FDA case study of Xenpozyme: A Clinical Dose Escalation Strategy for a Rare Disease Drug Program

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Outline

- **Introduction**
  - Highlight of FDA prevision policy summary for Olipudase alfa (Xenpozyme)
  - Xenpozyme for treatment of acid sphingomyelinase deficiency (ASMD)
- **Two key questions for rare disease development program?**
  - **How to find the best doses or dosing algorithm?**
    - Non-clinical ASM Knockout mouse model
    - Phase 1 SAD and MAD study
    - Phase 2/3 adult study
  - **How to prepare evidence for pediatric indication with proper pediatric extrapolation plan?**
    - Phase 1/2 pediatric study
- **Summary and reflection**

13March2025 FDA prevision policy summary

FDA's summary document: Olipudase alfa-rpcp (Xenpozyme): A Clinical Dose Escalation Strategy for a Rare Disease Drug Program

Key highlights by FDA

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.

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).

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.

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.

Acid Sphingomyelinase Deficiency (ASMD)

- Mutations of the SMPD1 gene result in deficiency of acid sphingomyelinase (ASM) activity with accumulation of unmetabolized sphingomyelin in cells, leading to organomegaly, dysfunction, and inflammatory response
- Global prevalence is estimated at birth to be ~0.5 per 100,000 (<2,000 patients in US &EU)
- Leading causes of death in ASMD types A/B and B are **liver and respiratory disease**

Clinical spectrum

Most severe → **Intermediate severity** → **Least severe**

Type	ASMD Type A	ASMD Type A/B	ASMD Type B
Onset	Early infancy	Infancy to childhood	Infancy to adulthood
Phenotype	**Neurovisceral,** rapidly progressive, severe visceral disease and neurodegeneration	**Chronic neurovisceral**, slowly progressive, variable visceral disease and neurodegeneration	**Chronic visceral**, slowly progressive, variable visceral disease with little or no neurologic involvement
Life expectancy	Death by age 3	Death from childhood to mid-adulthood	Death from childhood to late adulthood

Chronic ASMD

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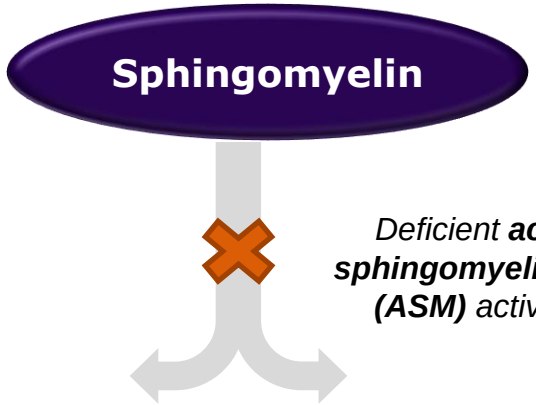
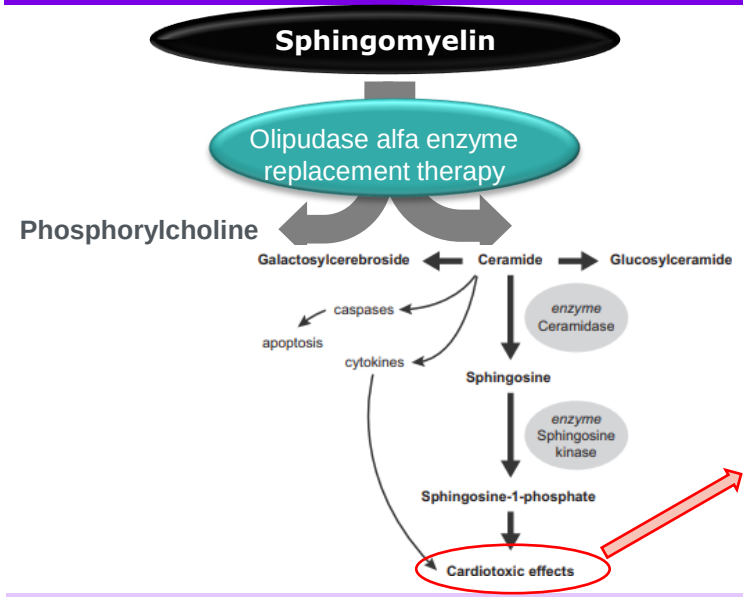
Olipudase Alfa For the Treatment of ASMD

Olipudase restores the enzymatic hydrolysis of sphingomyelin (SPM) to ceramide and phosphocholine and reverses the accumulation of SM in critical organs such as liver, lung and spleen.

