Olipudase alfa-rpcp (Xenpozyme)

A Clinical Dose Escalation Strategy for a Rare Disease Drug Program

Prior to reading this case study, please refer to the LEADER 3D Case Study User Guide as an informational resource. Please note this case study is not intended or designed to provide specific strategies for obtaining product approval. **Rare disease drug development is not one-size-fits-all.** The kind and quantity of data in each rare disease application will be different based on the unique considerations of each development program and must therefore be assessed on a case-by-case basis.

Introduction

This case study examines the clinical dose escalation strategy supporting the U.S. Food and Drug Administration's (FDA) approval of olipudase alfa-rpcp (Xenpozyme). For further details on this case study, please refer to the Integrated Review.

Olipudase alfa-rpcp is an enzyme replacement therapy used to treat Acid Sphingomyelinase Deficiency (ASMD), a rare autosomal recessive lysosomal disorder that results in liver and respiratory failure, which are the primary causes of death in patients with ASMD. In this case study, the Applicant engaged with the FDA, early and throughout development to leverage:

- Nonclinical data to inform a dose escalation strategy using the limited number of participants with ASMD in this drug development program (**Figure 1**).
- Early phase clinical data to achieve an optimal dose regimen.

Figure 1: *Summary of Studies and Participant Size Included this Case Study.*[1]

Study Protocol	n
Phase 1a, single dose, SPHINGO00605	11
Phase 1b, DFI13412	5
Phase 1/2, DFI13803	20
Phase 2/3, DFI12712	36

This case study describes dose escalation studies that incorporated data from multiple sources, including safety, toxicity, and pharmacokinetics. Dose selection is an important feature of rare disease trial design and generally, the effects of more than one dose should be studied. Given the limited number of participants, multiple data sources should be used to select the appropriate dose for efficacy trials to maximize therapeutic effect while minimizing toxicity.[2] Crossover or seamless phase two-three designs, including those with parallel groups, may be considered for dose optimization and efficacy assessment in the same trial.[3] Additionally, integrated analyses of all data from other clinical studies or "model-informed" approaches can aid in dose selection.[2]

FDA Guidance Corner

Note: The FDA Guidance Corner includes excerpts of draft FDA guidance documents which, when final, will represent the Agency's current thinking on topics within the case study. For up-to-date guidance documents, please search Guidance Documents for Rare Disease Drug Development | FDA.

In this case study, the Applicant engaged with the FDA early in the planning for their new drug application. Meeting with the FDA early in the drug development process is crucial so that potential issues may be addressed prior to pivotal clinical studies.

Draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (September 2023)

When a meeting is needed, a written request must be submitted to the FDA via the electronic gateway, or to CDER via the CDER NextGen Portal, as applicable. Requests should be addressed to the appropriate center and review division or office, and if previously assigned, submitted to the relevant application (e.g., investigational new drug application [IND], new drug application [NDA], biologics license application [BLA], pre-application tracking system [PTS] Number [CBER]).

If necessary, noncommercial IND holders may also submit the meeting request via the appropriate center's document room.

[1] Figure 1 was generated using information provided in the FDA Integrated Review for olipudase alfa-rpcp (Xenpozyme), BLA-761261.

[2] Wang, L, J Wang, J Feng, M Doi, S Pepe, M Pacanowski, and RN Schuck, 2022, Dose-Finding Studies in Drug Development for Rare Genetic Diseases, Orphanet J Rare Dis, 17(1).

[3] Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023).

Introduction to the Rare Condition

ASMD is a rare (1 in 250,000) autosomal recessive lysosomal disorder resulting from biallelic pathogenic variants (mutations) in the sphingomyelin phosphodiesterase 1 (SPMD1) gene. These variants cause a shortage of the SPMD1-encoded acid sphingomyelinase (ASM) enzyme, which is responsible for breaking down sphingomyelin (SPM) into ceramide and phosphocholine. Sphingomyelin (SPM) is a lipid found in cell membranes, and mutations in the SPMD1 gene result in its accumulation in various organs and tissues, including the liver, spleen, lungs, and brain (**Figure 2A**).

The severity of the disease varies depending on the residual enzyme activity and the age of disease onset. Based on disease severity, ASMD is classified as Type A (most severe), Type B (least severe), or Type A/B (intermediate severity). Liver and respiratory failure are the primary causes of death in patients with ASMD.

Treatment Mechanism of Action

Before FDA approval of olipudase alfa-rpcp, there were no approved therapies for the treatment of ASMD. Olipudase alfa-rpcp is a recombinant human ASM protein that replaces the faulty ASM enzyme and reduces SPM accumulation in patient's organs. Reductions in SPM accumulation result in decreased accumulation of fats within cells and improved ASMD symptoms (e.g., improved lung function and reduced spleen volume) as shown in **Figure 2B.**[4]

FDA Guidance Corner

In this case study, the Applicant engaged with the FDA early in the planning for their new drug application for discussion on considerations specific to their drug development plans. Meeting with the FDA to discuss development plans is crucial so that potential issues may be addressed prior to pivotal clinical studies.

