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The impacts of treatment with olipudase alfa on adult patients with ASMD

Samantha Wiseman, Senior Research Associate

Madeline Pearson Dawson, Research Associate

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BACKGROUND

Acid sphingomyelinase deficiency (ASMD) is a rare recessive lysosomal storage disorder (LSD) caused by a deficient activity of the acid sphingomyelinase (ASM) enzyme. Deficient ASM enzyme activity causes varying degrees of sphingomyelin accumulation in all cells.[1] The resultant tissue damage leads to severe morbidity and a reduction in life expectancy. Respiratory failure and liver failure are the most common causes of death, irrespective of age.[2]

As with other LSDs, the phenotype is variable and occurs in a spectrum from severe early onset and rapidly progressive disease (historically known as type A) to more attenuated disease (type B). Most untreated children with type A die before they reach the age of three years. The life expectancy of patients with type B varies, but survival into adulthood can occur.[1]

Early onset (type A) ASMD is characterized by hepatosplenomegaly, growth failure and psychomotor developmental stagnation followed by neurological deterioration. Interstitial lung disease results in frequent respiratory infections and often to respiratory failure.[1] Type B usually presents later than type A and is characterized by progressive hepatosplenomegaly, deterioration in liver and lung function, osteopenia and atherogenic lipid profile. No central nervous system symptoms are manifest in the most attenuated forms of the disease.[1]

Before the development of enzyme replacement therapy (olipudase alfa), there were no approved disease modifying therapies available for ASMD paitents. There is literature describing hematopoietic stem cell transplant (HSCT) as a possible treatment for ASMD, but the use of HSCT is limited by its associated morbidity and mortality.[1] As the new enzyme replacement therapy option undergoes review in Health Technology Assessments (HTA), there is a need to gather evidence on the patient experience of using olipudase alfa and its impact on their ASMD and quality of life to support HTA decision making.

To collect this evidence, the International Niemann-Pick Disease Registry (INPDR), National Niemann-Pick Disease Foundation (NNPDF), Niemann Pick Disease Group (NPUK), and International Niemann-Pick Disease Alliance (INPDA) commissioned a study of adult ASMD patients treated with olipudase alfa.

STUDY AIMS

The study aimed to:

- Describe the burden of disease on patients and their families
- Understand the impact of olipudase alfa on both ASMD patients and their families
- Explore patient views on the future in relation to ASMD treatment

METHODS

This was a qualitative study consisting of semi-structured interviews with participants that had completed the ASMD Patient Experience with Olipudase Alfa Survey conducted by the INPDR in collaboration with the NNPDF, INPDA & NPUK.

The semi-structed interviews were conducted by Rare Disease Research Partners (RDRP) with participants from Canada, the UK & USA. All interviews were conducted in English via Zoom and were audio recorded.

Inclusion criteria

- aged 18 years or over
- fluent in English (including non-native English speakers)
- able to give informed consent
- confirmed diagnosis of ASMD
- completed the online survey
- receiving treatment with olipudase alfa

Study activities

Recruitment

Patients were recruited to the on-line survey through outreach from national patient organizations including NNPDF, NPUK and INPDA through emails and social media. Participants who were interested in taking part in an interview indicated this on the on-line survey and provided their consent to be contacted by RDRP. Interested interview participants were contacted by RDRP between the 20th April and 24th May 2023.

Consent

Potential participants were sent a Participation Information Sheet and Consent Form to be completed before the interview took place.

Interviews

A semi-structured interview guide covering questions from the survey in more depth was developed. One hour interviews were conducted via Zoom by two experienced qualitative researchers to ensure a consistent approach to data collection.

Analysis

Descriptive statistics were applied to the qualitative data collected. A quantitative analysis of the interview transcripts was undertaken, applying an inductive thematic approach and using NVivo software.

Ethical considerations

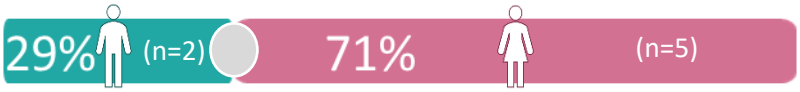
RDRP is a corporate member of the British Healthcare Business Intelligence Association, and the study was conducted in adherence to their legal and ethical standards.

RESULTS

Patient demographics

Two patients from the UK undertook interviews on 22nd February 2022. Five patients from USA (n=4) and Canada (n=1) undertook an interview between 4th May 2023 and 6th July 2023.

Median age of patients was **42 years**
(Mean± SD 42.7 ±11.6, range 26–58)



Median age of males: 34 years
(mean ±SD 34.0 ±11.3, range 26–42)

Median age of females: 42 years
(mean ±SD 46.2 ±10.7, range 34–58)

The **age at symptom onset** varied, but most patients presented with symptoms before the age of 6 years. Patients were diagnosed between the ages of 2–11 years.

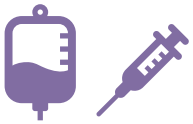
Age first symptoms appeared	n
From 2 months—less than 2 years of age	4
From 2 years—less than 6 years of age	2
From 6 years—less than 18 years of age	1

Median age at diagnosis 2.5 years
(mean ± SD 3.6 ±3.3, range 2–11 years)

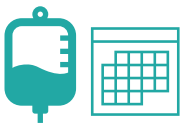
Three patients had experienced **neurological symptoms**, which included neuropathy, ataxia and migraines.

Treatment

The **median** length of **time between diagnosis and starting treatment** was **31.0 years**, mean ±SD 33.4 ± 10.7, range 17.0 – 52.5.



The **median age when started treatment** was **33 years**
(mean ±SD 37.0 ±11.4, range 20–55)



The **median length of time on treatment** was **4 years**
(mean ±SD 4.7 ±3.9, range 0.5–9.8)

Experience of ASMD in childhood and adolescence

In childhood and adolescence, the most reported symptoms included:

Gastrointestinal system:

- Enlarged liver
- Gallbladder stones
- Fluctuation in appetite
- Difficulty gaining weight
- Upset stomach

Constitutional:

- Pain (stomach)
- Discomfort
- Fatigue
- Developmental delay (including delayed growth and puberty)

Infections:

- Respiratory infections (sinusitis)

Neurological:

- Sleep disturbance (insomnia)
- Headaches and migraines

Hematologic:

- Enlarged spleen
- Easily bruised
- Frequent nosebleeds

Musculoskeletal:

- Fractures

Respiratory:

- Shortness of breath

Impact on ability to attend school and work

Patients reported a significant impact of ASMD on the schools they were able to attend and the activities they could take part in. In some instances, patients were denied admission to mainstream schools as they were considered too delicate. Those who were admitted to mainstream school were segregated from their peers and prohibited from engaging in any form of physical activity out of fear of harming their liver and spleen.

> "When I started school, the school board insisted that I start at a school for the disabled because **I was considered to be too fragile to be in a regular school system.** I did kindergarten and junior kindergarten in a school for the disabled.
>
> My parents continued to push, and I was moved to a regular community school for Grade 1, which is where I stayed until Grade 8, with the support of some fabulous teachers, despite some pushback from some others.
>
> But when I went to transition to high school, our local community high school refused to allow me to attend. Saying that I needed to be home-schooled because it was **too much of a risk** for me to be bumped in the hall and end up with a liver

or spleen rupture. They were **unwilling to accept that liability."**

"And at the time, they wanted to put me into a special needs school for children who had more learning disabilities and things like that. Because **the primary school didn't want to take responsibility for the fact that my abdomen was fragile.**

And also, there was **this element of risk**, if I was in normal school, getting pushed about, knocked over. So, my parents had to fight hard to get me into mainstream school. And then when I was in mainstream school, **I wasn't allowed to do anything that was remotely physical with any of the other children.** So, **playtimes I was segregated.** I wasn't allowed to play with them. I wasn't allowed to do sports. I wasn't allowed to do any form of PE or Sports Days. They used to find me other things to do like puzzles and handwriting club."

Patients found it hard to keep up with their peers and missed a lot of school due to recurrent infections, migraines, and doctor's appointments. It was hard to manage symptoms such as fatigue in educational settings and frequent absences from school resulting in some patients transitioning to home schooling out of necessity.