Acid sphingomyelinase deficiency



Targeting the underlying metabolic defect by supplementing the deficient enzyme activity



Accumulation of sphingomyelin in splenic and alveolar macrophages, hepatocytes

Spleen volume, liver volume, and hemoglobin-adjusted % predicted DL_{CO} are key clinical endpoints

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DL_{CO} = Carbon monoxide diffusion capacity

Non-clinical studies: dose optimization in ASMKO mice

Complete ASM knock-out(ASMKO) mice with disruption of the ASM gene lack ASM activity and accumulate SPM in a manner similar to humans with ASMD.

Q:To find optimal dose to balance **efficacy vs safety,** animal study (in ASMKO and wild-type mice) were conducted.

A:The presence of dose-dependent biomarker (Cytokine levels), AEs and histological findings in ASMKO mice, but not in normal animals, suggested that:

- **toxicity may be related to the rapid breakdown of accumulated sphingomyelin that is present only in ASMKO mice**.

Efficacy (reduction of SPM in liver, spleen and lung (higher dose needed))

Safety (ceramid toxicity including cardiovascular & inflamation)

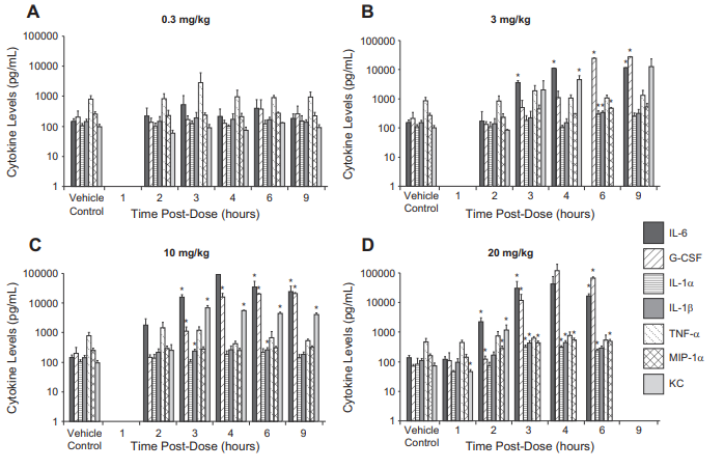


Fig. 5. Dose-responsive increases in pro-inflammatory cytokines in ASMKO mice following single doses of rhASM: (A) 0.3 mg/kg, (B) 3 mg/kg, (C) 10 mg/kg, and (D) 20 mg/kg. All results were compared to a vehicle control. *p < 0.05.

Reference: Murray JM, Thompson AM, Vitsky A, Hawes M, Chuang WL, Pacheco J, Wilson S, McPherson JM, Thurberg BL, Karey KP, Andrews L. **Nonclinical safety assessment of recombinant human acid sphingomyelinase (rhASM) for the treatment of acid sphingomyelinase deficiency:the utility of animal models of disease in the toxicological evaluation of potential therapeutics**. Mol Genet Metab. 2015 Feb;114(2):217-25. doi: 10.1016/j.ymgme.2014.07.005. Epub 2014 Jul 12. PMID: 25092414.

Non-clinical studies: Debulking studies in ASMKO mice

Q: Whether reducing the initial sphingomyelin load in ASMKO mice through debulking with lower doses prior to dose escalation could protect against high dose toxicity

A: Slow reduction in the sphingomyelin load over time using multiple low doses of rhASM (4 doses of 3.0 mg /kg over 8 days) followed by a single high dose (20 mg /kg 3 days later) (**Figure D**) prevented the toxicity associated with the high doses.