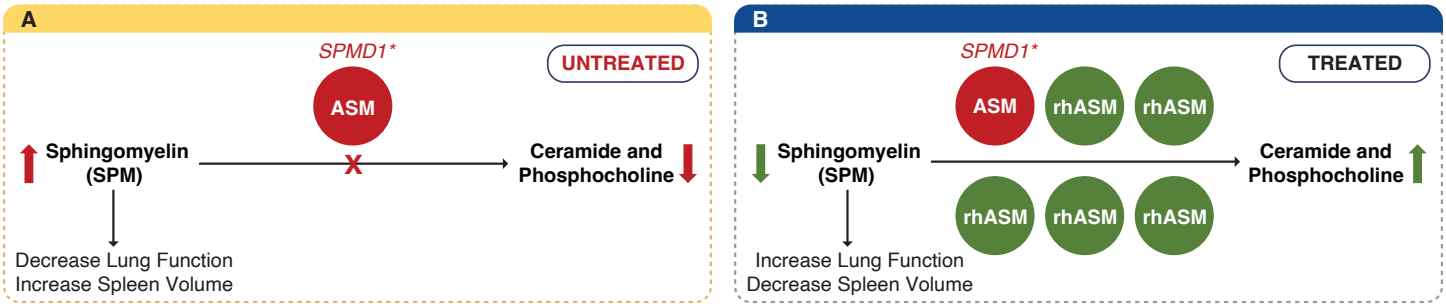
This guidance highlights important considerations in rare disease drug and biologics development:

Guidance for industry *Rare Diseases Considerations for the Development of Drugs and Biological Products* (December 2023)

Many rare diseases are serious conditions with no approved treatments, leaving a substantial unmet medical need for patients. FDA recognizes that rare diseases are highly diverse with varying prevalence, rates of progression, and degrees of heterogeneity that can affect both clinical manifestations and disease course even within a condition.

Further complexity is added depending on what is known about a disease's natural history and pathophysiology. As such, no one program can be designed exactly like another. FDA is committed to helping sponsors create successful drug development programs that address the particular challenges posed by each rare disease and encourages sponsors to engage early with the Agency to discuss their drug development program.

Figure 2: *A simplified overview of the effects of Acid Sphingomyelinase Deficiency (ASMD) and its treatment.* ***A****. Untreated Acid Sphingomyelinase Deficiency (ASMD): Acid sphingomyelinase (ASM) (red circle) is encoded by the sphingomyelin phosphodiesterase 1 (SPMD1) gene (red italics). Pathogenic variants in the SPMD1 gene (asterisk) limit the production of ASM, which is responsible for breaking down sphingomyelin (SPM) into ceramide and phosphocholine. The accumulation of SPM in different tissues causes decreased lung function and increased spleen volume.* ***B****. Olipudase alfa-rpcp treatment: Olipudase alfa-rpcp (recombinant human ASM; rhASM [green circle]) replaces the deficient ASM enzyme, allowing SPM to be broken down into ceramide and phosphocholine, which helps lung function and decrease spleen volume.*



[4] Animal model information located on pg. 79 of the Integrated Review.

Animal Model Considerations to Inform Dose-Finding Studies

The selection of appropriate animal models can be helpful to establish whether an investigational drug is reasonably likely to produce the intended clinical benefit in humans and may aid in initial dose selection for clinical trials.

The sponsor of an investigational drug development program should provide scientific justification that the animal model is translational, meaning that it exhibits key characteristics of the human disease or condition of interest and is appropriate to use with the investigational drug.

The animal model used in this case study was accepted by the FDA because:

- The ASM knockout (KO) mouse is a widely accepted and used model of ASMD.[5]
- ASMKO mice homozygous for disruption of the ASM gene lack ASM activity and accumulate SPM in a manner similar to humans with ASMD.[6]
- SPM reduction was dose- and duration-dependent when single doses of either native mouse (murine) ASM or olipudase alfa-rpcp (at 1.0, 3.0, or 5.0 mg) were administered to ASMKO mice.

Highlights

- In this study, the starting dose was based on no observed adverse effect level (NOAEL) data from the ASMKO mouse model.
- The titration upward to the maintenance dose of olipudase alfa-rpcp is based on the debulking of stored SPM.
- The unique safety issues specific to this disease (i.e., ceramide toxicity) necessitated the use of a non-traditional assessment of toxicity. Because rapid debulking of stored SPM can produce ceramide toxicity, a nonclinical study in the ASMKO mouse model was conducted, and additional safety data were obtained from a healthy animal species. Collectively, these data were used to evaluate the safety of regimens intended to support a gradual debulking regimen for clinical trials.
- For questions about selecting the appropriate animal model for a rare disease drug development program, including selection of healthy animal models for toxicology studies, please contact the FDA for guidance.

FDA Guidance Corner

This case study highlights the Applicant's dose escalation plan which was informed by certain safety considerations. This guidance outlines best approaches for nonclinical safety studies:

Guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)

The development of a pharmaceutical is a stepwise process involving an evaluation of both animal and human efficacy and safety information. The goals of the nonclinical safety evaluation generally include a characterization of toxic effects with respect to effects on target organs, including the dose-exposure relationship to toxicity, and, when appropriate, potential for reversibility from toxicity. This information is used to estimate an initial safe starting dose and dose range for the human trials and to identify parameters for clinical monitoring for potential adverse reactions. The nonclinical safety studies, although usually limited at the beginning of clinical development, should be adequate to characterize potential adverse reactions that might occur under the conditions of the clinical trial to be supported.