"**I missed half of high school with my migraines**. I had a lot of issues with being sick."

"Well, **I definitely missed out a lot**, as far as socialising, on both those last two halves of years at high school. I missed a lot there, but I was missing a lot anyway because I was having to stay home or go to doctor's appointments."

"I know, even when I was younger, it was bad **because I would go to school, and I would be so tired by the end of the day.** Most kids come home, eat a snack, go out and play. I would come home, eat a snack, go to sleep. I was having a very hard time. When I got up into high school, the last class of my day actually contacted my parents and said they could tell that **I was extremely tired. There were times where I would just fall asleep doing my work** […]."

"My activity tolerance was a significant issue when I was very young. When I was a child, **I did use a wheelchair for distances because I simply couldn't keep pace with my classmates, or friends, or on family outings.** I used a mobility scooter to get through university because of the distances required to get around campus."

"**I had to stay at home**, and they would send a teacher out, and she would bring all my work and just trade off. […]. But I had to do that because I was missing a lot because I would get sick, because when you're extremely tired, your immune system, mine being crazy as it is, would just… **I was catching everything**."

"I didn't go to high school. I was home schooled. **I had home schooling because of the migraines.**"

Having an enlarged liver and spleen meant that patients had to avoid vigorous activity (such as playing ball games) and were unable to participate in physical education classes. One patient mentioned having to wear a spleen guard.

> "**I had to be careful as to what sports I could and couldn't play**. I used to love playing softball, but **my mom made me stop that** because the balls, they're told to pitch right towards where your spleen or liver are, and she was worried about that. Plus, **I couldn't keep up all the time because I would get winded and tired**. I did do swimming, and I seemed to do pretty good with that one but had to teach myself how to breathe in that one."

> "Before, I didn't do anything. […]. **I wasn't allowed to because they were afraid that I was going to rupture my spleen or hurt my liver**."

> "Certainly, growing up, the enlarged liver and spleen, which meant that **I couldn't be part of physical education classes** […]."

> "**I was never able to participate in gym class because they were afraid I would get hit in the liver and spleen.** And my mum said actually in grade school, I had to wear a spleen guard."

Impact on mental health

The symptoms of ASMD had a negative impact on patients' mental health. Patients reported feeling self-conscious about their enlarged abdomen which gave the appearance that they were pregnant. It was difficult to find clothes that fitted properly. Oftentimes, classmates were unaware of the condition, which resulted in patients being bullied as children for their physical appearance.

> "[…] and then you get where kids also don't understand, and **you get bullied because you look like you're pregnant when you're a little kid**. I was, not now, but I used to be, real tiny, tiny, like you could look at me, I looked like a little elf, but I had a large belly."

> "Certainly, growing up, the enlarged liver and spleen, which meant that I couldn't be part of physical education classes **and looked different than everyone else.** And getting clothes to fit was a challenge. The first time I ever got asked if I was pregnant, I think I was only eight or nine, by a clown. And I've developed a significant aversion to clowns."

One patient reported that their mental health greatly suffered as a result of their ASMD diagnosis. They suffered severe depression as a teenager and were institutionalised following an attempted suicide.

> "Well, I touched on it, that when I was younger that **I had psychological problems**. But I actually was institutionalised when I was 17, for a few months. **Like I tried to kill myself.**
>
> *Interviewer: Yes, you said in your survey responses that you had experienced extreme depression as a teenager.*
>
> Yes.
>
> *Interviewer: Was that in relation to your ASMD?*
>
> I would say it had a lot to do with it. If you think you're going to die some excruciating death. […]. And then acting out a lot, if you think you only have a short time to live. Yes, definitely. It's hard to say what it would have been like without it, but I can point to direct effects that that had on me. The medical student told me I was going to die. It was like, that's huge. Let me add to it too, **I had no emotional counselling at all after that**."

Impact on families

Patients also considered how having ASMD affected their families. Patients in the sample reported that their illness was a factor in many family stress problems, such as having overbearing, controlling parents or parents who turned to alcohol as a coping mechanism.

> "I would say my dad's relationship with me is normal. But **my mum has a controlling relationship over me**. She worries when I go to work. If there's a strong wind, like there is at the moment, she frets before I go out. And that's because my entire life, **she's stood in my shadow making sure that nothing happens.**"

> "I know that my mum was an excellent advocate, who went to bat for me on many occasions. **My dad, unfortunately, was an alcoholic, and I do not know whether the stress of this contributed to that.** He stopped drinking completely when I was in university, but **I suspect the stresses added to that, in terms of that as being a coping strategy for him at that point**."

> "So, from my family's point of view, **it put a lot of stress on our relationship as a family**. Because at that point there was no cure, there was no treatment, and we didn't know anybody who lived beyond 40, 45. **Everybody I know who I grew up with were either really poorly with it or had passed away.**"

Siblings were impacted by the patients' ASMD, being involved in their care and worrying about their ASMD. As a result, patients frequently discussed how their siblings' childhoods had been taken away from them and that siblings were not always given enough attention.

> "It has been a bit of a thing, growing up, that [sibling] was not necessarily taught

to worry about me but **taught to look out for me**."

> "It didn't really stop us doing things, but **it massively affected my brother's childhood.** Because my brother's three years younger than me, but he was told as soon as he could walk and he could move around and get about, you need to look after your brother, he's vulnerable. So, **he's spent his entire life following me around,** making sure that nobody pushed me, nobody got too close to me if we went out. **He was forced to grow up from about the age of five to make sure that I was okay.**"

> "He was unaware of how sick I was. He's older. **He just knew not to roughhouse with me. He knew to be careful.** But I don't think he really... It's not like this day and age that everybody is aware of things. It was different."

> "When I was eight, nine years old living my own life in my own blissful ignorance. **And he spent his entire life in my shadow.** And that has massively affected his life as well. Because as he's grown up, he's followed my career path and followed everything I've done right behind me all the time. And literally copied everything I've done. Even if it didn't make him happy. Because **he's mentally programmed to follow me, make sure I'm all right, look after me,** that sort of thing."

One patient also discussed how their siblings' lives were impacted by their frequent hospital stays and how their family sought to find ways to accommodate the patient's ASMD symptoms and include them in the same activities as their siblings.

> "So, I have an older brother and a younger sister. My younger sister was adopted just prior to me being diagnosed. Certainly, for my family, when I was growing up, and **I tended to spend more time in hospital, very disruptive to the flow of things**.
>
> My parents worked very hard to try and make sure that [Name]and [Name] could still engage in the things they wanted to be in, so playing competitive soccer, doing all those kinds of activities, but find a way that I could still be included.
>
> So that was the motivation, initially, behind getting a wheelchair was so that I could still go on those family outings. [Name] and [Name] could still go to a theme park for the day, and not have to cut it short because I was done, but that we'd have options and strategies to be able to do that."

Symptom progression

ASMD is a chronic and progressive disease. The patients in the sample experienced similar ASMD-related symptoms and reported having similar rapidly progressing clinical manifestations, with shortness of breath, fatigue, and enlargement of the liver and spleen being the most prominent in the sample.

Spleen and liver

One of the most frequently mentioned progressive symptoms experienced in this group of patients was the enlargement of the spleen and liver. Patients who recalled their symptoms before treatment reported worsening of symptoms as their liver and spleen continued to grow. This led to spleen infarcts, fibrosis, and experiencing regular unsettled stomachs. The thickening of the bowels, in this example, caused patients to have regular upset stomachs and diarrhoea which can occur independently of organomegaly. Patients described how having an enlarged spleen and liver affected their daily lives, making it difficult for them to perform simple things like tying their own shoelaces.

> "Yes, so I'm badly affected in comparison to the other people that I know. I developed a lot of storage, and so from the age of diagnosis through to about 12 years old, **my condition progressed quickly**. My abdomen got big, distended, my spleen was from not long after diagnosis, around three, four years old was markedly distended and wasn't functioning properly. **I was bruising all the time as a toddler, my stomach was constantly upset because of the thickening of my gut.** So, I was constantly having upset stomachs all the way through primary school, well into secondary school."

