Molecular Genetics and Metabolism Reports 43 (2025) 101210

Contents lists available at ScienceDirect

Molecular Genetics and Metabolism Reports

journal homepage: www.elsevier.com/locate/ymgmr

Benefits of early intervention with olipudase alfa in symptomatic children with acid sphingomyelinase deficiency: A sibling case-comparison study

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A B S T R A C T

Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disease with multisystem complications including neurodegeneration, hepatosplenomegaly, interstitial lung disease (ILD), bone marrow disease, and growth failure. Non-neurological manifestations of this disease are amenable to enzyme replacement therapy (ERT) with olipudase alfa in both adult and pediatric patients. In this study, we offer evidence for the role of intervention in early childhood pediatric cases. We present longitudinal follow-up for two siblings with ASMD (*SMPD1* p.R498L/p.R610del compound heterozygous genotype) who were started on ERT at different ages (ages 3 and 7, duration of treatment >4 years). After initiation of ERT, both siblings demonstrated significant radiographic improvement of interstitial lung disease (ILD), organomegaly, and growth. Notably, the younger sibling who had started earlier on treatment did not experience any deceleration in growth parameters and has normal height and weight for age, while the older sibling showed a decline in growth velocity that improved once treatment was initiated. Similarly, the older sibling showed similar-to-worse ILD and more persistent organomegaly compared to the younger sibling. Treatment has resulted in sustained improvements in both patients. These findings suggest that early intervention with ERT in ASMD may have cumulative benefits for pediatric health and motivate early screening for ASMD in pediatric patients.

1. Introduction

Acid-sphingomyelinase deficiency (ASMD; also historically known as Niemann-Pick disease A and B) is a lysosomal storage disorder caused by loss-of-function variants in the gene *SMPD1* and impaired activity of lysosomal enzyme acid sphingomyelinase. Deficiency of enzyme activity causes accumulation of sphingomyelin in the cells of the reticulo-endothelial system and causes multisystem disease. Manifestations include hepatosplenomegaly, growth failure, interstitial lung disease (ILD), bone marrow infiltration, abnormal atherogenic lipid profile and, in severe cases, neurological involvement. Growth failure is especially common in childhood-onset disease [1,2]. The degree of enzyme deficiency dictates the clinical phenotype: ASMD falls on a spectrum ranging from severe, early-onset neurodegeneration with early demise (Niemann-Pick type A); chronic combined neuro-visceral disease (type A/B); and, isolated chronic visceral/non-neurologic disease (type B).

Olipudase alfa (Sanofi) was developed as an enzyme replacement therapy (ERT) for Non CNS manifestations of ASMD. The first clinical trials in adults demonstrated promising outcomes with improvements in organomegaly, liver function tests, and lipid profiles [3,4]. Subsequently, a multinational pediatric trial of pediatric cases was initiated with 20 patients enrolled [5]. We present a single case-comparison study of two siblings enrolled at chronologically different periods in their disease course with the older sibling initiated at seven years of age and the younger sibling initiated at three years of age. Treatment improved disease biomarkers and normalized growth in both siblings. These cases suggest that early diagnosis and treatment prior to irreversible organ damage will improve outcomes in affected children. Newborn screening will be a valuable tool in identifying affected patients presymptomatically.

2. Methods

2.1. Subjects

This retrospective case study analyzes data from two siblings

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https://doi.org/10.1016/j.ymgmr.2025.101210
Received 6 January 2025; Received in revised form 23 March 2025; Accepted 24 March 2025

previously in the olipudase alfa ASCEND-Peds open-label pediatric clinical trial with extension per Sanofi (trial NCT02292654/NCT02004704) prior to continuation after FDA approval of olipudase alfa.