This case study highlights the Applicant's dose escalation plan, and the considerations made in selecting the safest starting dose. This guidance outlines a process for deriving the maximum recommended starting dose (MRSD) for first-in-human clinical trials:

Guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005)

The first step in determining the MRSD is to review and evaluate the available animal data so that a no adverse effect level (NOAEL) can be determined for each study. Several definitions of NOAEL exist, but for selecting a starting dose, the following is used: the highest dose level that does not produce an increase in adverse effects in comparison to the control group. In this context, adverse effects that are biologically significant (even if they are not statistically significant) are considered in the determination of the NOAEL. The NOAEL is a generally accepted benchmark for safety when derived from appropriate animal studies and can serve as the starting point for determining a reasonably safe starting dose of a new therapeutic in healthy (or asymptomatic) human volunteers.

[5] Horinouchi, K, S Erlich, DP Perl, K Ferlinz, CL Bisgaier, K Sandhoff, RJ Desnick, CL Stewart, and EH Schuchman, 1995, Acid Sphingomyelinase Deficient Mice: A Model of Types A and B Niemann-Pick Disease, Nat Genet, 10(3):288-293.

[6] For more information regarding the selection of the animal model for this approval, please see the Integrated Review on page 79.

The multiple within-participant human dose escalation strategy was based on dose-dependent reductions of in-tissue SPM.[7] Because rapid debulking of accumulated SPM can produce acute severe ceramide toxicity, the studies in the ASMKO mouse model also evaluated the safety of regimens intended to support a gradual debulking regimen for clinical trials.

First-in-Human Dose Escalation Trial Design (SPHINGO00605)[8]

The safety and tolerability of olipudase alfa-rpcp was assessed in SPHINGO00605, a first-in-human, single ascending dose (SAD),[9] phase 1a trial in a total of 11 adult participants with Type B ASMD (Figure 3) who received olipudase alfa-rpcp in five separate dose cohorts.

The initial dose, 0.03 mg/kg, was chosen based on a 10-fold safety factor in comparison to the single-dose NOAEL in the ASMKO mouse animal model and was administered to three participants. Subsequently, the Applicant increased the dose in a stepwise manner to 0.1 mg/kg (three participants), 0.3 mg/kg (two participants), 0.6 mg/kg (two participants), and 1.0 mg/kg (one participant), as shown below in Figure 3.

SPHINGO00605 was terminated after dosing of 1.0 mg/kg because the participant experienced hyperbilirubinemia and constitutional symptoms, such as nausea, vomiting, pyrexia, fatigue, and/or pain.

After analyzing the pattern of adverse reactions that occurred during this trial, the Applicant identified the **maximum tolerated starting dose to be 0.6 mg/kg**, allowing for the start of the multiple ascending dose (MAD)[8] phase of the trial in adult participants.

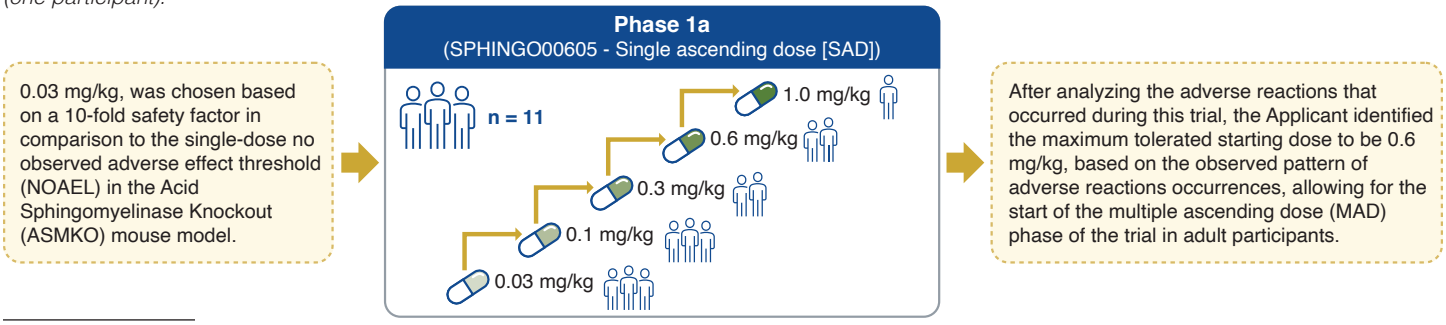
FDA Guidance Corner

This case study highlights the Applicant's nonclinical study approach for dose-finding. This guidance provides important considerations in rare disease drug and biologics development:

Guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023)

- The data generated from nonclinical studies are important to the design of early-phase clinical investigations, particularly for defining the toxicity profile, selecting the starting clinical dose, dose escalation plan, dosing regimen, and route of administration.
- Generally, healthy animals are used in traditional toxicology testing and, in most circumstances, would be used to support initiation of clinical investigations.
- Toxicology testing in an animal model of disease may contribute to the nonclinical support for clinical investigations but usually will not substitute for toxicology testing in healthy animals. However, safety evaluation in an animal model may be needed when drug toxicity is predicted to be more severe in the presence of underlying disease.
- When an animal model of the disease is available, pharmacology studies in cultured cells and animal models of disease may contribute to understanding the actions of the drug on disease pathophysiology, inform safety in the context of that disease, and guide plans for measuring biological effects in patients.