> "But I do know that, **as time went on, I could tell it was progressing**. The liver and spleen continued to grow. I had a lot of splenic infarcts, and I have scarring, and I've got a lot of it over time on the spleen. **And then the liver continued to progress.**"

> "But the enlarged liver and spleen also meant challenges for things like picking up off the floor because as my abdomen, and things, got larger, **it was harder and harder to be able to reach to tie shoes, to pick things up off the floor.** And then, combine that with being short of breath when doing those tasks, it's just like, oh, come on, guys."

Breathlessness and fatigue

Shortness of breath and fatigue frequently coexisted and were among the most common symptoms that progressed overtime. Patients considered fatigue to be one of the symptoms that had the most severe impact on their everyday lives. Consequently, patients had to reduce or avoid activities altogether to conserve energy.

> "The fatigue continued to get worse and worse as well. That one was really, really hard, and I still deal with that. I noticed that my eyes and things would get real puffy, real bad, and that was… **Over time, just everything continued to progress**"

> "Fatigue and shortness of breath have always been part of my picture with ASMD, but **it had become progressive over time**. Prior to starting on treatment, it had

gotten to the point that **in order to have enough energy to get through the work week, I could really cut out pretty much everything else** in terms of social activities or things. I got the bare essentials done at home. I spent the weekends at home recharging in order to be able to get back through the work week, the following week."

Experience of ASMD in adulthood

Patients' ASMD-related signs and symptoms worsened with age, and new symptoms and challenges appeared. Once patients reached adulthood, the most reported signs and symptoms included:

Respiratory:

- Shortness of breath
- Asthma
- Lung disease
- Pleurisy

Neurological:

- Sleep disturbance
- Headaches and migraines
- Cerebellar ataxia
- Neuropathy

Gastrointestinal system:

- Nauseousness
- Enlarged liver
- Gallbladder stones
- Fluctuation in appetite
- Difficulty gaining weight
- Liver fibrosis
- Appendix rupture

Heart:

- Septal wall thickening
- Irregular heartbeat
- Coronary artery disease (calcification and mild blockages)
- Aortic stenosis and other valvular heart disease (valve thickening and systolic murmur)

Infections:

- Infectious mononucleosis
- Respiratory infections (sinusitis and pneumonia)
- Swine flu
- Urinary tract infections
- Weak immune system

Musculoskeletal:

- Arthritis
- Fractures
- Joint pain / stiffness
- Osteopenia
- Osteoporosis

Hematologic:

- Enlarged spleen
- Low platelets
- Easily bruised
- Frequent nosebleeds

Psychological:

- Depression
- Anxiety
- Overthinking
- Excessive worrying

Constitutional:

- Pain
- Discomfort
- Fatigue

Lymphatic system:

- Abnormally enlarged tonsils

Symptom management

Prior to treatment of olipudase alpha, patients were treated symptomatically. The most common ways to manage symptoms included:

Pain relief medicine:
- Tylenol
- Targeted migraine pain relief

Other medication:
- Steroids for infections
- Statins for cholesterol
- Targeted medication for low platelets

Exercise:
- Swimming
- Physiotherapy
- Running

Rest:
- Resting often
- Taking frequent naps during the day

Other symptom management mentioned by patients included the use of vitamins, Chinese herbal tea medicine for low platelets, arnica gels and heat pads for pain relief, antibiotic infusions for infections, having water nearby for coughing, and anti-nausea medication.

Impact on activities of daily living

Patients would commonly experience shortness of breath while performing simple actions, such as walking and talking.

> "**When I run, it was real hard for me to breathe**. I get shortness of breath. Just walking or doing a flight of stairs**, I would be winded,** or even, at times, sitting, having a conversation, having to talk long, long sentences. I would get winded even doing that.
>
> *Interviewer: Yes, and how long would it take you then to regain normal breathing?*
>
> Well, I started doing swimming, and it helped coach me on how to breathe. But I would say, it would take me a couple minutes to just get back to what… I'd have to stop and stand there for a minute. **I couldn't always keep up with everybody else walking.**
>
> *Interviewer: and do you feel that gradually got worse over time, or just stayed?*
>
> Yes, certainly got worse, because I was able to stay more active when I was younger. I think it does that over time with anybody, but **I eventually got to the point where, even just walking or hiking, that was even hard on me**."

> "Prior to starting olipudase alfa, at the point that I would get short of breath talking. Family and friends would ask me why I had run to the phone when I had just walked across the living room to pick up the phone. **And shortness of breath**

> **was a limiting factor for things like climbing stairs**."

Shortness of breath could impact patients' ability to complete physical therapy.

> "Probably only I guess physical therapy, with the exercises, but I'm supposed to do five minutes, but **I would only do it two minutes and I'd be out of breath**. Once I've stopped and got off, it only took five minutes. **I just had to deal with it**. There's not really much I could do."

Fatigue could make it difficult to keep up with family members during leisure activities.

> "The only time **I remember it impacting was going skiing, a holiday**, and that would be a thing of fatigue where I would want to go home and rest before anyone else, because of **the physical exertion weighing more on me than it did others**."

Patients often recalled how their enlarged spleen and liver interfered with their everyday activities. Patients faced physical challenges with simple tasks like tying shoelaces and finding a comfortable position in bed leading to disturbed sleep.

> "[…] the enlarged liver and spleen also meant challenges for things like picking up off the floor because as my abdomen, and things, got larger, **it was harder and harder to be able to reach to tie shoes**, to pick things up off the floor."

> "**Sleep was a massive thing**. There were a lot of things I didn't take into consideration as being part of the condition until they stopped. Sleep was a significant thing and what I learnt which now I still do even though I've had the treatment is that **I will wake up in the night**. And because my spleen was uncomfortable, my liver was uncomfortable, a bit like being pregnant, my abdomen was distended. I would roll around a lot, so I wouldn't be comfortable in one position, then I'd move to get into another position.
>
> And in order to do that, I couldn't roll over because of the size of my stomach, so I used to sit bolt upright almost, turn into a better position, and lie back down and go to sleep."

There were substantial parts of the patients' lives that were also severely affected by ASMD-related pain. One pain was joint pain, with patients explaining that they had a permanent ache and that there was significant sleep disruption, which restricted their everyday function.

> "Oh yes, because it [joint pain] **disturbs your sleep**. […]. And then **it's hard to function** when you're sleepy. […] it's just a **permanent ache all the time**. It's not

fun. It's noticeable."

Impact on work

Patients often encountered issues at work comparable to those they faced in school, as fatigue, tiredness, shortness of breath, acquiring illnesses, and low energy levels would be a problem for them throughout their working day. This influenced their capacity to function throughout the day and made it difficult for them to perform everyday tasks like climbing a flight of stairs or speaking with co-workers while walking as they would become easily tired and out of breath.

> "At work, everybody is talking maybe about the meeting as we're walking, and **I noticed I would get out of breath**. So, I tried really hard not to talk much when I was walking to meeting."

> "**I couldn't climb a full flight of stairs without being short of breath**. I was too short of breath on a full flight of stairs to carry on a conversation by the time I got to the top. It would probably take about five minutes to get back to a state where my colleagues didn't think I was going to die on them."

> "It's not helpful when your [identifiable information] colleague tells their student, who asked what cyanosis is to just walk up a flight of stairs with [Patient's name] and turn around and look at her. It's like, you can stop using me as a teaching model any time now."

Patients mentioned that having an empathetic employer that made sure they were comfortable in their workplace and made sure they could work safely to accommodate their disease was beneficial to a certain extent. Despite this, patients continued to feel limited in their ability to engage in work activities due to the health effects of ASMD. Some patients would experience constant exhaustion at work, while others would frequently contract infections from their co-workers.

> "Well, when they hired me, I made sure they knew about everything, and I had a wonderful boss who was willing to work with me.
>
> […]
>
> **I almost passed out on my first day.** And so, she was like, well, we want you to stay, and so she moved me. […]. But I think, having the interactions with everybody coming in and out constantly, **because it was face to face, I was catching a lot of the same [infections], like at school**… And I think that's why they told me to stop, because that, and then just energy level-wise, I think I was pushing myself hard."

> "Yes, I was tired and fatigued. I had my good days and my bad days. I did work until 2012. I was working every single day, 40 hours, but then after that **I couldn't do it anymore. It was just too much for me. I had to stop. I was like a lot.** I was

fatigued, it was a lot."