2.2. Participant characteristics

The older of two siblings was referred to the Lysosomal Storage Disorders Program at our institution at age 38 months for splenomegaly. Splenomegaly was initially noted at age 2; it was initially presumed due to intercurrent Parvovirus B19 infection but persisted on serial abdominal ultrasounds after resolution of infection. He received a bone marrow biopsy revealing foamy macrophages. A diagnosis of Gaucher disease was considered initially but glucocerebrosidase enzyme activity was normal. Lysosomal enzyme panel testing revealed deficient acid-sphingomyelinase activity confirming ASMD. He had no history of fevers, bleeding diatheses, recurrent infections, respiratory difficulties, or bone fractures. His family ancestry was French Canadian/Greek/Italian (maternal) and Irish/Dutch (paternal). On initial evaluation, his exam was notable for height of 90 cm (4th percentile) and weight of 13.5 kg (30th percentile). He had hepatomegaly of 3 cm below the costal margin and splenomegaly 8 cm below the costal margin. Subsequent molecular testing revealed compound heterozygosity for the pathogenic variants p.R498L & p.R610del in *SMPD1*. A complete blood count and basic metabolic panel were normal. Liver function testing was also normal except for an elevation of AST at 60 units/L (normal <50 units/L). A fasting lipid profile at age 50 months revealed high LDL cholesterol (120 mg/dL; normal <110 mg/dL) and low HDL cholesterol (29 mg/dL; normal >45 mg/dL); these measurements were consistent with an atherogenic profile typical of ASMD. He also had a low vitamin D level (17 ng/mL; normal >30 ng/mL). As clinical trials for olipudase alfa in pediatric patients were not approved at the time of diagnosis, he was initiated on standard of care treatment with dietary management, vitamin D supplementation, and anticipatory guidance given high risk for spleen injury. Monitoring included serial chest radiographs and pulmonary function testing; these examinations demonstrated interstitial lung markings and reduced diffusion capacity of carbon monoxide of the lung consistent with ILD. An ophthalmological examination did not show macular halos or cherry-red spots as seen in some patients with ASMD-B disease. He was subsequently enrolled in the ASCEND-Peds clinical trial with olipudase alfa treatment at age 7 years 5 months. Prior to initiation of treatment, his serum lyso-sphingomyelin level was 484 μg/).

Based on his brother's previous diagnosis, the patient's younger brother was tested for ASMD and the diagnosis was confirmed at 6 months of age. He had normal liver function testing at initial evaluation and follow-up. He had a normal complete blood count at age 11 months; however, follow up at 23 months of age revealed leukopenia (4.2×10^3 cells/μL; normal $>4.5 \times 10^3$ cells/μL) and thrombocytopenia (108×10^3 cells/μL; normal $>120 \times 10^3$ cells/μL). Lipid profile at 11 months also demonstrated an atherogenic profile with elevated LDL (148 mg/dL) and low HDL (30 mg/dL). He was enrolled in the ASCEND-Peds clinical trial with olipudase alfa treatment at age 3 years. Prior to initiation of treatment, his serum lyso-sphingomyelin level was 293 μg/L.

2.3. Clinical disease monitoring

While enrolled in the ASCEND-Peds clinical trial and its long-term continuation, the patients followed with regular semi-yearly to yearly in-clinic appointments. Anthropometric data were obtained by chart extraction of growth parameters from clinic visits with our program and in-network subspecialists. Volumetric spleen and liver size measurements for organomegaly were quantified via MRI and calculated as multiples of normal (assuming nominal liver and spleen sizes of 25 mL/kg and 2 mL/kg, respectively); both patients had MR imaging at baseline and yearly for at least two years post-initiation of ERT. Additionally, ILD was monitored yearly per trial protocol with high-resolution CT imaging at baseline and at least two-years post-initiation of ERT. A severity score for ILD was scored as follows: 1 for imaging with minimal subpleural lines without ground glass density; 2 for moderate involvement with mildly thickened inter- and intralobular septa and/or scattered patchy areas of ground glass density; and, 3 for severe involvement with thickened inter- and intralobular septa and/or diffuse ground glass density. Chest imaging was scored by the same radiologist (WLS). For visualization, chest imaging was selected to demonstrate the same relative plane within the thorax across timepoints and participants. Routine pulmonary function tests were performed by the same pediatric pulmonologist (AT).