Figure 3: *Olipudase alfa-rpcp clinical trial dose schematic and justifications for phase 1a. The Applicant gave a single dose injection to 11 participants, increasing the dose in a stepwise manner starting at 0.03 (three participants) to 0.1 mg/kg (three participants), 0.3 mg/kg (two participants), 0.6 mg/kg (two participants), and 1.0 mg/kg (one participant).*[10]



[7] For information on dose conversion from animal model to humans, please refer to Integrated Review.

[8] For more information on First-in-Human dose escalation trial design (e.g., selection of doses), please refer to Integrated Review on page 29.

[9] Single Ascending Dose (SAD): Participants only receive one dose of study drug. Multiple Ascending Dose (MAD): Participants receive more than one dose of the study drug.

[10] Figure 3 was generated using information provided in the FDA Integrated Review for olipudase alfa-rpcp (Xenpozyme), BLA-761261.

Highlights

- The Applicant identified the maximum starting dose of olipudase alfa-rpcp, by using histopathology data related to liver injury, which was collected in the ASMKO animal model.
- The Applicant used a dose escalation strategy in the SAD phase (i.e., Phase 1a) of the clinical trial due to the unique safety issues specific to this disease (i.e., ceramide toxicity).

Dose Escalation (DFI13412)[11]

To better understand the safety and tolerability of **repeated administration** of olipudase alfa-rpcp in adults with ASMD, five participants were enrolled in the phase 1b (DFI13412) trial which used a multiple within-partcipant dose escalation strategy (**Figure 4**). The Applicant noted that, in the ASMKO mouse model, this debulking method reduced the in-tissue SPM accumulation and limited the toxicity associated with ceramide release.

The starting dose for the phase 1b trial was 0.1 mg/kg, the highest dose in the phase 1a trial, SPHINGO00605, that did not show any treatment-related AEs, and based on nonclinical findings, was predicted to efficiently reduce SPM in the lungs of adults with ASMD. To maintain the reduction of SPM, the Applicant chose the intravenous (IV) dosing frequency of every two weeks—a dosing regimen also based on nonclinical study results.

The within-participant dose escalation was 0.1, 0.3, 0.3[12], 0.6, 1.0, 2.0, and 3.0 mg/kg every two weeks for 14 weeks followed by a maintenance dose of 3.0 mg/kg every two weeks until Week 26. The maintenance dosage of 3.0 mg/kg was based on nonclinical results predicted to efficiently reduce SPM in the kidney, liver, and spleen of adult patients with ASMD. After the treatment period, participants were enrolled in the long-term open-label clinical trial LTS13632.

Adult participants with ASMD tolerated the gradual, within-participant dose escalation protocol well, and no major or severe AEs or deaths were reported, allowing the Applicant to initiate the phase 2/3 trial.

FDA Guidance Corner

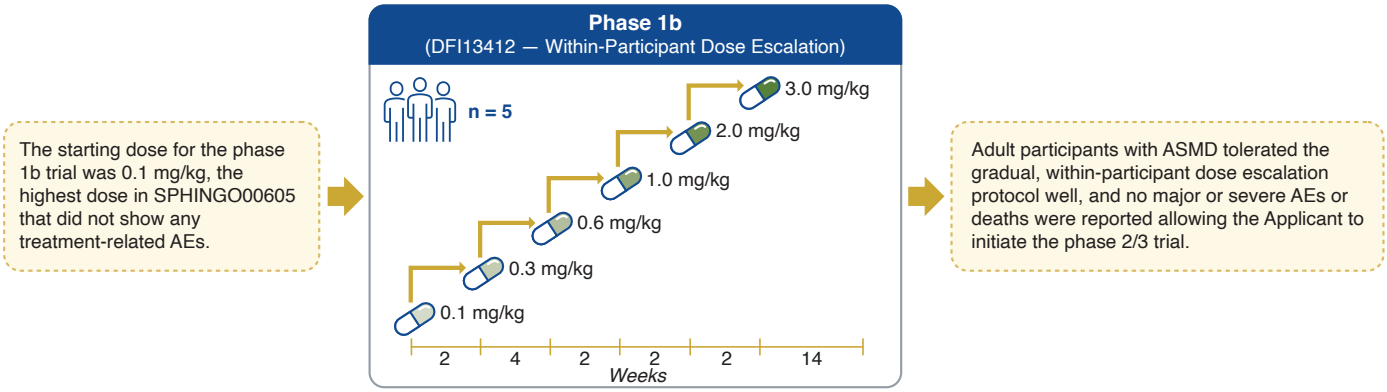
This case study highlights the Applicant's dose escalation plan which was informed by certain safety considerations.

This guidance outlines safety approaches to consider when designing a dose escalation strategy:

Guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010)

Human clinical trials are conducted to investigate the efficacy and safety of a pharmaceutical, starting with a relatively low systemic exposure in a small number of subjects. This is followed by clinical trials in which exposure to the pharmaceutical usually increases by duration and/or size of the exposed patient population. Clinical trials should be extended based on the demonstration of adequate safety in the previous clinical trial(s), as well as on additional nonclinical safety information that becomes available as clinical development proceeds.

Figure 4: *Olipudase alfa-rpcp clinical trial dose schematic and justifications for phase 1b. The Applicant gave each of the five participants a within-participant dose escalation every two weeks followed by a maintenance dose of 3.0 mg/kg every two weeks until Week 26.*[13]



[11] For more information (e.g., selection of doses), please refer to the Integrated Review on page 29.