Interviewer: Do you think your tiredness and fatigue increased over time or just maintained the same level that you could get to and that was it, from high school to working?

It was difficult. I was definitely more than the average person. When I came home from work, I had to sleep for a couple of hours and then eat and back to sleep right afterwards. It's not something that I'm like, oh, let's go party."

"But the reality of it was I was working with poorly people by my career choice, and every time I went to somebody who had something, **nine times out of ten I caught it**. And brought it home. And **there was no getting away from that**."

Patients with ASMD frequently had to miss work owing to illness and medical appointments. One patient used all their annual leave days for appointments and hospital stays. Another patient described the recurrent cycle of falling ill, returning to work for a month, and then falling ill again.

"**I would take days off for hospital appointments and for doctor's appointments**, but usually what I would do is utilise vacation time days. So, I would schedule the appointments, or I would schedule so that I could go first thing in the morning, and my employer would allow me to shift my work hours. So, I would work eleven until six, instead of nine to five, or whatever, to make up the hours."

"And the other thing is I spend my entire working career, up until enzyme replacement therapy, on a Stage 3 sickness review. I don't know how much you know about the National Health Service, but you go through key points and then that puts you in different stages of review. So, while my sickness was never for massive periods of time, **I would be sick and back to work for a month. And then I'd be sick again. So, I quickly racked up sickness stages.**"

One patient disclosed that they had been unable to resume work following childbirth because their immune system and platelets had not fully recovered, which they considered to be the impact of ASMD.

"**I had to stop working when I was pregnant with him because I was having some issues, and they told me that I should stop working.**

[…]

And then, after I had him, my immune system never really recovered. And so, that was when my platelets started going haywire again. And the doctors, they were trying to keep me away from everybody being sick, and they recommended me not work."

Impact on mental health

Before starting treatment, some patients described their coping strategies as going about their everyday lives and acting as if nothing were wrong, while others opted to talk to a councillor.

Patients acknowledged that it is challenging to be happy while experiencing pain and how stressful having severe pain can be.

> **"It's hard to be happy when you're hurting."**

> "You know you have a lot of stomach pains with this, and you don't know what they are. One time I went, and they said maybe it was gas. **But I was doubled over thinking I'm going to die.**"

Patients continued to struggle with the appearance of their swollen abdomens and felt burdened by the comments that they looked pregnant.

> "But, somehow, in my brain**, I assumed that would go away as I got older. But of course, it didn't.** The tone of it changed as I got older because it became an age that it was socially acceptable if you're pregnant, and people would say things that they thought were very positive, like oh, you look like you're having a boy. And they were trying to do it in a very positive framework, but it just was like, really? Because I work in a hospital, I would have patients saying oh, I'm sure that's a boy, and my colleagues are standing there going, no.

> "**I said I'm just fat**. […]. **I was skinny. I was 134 pounds and I'm 5.1 and a half. I had a big belly.** […]. An older women came up and she said, when are you due, and I was like, no, I'm just fat."

Another patient revealed that they were scared of their ASMD and the repercussions it would have on their future health because they had been in fairly good health throughout their childhood and adolescence.

> "[…] and, when I went to college, I graduated, I got my own health insurance. And **I was terrified that I would get sick one day**, and it would be considered a pre-existing condition, and wouldn't be covered. […] it was really weird being really healthy but then **thinking something terrible might happen**."

Impact on family and friends

Patients with ASMD had trouble socialising with their partners, friends, and family. Patients remembered that they regularly felt unwell, were in the hospital, and had frequent medical appointments, which left them without the energy to meet with family or friends.

> “I’d love to be there, an anniversary party for friends. I would absolutely love to be there, but it’s a two-hour drive one direction and a two-hour drive back, and I simply can't. **I don't have the energy reserves to do it**.”

> “There's a ten-year age difference between my youngest niece and my youngest nephew. The things I could do with my nieces when they were young and my nephews when they were young had changed. So, I could take my nieces to the zoo. **I didn't have the energy to do that with my nephews**.”

There were challenges with patients having to put their social lives on hold to prioritise their work. Adult ASMD patients would frequently get so exhausted that they had to choose their work over spending time with friends and family to get through the working week. Patients had to use their weekends to finish chores and so they could rest up for the approaching work week and there were times when patients couldn’t bring themselves to do household chores because of work exhaustion.

> “I got the bare essentials done at home. **I spent the weekends at home recharging in order to be able to get back through the work week the following week**.”

> “It really meant that **I was using my energy and directing my energy and time to doing the absolute essentials.** So, get the groceries, get the laundry done, get some meals, get through the workweek. **I gradually cut out going out with friends**.”

> “Prior to starting on treatment, it had gotten to the point that in order to have enough energy to get through the work week, I could really cut out pretty much everything else in terms of social activities or things.”

Patients also talked about the difficulties of dating later in life, how their ASMD made them feel like a burden at times, and the strain of living with a spouse with ASMD. They also described the difficulties of communicating their ASMD to potential partners and how their symptoms affected their intimacy with their partner.

> “I think so. I think it’s a combination of pieces. **I think the fact that when you're 19 and you look pregnant does not make it easy to date.** The energy piece, meaning that I'm not out socialising a lot. My sister often said you're not going to find Prince Charming sitting on your couch, and it’s like, well, darn it, he should just show up here because I'm too tired to go looking for him.
>
> *Interviewer: It would be so much easier, wouldn't it?*
>
> Exactly. Seriously? You don't have the energy for this.
>
> **Plus, it is intimidating to try and explain all of this to someone because it isn't just... You don't want someone to walk into a relationship blind and spring it on them later.** But yes.”

> “But it’s something that when we were early on in our relationship, and two, three years and we got married**, it was a dark cloud that was over our future**. And we didn’t know whether the land was going to lie with that. So, it made family life stressful.”

> “But **I would say one of the big impacts**, more recent than I can remember, is when I had the hip pain for so long, and being so tired and not able to sleep, **it impacted my sex life with my current husband**. Because I was tired and hurt and grumpy, so yes, that was an impact. Yes.”

Additionally, patients frequently had to make difficult decisions such as choosing whether to have children based on their ASMD. Patients shared their worries about how their ASMD diagnosis could impact their children and family, especially given how unpredictable their future would be without treatment.

> “**We’ve made decisions based around my condition**. […]. So, when I got with my wife we were talking about having children. […]. And we made the decision together that actually, it’s probably better in the long run if we didn’t. I’ve got two lovely stepchildren and this [ASMD] stops with me now.”

> “And when I got with my wife at the time, she had a young daughter, my step daughter, and **it was a discussion that we had to have**. That ultimately, we don’t know how my health was going to go and what I would need later on and how long I would live.
>
> […]
>
> And in sad circumstances, my stepdaughter picked up on that early, and when she was about nine or ten years old, she’d come down having looked on the internet to see whether she was suitable to donate part of her liver if I needed that. **Which is a horrible thing for a nine- to ten-year-old to be thinking of or looking into or doing**.”

IMPACT OF OLIPUDASE ALFA ON ADULT ASMD PATIENTS

Patients started treatment between the ages of 20–55 years and were on treatment for 6 months–9 years at the time of the interviews.

Experience of olipudase alfa

First impressions of treatment

Patients admitted to feeling a little apprehensive at first when they began treatment as they did not know how their body would react and whether it would work for them. They also had to get used to the frequent infusions and fitting these in with their lives.

> "**It was a shock to start off with** because my entire medical hospital-based treatment was one appointment every 12 months with a consultant in London, because there was nothing they could actively treat me for or do. So, at the time, it was giving up a day every fortnight that I planned for other things. It was new, that's the best way to describe it.It was new. **I had to make time for it**. Now, it's a given. I don't think about it. I discussed it with work because the hospital in Manchester said they could give you the time. You could take that as sick because **it's something you need to have done.** And I've never done that."

> "I think there was, initially, **just a little bit of anxiety**, in terms of this is all an entirely new process and trying to figure out how to make it fit in life, as well."

> Just **worried and anxious about what was going to happen to me**. And when the medicine did come out, I was reluctant to start it at first because I've been without the enzyme for 32 years, so **I didn't know how my body was going to react.**

> "Concerns? Like I said, at first**, I didn't know how it would affect me, or if my body would reject it, but my body seems to like it**."