3. Results

3.1. Olipudase alfa treatment in chronologically early disease promotes age-appropriate growth

At initiation of ERT, both siblings were short-for-age (older sibling: 4th percentile at 7 yr old; younger sibling: 3rd percentile at 3 yr old), and anthropometrics of both siblings improved with ERT (Fig. 1A). The older sibling's height improved by approximately 0.5 SD within 1.25 yr of treatment (but still remained at the 7th percentile) and surpassed the 10th percentile by 3.75 yr into treatment. The younger sibling showed faster catch-up growth: he surpassed the 10th percentile by two years into treatment and showed higher height velocity at any given age compared to the older sibling (Fig. 1A). Prior to initiation of ERT, both siblings had weight appropriate for age (at 17th and 27th percentile for older and younger siblings, respectively), but lower than average ($Z = -0.99$ and -0.67, respectively; Fig. 1B). Their weight improved to above the 60th percentile for age (equivalent to improvement of 1.7 and 1.3 SD). These findings suggest that early intervention is associated with improved growth over time.

3.2. Olipudase alfa treatment reverses organomegaly and improves markers of lung function

While undergoing ERT, both siblings showed longitudinal improvement in organomegaly and ILD. Initial liver and spleen sizes prior to start of treatment were grossly enlarged (liver multiple-of-normal 1.8 and 2.2; and spleen multiple-of-normal ~20 and 13 for younger/older siblings, respectively; Figs. 2A & 2B). One year into ERT, both siblings had substantially improved organ volumes. By the end of the study period, both siblings had essentially normal liver size (defined as ≤1.25 MN; Fig. 2A). However, the younger sibling achieved this goal after one year into ERT, while the older sibling required three years of ERT for liver volumes to normalize. Both siblings had improved, but persistently above-normal spleen volumes (~5 MN, normal <2.5 MN; Fig. 2B). Overall, organ size improved initiation of ERT with faster resolution of splenomegaly for the sibling treated earlier in childhood.

Prior to initiation of ERT, both siblings had severe burden of ILD involving the whole lung (Fig. 3, left-column). With ERT, the extent of disease persisted throughout the lung (Fig. 3, middle−/right columns), consistent with previous observations of ERT in older pediatric patients [5]; however, the severity of parenchymal disease improved. To assess severity over time, we developed a severity score based on degree of septal involvement and burden of ground glass opacities. This score was defined on a 1–3 scale (see Methods/Clinical Disease Monitoring). The older sibling started at initiation of ERT with a severity score of 3, while the younger sibling started with a severity score of 2. Sequential imaging at 1 and 2 years post-initiation of treatment revealed radiologic improvement in disease severity (Fig. 3, middle- and right-columns) with decreasing disease severity to a score of 1 by two years post-initiation. These findings suggest that olipudase alfa treatment improves pulmonary disease in children.