[12] The repeat dosing was to decrease toxicity from ceramide release.

[13] Figure 4 was generated using information provided in the FDA Integrated Review for olipudase alfa-rpcp (Xenpozyme), BLA-761261.

Highlights

- The starting dose for the phase 1b trial (0.1 mg/kg) was based on the highest dose in the first-in-human trial (SPHINGO00605) that did not show any treatment-related AEs.
- The dosing frequency (every 2 weeks) was based upon the demonstration of maintained reduction of sphingomyelin in the nonclinical studies. Repeating multiple within-participant doses was based on the demonstration of less toxicity (associated with ceramide release) in the ASMKO animal model.
- The target dose (3.0 mg/kg), based on nonclinical study results, was selected because it was expected to effectively clear sphingomyelin from the lungs in patients with ASMD.

Adult Clinical Trial Design for DFI12712 (ASCEND)[14]

To further expand the investigation of dosing and efficacy for olipudase alfa-rpcp, the Applicant conducted a phase 2/3, multicenter, repeat-dose, clinical trial. The trial included two consecutive time periods: a 52-week randomized placebo-controlled, double-blind primary analysis period (PAP) followed by an extension treatment period (ETP).

In the PAP, 36 participants with Type B ASMD were randomly assigned in a 1:1 ratio to receive either IV infusions of olipudase alfa-rpcp or placebo every two weeks (**Figure 5**). Participants in the active treatment group underwent a dose escalation of olipudase alfa-rpcp starting from 0.1 mg/kg and incrementally increasing every two weeks to 0.3, 0.3[15], 0.6, 0.6[16], 1.0, 2.0, and 3.0 mg/kg over the initial 14 weeks and then received a maintenance dose at 3.0 mg/kg (or the maximum tolerated dose if the 3.0 mg/kg dose was not tolerable) for the remainder of the PAP and ETP.

The primary objective of the ASCEND trial was to assess the efficacy of olipudase alfa-rpcp by measuring changes from baseline to Week 52 in two endpoints:

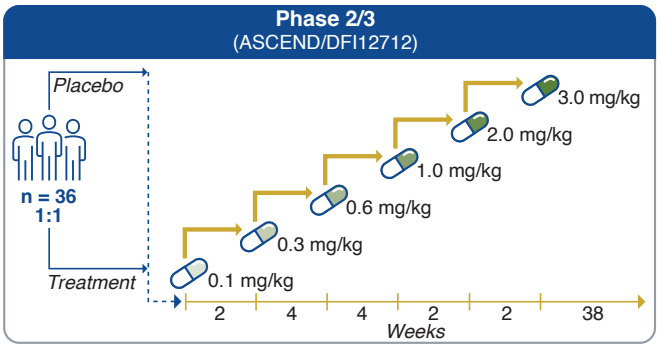
- Infiltrative lung disease evaluated by diffusing capacity of the lungs for carbon monoxide (DLCO), and;
- Spleen volume measured by magnetic resonance imaging (MRI) along with participant perception related to spleen volume as measured by splenomegaly-related score (SRS).

Key Takeaways

- Repeat dosing was utilized in the dose selection study design to reduce toxicity from ceramide release.
- In the ASCEND trial, a second dose of 0.6 mg/kg was implemented to provide an even more gradual within-patient SPM debulking regimen, thereby mitigating the toxicity associated with ceramide release.
- FDA can help advise sponsors on how best to incorporate evidence from dose selection studies into the overall trial design. Therefore, alignment with FDA should be sought early (i.e., before conducting the adequate and well-controlled investigation) with regard to the choice of endpoints in the statistical analysis plan.

Figure 5: *Olipudase alfa-rpcp clinical trial dose schematic and justifications for phase 2/3. The Applicant randomly assigned 36 participants with Type B ASMD in a 1:1 ratio to receive either IV infusions of olipudase alfa-rpcp or placebo every two weeks. The participants who received olipudase alfa-rpcp had a within-participant dose escalation for 14 weeks followed by a 38-week maintenance dose of 3.0 mg/kg.*[17]

Adult participants with ASMD tolerated the gradual, within-participant dose escalation protocol well, and no major or severe AEs or deaths were reported, allowing the Applicant to initiate the Phase 2/3 trial. Treatments were administered every two weeks.



The primary objective of the ASCEND trial was to assess the efficacy of olipudase alfa-rpcp by measuring changes from baseline to Week 52 in two endpoints:

1. Infiltrative lung disease evaluated by diffusing capacity of the lungs for carbon monoxide (DLCO) and;
2. Spleen volume measured by magnetic resonance imaging (MRI) along with participant perception related to spleen volume as measured by splenomegaly related score (SRS).

[14] For more information on adult clinical trial design (e.g., endpoints, inclusion/exclusion criteria, statistical analysis plan), please refer to the Integrated Review on page 32.

[15] The repeat dosing was to decrease toxicity from ceramide release.

[16] The repeat dosing was to decrease toxicity from ceramide release.

[17] Figure 5 was generated using information provided in the FDA Integrated Review for olipudase alfa-rpcp (Xenpozyme), BLA-761261.