> "Well, I know that I wasn't apprehensive about actually going onto it. **I just was, I guess, antsy as to how long it was going to take to start seeing everything change.** And I was worried that I might be that one patient that it didn't work for, because sometimes it doesn't always work for everyone. But I didn't have any of those issues, and **it's been wonderful**."

Overall change in quality of life

One of the most important impacts of treatment to patients was a positive influence on their health and quality of life. Patients reported feeling that their health was better and were able to see a difference in themselves from prior to treatment.

> "**It's overall beneficial that I've taken it**. **My health has overall improved. It's beneficial.** Everything has gotten better, overall, since I've been on it for ten years. I can see with my bloodwork, my MRIs, my CAT scans, everything in general. Even doing things, like I'm more active**. I can see a difference in myself, overall, from prior to taking olipudase alfa**."

> "**I feel better in general.** I still have my good days and my bad days. That's the only thing. I was hoping that I'd feel good all the time. I'll take the good and the bad."

> "**It's a massive positive**. […]. And when I started the enzyme replacement therapy, my health flipped, completely turned on its head. All these things I've never been able to do I could do. […]. **Because the only thing that's giving me my quality of life right now is the enzyme replacement therapy**."

> "Whereas with this enzyme replacement therapy, literally from starting it in May, by Christmas **I was a totally different person**. **And within 12 months, a**

> **completely normal healthy person.** And the nurses who were working on the research ward were blown away by it."

Symptom improvement or stabilisation

There was an overall improvement in ASMD-related symptoms since treatment which impacted patients' quality of life. Adult ASMD patients had reported first seeing improvement in symptoms from 3 weeks to 1 year after beginning infusions of olipudase alfa. These symptoms included:

Respiratory:

- Increased lung capacity
- Normal pulmonary functioning
- Little to no shortness of breath

Neurological:

- Improved sleep
- Less headaches and migraines
- Neuropathy had improved

Gastrointestinal system:

- Less nausea
- Gallbladder stones had improved
- Regular appetite
- Ability to gain weight
- Scarring on the liver had healed

Hematologic:

- Shrinkage of the spleen, liver and abdomen
- Improved platelet levels
- Improved clotting
- Reduced bruising
- Fewer nosebleeds

Heart:

- Healthier cardiovascular system

Infections:

- Less infections

Musculoskeletal:

- Improved bone density
  Lessened joint pain / stiffness

Psychological:

- Overall improvement in mental wellbeing (less anxious and depressed, improved self-confidence)

Constitutional:

- In less pain and discomfort
- More energy thus less fatigued

Lymphatic system:

- Reduced size of tonsils

Pulmonary function	"And I said where do my lungs stand now? Because when I started the trial the pulmonary function chap had said to me the best way to describe it is you're working on one lung. Although you've got two lungs, because of the storage, they're not working effectively, so you're working on the one lung. **And my last test in January, my lung function was 25% better and healthier than the average male of my age. So, it's a huge improvement.**"
Liver and spleen	"And in the initial safety trial that I did in Manchester, **in the eight-month period that I was being given the initial enzyme replacements therapy, I'd gone from having an obviously distended abdomen and overcrowded abdomen to almost a normal abdomen. My spleen had shrunk.** Before I started my spleen was that big, it had gone down and in my pelvis and up towards my liver."
Infections	"II have like an allergy sinus. Everyone's dealing with it right now in [Location], a sinus infection type of thing. **I haven't been sick in seven months**, thank God. I'm dealing with it right now. **Seven months is good not being sick**."
Appetite	"[…] **I was eating food and gaining weight. And not only that, I didn't need to eat a lot.** I was eating a normal meal, and then I was fine for four, five, six hours. I wasn't even hungry. Whereas before, I would have eaten that and then 20 minutes later looking for something else to have to eat. So, my meal sizes had cut down."
Heart	"The sonographer who was doing my echo as part of the trial was like 'your heart's better.' **Immediately post enzymes your heart looks better, it looks stronger**. And this was within two, three months of having the treatment."

There were patients who also mentioned that some of their ASMD-related symptoms had only slightly improved or had not progressed further, which still positively impacted their lives.

Headaches	**"So, I take ibuprofen, but I don't get them as much as I used to, but I still get them once in a while."**
Nosebleeds	"But now, since the treatment, **I might get a nosebleed maybe every six months and it would just be the one**, and that's it. […]. It's better now, yes. I mean, I had a nosebleed maybe about two or three weeks ago, I had one. Or did I have two? I think I had one. But it was the first time in about six months I'd had one."
Pulmonary functioning	"And **I don't get as winded as I used to**. I still get a little winded, but not like I used to. *Interviewer: Okay, that's fantastic. And how quickly did you start noticing those changes?*

> It probably took about a year, only because [Name] thinks that it took 32 years to develop all that sphingomyelinase."

Impact on activities of daily living

Patients reported that their ability to perform routine tasks had greatly improved since receiving ERT. Prior to ERT, patients frequently experienced shortness of breath and exhaustion, making it difficult for them to complete typical home duties. Patients on treatment reported many changes in their ability to conduct everyday tasks and could perform more household chores without feeling unduly tired out. These improvements included the ability to climb a flight of stairs and talk without becoming out of breath.

> "[…] **I could do more around the condo** so that it wasn't just getting the bare minimum done. It was getting some of the nice-to-dos done, instead of just the absolute essentials, and not coming home from work, making dinner, and going to bed."

> "**I can climb a flight of stairs**. I still am a little bit short of breath on a full flight of stairs, but not to the degree that I was. **I can carry on a conversation while I'm walking on a level. I can tie my shoes without getting out of breath.** My friends and family report that **my voice sounds much stronger** when I answer the phone, and they no longer worry that they need… A friend, last night, said I no longer worry that I need to phone 911 when you answer the phone. It's like, excellent. I appreciate that."

As patients' pulmonary function and enlarged organs improved, they also began to feel more at ease with physical activity. As a result, they returned to the gym, began participating in sports, and started running marathons. Furthermore, as more and more ASMD-related symptoms improved, patients' attitude towards their condition had a positive change.

> "But yes, **my quality of life has gotten a lot better**. Like I said, I started working out more."

> "I often go and play football on the days after my treatment**. I do feel like I can carry on with the rest of my normal life.**"

> "**I do partake more in sport at the moment than I did before the treatment**. I think part of that is maybe a mental thing, because I was always very cautious of my enlarged organs because they were more vulnerable as well. And I was maybe less readily partaking in sport than I do now, when I know **I'm less at risk of getting hurt now.**"

> "And when I started the enzyme replacement therapy, my health flipped, completely turned on its head. **All these things I've never been able to do I could do.**"

> “And the other thing was often I spent most of my working career ill. So, nine times out of ten, I would be going to work with a temperature and on antibiotics because of my sickness review. And the last thing I wanted to do when I finished work was walk home. **Whereas when I was on the trial, and I’d done a shift, I wasn’t exhausted. I had the energy to cycle home, and I recovered quickly when I got in, so it wasn’t a massive impact**.”

Patients also mentioned how a reduction in the size of their spleen and liver allowed them to sleep better and be more comfortable. One patient also mentioned that they were now able to button up their shorts easier and had dropped down two sizes in clothing.

> “And by the time I’d done the eight months trial, it was on the same level as my kidneys. So, massively reduced. My right leg of my liver had shrunk up to almost my ribs. And my left leg of my liver had moved back across underneath my diaphragm. **So, my abdomen was much smaller, much more comfortable. I was sleeping better,** all be it sat up and turning over. **I wasn’t getting any discomfort during the night.**”

> “But as far as my liver and spleen, I always used to have trouble buying clothes before, and my shorts, having trouble buttoning them and stuff. But **I used to wear a size five, and now I’m in a three and they’re easier for me to button**.”

One patient reflected on their improved stamina and the fact that they could now keep up with their family members during leisure activities.