Conclusion:

- The step-wise removal of substrate appears to mitigate the toxicity observations in the ASMKO mouse.
- The toxicity associated with an initial dose of 3.0 mg /kg was reversible and not observed after repeat dosing at 3 .0 mg /kg.

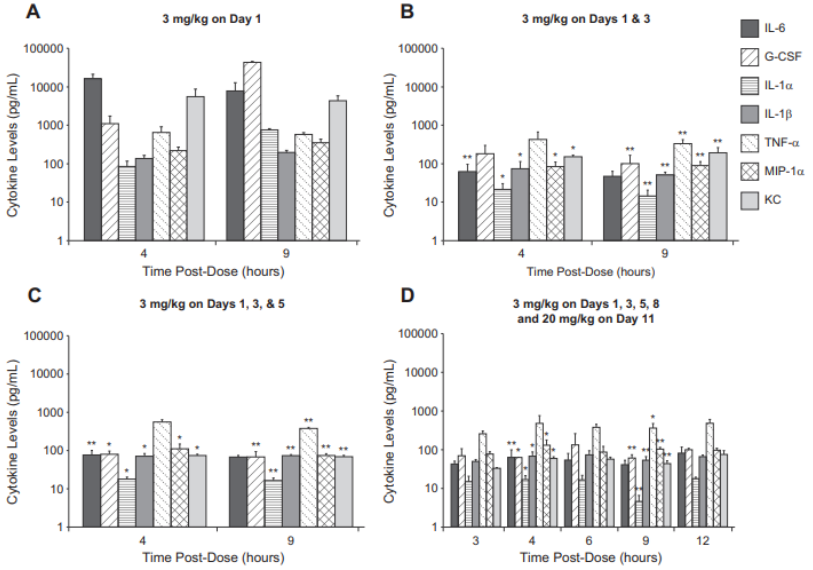


Fig. 6. Pro-inflammatory cytokine increases noted in ASMKO mice following an initial dose of 3 mg/kg rhASM, but not following subsequent administrations, which also prevented death associated with the administration of a known toxic dose of 20 mg/kg rhASM. A: 4 and 9 h following a single 3 mg/kg dose of rhASM. B: 4 and 9 h following two 3 mg/kg doses of rhASM. C: 4 and 9 h following three 3 mg/kg doses of rhASM. D: Cytokine levels measured at 3, 4, 6, 9 and 12 h following four 3 mg/kg doses and a single 20 mg/kg dose of rhASM. All results were compared to 45 and 9 h following a single dose of rhASM at 3 mg/kg. $^{*}p < 0.05$, $^{**}p < 0.01$.

Reference: Murray JM, Thompson AM, Vitsky A, Hawes M, Chuang WL, Pacheco J, Wilson S, McPherson JM, Thurberg BL, Karey KP, Andrews L. **Nonclinical safety assessment of recombinant human acid sphingomyelinase (rhASM) for the treatment of acid sphingomyelinase deficiency:the utility of animal models of disease in the toxicological evaluation of potential therapeutics**. Mol Genet Metab. 2015 Feb;114(2):217-25. doi: 10.1016/j.ymgme.2014.07.005. Epub 2014 Jul 12. PMID: 25092414.