Individuals with ASMD-related ILD have abnormal pulmonary

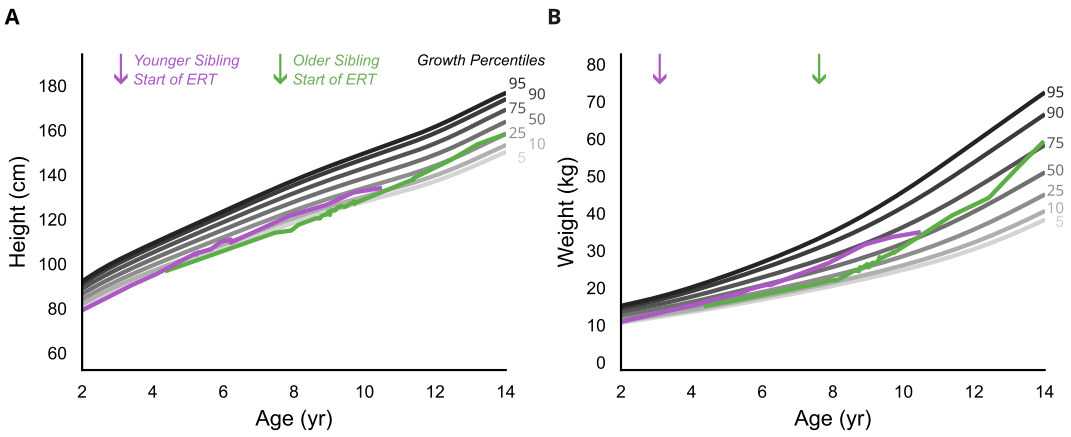

Fig. 1. Early initiation of olipudase alfa treatment improves stature in two siblings with ASMD. Trendlines for (A) height-for-age and (B) weight-for-age for the older (green) and younger siblings (purple) with percentiles as noted per CDC growth tables (age 2–20 years old). Arrows indicate respective age-of-onset of olipudase alfa/ERT.

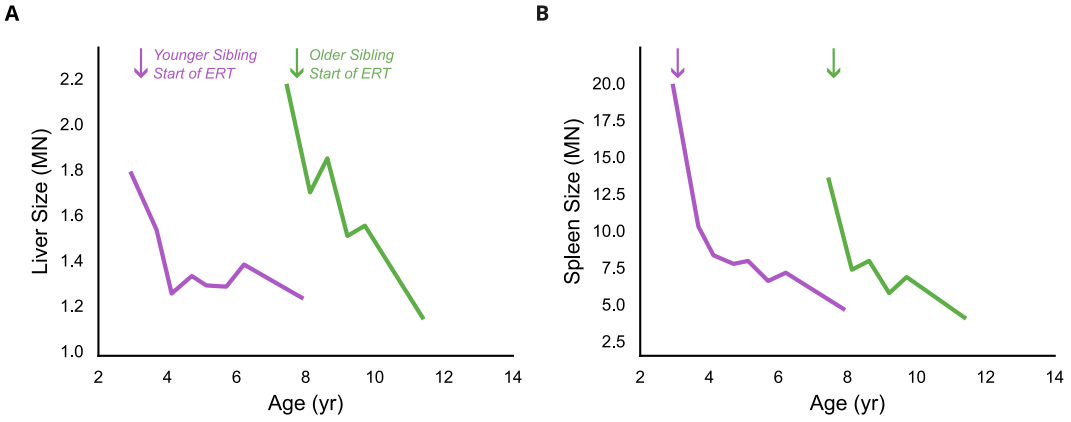

Fig. 2. Initiation of olipudase alfa in early childhood decreases organomegaly. (A) Liver size and (B) spleen size (measured as multiples-of-normal) for the older (green) and younger siblings (purple) via sequential volumetric assessment by MRI. Arrows indicate age-of-onset of olipudase alfa/ERT.

