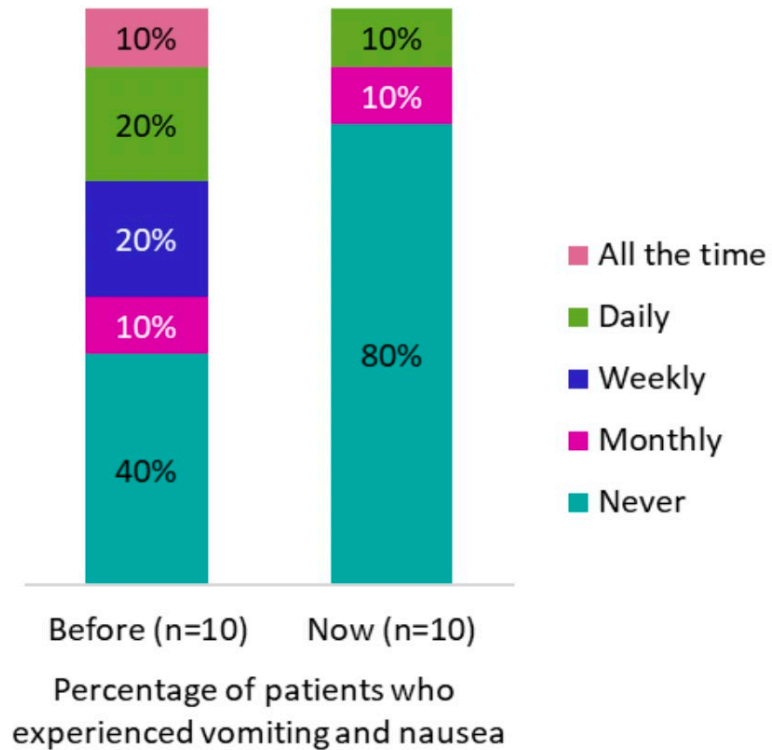
“...the belly is completely gone.”

Interview, started treatment at 4 years of age, 3 years and 6 months on treatment

“We were noticing that she was having a very challenging time eating. She would say I’m hungry, I’m hungry, I’m hungry, then we’d feed her, she’d take one bite and say I’m full, and get up and walk away from the table.”

Interview, before treatment, started treatment at 7 years of age

Nausea and vomiting



“

Before treatment:

“So when he was first born, he was a pretty typical developing baby. He did have a lot of vomiting issues, which we had been told numerous times that it was just reflux, but we felt like this seems a little more severe than reflux. But we were first-time parents, so we didn’t know, really. So, that, the vomiting got progressively worse before he started on olipudase. There were days he would vomit upwards of five times a day.”

After treatment:

“He went from throwing up five times a day to now maybe he vomits once every four, five days. So, he still does have occasional vomiting, but it’s immensely better than what it was, and it’s manageable now.”

Interview, started treatment at 2 years of age

“

“He would eat a full meal and he would eat a lot. And then after he was finished eating, he would throw up, which it makes sense now, with everything being so enlarged. But yes, so he would eat. And that’s why I didn’t understand why he wasn’t gaining weight. Because he would eat a lot and then he would throw up, not at the end of every meal, but enough to make you wonder, why is this happening?”

Interview, before treatment, started treatment at 1.5 years of age

Some children had to take meal supplements to be able to gain the calories before treatment because their nausea and gag-reflexes would not allow them to eat enough solid food, but after treatment these issues resolved.



Before treatment:

“It would be every third or fourth day he could have a vomiting episode, it just seemed like he would get backed up or too big a bite, something would cause the gag reflex in him. He didn’t have any problems swallowing, [...] 90% of his calories came from a PaediaSure or like a very thick liquid that he drank with a little bit of food on the side of that.”

After treatment:

“About six months into treatment he... We’d started watching him wolf down food and we were just ready for him to gag, because you just... All of a sudden he’s just taking orange slices like nothing. And I think I just remember looking up at each other like holy cow, he’s just like downing food. And so all of a sudden he could eat no problem, everything and anything. We slowly phased out the fortified drink, it was probably decrease, decrease, decrease, it took a year.”

Interview, started treatment at 6 years of age

He is still a very happy boy, but no child wants to be throwing up five times a day. And he’d wake up first thing in the morning throwing up, and it was just uncomfortable for him to sit for really short periods of time. You could just tell it was uncomfortable in his belly. So, it affected really all areas of his development.

Overall impact on “abdominal problems”

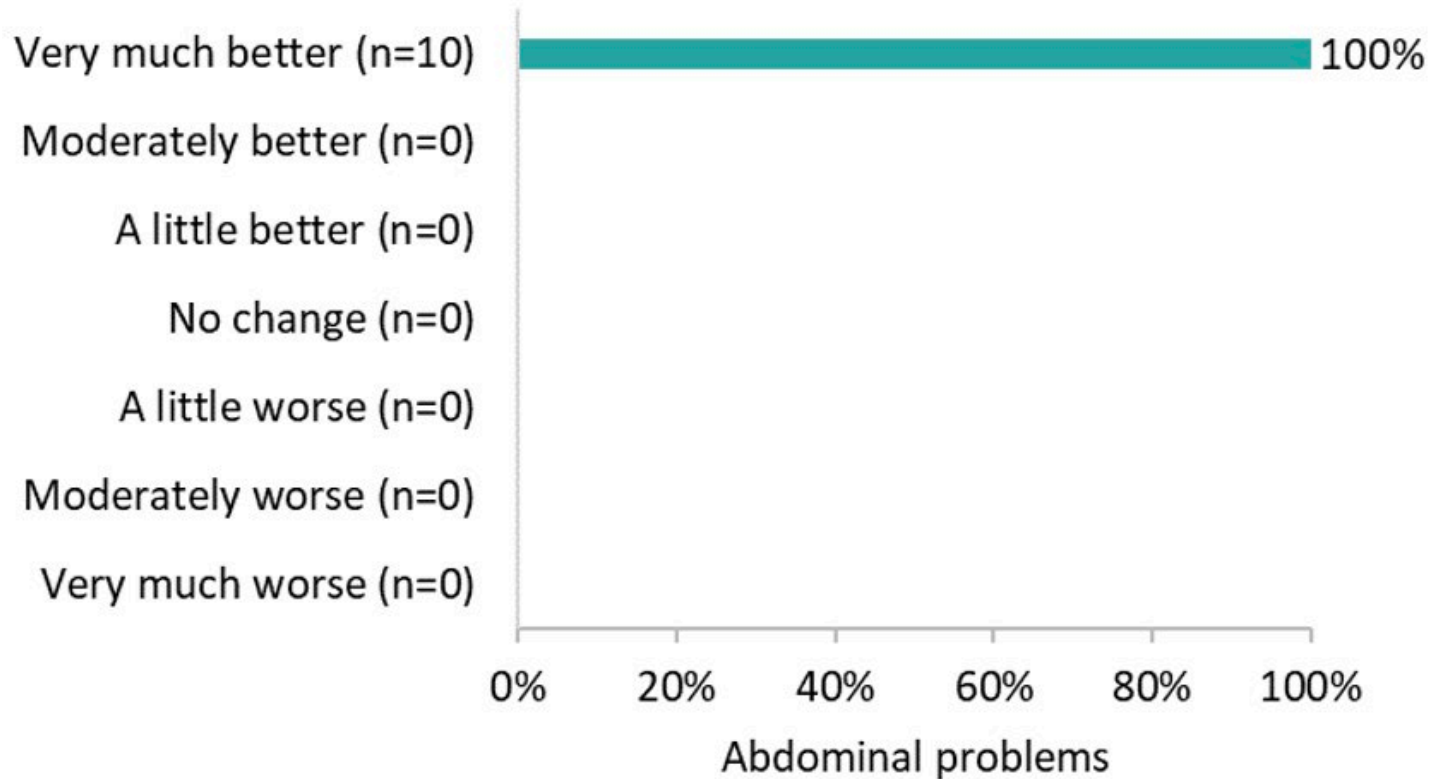
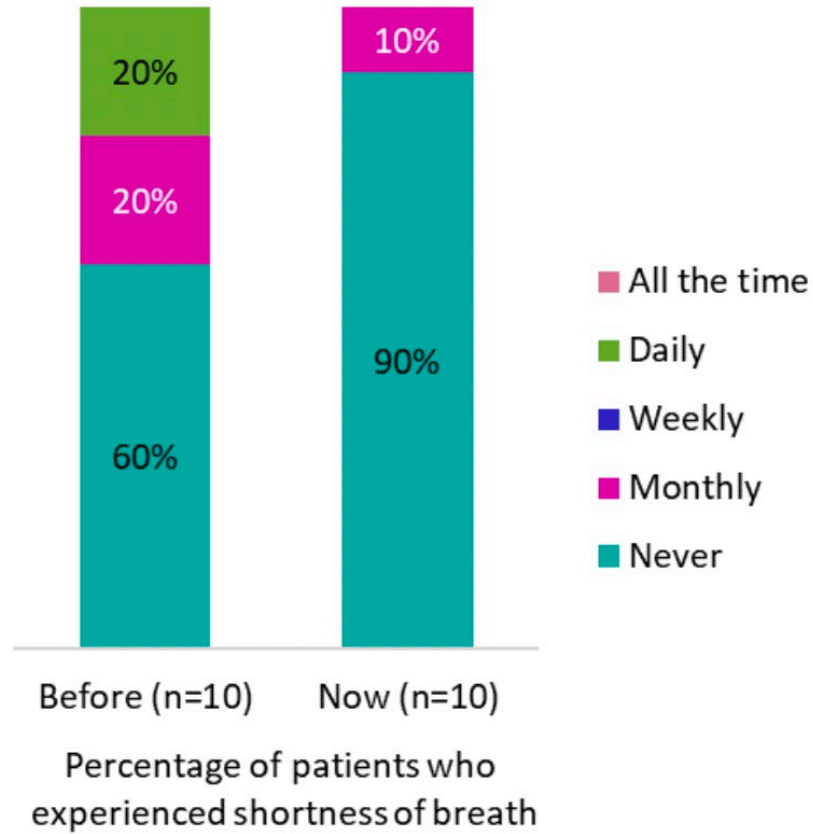