Pediatric Clinical Trial Design for DFI13803 (ASCEND-Peds)[18]

The Applicant was able to expand their investigation into pediatric participants due to the similarity of disease pathogenesis and anticipated response to olipudase alfa-rpcp between adults and pediatric participants with ASMD, the mechanism of action of olipudase alfa-rpcp, and use of the same endpoints as the ASCEND trial. The ASCEND-Peds trial was a phase 1/2 open-label, multicenter, repeat-dose trial conducted in participants under 18 years of age with non-central nervous system manifestations of ASMD and measured the same efficacy endpoints as the ASCEND trial. The trial enrolled a total of 20 participants with Type B or A/B ASMD (adolescents 12 to <18 years, n=4), children (2 to <12 years, n=15), and infants (<2 years, n=1).[18] These participants received IV infusions of olipudase alfa-rpcp every two weeks for a total duration of 64 weeks.

During the investigation, the participants underwent dose escalation of olipudase alfa-rpcp (**Figure 6**) starting from 0.03 mg/kg and gradually increasing to 0.1, 0.3, 0.3, 0.6, 0.6, 1.0, 2.0, and 3.0 mg/kg within the first 16 weeks or longer. The lower starting dose and the slower dose escalation schedule for pediatric participants was selected for safety reasons as the drug can create toxicity from ceramide release. The pediatric participants were then maintained on 3.0 mg/kg (or the maximum tolerated dose) for the remainder of the 64-week trial. After completing the 64-week treatment period, participants had the option to enroll in the long-term trial LTS13632.

The focus of the ASCEND-Peds was to evaluate the safety and tolerability of olipudase alfa-rpcp in pediatric participants. The Applicant also measured the efficacy endpoints of spleen volume expressed as multiples of normal (MN), percent predicted DLCO, and liver volume (MN).

Figure 6: *Olipudase alfa-rpcp clinical trial dose schematic and justifications for pediatric phase 1/2 trial. The Applicant enrolled a total of 20 participants with Type B or A/B ASMD who were divided into three age cohorts: 4 to the adolescent cohort (12 to <18 years), 9 to the child cohort (6 to <12 years), and 7 to the infant/early child cohort (<6 years). The participants received a within-participant dose escalation for 16 weeks followed by a 48-week maintenance dose of 3.0mg/kg.*[19]

FDA Guidance Corner

In this case study, the Applicant conducted a dose escalation scheme in pediatric participants. This guidance which, when final, will reflect the Agency's current thinking, provides considerations for planning clinical studies in a pediatric population:

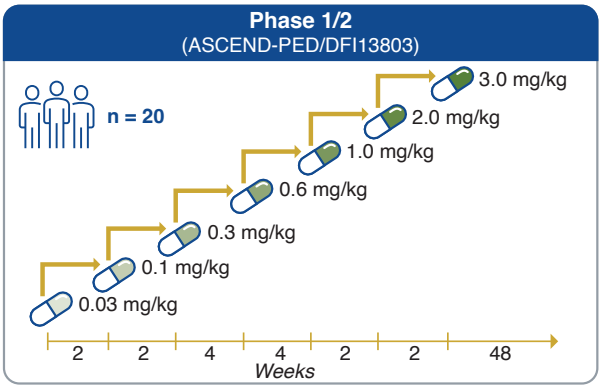
Draft guidance for industry *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations* (May 2023)

Well-designed early phase dosing studies are critical to a successful pediatric development program. Inadequate dose-ranging studies in the past have contributed to failed efficacy studies and have delayed or prevented approval in pediatric age groups. Modeling and simulation, when appropriate, should be used to inform dose selection and/or trial design. Confirmatory PK studies is critical, particularly in younger children, in whom dosing is not necessarily predictable based on the experience in adult or adolescents.

Key Takeaways

- In this specific case study, the Applicant was able to perform an open-label pediatric clinical trial for the drug by extrapolation from the adult study due to (a) similarity in disease pathogenesis, and (b) anticipated response to therapy.
- Apart from a lower starting dose and slower dose ascension, the Applicant used a similar dose escalation as the adult study.

The lower starting dose and the slower dose escalation schedule for pediatric participants was selected for safety reasons as the drug can create toxic metabolites.



The focus of ASCEND-Peds was to evaluate the safety and tolerability of olipudase alfa-rpcp in pediatric subjects. The Applicant also measured the primary endpoints spleen volume expressed as multiples of normal (MN), percent predicted DLCO, and liver volume (MN).

[18] For more information on pediatric clinical trial design (e.g., inclusion/exclusion criteria for pediatric participants), please refer to the Integrated Review on page 59-60.

[19] Figure 6 was generated using information provided in the FDA Integrated Review for olipudase alfa-rpcp (Xenpozyme), BLA-761261.

FDA Conclusion of ASCEND and ASCEND-Peds Trials

Dose Selection of Olipudase alfa-rpcp in Adult and Pediatric Participants

Carefully performed dose selection studies contributed to the design of the ASCEND investigation, an adequate and well-controlled investigation demonstrating the efficacy of olipudase alfa-rpcp.

FDA concluded that the results were clinically meaningful because progressive loss of pulmonary function and liver failure are the most common causes of death in patients with ASMD. In addition, FDA allowed for partial extrapolation of positive adult ASCEND trial results to be used for pediatric populations due to similar disease pathogenesis, drug mechanism of action, and comparability of efficacy results (i.e., change from baseline for endpoints in common between the adult and pediatric studies).[20]

Conclusion

The Sponsor used a well understood disease pathology, clinically meaningful and measurable endpoints, and a nonclinical animal model, to build a drug development program that enabled them to select doses for the approval of olipudase alfa-rpcp for ASMD. This case study demonstrates that, similar to more common disorders, sponsors can perform a well-defined dose selection trial for rare diseases with inherently small patient populations.