> “But it was my dad on a skiing holiday who, after one day, and this is after I’d started the treatment, went, ‘you know what you did, don’t you?’
>
> I went, what?
>
> He went, ‘you didn’t finish early. **Before the treatment, you wouldn’t be here now**.’
>
> And I sort of went, ‘yes, you’re right.’ I hadn’t noticed it myself, because it wasn’t something I was thinking about, but it was something that he was thinking about, because he’s my dad. And so, yes, **it was him noticing it more than me. And then I started to take notice.**”

Impact on ability to attend school and work

Prior to receiving treatment, several individuals had left education, left employment or were considering leaving employment due to their ASMD. Once on treatment, patients were able to cope with work much better and continue their education.

> “**I think it improved my ability to be able to continue at work.** I think it was getting to a point where I was deciding whether I could or couldn't continue in this. Several of my colleagues had asked about would I consider looking at a non-clinical role because of the demands of my clinical role. So, I certainly think **it has started to make a positive impact on my ability to maintain that**.”

> “So, not long after starting, I started college in 2015, so maybe even 12 months after being on enzyme replacement therapy, I’d gone from working three shifts and being absolutely wiped out to working four, including nights, and coming straight off of nights and going to college all day, doing my college, coming home in the evening and doing something and going back into day shifts straight on the bounce with no breaks. **It’s a massive difference**.”

Patients were less vulnerable to infections, which meant less days off work due to illness and one patient detailed how they were able to continue working throughout the COVID pandemic after being removed from the shielding register because of their good health.

> “The guy I work with has had coronavirus three times, brought it into work and then gone home on the sick. And **I’ve never caught it**. And although we’re using a lot of protection, years ago that probably would have killed me, to be perfectly honest. I certainly wouldn’t have been working.
>
> And my consultant took me off the shielding register because I was immediately shielded when the coronavirus started. **And within about six months of the initial start, he had me removed from the shielding register because my health was as good as anybody else. And I returned to work and worked all the way through it.**”

Impact on mental health

Since beginning treatment, patients' mental health had improved as their health had improved and they felt less negative about living with ASMD.

> “**I'm happier that taking the enzyme treatment**, overall, I'm very happy that I decided ten years ago to take this enzyme treatment.”

> “**I think it’s better now than it was before**. Maybe I’m a little less… Anxious isn’t the word. Maybe paranoid. Although they kind of mean the same thing. I do feel a little bit less that way after the treatment, beca**use I know that ASMD is less of a factor in my life now**. Not to say that it’s not still a factor. But yes, I would say that there’s only a slight improvement in my mental health now than then.”

> Yes. I think, again, a biproduct of just having the treatment is that **it affects my mental health in that I know I’m being treated and that, in itself, improves my mental health, because I know my physical health is being improved.**

> And again, having the treatment, is it almost… I would say maybe almost, even though the treatment itself isn't a placebo, it's almost a placebo effect, in that I know I'm being treated and therefore there are things I don't have to worry about. And almost not worrying about them means I don't focus on my symptoms and therefore I feel better. And it's almost like I don't have my… It's a strange thing to think about sometimes, because it's almost like the treatment, **the drug is helping me and just the act of being treated as well is helping me**."

> "I don't think my mental health has actually changed because **I've always tried to look at things in a more positive way**, because when you look at all the bad that you have, it just makes it worse. You can't really help yourself that way. It actually makes things worse, I think. But like I said to [name], I always try to stay positive. I didn't know anything else growing up anyway. But I would definitely say **we're more excited because we know what's happening. So, we're very excited about everything that's been happening.**
>
> And **there were happy tears cried the first day that I started the medicine**, and then tears when we see the different lab results coming out now. So, **it's all very positive**.

Patients who had previously struggled with body image discussed the effects of treatment and how their spleen, liver, and abdomen have shrunk, making them considerably less self-conscious about their appearance.

> "**It's made my mental health better**. I like that my spleen is better. Overall, looking at myself, **I look normal**.
>
> I'm happy that no one is coming up to me saying, when are you due? What do you do? Because my stomach is so big."

> "If you put two pictures together, **anybody could see there was a huge difference**. And **that was great for my own mental health**, because I was conscious of the fact that I had a big abdomen."

An emotional weight has been removed from patients who are parents, who no longer worry if they will be around to see their children grow up.

> "I'm extremely excited, and when I will do different interviews, before it was actually approved, I'd break down crying because I was worried about being able to be here and spending time with my son and watching him grow up. **And now I know I have that opportunity, so it's a big deal to me, it really is**."

Impact on family and friends

Patients considered the hardships and obstacles their initial ASMD symptoms and diagnosis had on their family and friends. There had been a shift in the impact of the disease on their family and friends once they had started treatment. Patients felt their energy levels and fatigue had improved as a result of being on treatment and acknowledged that they were able to socialise more without feeling tired.

> "So, **I go out more and do stuff, and I don't get as tired as I used to**. […]. I can go out and do stuff and not get really tired and stuff."

> "Yes, I definitely have made a lot more friends, especially being on the PTC, because that whole group of ladies, we're all very close now. Even over the summer, we're close. And they're my son's friends' parents, so it makes it better because he's involved. **It's just definitely a lot more energy, a lot more socialising, the ability to be able to do things together as a family or with friends**."

> "Definitely on the positive, in terms of I'**m able to engage more in activities with friends and family.** Being able to do more of the things that have always lived in the back of my head saying I'd really like to be able to say yes to this invite, but I just can't. Being able to say yes to those, for a change, is a nice concept."

> "And still doing family things in the evenings and that sort of thing as well, **which I never would have been able to do before**."

Patients initially believed their parents and siblings were worried about the treatment, but once they started the treatment, their parents and siblings quickly felt a significant release of stress. Patients remembered that their parents had been supportive, enthusiastic, and positive ever since the patient began treatment.

> "I think my parents, for them, one of the big things they worried about ASMD is they were worried about the treatment. When I was going to put on the treatment. **So being on the treatment, that in itself is a big release, especially for my parents**."

> "Yes. The first day that I started it, him, my mum and dad, all my doctors, we were all in the room together, and you could just tell, everybody, that it was a very, **very emotional day**."

> "I've got one younger brother. **I think maybe he worries about me less now**, maybe. I'm not sure. It has been a bit of a thing, growing up, that he was not necessarily taught to worry about me but taught to look out for me. **Maybe he feels less responsibility for me now**."

Throughout the course of their treatment, patients regarded their friends' and family's support as extremely important. Patients said that with this support, their lives felt much more "normal."

> "**But luckily, I have a lot of support. My family is wonderful. I have very understanding friends**, and as you can see, I have [Name], but I ended up with everything I wanted. **I still think I have a normal life. It's just a little bit different**."

> "**I am quite lucky in that my family are very involved with ASMD and therefore know a lot about it and are very supportive.** And not just my parents and my brother. One of my grandparents is on the board of trustees at [patient organisation] and my uncles and my aunts have all been involved. So I'm very lucky. And I'm very lucky that, as a teenager, **I had some very understanding friends as well**."

Additionally, patients believed that because their future was much more unambiguous, they could now plan for retirement and make preparations for the future with their families.

> "And that's one of the biggest things that's changed since I've been on enzyme replacement therapy is that I was convinced that when I started it, I would still look at life that way. I would still look at the well live it for now, don't make any plans, do everything you want to do. And in actual fact, **after a couple of years of being on it, I'm planning a retirement, looking at long-term things because I have totally different health.**"

> "I'm probably f**eeling more positive about my future related to my health than I have in a very long time,** because even if the answer were that things were to stabilise as they are right now, that would be stellar. Because **it means that I can make plans,** based on where things are now. I don't have to worry that everything is going to go upside down tomorrow. **I do have enough energy at this point to be able to do some of those things that I place high value on.**"
>
> *Interviewer: What are those things you place high value on?*
>
> "Being able to spend time with my family and my friends. Being able to do some travel and see some folks that I haven't seen in a long time."

Disadvantages of treatment

The disadvantages of treatment were mainly related to the infusion itself and having to plan life around regular infusions. The impact on day-to-day life was most acute while patients were on the clinical trial, but once this was over, infusions became more manageable although life still has to be planned around them. One patient mentioned the impact on planning a family.

Infusions

There were some concerns raised with patients regarding infusions. Patients claimed that while the treatment itself didn't worry them, their primary concerns were that they would bruise every time they received an infusion and that they didn't appreciate having to use needles repeatedly.