Figure 22. Overall change in abdominal problems since starting treatment with olipudase alfa (n=10).

Shortness of breath



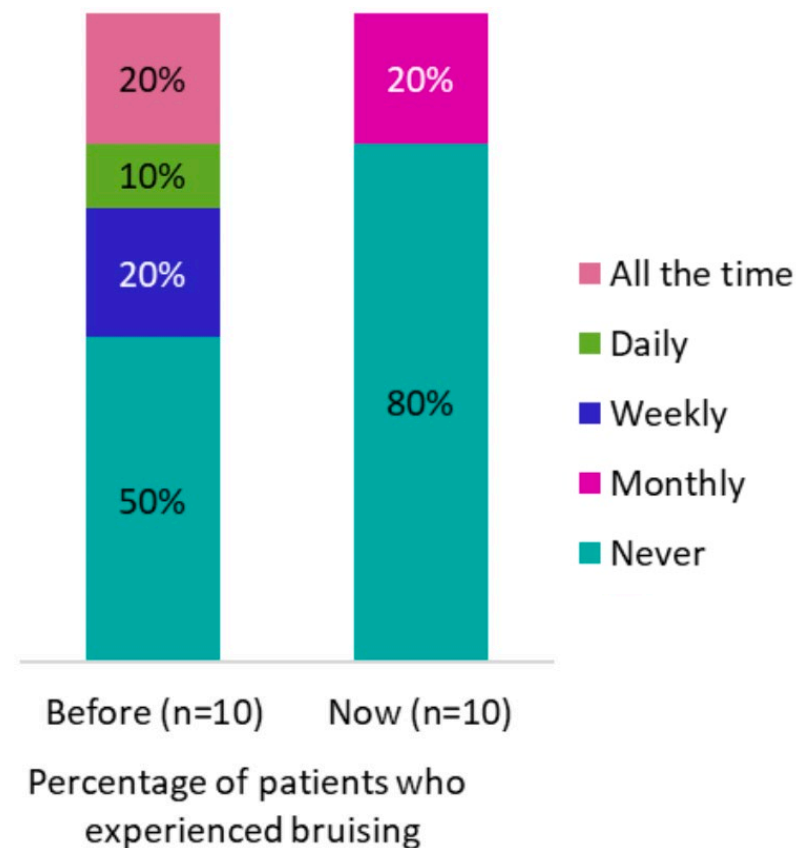
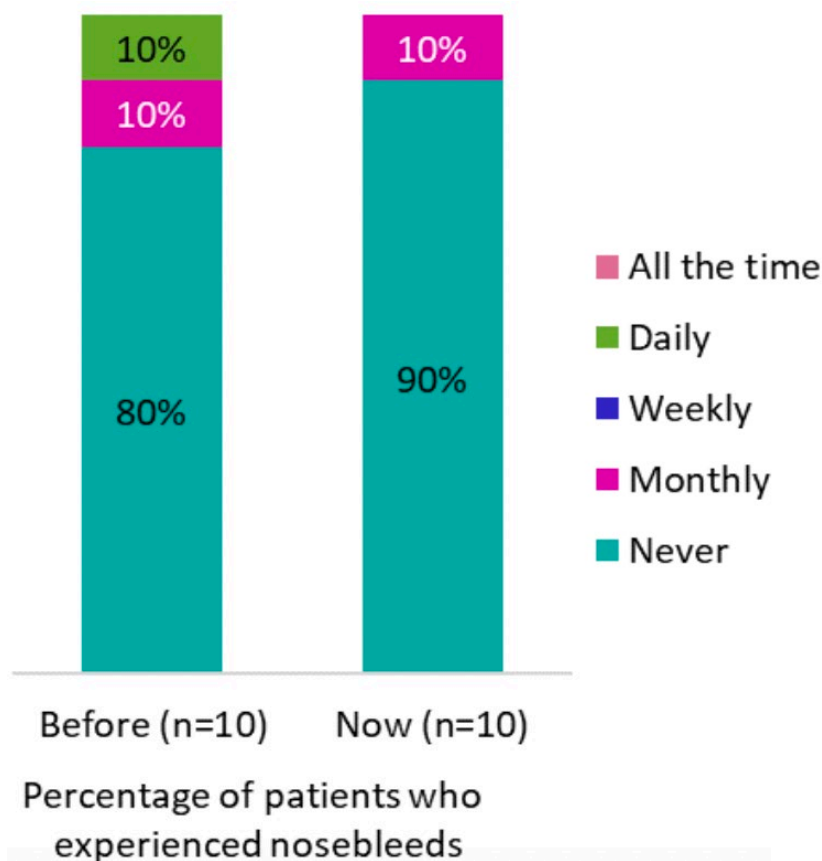
“It was her favourite thing to do is play tag. [...] And when she’d run and she’d be holding her stomach to get away, she’d get to the safe spot, and you could see her just always out of breath.” *Interview, before treatment, started treatment at 7 years of age*

Bleeding and bruising

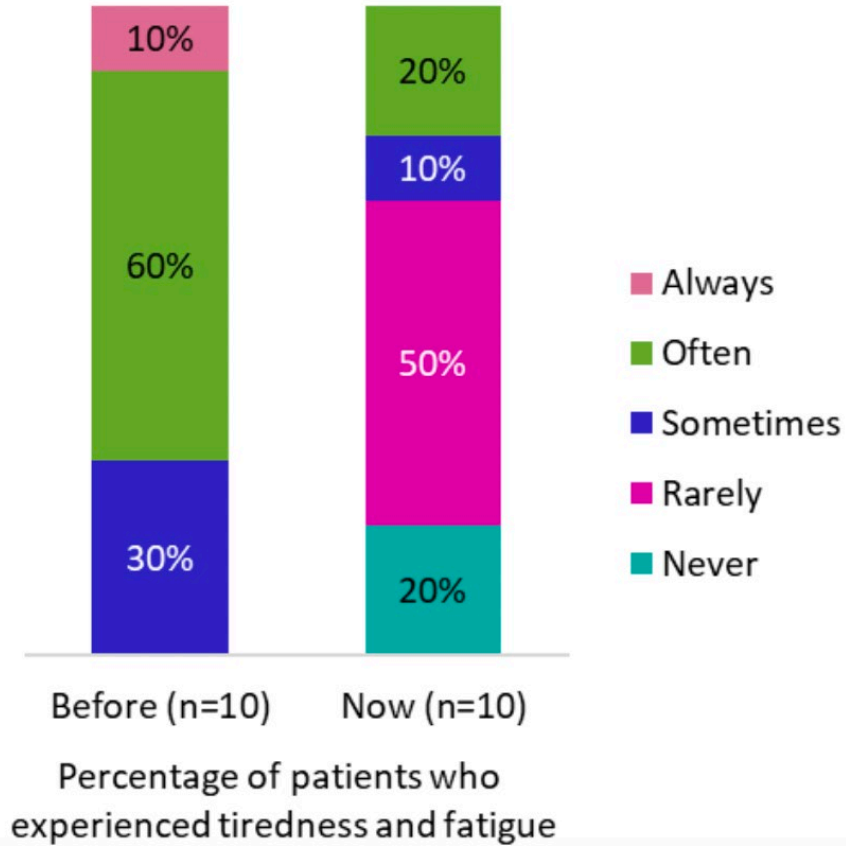


“And then really hard to stop his bleeding, he didn’t have nosebleeds, but if he got a cut or a scrape like the... You could see the effect of the disease on the spleen, like that part was hard, it was very to get his bleeding to stop, although he never really had nosebleeds, which was interesting with him.”