Key Takeaways

- Effective dose-finding strategies can be used in rare diseases.
- The ASMKO mouse model is a well-defined animal model that recapitulates the disease and was used to inform the initial safety assessment for the phase 1a clinical trial.
- The design of the dose escalation study facilitated the gradual debulking of accumulated sphingomyelin, which limited ceramide toxicity in both participants and animals.
- Patient data from early phase tolerability and pharmacokinetic/pharmacodynamic (PK/PD) studies can be used to inform safety and subsequent dosing strategies.
- Use of adult clinical investigation data can be used to inform dosing in a pediatric population if the pathogenesis of the disease, mechanism of action of the drug, and efficacy endpoints are similar.[21, 22, 23]

Dose Selection Recommendations

Sponsors may have concerns about the feasibility of conducting dose selection studies for drugs developed to treat rare diseases. Sponsors should consider the following:

- Multiple data sources (e.g., animal models) which can be used to help optimize the dosage and select the appropriate doses for efficacy and safety trials.[24]
- Crossover or seamless phase two-three designs, including those with parallel groups, may be considered for dose optimization and efficacy assessment in the same trial. Integrated analyses of all data from other clinical studies or "model-informed" approaches can also aid in dose selection.
- FDA recommends identifying and studying biomarkers relevant to the drug's pharmacology and the disease process using validated assays.[25]
- FDA recommends storing specimens for future analysis if novel biomarkers are discovered.[26]

In addition, sponsors should consider the following sources of information to inform dose optimization:

- Studies conducted in healthy participants (when feasible) to evaluate pharmacokinetics and tolerability in populations that may be sensitive to the amount of drug administered.[27]
- Patient data from tolerability and PK/PD studies from early phase efficacy and safety trials.

[20] For more information on the extrapolation of positive adult ASCEND trial results used for pediatric populations see page 73 of the Integrated Review.
[21] Guidance for industry *Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (April 2003).
[22] FDA CDER & NIH NCATS Regulatory Fitness in Rare Disease Clinical Trials Workshop, May 2022, Day 1, slides 128 - 147.
[23] Liyun, J and Y Ying, 2023, Seamless Phase II/III Design: A Useful Strategy to Reduce the Sample Size for Dose Optimization, J Natl Cancer Inst 115(9):1092 1098.
[24] See footnote 2.
[25] Draft guidance for industry and FDA staff *Biomarker Qualification: Evidentiary Framework* (December 2018). When final, the draft guidance will represent the Agency's current thinking.
[26] Guidance for industry *GE18 Genomic Sampling and Management of Genomic Data* (March 2018).
[27] Guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005).

Critical Thinking Questions for a Rare Disease Drug Development Program

When planning for and designing a rare disease drug development program for a medical product, FDA encourages consideration of the following questions:

1. **What is the plan for establishing a maximum recommended starting dose for the clinical trial?**
   - Is there a suitable animal model for the nonclinical studies?
   - Have the parameters been identified for clinical monitoring for potential adverse reactions related to dose?
2. **What is the plan for designing dose selection studies that include SAD and MAD?**[27]
3. **Does the nonclinical safety evaluation include a characterization of toxic effects with respect to target organs, dose dependence, relationship to exposure, and when appropriate, potential reversibility?**

We recommend speaking to the Agency to reach alignment regarding the design of the dose-finding and dose escalation strategy.

Additional Resources

Literature

- Hon, YY and A Zaidi, Review Team, K Donohue and C Nguyen, 2024, Regulatory News: Olipudase alfa-rpcp (Xenpozyme™) for Treatment of Non-Central Nervous System Manifestations of Acid Sphingomyelinase Deficiency (ASMD) in Adult and Pediatric Patients—FDA Approval Summary, J Inherit Metab Dis, 47(4):575-577, https://doi.org/10.1002/jimd.12754.
- Kempf, L, JC Goldsmith, and R Temple, 2018, Challenges of Developing and Conducting Clinical Trials in Rare Disorders, Am J Med Genet A, 176(4):773–783, https://doi.org/10.1002/ajmg.a.38413.
- Schuller, Y, C Gispen-de Wied, CEM Hollak, HGM Leufkens, and V Stoyanova-Beninska, 2018, Dose-Finding Studies Among Orphan Drugs Approved in the EU: A Retrospective Analysis, J Clin Pharmacol. 2019;59(2):229-244, https://doi.org/10.1002/jcph.1304.
- Shen, J, B Swift, R Mamelok, S Pine, J Sinclair, and M Attar, 2019, Design and Conduct Considerations for First-in-Human Trials, Clinical and Translational Science, 12(1):6–19, https://doi.org/10.1111/cts.12582.