> “**I don’t really have concerns about the actual drug, it’s more the IV process.** Because I don’t know if you can see, I’ve got a big bruise. That’s it.”

> “And then **it gets tiring getting stuck with needles all the time**. **Sometimes I get stuck multiple times.** I don’t want a port, because I’m very active. And if I need this for the rest of my life, maybe I’ll wait until I’m a really old lady to get a port.”

Patients felt that it was sometimes difficult for them to function or finish duties right after an infusion, and that they felt worn out and unmotivated for the rest of the day. Patients often experienced tiredness and mood related symptoms directly after receiving an infusion.

> “Sometimes on the Saturday afterwards, I’m fine. And other times I feel myself frustrated and screwed up. Which passes once I’ve eaten something.”

> “It’s not even really a side effect, but **I do suffer from a short fuse the second day**. And the only way to describe it is **like when you’re hungry or frustrated or tired, you’re short.** You feel short with things.

> “It has changed a little bit. I don’t get as fatigued as I used to, **but some days, like infusion days, are really bad with fatigue**.”

> “Yes, I do take the day off work on that day every fortnight, purely because it’s… Maybe I could work whilst having the treatment, but pretty much **one of my arms is out of commission and it does make me very lethargic, the treatment. Very unmotivated.**”

One patient had lupus and believed that the infusions increased their inflammatory levels, resulting in a fever, headaches, and muscle pain. Nevertheless, they would rather deal with these effects than go without treatment for ASMD.

> “Especially in the beginning with olipudase alfa, and because I have the autoimmune disorder, I got a side effect on the second week. It was a really hard thing to figure out why I was getting so sick. I had an inflammatory reaction with the olipudase alfa. I was getting 106 fevers and shakes and pain all over my body, muscle, bone and joint pain. I thought I was dying. It was terrible. It was a lot on me. I still get it but I deal with it better. I mentally deal with it better. I know it's coming, so I know. But in the beginning, I was like what’s going on? No one knew. It's a new drug.”
> […]

> "I'm dealing with other things with the enzyme treatment, with side effects, but **I'll rather deal with that than deal without it**."

Participating in the clinical trial

Patients mentioned that ERT had caused some disruptions to their everyday life. The most frequently discussed disruptions were having to plan around infusions. When on the clinical trial, travel to the clinical site for infusions, having no flexibility on the day infusions were given and restrictions on alcohol consumption meant that life had to be managed around infusions. It was difficult for patients to attend certain social gatherings or major events like weddings and some found the travel stressful.

> During the clinical trial **I had to plan around,** because in the clinical trial they had a big thing about you can't have alcohol the day before, the day of, three days after. So, if it's going to be New Years, or your birthday, or somebody's wedding, and you might want to have a drink. **It would be like, I have to move my infusion. And at first, we couldn't move our infusions around.**
>
> So, **I had a miss a wedding**, **but later on we could move them around**. So, then it was like okay if I move it here, then I could still have a glass of champagne on New Years. **It just makes life more complicated**. Have to plan, but I'm very thankful to have it, obviously.

> "Well I would say that I definitely got, and this happened super early in the study, but **I definitely got depression and anxiety**. And I think that started probably with work. Because it looked to me like I was going to get laid off, and anyway, **all the travel was hard on my relationship and all that**. And the packing, and I just got really weird to wear, like if I had to pack, I would just get really anxious and stressed out and grumpy."

> "So, because I was travelling to and from New York, I would work eight days out of a ten-day stretch. I would work up until Wednesday afternoon, leave Wednesday afternoon to the airport, fly to New York, do an infusion Thursday, the eval Friday, fly back home Friday night, start my work week, again, on Monday.
>
> […]
>
> It's now, here, in [City], so it's just drive to a clinical site, infusion site. **So, no longer spending enormous amounts of time at the airport**, and getting to know all the customs agents, and the airline agents."

The need for regular infusions

As time went on, treatment became more manageable as patients were able to plan infusion days to suit their schedule and receive infusions more locally. Travel could still be an issue, with travel disruption meaning that infusions were missed.

> “**It just makes life more complicated**. Have to plan, but I’m very thankful to have it, obviously.”

> “It’s just that I need a day, at the moment, in my schedule every two weeks to participate in the treatment. **That’s the disruption to my schedule at the moment**.”

> “And on a couple of occasions, because I live in the West Country and **I have a long train travel to get to London to get my treatment initially.** There was often where the train wouldn’t travel because the lines were shut. And I would miss it and would land up missing an enzyme and then going a month before I got it again. […]. And in that month, I could feel changes. I could feel differences.
>
> […]
>
> **And that feeling of anger, frustration, tiredness, that whole hangry situation, is worse if I’ve missed an enzyme**.”

Planning a family

One patient mentioned that they would have liked more information about family planning before starting treatment so that they could make informed decisions before starting treatment.

> “**I can't have kids, so that’s it.** That was the only other thing. That’s the only worry. I asked many times throughout the research and they never really gave me an answer about children and stuff like that. I think it's passed that. It's the only other thing. They actually came out and said that you'd have to stop to have children. I wish they had told me that before. I would have planned a little bit differently before I would have started. I had a couple of months, maybe I would have planned it a bit differently.”

Current challenges for adult patients with ASMD

Relationships and mental health

One patient spoke about how their relationships were still affected by their ASMD, how it continued to be challenging to find a life partner who understood the illness, or finding friends.

> “I want to find a life partner. **Nowadays it's hard to find anybody to talk to. It's hard to explain to people.** I've had many boyfriends and it's very hard to find somebody to understand this disease. It's very difficult.”

> *Interviewer: So, did receiving treatment with olipudase alfa impact your mental health? You mentioned there that the depression…*
>
> “Yes, a lot of it’s gone. I still have a tiny bit.
>
> *Interviewer: And why do you still have a tiny bit, do you think? What is it, then?*
>
> **It’s more because of my walker and having trouble making friends, and accepting that I’m different.** But also, it’s hard explaining ASMD to people. So,

> this kid with my disease, he wrote a book about my disease, and the foundation sent me a bunch of copies, so I give that to my friends and I tell them to read that, and then I explain how it affects me."

THE FUTURE

Patients' perspectives on their future health have shifted as a result of their treatment. Patients believed that if treatment stopped there was a chance that their health could deteriorate and would prevent them from having a future. Due to the profound impact that treatment has had on adult patients, they believed there was a need to start treatment early and for it to be available for everyone with ASMD.

Outlook on future health

Treatment had given patients hope and put them in a positive headspace regarding their future health.

> "As long as I can keep receiving the treatment, **I feel more optimistic about my future when it comes to my health than before I started the treatment.** I was told or made aware before I started the treatment that my health would decline as I got older. And that's less of a factor now that I'm being treated. That's what I would say."

> "**Good, optimistic. I feel happy that I'm on the enzyme treatment**. I hope that I can sustain this somewhat healthy lifestyle with the enzyme treatment and continue to keep this going for many years to come and not have any hiccups. We'll see what happens. Hopefully, better and better."

> "But **I'm very excited now for what the future holds**, and hopefully be able to do something positive and good with it."

> "Yes. The first day that I started it, him, my mum and dad, all my doctors, we were all in the room together, and you could just tell, everybody, that it was a very, very emotional day."

Furthermore, patients frequently commented on the fact they now have a longer lifespan and a future to look forward to.

> "**Overall, it's given me hope that I know that it's prolonged my life.** Because before, to be honest, the first doctor that I spoke to ten years ago said that I would be on oxygen for my lungs, because my lungs were bad, and I wouldn't live that long is what they told me. Niemann–Pick disease isn't a great disease to have

without a treatment, so I'm happy that it's prolonged my life. **I have a good headspace knowing that I have a treatment that's prolonged my life**."

"**I'm extremely excited**, and when I will do different interviews, before it was actually approved, I'd break down crying because I was worried about being able to be here and spending time with my son and watching him grow up."

"Oh sure. I mean now I'm like, well **I might live to be 100 or something**. We never thought that. Yes."

"With regards to my health, **now I know that I do have a future.** Before, I was actually worried about whether I would have a future. I lost another friend at 27 from a spleen aneurysm, so I didn't know if anything like that was going to happen to me. Like the splenic infarct, I didn't know if it would come back."