Interview, before treatment, started treatment at 6 years of age



Fatigue



Before treatment:

“Yes, often tired. Didn’t want to do anything.”

After treatment:

“He’s able to be active. He’s doing push-ups.”

Interview, started treatment at 7 years of age, 4 years and 1 month on treatment

Before treatment:

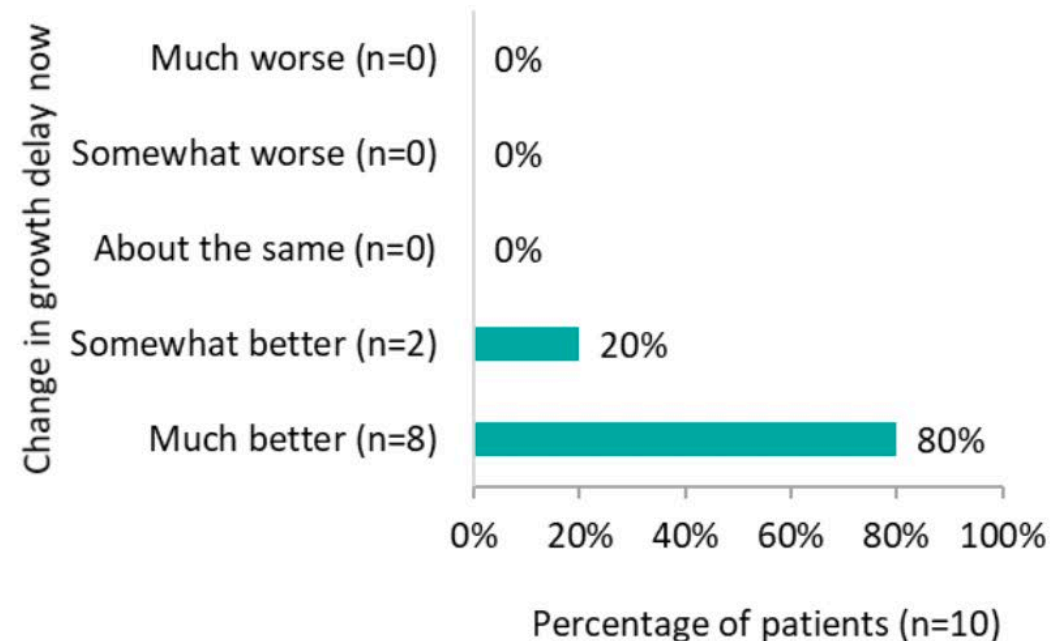
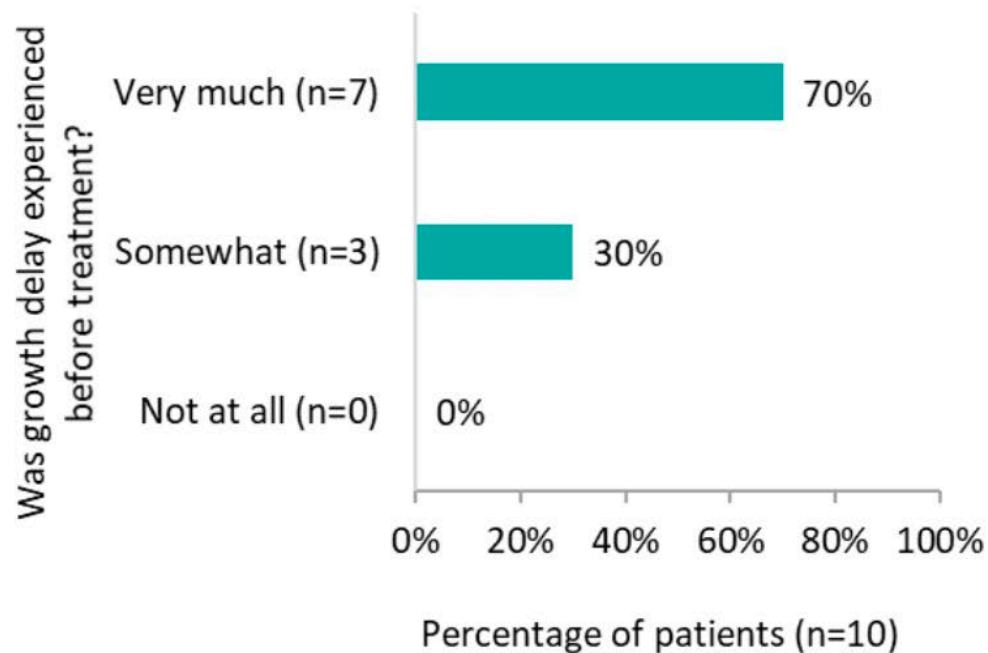
“...when she was really young, she never wanted to sleep. She was always very happy, very joyful. And as time passed by, we noticed that her energy level decreased, and when she got home from school, she asked us to go to bed.[...] And we also noticed that if she had to walk a certain distance, that it was difficult for her to catch up with the other children because she was always tired.”

After treatment:

“Also, the energy, she is really full of energy now. It’s amazing. She’s very active and she likes to do sports, [...] Now she’s really an early bird, she’s awake very early, and it’s not a problem for her to handle these long schooldays anymore.”

Interview, started treatment at 4 years of age, 3 years and 6 months on treatment

Growth Delay





“You wouldn’t think it, if you saw her today you would not think that that child could not walk, that she was a bag of bones, that she was nine months old and in three month old clothes because she was so small. You wouldn’t think it.”

Interview, after treatment, started treatment at 3 years of age, 4 years and 11 months on treatment

“Before beginning the drug, he was I think in the 15th percentile of his age for height and weight. He is now, I believe, in the 85th to... I think it’s the 85th percentile. But he has a head full of hair. He is over three feet tall. He is weighing about 40 lbs. He’s a little skinny but he’s tall.”

Interview, started treatment at 1.5 years of age, 3 years and 10 months on treatment

“He has grown a ton. He went from not being on the growth chart at all, to he’s now at the 50th percentile for weight and height. So, he grew a lot, put on a lot of weight, and he’s a healthy size now.[...] His body is just absorbing nutrients a lot better now.”