Xenphozyme clinical development program in ASMD patients

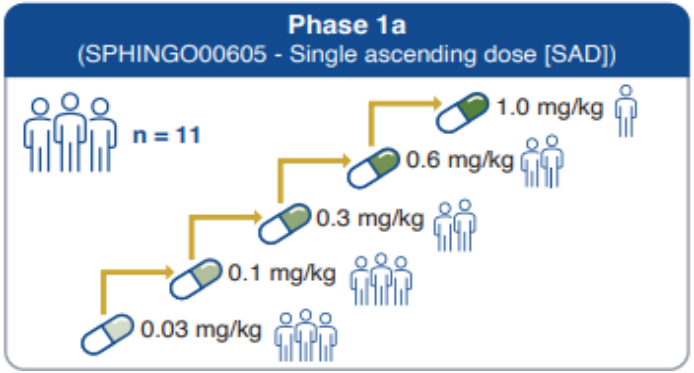
	Phase	Age	N	Key design feature	Duration
SPHINGO00605	1a	Adult	11	SAD study	Single dose
DFI13412 (SPHINGO00812)	1b	Adult	5	MAD study	26 weeks
DFI12712 (ASCEND)	2/3	Adult	36	1:1 randomization to placebo or Xenphozyme, blinded within patient **dose escalation of 0.1 mg/kg to 3.0 mg/kg**	52 weeks PAP & up to 4 years extension
DFI13803 (ASCEND-Peds)	1/2	Pediatric	20	Single arm, within **dose escalation of 0.03 mg/kg to 3.0 mg/kg**	64 weeks
LTS13632	2	Pediatric/ Adult	25	Long term study with **maintenance dose of 3.0 mg/kg** for patients rolled over from DFI13412 and DFI13803.	Up to 9 years or marketing approval

Clinical study (Ph1a): Finding maximum tolerated dose (MTD)

Between patient dose escalation in SAD study (SPHINGO00605)

Modified 3 + 3 design (N=11, 5 dosing cohort of 3+3+2+2+1)

- Starting dose of **0.03 mg/kg** is **one tenth of the single-dose no-observed-adverse-effect level (NOAEL)** in ASMKO mouse
- Dose escalation proceeded in smaller increments for added safety.



Study was terminated after 1.0 mg/kg due to hyperbilirubinemia and acute phase inflammatory reaction.

Results:

- Dose-dependent **increase of ceramide** with peak of 24 to 48 hours and return to normal by **day 14**.
- **No decrease on SPM** was observed, indicating not reaching therapeutic dose yet.
- Based on observed AE profile, maximum tolerated starting dose **(MTD) is determined as 0.6mg/kg** for MAD study.

SAD = Single ascending dose study; MAD = Multiple ascending dose study; NOEL: No-observable-effect-level; SPM = Sphingomyeline

Clinical study (Ph1b): Finding within-patient dose escalation algorithm

Ph1b MAD study (DFI13412): 12 weeks dose-escalation + 14 weeks maintenance dose

Within patient dose escalation Rationale

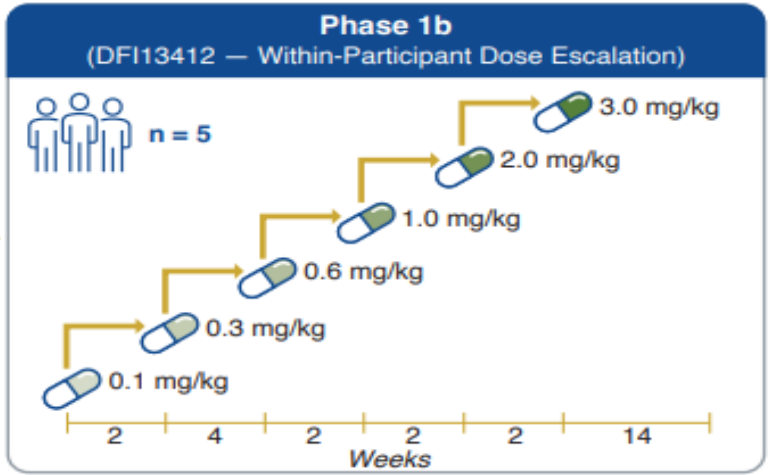
The starting dose of 0.1 mg/kg
- Highest dose not associated with any treatment-related AEs , and lower then MTD (0.6 mg/kg) in **Ph1a SAD study**
- NOEL **in ASMKO mice**
- 3 times lower than NOAEL **in ASMKO**.

The second dose of 0.3 mg/kg
- Lowest dose that reduced SPM in **ASMKO**

The target and maintenance dose of 3.0 mg/kg
- Maximize the lung clearance of SPM in **ASMKO**

The in-between doses of 0.6, 1 and 2mg/kg
- To allow controlled Sphingomyelin degradation

Q2W dosing frequency
- Due to **SAD study** PD finding (Ceramide) which return to pre-infusion by day 14.