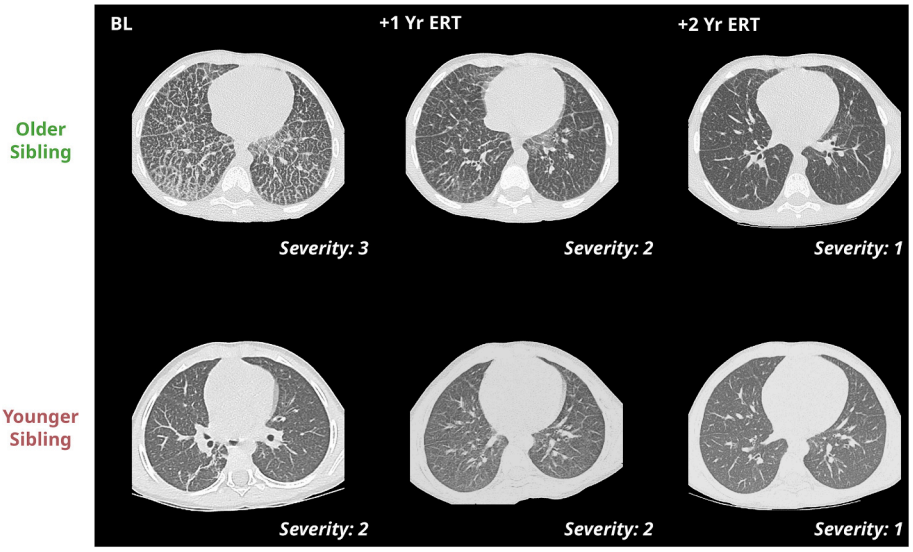

Fig. 3. Early olipudase alfa treatment improves radiographic severity ILD in patients with ASMD. Sequential assessment of ILD by high-resolution CT at baseline (BL) and at 1- and 2 years into ERT. For illustration purposes, a representative image of bilateral lower lung fields is used to visualize the same area across siblings and examinations. Excess background was stripped using automated image segmentation to isolate the body of the patient. Severity improved to a score of 1 for the both patients on ERT (see Methods for details on scoring).

function tests (PFTs) including decreased diffusion capacity of carbon monoxide of the lung (DLCO) and functional vital capacity. The older sibling was noted to have decreased DLCO (53 % of reference adjusted for hemoglobin) with improvement to 93 % within the first year of treatment (Fig. 4A). Similarly, the older sibling had decreased FVC at ~87 % at initiation of ERT with improvement to 100 % within one year of treatment (Fig. 4B). Unfortunately, the younger sibling did not complete PFT evaluation due to inability to tolerate PFT testing at age of enrollment and limited follow-up during the COVID-19 pandemic. The older sibling's recovery of DLCO and FVC suggests that olipudase alfa treatment reverses pulmonary function defects caused by ASMD.

Serial serum lyso-sphingomyelin levels were obtained to monitor both patients' response to therapy; both siblings experienced a sustained >80 % decrease in serum lyso-sphingomyelin within the first 6 months of initiation of ERT (Fig. 5).

4. Discussion

In this report, we investigated the role of early ERT on chronic visceral ASMD/ASMD-B by comparing two affected siblings who initiated ERT at different ages. Multiple parameters of disease involvement showed improvement, including height, organ size, and lung disease burden; these findings coincide with those noted in the one major pediatric study of pharmacokinetics and safety of ERT in ASMD [5] as well as prior trials in adults [3,4]. Notably, treatment with olipudase alfa in the sibling with earlier age of initiation resulted in improved growth at any age and faster resolution of hepatomegaly compared to the other sibling. These findings not only confirm general benefits of ERT in pediatric ASMD-type B patients, but also suggest that earlier initiation of ERT provides improved and cumulative benefits for childhood health and development.

An important limitation of this study is the small sample size. Even in siblings the severity of ASMD can vary so a single sibling pair may not be sufficient to draw any particular conclusions. Given our reported benefits, we hope that this longitudinal assessment motivates further assessment of the role of ERT in early-onset pediatric ASMD type B.

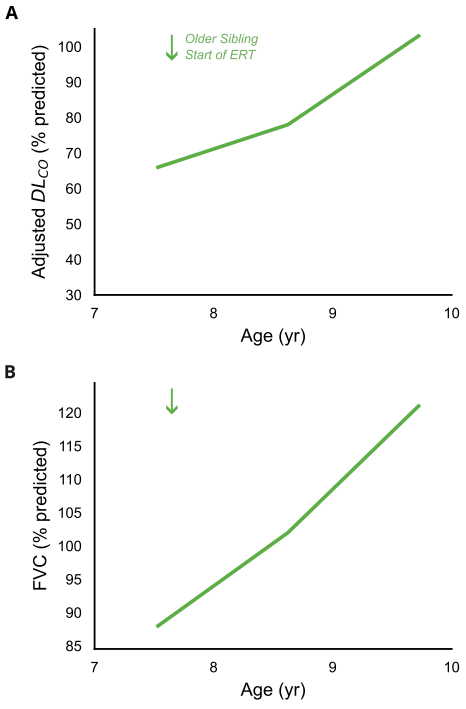

Fig. 4. Olipudase alfa treatment improves pulmonary function testing in ASMD patients with ILD. Sequential (A) diffusing capacity of lungs for carbon monoxide (DLCO) adjusted for age & body hemoglobin, and (B) functional vital capacity (FVC) for the older sibling at baseline and yearly thereafter.