Interview, started treatment at 2 years of age, 1 year and 3 months on treatment

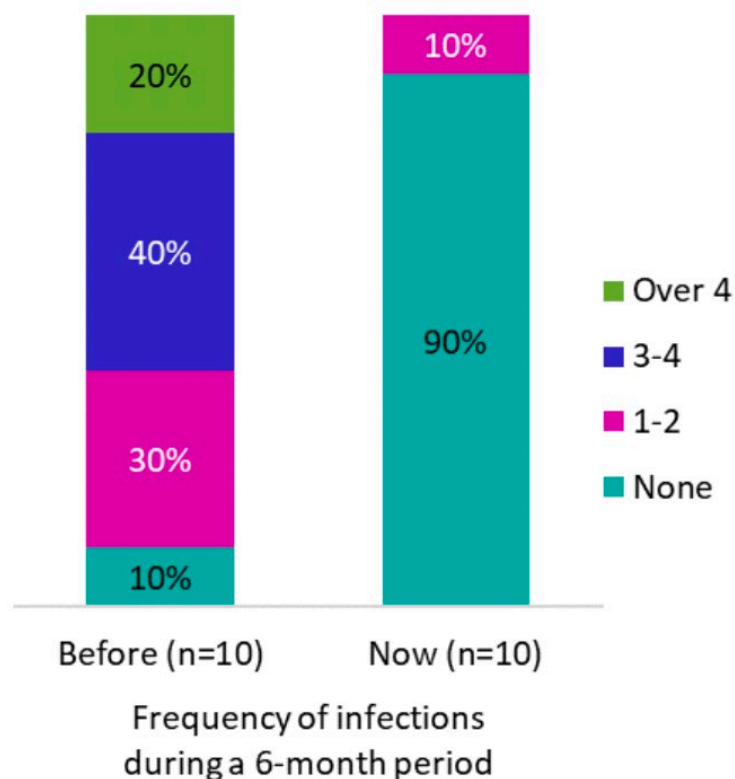
“He was always on that 3% growth curve, he’s up in the 30%, 40% growth curve now. So, he’s still, I wouldn’t say small at all, but he’s not the tallest in his grade. But he’s not the shortest. So, he’s grown quite a bit. We’ve seen a huge impact on growth.”

Interview, started treatment at 7 years of age, 4 years and 1 month on treatment

“But we had the impression that before, she was really small, and it was also confirmed when they measured her, that she is somewhat small. But now, if you compare her to other people from school, of the same age, it’s rather normal now.”

Interview, started treatment at 4 years of age, 3 years and 6 months on treatment

Infections



The number of ear infections were dramatically reduced after starting treatment.

“

Before treatment:

“He would constantly have an ear infection. He’s had two sets of tubes in his ears.”

After treatment:

“Before the fall, he had not had an ear infection in probably at least two years. It has been a long time.”

Interview, started treatment at 1.5 years of age

Some parents/caregivers explained that before treatment, infections such as the common cold would imply a stay in hospital, but this changed after receiving treatment.

“

“... whenever he got sick before ERT, he would nine times out of ten end up in the hospital, even if it was a common cold, just because his lungs weren’t in the greatest shape [...]. Actually, the first time he got a cold after being on the infusions was the only time he didn’t end up in the hospital....”

Interview, before treatment, started treatment at 2 years of age

“She would get ear infections a lot. And they would give her a ten-day supply of medication, and it would never heal her. She would have to go through two ten-day cycles. But it was on a monthly basis that she was getting ear infections.”

Interview, before treatment, started treatment at 7 years of age

“Yes, over four [over 6 months]. [Name] got a lot of ear infections... It was so bad to the point where we got the tubes put in his ears at a young age, just because that’s how bad. It was constantly ear infections, it was constantly colds, everything.[...] And a fever always comes along with it, so it was tough.”

Interview, before treatment, started treatment at 2 years of age

“So for his first year, we noticed that [Name] developed RSV when he was a few months old. He always seemed congested. But we were always met with it’s allergies. But he’s so young. You really can’t diagnose a child with allergies this young. So we just noticed he always had some type of respiratory something going on that just never seemed... It would clear up and then it would come back.”

Interview, before treatment, started treatment at 1.5 years of age

“He had to be on CPAP briefly with some oxygen, and what started that was a bad virus and we had to cure him of that virus and then get the tonsils and adenoids out. And then the other infections, it was basically just... The one hospitalisation came from the flu that turned into pneumonia and he was on BiPAP for a while. And then other infections might have been just a regular cold...”

School attendance



80% | Attending mainstream school (n=8)



10% | Attending further education (i.e. college or university) (n=1)

“Before the treatment, she was always very tired when she came home from school, and that is not the case anymore. In the mornings she had difficulties getting up, and she was still very tired, and it was a struggle to get her to school. If we walked to school, it was really a struggle, and that is not the case anymore. Now she's really an early bird, she's awake very early, and it's not a problem for her to handle these long schooldays anymore.[...] she is really full of energy now. It's amazing. She's very active and she likes to do sports.”

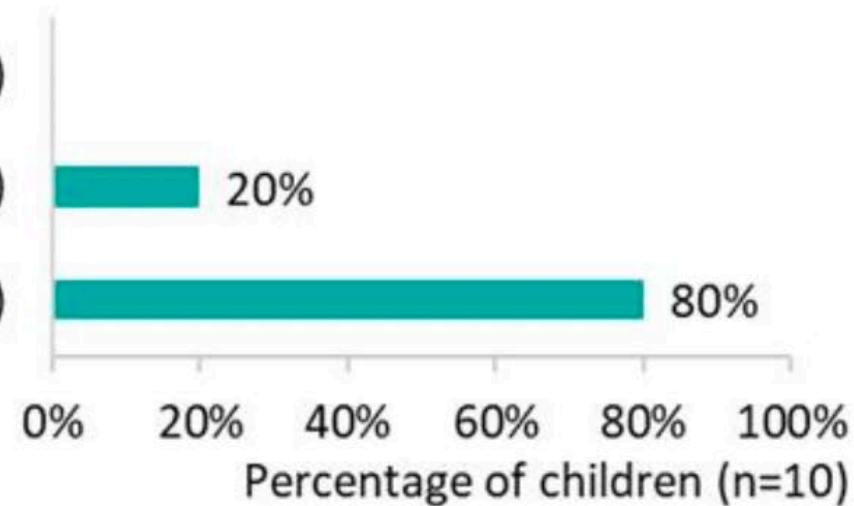
Interview, started treatment at 4 years of age, 3 years and 6 months on treatment

Physical activity/ participation in sports

Decreased ability to participate in physical activity/sports (n=0)

No change (n=2)

Increased ability to participate in physical activity/sports (n=8)



“

Before treatment:

“We did let her participate in everything she wanted to participate in, except for gymnastics, which we deemed to be a little bit too dangerous, especially if she landed on her stomach.[...] she couldn't do a cartwheel. Her body was so just not normal, her cartwheels, she would just plop to the ground because her stomach was sticking out. [...] Not being able to do what she really wanted to do, which was gymnastics, I think, was really tough on her.”

After treatment:

“so it must have been about six months after she started the treatment, we allowed her to do gymnastics. And she literally went from not being able to do a cartwheel to being a state champion. So, now she's a competitive gymnast. So, she is completely done a complete 180, 360, whatever you want to call it. Everything has completely changed. I never, ever worry anymore about her health.”

Interview response, started treatment at 7 years of age

“

“He got the okay to start participating in contact sports a couple of years ago. Now he plays, he's on a travel soccer team where he plays year-round. [...] No issues running, he plays midfield, and he's up and back all game long. So, running is not an issue. [...] He actually does kickboxing [...] The doctor gave him the okay to ride a bike, so he's been riding a bike for a couple of years.

Interview response, started treatment at 7 years of age, 4 years and 1 month on treatment

ASMD impact on mental health

- 60% of parents reported ASMD impacted their child's mental health

Changes before treatment included:

- Being bullied for being short
- Being bullied for having a big belly
- Poor self-image
- Feelings of isolation
- Anxiety
- Depression
- Feelings of guilt

Mental health changes before and after starting olipudase:

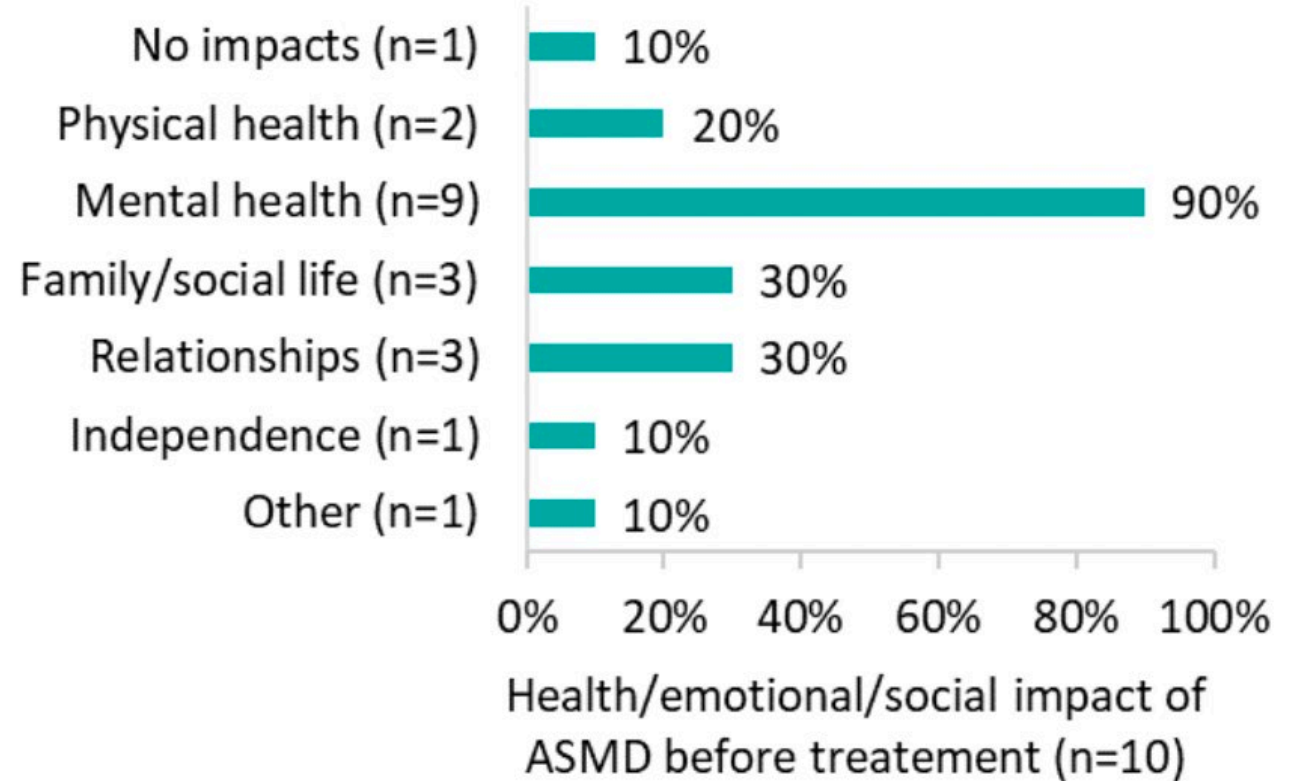
Changes after treatment included:

- + Bullying is better
- + Better self-image and confidence
- + Parents feeling better knowing the child is physically more comfortable
- + No limitations
- ± Some have less feelings of isolation but others still have those feelings
- ± For some, there are less feelings of anxiety and depression, others are still suffering anxiety and depression
- Having to miss school for treatment and having to explain why feels different
- Anxiety about being sick and dying
- Feelings of guilt

Observations

- “I feel like with him being in the trial and his liver and spleen being normal sizes, when you help him walking around, he’s happy because he knows he can do it.”
- “The drug has drastically improved our son's life. He looks and acts like any other kid his age. He is much more confident now that his belly is small and he is similar in size to his peers. [...] You would never know that he has ASMD.”
- “People just come to her. She attracts friends. So many friends, more friends than I ever had my entire life. People, just, are attracted to her, and she’s the centre of attention now. That definitely would not have happened if she hadn't received the treatment.” *Interview, started treatment at 7 years of age*
- “He was happier, he was able to do things that other kids were doing. He has a friend in the neighbourhood that would come over and always ask do you want to go on a bike ride? So, he was able to do those things which he wouldn’t have been able to.” *Interview, started treatment at 7 years of age*

Impact of ASMD on family/caregivers



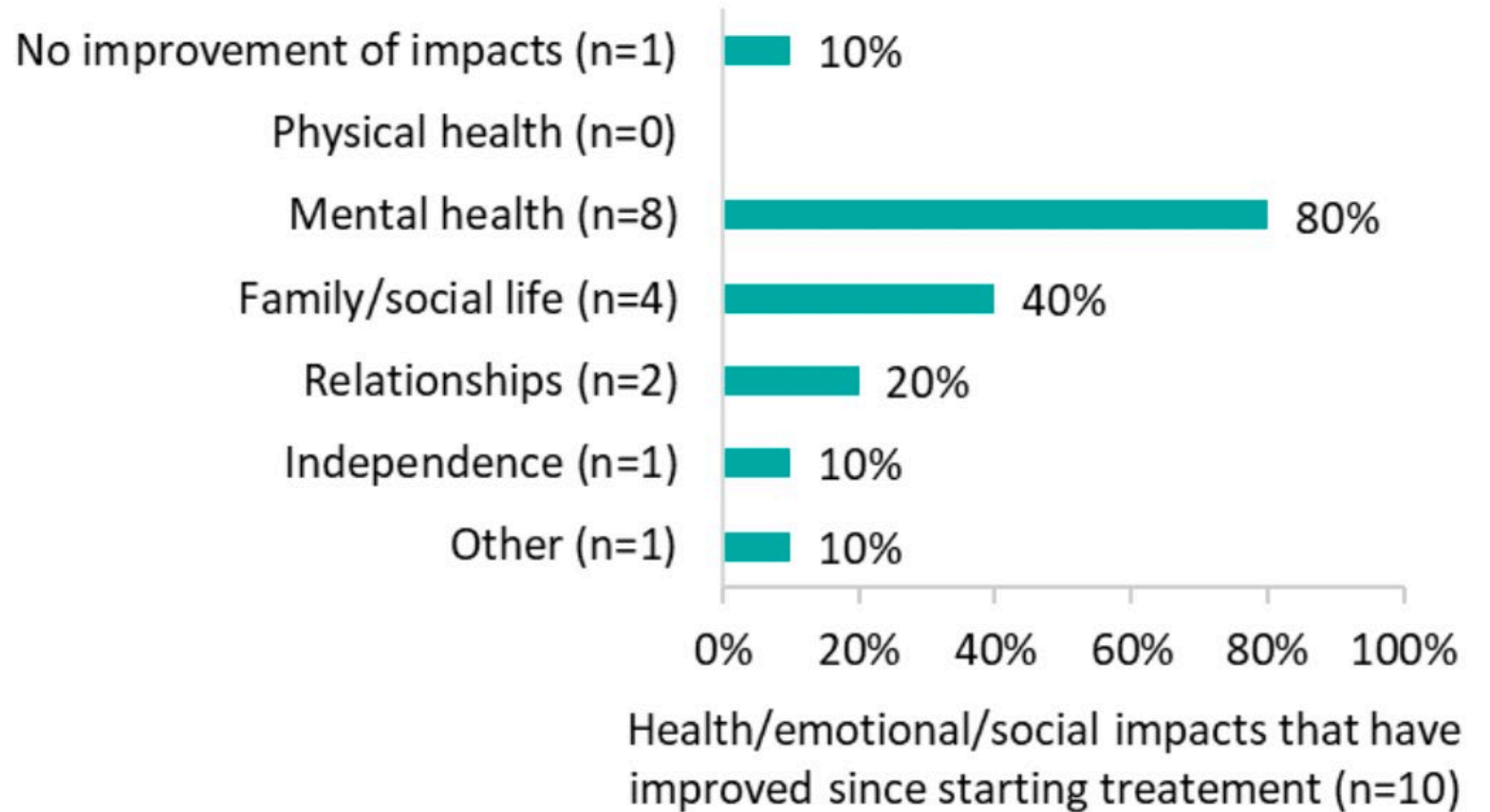
“I think you think of them every day and you think of them every night. You wake up thinking about it. That takes over your life, how am I going to normalise my child’s life? How is she going to be able to live normal and not be constantly sick and in the hospital?”