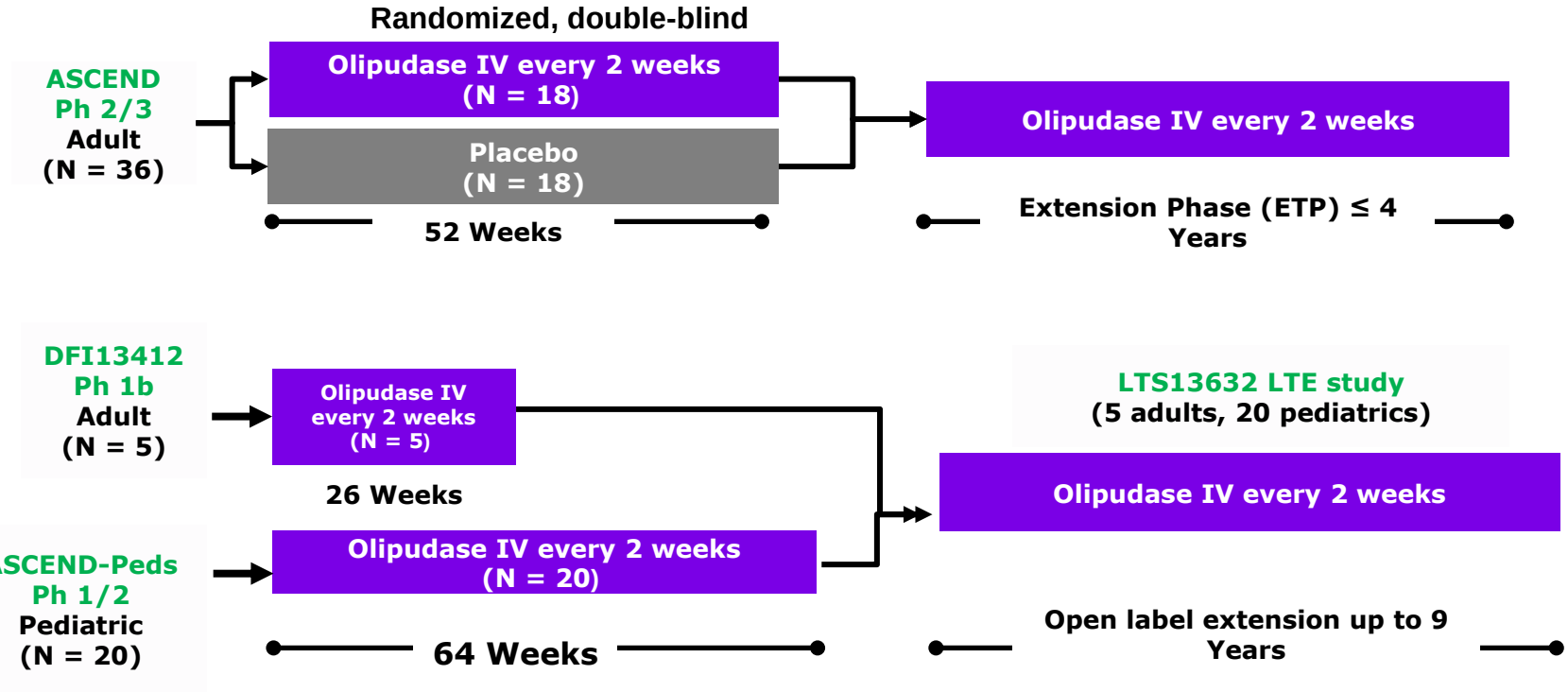
AE based dose escalation schema

- **No AE or a mild AE, escalate to the next dose.**
- **Moderate AE, repeat the same dose.**
- **Severe AE, decrease to the prior dose.**

- **Safety/Tolerability confirmed.**
- **Efficacy Effects were observed at week 26:**
  - Increase in spleen volume.
  - Reduction in % predicted DLco

SAD = Single ascending dose study; MAD = Multiple ascending dose study; NOEL: No-observable-effect-level; SPM = Sphingomyeline
PD = Pharmacodynamic ; DLCO = Carbon monoxide diffusion capacity