FDA Resources and Guidance Documents

- Draft guidance for industry *General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products* (September 2022) available at https://www.fda.gov/media/90358/download. When final, the draft guidance will represent the Agency's current thinking.
- Guidance for industry *Population Pharmacokinetics Guidance for Industry Clinical Pharmacology* (February 2022) available at https://www.fda.gov/media/128793/download.
- Opportunities to Improve Dose-Finding and Optimization for Rare Disease Drug Development, 2024, Duke Margolis Institute for Health Policy, accessed 2025 Jan 17, https://healthpolicy.duke.edu/events/opportunities-improve-dose-finding-and-optimization-rare-disease-drug-development.
- Smpokou, P, 2018, Clinical Trial Design in Rare Diseases: Special Considerations FDA Clinical Investigator Training Course, FDA Office of New Drugs Center for Drug Evaluation and Research, https://cersi.umd.edu/sites/cersi.umd.edu/files/S01%20-%20 08%20Smpokou.pdf.

[27] Guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005).

Case Study References by Order of Appearance

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- See the LEADER 3D Case Study User Guide available at https://www.fda.gov/media/185425/download.
- See FDA Integrated Review document for olipudase alfa-rpcp (Xenpozyme) available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.
- See the FDA webpage with a list of guidance documents for Rare Disease Drug Development available at https://www.fda.gov/drugs/guidances-drugs/guidance-documents-rare-disease-drug-development.
- See draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products Guidance for Industry* (September 2023) for more information on how to engage with the FDA early in the drug development process, available at https://www.fda.gov/media/172311/download. When final, the draft guidance will represent the Agency's current thinking.
- See Wang, L, J Wang, J Feng, M Doi, S Pepe, M Pacanowski, and RN Schuck, 2022, Dose-Finding Studies in Drug Development for Rare Genetic Diseases, Orphanet J Rare Dis, 17(1), available at https://doi.org/10.1186/s13023-022-02298-6.

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- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) for important considerations in rare disease drug and biologics development, available at https://www.fda.gov/media/119757/download.
- See page 79 of the FDA Integrated Review document for more information on the animal model used for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.

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- See guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) for more information on the approaches for nonclinical safety studies, available at https://www.fda.gov/media/71542/download.
- See guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005) for more information on the process for deriving the maximum recommended starting dose (MRSD) for first-inhuman clinical trials, available at https://www.fda.gov/media/72309/download.
- See Horinouchi, K, S Erlich, DP Perl, K Ferlinz, CL Bisgaier, K Sandhoff, RJ Desnick, CL Stewart, and EH Schuchman, 1995, Acid Sphingomyelinase Deficient Mice: A Model of Types A and B Niemann-Pick Disease, Nat Genet, 10(3):288-293 for more information on the ASM knockout (KO) mouse model used for ASMD, available at https://pubmed.ncbi.nlm.nih.gov/7670466/.
- See page 79 of the FDA Integrated Review document for more information on the animal model used for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.
- See the FDA Integrated Review document for information on dose conversion from animal model to humans for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.

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- See guidance for industry *Rare Diseases: Considerations for the Development of Drugs and Biological Products* (December 2023) for more information on the nonclinical study approach for dose-finding in rare disease drug development, available at https://www.fda.gov/media/119757/download.
- See page 29 of the FDA Integrated Review document for more information on the first-in-human dose-escalation trial design (SPHINGO00605) used for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.

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- See guidance for industry *M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals* (January 2010) for more information on safety approaches to consider when designing a dose escalation strategy, available at https://www.fda.gov/media/71542/download.
- See page 29 of the FDA Integrated Review document for more information on the selection of doses for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.

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- See page 32 of the FDA Integrated Review document for more information on the adult clinical trial design for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.

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- See draft guidance for industry *Pediatric Drug Development Under the Pediatric Research Equity Act and the Best Pharmaceuticals for Children Act: Scientific Considerations* (May 2023) for more information on considerations for planning clinical studies in a pediatric population, available at https://www.fda.gov/media/168202/download. When final, the draft guidance will represent the Agency's current thinking.
- See pages 59 – 60 of the FDA Integrated Review document for more information on the pediatric clinical trial design for olipudase alfa-rpcp (Xenpozyme), available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.

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- See page 73 of the FDA Integrated Review for olipudase alfa-rpcp (Xenpozyme) for more information on the extrapolation of positive adult ASCEND trial results used for pediatric populations, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf.
- See guidance for industry *Exposure-Response Relationships—Study Design, Data Analysis, and Regulatory Applications* (April 2003) for more information on the use of adult clinical trial data to inform dosing in pediatric populations, available at https://www.fda.gov/media/71277/download.
- See FDA CDER & NIH NCATS Regulatory Fitness in Rare Disease Clinical Trials Workshop, May 2022, Day 1, slides 128-147 for more information on dose optimization for rare diseases, available at https://www.fda.gov/media/162732/download?attachment.
- See Liyun, J and Y Ying, 2023, Seamless Phase II/III Design: A Useful Strategy to Reduce the Sample Size for Dose Optimization, J Natl Cancer Inst 115(9):1092 1098, available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC10483325/.
- See draft guidance for industry and FDA staff *Biomarker Qualification: Evidentiary Framework* (December 2018) for more information on biomarker qualification, available at https://www.fda.gov/media/122319/download. When final, the draft guidance will represent the Agency's current thinking.
- See guidance for industry *E18 Genomic Sampling and Management of Genomic Data* (March 2018) for more information on storing specimens, available at https://www.fda.gov/media/98596/download.
- See guidance for industry *Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers* (July 2005) for more information on dose optimization, available at https://www.fda.gov/media/72309/download.