“We already thought that he was on borrowed time, but I think there’s emotional exhaustion that you don’t even notice, you’re just kind of waiting for the ball to drop sort of, like the whole time you’re just waiting for him to lose an ability. [...] you’re always looking for the regression.” *Interview, before treatment, started treatment at 6 years of age*

“I can’t even tell you how mentally exhausting it is to clean up vomit so many times a day. It just wears on you, not even physically, but emotionally it’s really hard to just watch your child constantly throwing up, and just looking like they feel awful.”
Interview, before treatment, started treatment at 2 years of age

“Really trying to learn how to cope and still be a parent to another child that doesn’t have a medical diagnosis is a whole another chapter in our lives that we had to learn how to do.”
Interview, before treatment, 5-year-old sibling

Impact of olipudase on caregiver's health





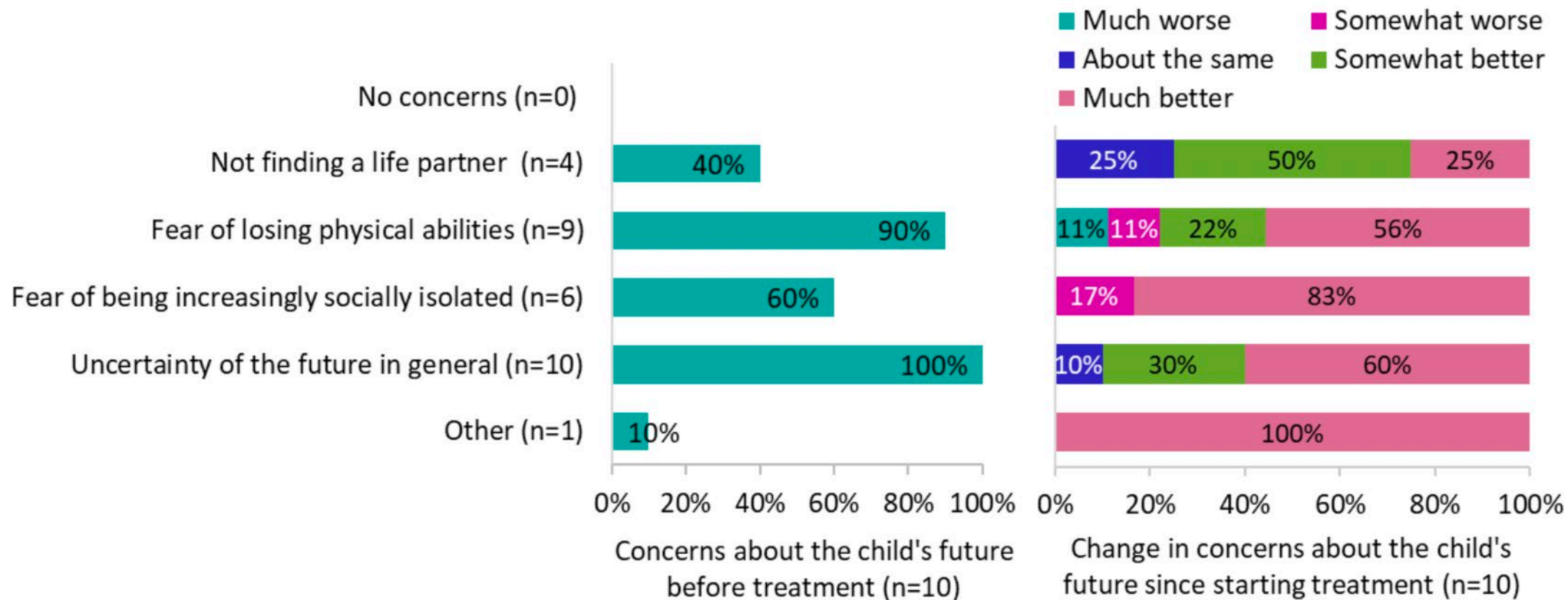
“We kind of breathed again. Before you just felt like you were no sleep, so fearful to look forward to the future. Now we just, it’s hard to describe without getting emotional. Everything has just changed. It’s completely changed. We’re able to breathe again, we’re able to have hope again, we love sharing about it.[...] Our anxiety level has reduce tremendously, our depression has lifted.”

Interview, started treatment at 3 years of age, 4 years and 11 months on treatment



“After [name] started treatment with olipudase alfa my stress level went way down. I no longer felt like he was running out of time, and it was amazing to watch him grow, eat, and gain strength.” *Survey, started treatment at 6 years of age, 5 years and 8 months on treatment*

Caregiver's concerns about their child's future



Impact on mental health of caregivers

“We had such negative thoughts about his future early on that right now if you can tell us this is the best it’s going to get, that’s incredible. We’re thrilled. Because he’s able to live a normal life and there’re no concerns I have at all about it.”

Interview, started treatment at 7 years of age, 4 years and 1 month on treatment

“It has been life changing for us as parents. Just to know that his organs are normal sized, and just to know that he’s not in that pain and discomfort all the time, is everything to us. And getting him off of oxygen, and just having him feel more like a normal child, not being hooked up to things all the time, is a really big deal for us and for him, where it’s been a lot easier to go places now. Because we’re not constantly having anxiety about him throwing up in the car, or when we get there, we’re not having to pack five changes of clothes to leave the house. So, it’s gotten drastically better.”

Interview, started treatment at 2 years of age, 1 year and 3 months on treatment

Cognition

BASELINE

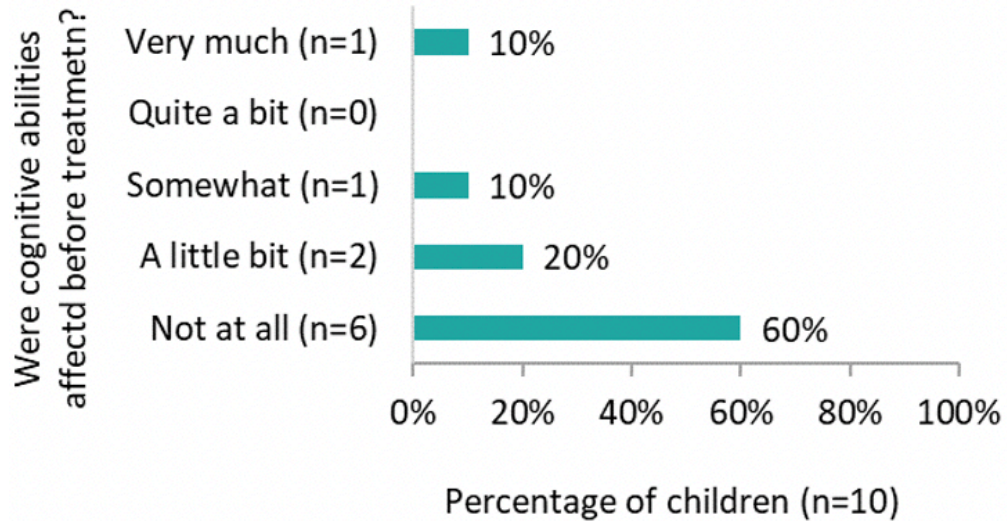


Figure 19. Effect of ASMD in cognitive abilities before treatment.

AFTER OLIPUDASE THERAPY

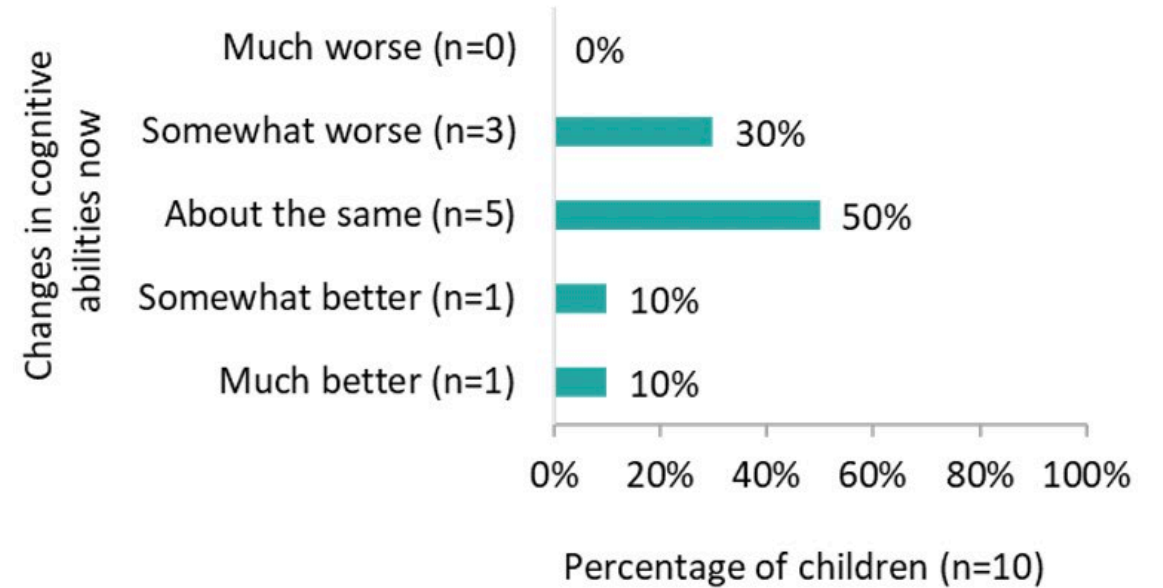


Figure 20. Changes in cognitive abilities now.