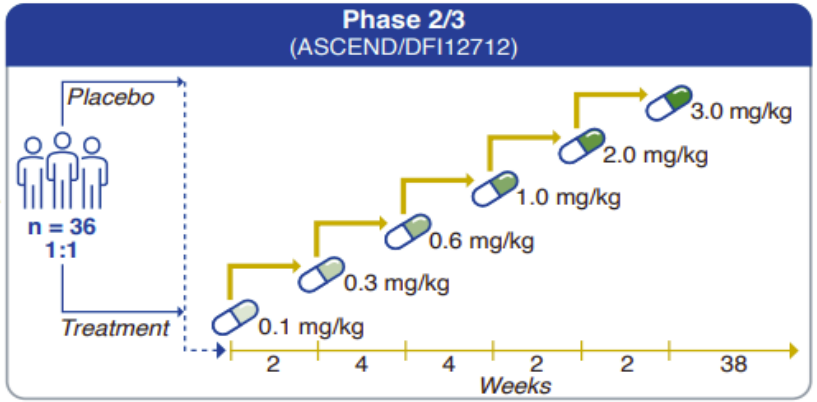
Clinical phase 2/3 adult and 1/2 pediatric study



Phase 2/3 adult (ASCEND) study design

Adult placebo-controlled study

14 weeks dose-escalation + 38 weeks maintenance dose



Dose selection/escalation Rationale

Same as phase 1b study

AE based dose escalation schema

Same as phase 1b study

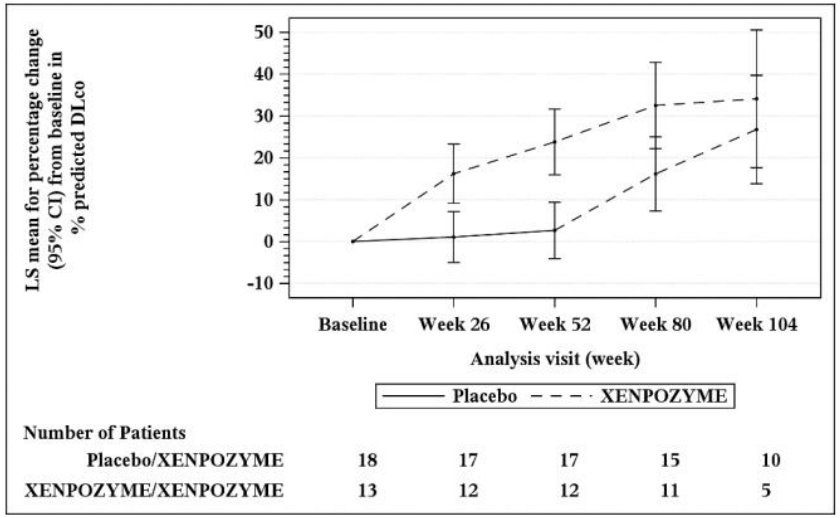
Primary endpoints (with Hochberg multiplicity adjustment method):

- Percent change from baseline in % predicted DLCO at week 52
- Percent change from baseline in Spleen volume (in multiple of normal) at week 52 and for FDA only (change from baseline in splenomegaly related score (SRS) at week 52 with a trend test, 2-sided p-value ≤ 0.15)

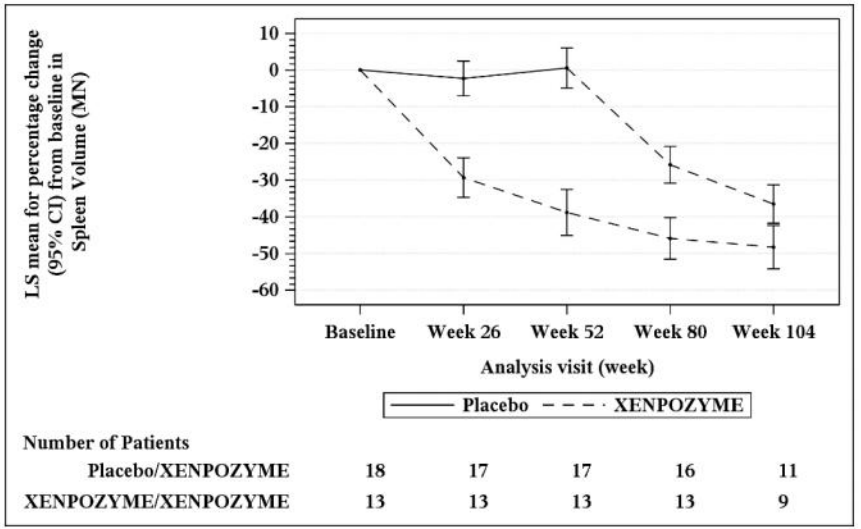
DLCO = Carbon monoxide diffusion capacity; MN = Multiple of normal