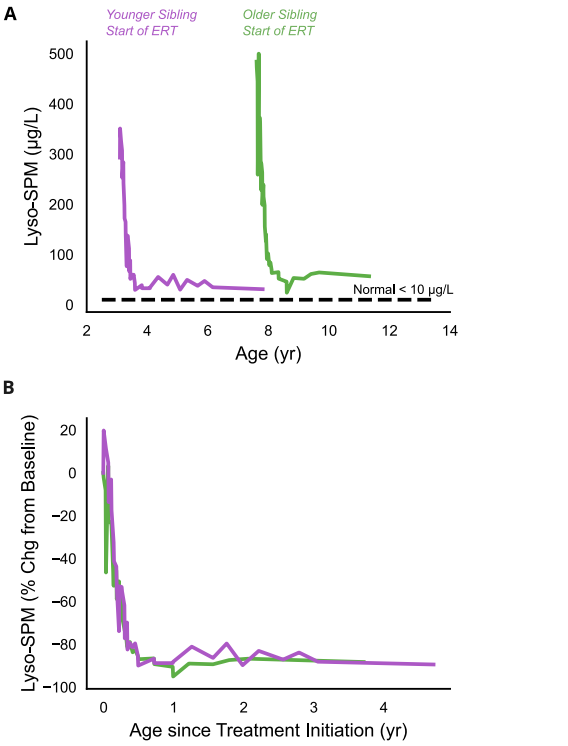

Fig. 5. Lyso-sphingomyelin (Lyso-SPM) decreases during ERT. (A) Absolute Lyso-SPM at absolute age for each sibling. (B) Percent change from baseline in Lyso-SPM since time treatment initiated.

After successful clinical trials in adults and children, olipudase alfa (Xenpozyme®; Sanofi) was approved by the FDA in 2022 as an ERT for management of non-neurological manifestations of ASMD [6,7]. In clinical trials of adult patients with ASMD- type B, olipudase alfa reversed elevations in serum biomarkers (i.e. lyso-sphingomyelin) and improved markers of organ disease (such as hepatosplenomegaly, liver function tests; lipid profile; DLCO; and bone marrow function) [3,4,8]. A phase 2 safety trial in pediatric patients reported endpoint data supporting olipudase alfa treatment in ameliorating these same markers of disease [5]. Using sibling-paired data, this is the first study providing evidence that early initiation of ERT improves clinical outcomes and may prevent some disease manifestations.

This case comparison illustrates the role for early monitoring and treatment with ERT in cases with high disease morbidity. To be clear, these siblings had ASMD type B and did not have neurological involvement associated with the more severe end of the ASMD spectrum. However, outside the standard classification of ASMD severity based on presence of neurological symptoms (i.e. ASMD-A vs ASMD-A/B or B disease), individuals with ASMD-B also fall on a spectrum with variable age-of-onset and severity of chronic visceral disease [2,9]. By known criteria for visceral ASMD [2], these patients' disease classify as moderate-to-severe, and more significant multisystem disease burden than the other patient with the same genotype (p.R610del/p.Arg498Leu) described in the literature [2]. It is likely that any child with significant disease burden would benefit from early initiation of ERT. Conversely, some ASMD typeB patients along within the milder ASMD type B spectrum may have less disease burden and may not need early ERT initiation compared to others; identifying this distinction requires close clinical surveillance and clinical judgement