Unmet need

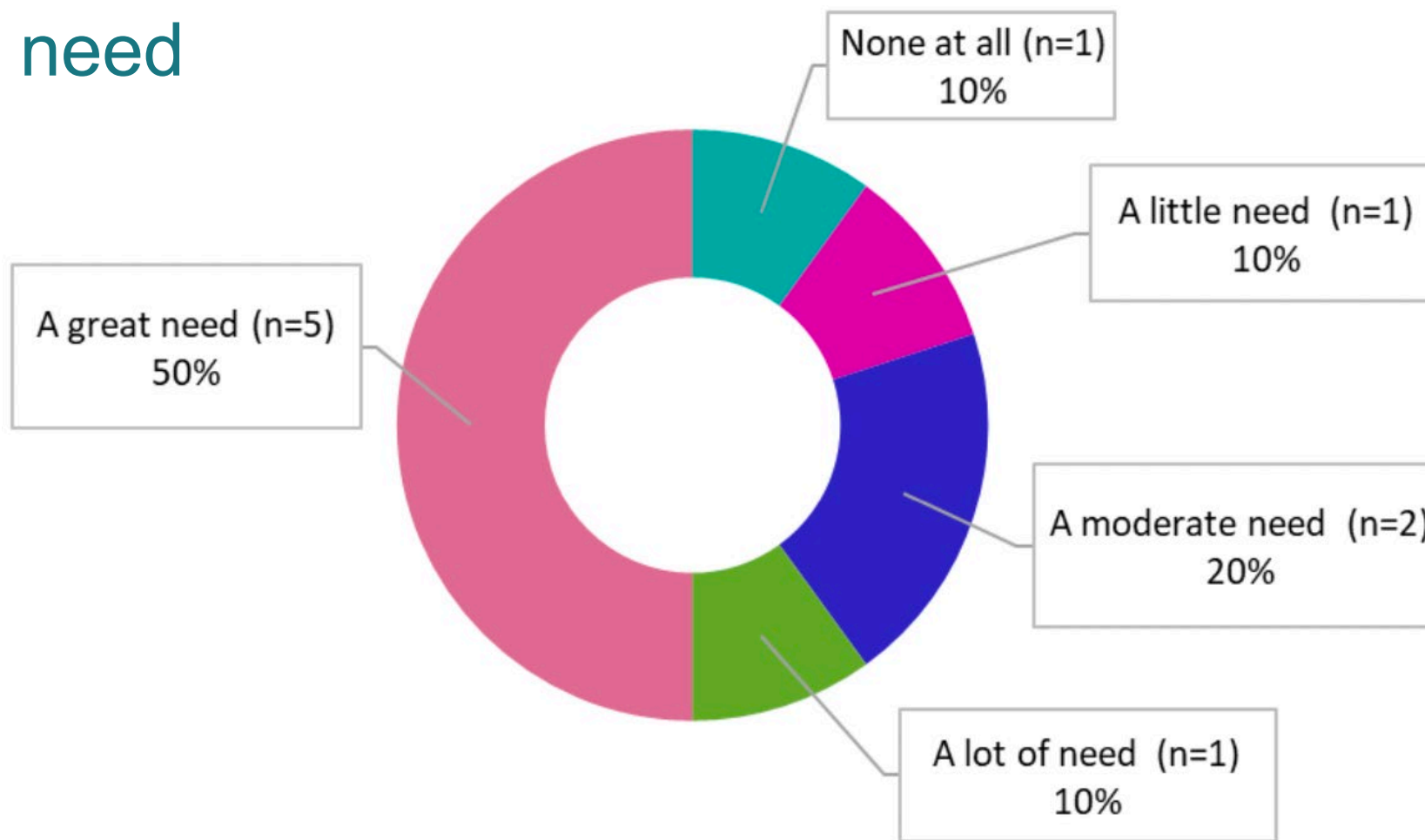


Figure 44. Level of need for a new treatment (n=10).

“This drug has saved my sons life, no doubt about that. We are so grateful and always will be, but it doesn’t cross the blood brain barrier to aid in neurological involvement.”

Survey, 3 years and 10 months on treatment

“Well, I feel like you couldn’t just jump in and save the brain in any other way, you would have to treat them with this drug first anyway before you went on another one. If there was a way for this drug to hit the brain, it would be great but... And there’s just going to be another need, not a replacement but just more.”

Interview, 5 years and 8 months on treatment

“I feel like this treatment is working beautifully at reversing damage done to their bodies and basically making their bodies normal again, but now the second piece to the puzzle is finding treatment to slow down or stop the neurological disease progression, or even reverse it. And it’s so important.” *Interview, 1 year and 3 months on treatment*

Clinical trial participation



“The hardest part of everything is the strict rules of the trial. The trial itself was the harder part than the drug itself. That is what caused the majority of the stress, getting the MRIs, getting the ultrasounds. And even something as little as them being done with their infusion and then having to wait an hour to get their vitals done, that hour time frame, that’s always been the hardest thing out there. Because the kids are done, they want to be up and go round. It’s just that extra hour after a four-and-a-half-hour infusion just adds to the point.”



“For the past year and a half, or two years, we’ve been getting in-home treatments. Where the nurses are able to come to the house and give them their infusions here at the house. Which has made a world of difference.”

Interview, started treatment at 7 years of age, 4 years and 1 month on treatment

Caregiver modifications of employment

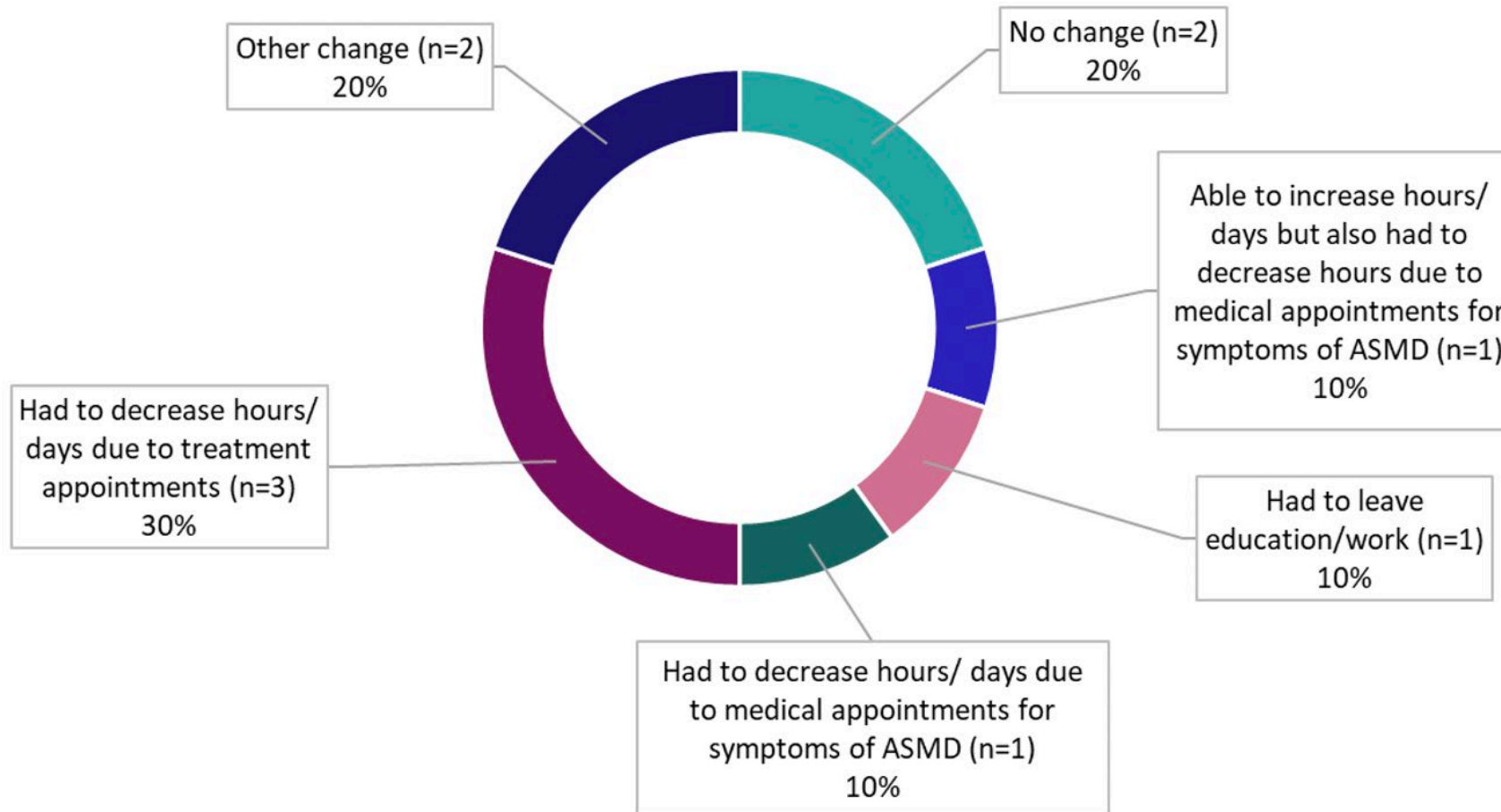


Figure 34.
Change in the parent/caregiver ability to attend education/work since the child started treatment with olipudase alfa (n=10).