Phase 2/3 adult (ASCEND) study design- primary efficacy results

Percent change in % predicted DLco



Percent change in Spleen volume (MN)

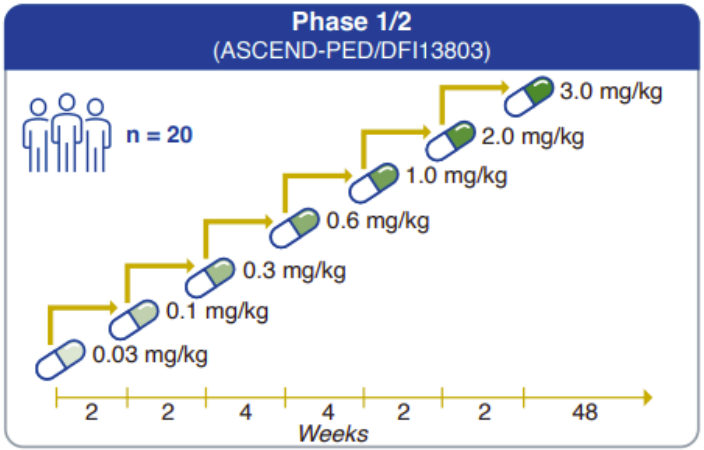


DLCO = Carbon monoxide diffusion capacity; MN = Multiple of normal
Xenpozyme USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761261s000lbl.pdf

Phase 1/2 (ASCEND-PEDS) pediatric study design

Pediatric Single arm open label

16 weeks dose-escalation + 48 weeks maintenance dose



Dose escalation Rationale

- Lower starting dose of 0.03 mg/kg, 10 times below NOAEL in ASMKO mouse, thus added 2 additional week on this lower dose with total dose-escalation of 16 weeks
- Rational for selection/escalation for other doses are the same as adults

Staggering of patient enrollment between age cohorts: start with 12 – 18 yrs, followed by 6 to <12 yrs, ending with <6 yrs.

AE based dose escalation schema

Same as phase 1b study

Primary objective is safety and tolerability.
Efficacy data (Spleen volume and % predicted DLCo) were also collected

Pediatric extrapolation plan

- **PK/PD model** using pooled data from 4 clinical trials
- **External control** from natural history study
- Utilization of **adult data**

- **Quantitative system Pharmacology (QSP model)** also use additional data including:
  - Natural history data
  - Nonclinical biodistribution data
  - In vitro enzyme kinetics data
  - Peer-reviewed literature for SPM metabolism and key ASMD disease processes

QSP = Quantitative system pharmacology; DLCO = Carbon monoxide diffusion capacity; SPM = Sphingomyelin
FDA guidance of "E11A Pediatric Extrapolation": E11A Pediatric Extrapolation | FDA

Pediatric Extrapolation plan for submission/approval

✓ **Dose selection**	Based on non-clinical ASMKO mice data and ph1a adult study data
✓ **Use of Biomarker**	Cytokine, SPM, Ceramide
✓ **Single arm study (safety/ tolerability as primary objective)**	Due to small sample size, ethic concern.