Including the current study, the increasing evidence for efficacy of olipudase alfa in childhood-onset ASMD-B raises an important question of whether early screening should be implemented for this condition. Early screening (i.e. on newborn screening panels) is reasonable for

conditions that have increased early-life morbidity and mortality if left undiagnosed in early life; have scalable biomarkers that facilitate screening; and, have a known treatment. Symptoms of ASMD-B manifest in early childhood (within the first 2–3 years of life) including impaired childhood growth [1]; these observations coincide with the observations in this report. Acid sphingomyelinase activity measurement is a readily available marker for disease that is currently used for newborn screening in 2 states in the US (Illinois [10], New Jersey) and is included on an expanded pilot newborn screening panel in New York State (ScreenPlus) [11] and in pilot newborn screening studies in the Shanghai, China [12]. Data from two of these prospective screening programs suggest that ASMD is up to two times more prevalent than previously noted [10,12]. Ongoing work also suggest that plasma lyso-sphingomyelin is a useful biomarker for identifying patients with ASMD; lyso-sphingomyelin can be tested from serum or dried blood spot samples [13,14] and its level may correlate with clinical severity [15]. Overall, ASMD is a screenable disorder with early-life morbidity, and early treatment has promising effects for alleviating visceral manifestations of ASMD faster. Expansion of early screening will assist in identification of pre-symptomatic patients and additionally those whom ERT for ASMD may prevent disease sequelae.

We present a single case-comparison study of two siblings treated at chronologically different periods in their disease course. Treatment improved disease biomarkers and normalized growth in both siblings and more rapid improvement in the younger sibling started earlier in childhood. These cases suggest that early diagnosis and early treatment initiation prior to irreversible organ damage will improve outcomes in affected children. Newborn screening will be a valuable tool in identifying presymptomatic patients, and the clinical benefits of early diagnosis, monitoring, and treatment justifies the addition of ASMD to the Recommended Uniform Screening Panel for universal newborn screening.

Data sharing statement

As per original consent for this trial, anonymized data are freely available upon request to the corresponding author.

CRediT authorship contribution statement

Drew B. Sinha: Writing – original draft, Visualization, Formal analysis, Data curation, Conceptualization. **William L. Simpson:** Writing – review & editing, Visualization, Methodology. **Andrew Ting:** Investigation. **Louise Bier:** Writing – review & editing, Resources, Project administration. **Mary Freeman:** Writing – review & editing, Resources, Project administration. **Lauren Mackenzie Mason:** Writing – review & editing, Resources, Project administration. **George A. Diaz:** Writing – review & editing, Project administration, Investigation, Funding acquisition. **Jaya Ganesh:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Conceptualization.

Ethics statement

The Icahn School of Medicine Institutional Review Boards (IRB) approved the study as described herein (IRB #15–00215). Patients/parents provided written informed consent prior to screening. All clinical data were de-identified. The study adhered to the principles set out in the Declaration of Helsinki.

Funding

Sanofi provided funding for clinical trial efforts and longitudinal patient Lyso-SPM data collected during the ASCEND-Peds trial & open-label extension. Sanofi was not involved in data analysis/interpretation nor manuscript preparation prior to submission. In review, Sanofi provided input on manuscript content for factual accuracy.

Declaration of competing interest

DBS has no conflicts of interest to declare. WLS was a participating investigator in the ASCEND-Peds trial and has been a consultant for Sanofi on other clinical trials for Gaucher disease. AT was a participating investigator in the ASCEND-Peds trial. LB has no conflicts of interest to declare. MF has no conflicts of interest to declare. LMM has no conflicts of interest to declare. GAD was a principal investigator in Sanofi-sponsored trials and has received honoraria and consulting fees from Sanofi; he was a primary investigator in the olipudase alfa ASCEND-Peds clinical trial. JG is a principal investigator in Sanofi-sponsored trials and has received research funding and honoraria from Sanofi; she is also a site investigator in the olipudase alfa ASCEND-Peds clinical trial open-label extension.

Acknowledgments

The authors thank the family discussed in this report for participation in this study.

Data availability

Data will be made available on request.

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