Impact if treatment were to be stopped

Patients reflected on their lives before treatment and stated that their lives would be much different if they stopped taking olipudase alfa. The prospect of falling ill again was daunting and patients felt that ERT made such a difference to their quality of life they now couldn't imagine life without it.

"I would get sick. I wouldn't feel good. **It would be devastating**."

"Yes. **And if it was taken away from everybody, I'd be depressed about the other people. I had a couple of friends that died before it got approved**."

Patients were also concerned about future access to ERT with worries about the treatment not being available to them in the future.

"It's a massive positive. **But there is a negative element to it and that is because it is terrifying if it stops.** And that's the reality of it. Like I was saying earlier, you live your life well. I can't make any plans because it's not going to happen. And when I started the enzyme replacement therapy, my health flipped, completely turned on its head. All these things I've never been able to do I could do. I could go out and do contact sports now if I wanted, I just don't fancy it. I've never done it, so I feel no need to do it.

So, although it's a massive positive having it and it's completely transformed my life, it's terrifying if it doesn't continue. Because the only thing that's giving me my quality of life right now is the enzyme replacement therapy."

"If I no longer had access, then I would be back concerned about, well, for one thing it's weird, because I'm so healthy. […]. **But I also think that I would notice the problems more.** Because going from being on treatment, if all of a sudden, I wasn't on it, that I would notice when I start having breathing problems and I would be going to the doctor more**. And back to worrying about, am I going to**

have to be on oxygen, am I going to get osteoporosis. I probably be a little more paranoid and going to the doctors even more to get testing to see where I was and all that."

"

Interviewer: And what impact would a loss of access to olipudase alfa have for you, do you think?

"A loss of olipudase alfa? It would have a really bad impact because things would go back to how they were."

Access to treatment

Patients also reflected on availability of treatment. They felt there was a need for the treatment to be approved for everyone to have access to.

"

"And since I've been on the enzyme replacement therapy, though not even thinking about it, my whole outlook on everything has completely changed. And even if I think to myself now you haven't got a future, because my health is so good, I closet it. I don't give it any thought. **Because there's no way I would have been able to do any of the things I was doing before.** So now, it's a given, reluctantly to say that because nothing's got licensed yet. And we're still in the situation where it's still a clinical trial. **But it's made such a difference that I can't imagine my life without it now.**"

"

Yes. **I think it is something that everyone should have made available to them if they have ASMD.** There are people who are affected with ASMD worse than I am who would benefit greatly from the treatment. I know several others who are on the treatment as well who maybe benefitted more than I do because of the severity of their symptoms. So yes, I think it should be made… If they can receive the treatment, they should.

"

"And now, it's about telling a story because it's important that people understand how much of a difference this drug makes. And how good it is. If I didn't sit and have the meeting and discuss it with you, then the chance of the licence is going to be less. **And the most important thing to me now is getting that drug licensed**."

One patient reflected on a friend who was not eligible to take part in the clinical trial and died at the age of 24 from liver complications.

"

"[Friend's name] didn't have that opportunity, she didn't understand any of it, so she took medical advice which was, well, 'you're not suitable at the moment.' I had my bilirubin redone, coming on the criteria and was accepted on the trial and started the treatment. **And within the first four months, I met her at one of the conferences. And said, look, I've already started noticing differences, this is going to be amazing, it will really help you out. And by the time I'd moved from**

> **the [location] trial to the [location] trial, which is a period of nine months, [friend's name] had died from liver problems. And she was 24. And she was so desperate when she'd seen me at the family conference because she'd seen how much it had improved me.**"

One patient also discussed access in other countries and the need for newborn screening.

> "No. One thing is that **I heard that it's not getting approved in Canada, or maybe, they're not even going to try. And so, that makes me feel sad too, because I don't know what the people in Canada are supposed to do.** I have one friend is on it, and supposedly [Company Name] is going to cover. But, somebody gets nearly diagnosed in Canada, what are they going to do?
>
> **And hopefully, that it gets put on the newborn screening and all of the states, so that people can catch it early.** I guess I have a lot of concerns for other people, because I see most people have more problems with it than I did. Yes."

Need for early treatment intervention

Patients frequently discussed the importance of early treatment intervention. They believed that this was necessary to prevent the adverse childhood experiences and symptom progression that they had experienced.

> "It was a rough road for me. **I'm glad we have something now for our young ones, that they can be on enzyme treatment, that they won't have to deal with what I dealt with when I was younger**.

> "**Oh, I think it's extremely important because I watched, being little and being diagnosed with it and living with it my whole life and how it progressed over time.** I think it's extremely important to have that because if you can catch it early on, before anything starts getting crazy and get on the medication, you can have, I guess, more of a, what people say, normal life. But you won't have to experience all the crazy stuff either, as far as you could play those contact sports.
>
> Your liver and spleen won't be the size that everyone has had to deal with lately. And I just think you'd be able to experience more life than if you're not on that, because it does, it starts to slowly poison your system.
>
> *Interviewer: Yes, so you think getting on olipudase alfa early is the better option?*
>
> Yes, because **they say it's easier when there are children who are on it, to start reversing everything and actually seeing the effects because they don't have as much scarring built up on their system. Whereas, an adult, it takes a lot longer to reverse anything, and that's if it can all be reversed.**

Need for treatment alternatives

Within the sample, patients strongly felt there was a need for less invasive treatment options for ASMD and treatments that could address neurological symptoms.

> "Another treatment? **So, I feel like there is, only because [Name] said olipudase alfa will not pass through to my brain.** But they're working on gene therapy, taking my bad gene and giving me a good gene, so yes."

> "Okay. Well, just thinking of what I would've been thinking then, it is still being attached to a drip for four hours. **If it was a pill I took every day, then I would be completely satisfied.**
>
> *Interviewer: That's what you meant, yes. No, just to clarify. That makes sense. And it even is a bit stressful to try and make up the working hours from taking that day off every week.*
>
> It can be, yes. And I do still need to have hospital visits. Once every quarter, I still have to go in for my treatment and have things like an ECG and blood tests. **Again, if it was just a pill I took every morning, that would be completely satisfying. Or there are other ways it could be less time consuming and, in some ways, less painful.**"

> "So, you want to shoot, if the sky's the limit. I would like to just fix me and let me. Looking at it, because you know MPS, had a clinical trial for gene therapy and some kids died.
>
> And I think they had to stop the study to see if it was because of the gene therapy or was it because you have a fatal disease. **It would be wonderful to have something that's not so invasive**."

Other comments on treatment

Patients made additional comments about having a treatment strategy, the need for newborn screening, the cost of treatment, and the importance of ASMD voices being heard.

Treatment strategy	"I recognise that the disease to someone looking at me is invisible, and they perceive well, then, why do we need to treat it? We need to treat it. It isn't okay to just say well, just because I can't see it, we don't need to treat that. That's the equivalent of saying, well, because I can't see that tumour, we don't need to treat it, we'll wait until it's visible. That's not an acceptable strategy."
Newborn screening in all USA states	"And hopefully, that it gets put on the newborn screening and all of the states, so that people can catch it early. I guess I have a lot of concerns for other people, because I see most people have more problems with it than I did. Yes."
Costs of treatment	"How it's going to be paid for. It's so expensive. We're in May. Towards the end of the year, it needs to be recertified. I always get worried how it's going to be paid for

	and how my nursing was going to be paid for. Again, I'm disabled. I'm on Medicare. Thank God, they help me get payment for it. A foundation is paying for my nursing, but I get very concerned on how everything is going to get paid for for next year."
Patient voices	"I think it's important that we raise our voice and make sure that the things we need get done, and our voice isn't lost in the shuffle because there's so much happening in the world. I get that we're a very small number, but that doesn't mean we're not valuable."
Access to counselling	"I think, yes, there is a need for it. Counselling has helped me deal with not some of my symptoms, but everything I'm going through, but yes, so I think it's beneficial."

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Rare Disease Research Partners

Rare Disease Research Partners

MPS House, Repton Place, White Lion Road

Amersham, Buckinghamshire, HP7 9LP, UK

t: +44 (0) 345 260 1087

e: info@rd-rp.com

w: rd-rp.com