✓ **Modeling and simulation via PK/PD and QSP modeling**

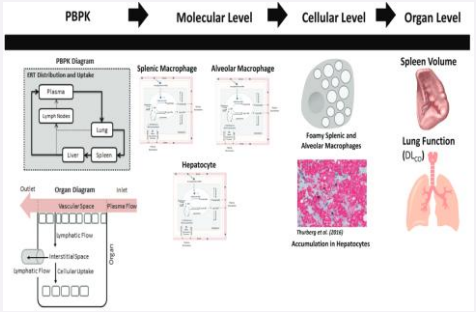
PK/PD modeling

- **E-R analysis** demonstrating no exposure dependence for efficacy with maintenance dose of 3mg/kg
- **Pop PK/PD** analysis showed that Olipudase alfa triggered reduction of SPM, which correlated with observed improvement in efficacy (Spleen volume and DlCo)

QSP model

Supported mechanistic disease and response **similarity** between pediatric and adult ASMD patients.

- Pediatric and adults only differs in baseline disease burden, not in pathophysiology that defines ASMD



✓ **Use of external control**	• Apply ASCEND-PEDS inclusion/exclusion criteria to external control • Balance of baseline covariates were checked
✓ **Use of adult data as prior distribution to quantify treatment effect in Peds**	• Bayesian fixed borrowing of historical adult data from ASCEND on both placebo and Olipudase alfa treated are was applied

QSP = Quantitative system pharmacology; E-R = Exposure Response; Pop= Population; DLCO = Carbon monoxide diffusion capacity; SPM = Sphingomyelin

Summary and reflection

How to find the best doses or dosing algorithm ?

- Use of a well defined Non-clinical **ASMKO mouse** model to select within patient dose escalation algorithm.
- In SAD study, **3+3 design** was used to find MTD (0.6mg/kg).
- Luckily, the **dose escalation algorithm** suggested by ASMKO mouse & SAD studies was confirmed in MAD study.
- Complex statistical approaches (such as model based BOIN design, mTPI-2 design, CRM, BLRM, etc) are not used, but could be considered in the future for similar situation.
- An adaptive dose escalation design could be used for MAD study in case pre-specified dose escalation algorithm did not work.

How to prepare evidence for pediatric indication with proper pediatric extrapolation plan?

For rare disease, if planning a single arm pediatric study, pediatric extrapolation plan needed incluisng:

- Proper dose/dosing algorithm
- Use of biomarker data
- Use of modeling & simulation, e.g., PK/PD & QSP modeling
- Use of external data as external control

MTD= Maximum tolerated dose; BOIN = Bayesian optimal interval design;
mTPI-2= Modified Toxicity Probability Interval-2 design
CRM= Continual reassessment method; BLRM= Bayesian Logistic Regression model;

References

1. FDA's summary document:; Olipudase alfa-rpcp (Xenpozyme): A Clinical Dose Escalation Strategy for a Rare Disease Drug Program
2. FDA guidance of "E11A Pediatric Extrapolation": E11A Pediatric Extrapolation | FDA
3. Murray JM, Thompson AM, Vitsky A, Hawes M, Chuang WL, Pacheco J, Wilson S, McPherson JM, Thurberg BL, Karey KP, Andrews L. Nonclinical safety assessment of recombinant human acid sphingomyelinase (rhASM) for the treatment of acid sphingomyelinase deficiency:the utility of animal models of disease in the toxicological evaluation of potential therapeutics. Mol Genet Metab. 2015 Feb;114(2):217-25. doi: 10.1016/j.ymgme.2014.07.005. Epub 2014 Jul 12. PMID: 25092414.
4. Kaddi, C.D., Niesner, B., Baek, R., Jasper, P., Pappas, J., Tolsma, J., Li, J., van Rijn, Z., Tao, M., Ortemann-Renon, C., Easton, R., Tan, S., Puga, A.C., Schuchman, E.H., Barrett, J.S. and Azer, K. (2018), Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and the Enzyme Replacement Therapy Olipudase Alfa Is an Innovative Tool for Linking Pathophysiology and Pharmacology. CPT Pharmacometrics Syst. Pharmacol., 7: 442-452. https://doi.org/10.1002/psp4.12304
5. Xenpozyme USPI: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/761261s000lbl.pdf

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