Level of satisfaction with olipudase

“We have seen a drastic improvement in our child's physical, social, and mental health. He is able to engage and participate in age appropriate play with his peers. He feels better about himself and his condition knowing that it can be treated.”

Survey, 4 years and 1 month on treatment

“We see that [name] is doing really well, there is not one symptom that we could wish to be further decreased. She has lots of energy, her belly is normal, she eats normal, she can play and do physical exercise like a normal 7-year-old girl. Also the doctors tell us that they could not have wished for any better result since all the parameters that are measured/followed up have gone towards normal a lot.”

Survey, 3 years and 6 months on treatment

“I have seen almost complete resolution of disease manifestations with the treatment.”

Survey, 6 years and 1 month on treatment

“Our daughter leads a life just like any other 7-year-old without ASMD and that's all you ever want for your child.”

Survey, 4 years and 11 months on treatment

Perceived disease progression since starting olipudase alfa

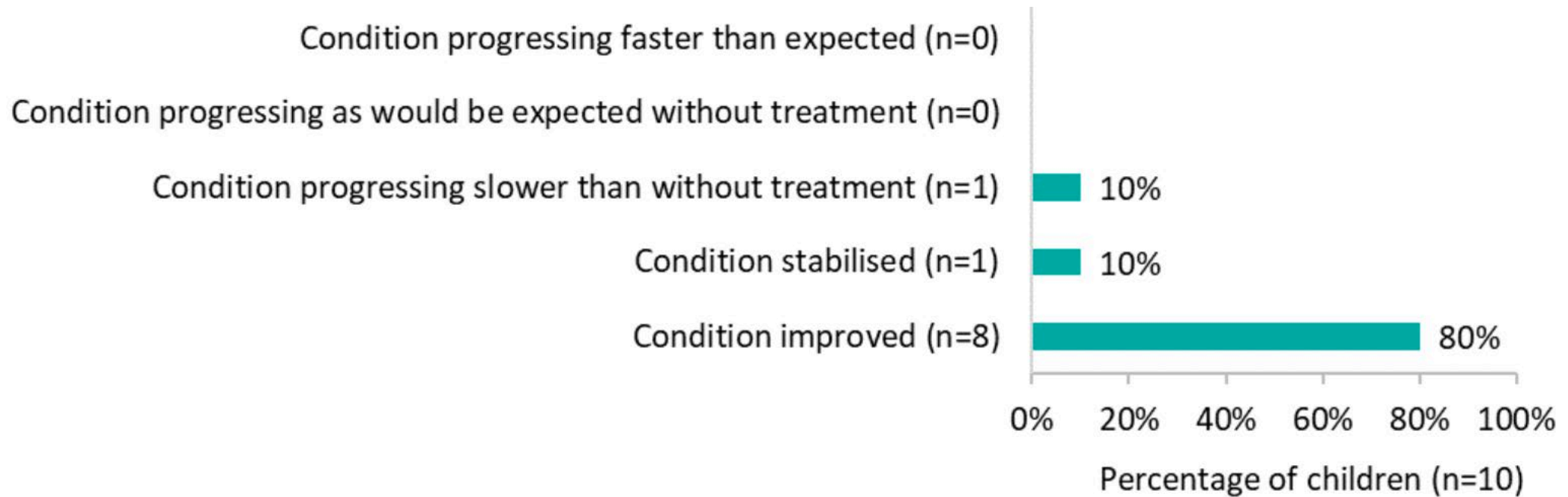


Figure 43b. Overall progression of ASMD while receiving treatment with olipudase alfa (n=10).

“The best way to describe it is that she’s just like a typical child. Like when we share now that [name] has an underlying metabolic genetic disease people are totally shocked and surprised, I have to fill that information out when she attends like trampoline parks or attends school and teachers and people are so confused because they look at her and they’re like wait a minute what?” *Interview, 4 years and 11 months on treatment*

“**It’s a complete 360. Really, the healthiest person I think I probably know on the Earth right now is her.** So, she completely changed. It was not only her health but just her overall bodily figure just completely was altered. **She was a completely different person after receiving the treatment. And we noticed, I would say, within three months, that her figure was changing.** She didn’t have the distended stomach anymore.”
Interview, 5 years and 9 months on treatment

“**Honestly, it has saved his life. And I will tell anyone that this trial saved his life.**”
Interview, 3 years and 10 months on treatment

“Everything changed for [name], physically, mentally, it changed our family for the better.”
Survey, 4 years and 11 months on treatment

“it was life saving for him, I mean it was really was, I don’t... I think his organs were failing, I think he couldn’t sustain his system much longer, definitely was.”
Interview, 5 years and 8 months on treatment

“We are absolutely thrilled with the treatment. The demands of the trial have presented numerous challenges, however the benefits of the treatment greatly outweigh them.”
Survey, 4 years and 1 month on treatment



“My heart breaks for the parents whose children have ASMD and they’re not in the trial and they’re not receiving anything. [...] And one particular family talks about how they’ve noticed their child doesn’t do this anymore, and that. And it is heart-breaking, because you [...] honestly also feel guilty because your child is receiving this medicine and you have seen the benefits of it. And you know they wake up every day and they’re just... Oh. It’s just devastating. It is devastating. And this medicine can... **It saved my child’s life.”**

Interview, 3 years and 10 months on treatment



“They’re the best kids, and they deserve every single opportunity that life can give them, and I’m just hoping and praying that this treatment gets FDA approved. And I’m hoping it can help so many other families in our position....”

Interview, 1 year and 3 months on treatment



Retrospective Case Series

- Negatives -
 - Recall bias
 - Confounders
- Positives -
 - Useful in rare diseases
 - Useful when study time is extended
 - Useful when it takes an extended period of time to reach an outcome

Strengthening the Natural History evidence base

- Building on the natural history cohorts collected by Wasserstein et al
- Contributing to the newly developed patient-reported database in the International Niemann-Pick Disease Registry (INPDR)
- To create robust resource reporting the longitudinal patient-reported experience of ASMD
- To support further development and validation of patient-reported outcome and experience measures in ASMD

Take Home Points

- ASMD is a systemic disease with a wide array manifestations that significantly impact quality of life
- Olipudase alfa was associated with improvements in all non-neurologic manifestations
- The emotional and mental health impacts of ASMD on both patients and family is significant, and olipudase mitigated those impacts in a meaningful way
- Participation in a clinical trial impacted patients and families but this burden was felt to be outweighed by the perceived benefits
- Despite the benefits of olipudase, there is an unmet need to treat the neurologic manifestations of the disease
- Families feel all patients with ASMD need access to olipudase based on the life-changing experience they have perceived



Thank You

- We appreciate all patients and families who participate in clinical trials. As leaders in the Niemann Pick space, we recognize the sacrifices you make every day and the impact this has on you and your families.
- We also appreciate you taking the time to bravely share your experience and your stories in this clinical trial.

Resources

- Diaz, G., et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genetics in Medicine. (2021) 23:1543-1550
- Wasserstein, M., et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency(ASMD) in adults: One-year results. Genetics in Medicine. 2022. doi: <https://doi.org/10.1016/j.gim.2022.03.021>