ASMD—historically known as Niemann–Pick disease types A, A/B, and B—is caused by reduced activity of the enzyme acid sphingomyelinase (ASM). Deficient ASM activity can result in intra-lysosomal accumulation of sphingomyelin in various tissues.1,2

XENPOZYME™ (olipudase alfa-rpcp)

**XENPOZYME™**

**THE FIRST AND ONLY DISEASE-SPECIFIC TREATMENT FOR ASMD (NON–CNS MANIFESTATIONS)**

**ASMD** is an enzyme replacement therapy that provides an exogenous source of ASM. XENPOZYME is not expected to cross the blood–brain barrier or modulate CNS manifestations of ASMD.1

The safety and efficacy of XENPOZYME were evaluated in 3 clinical trials including adult and pediatric patients with ASMD.1

XENPOZYME is administered in 2 phases: (1) dose escalation, followed by (2) maintenance phase,* with an option of home infusion during the maintenance phase.1

*3 mg/kg is the target maintenance dose, which can be administered following the dose escalation schedule.1

ASMD=acid sphingomyelinase deficiency; CNS=central nervous system.

**INDICATIONS AND USAGE**

XENPOZYME™ (olipudase alfa-rpcp) is indicated for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

**IMPORTANT SAFETY INFORMATION**

**WARNING: SEVERE HYPERSENSITIVITY REACTIONS**

**Hypersensitivity Reactions Including Anaphylaxis**

Patients treated with XENPOZYME have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during XENPOZYME administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, XENPOZYME should be discontinued immediately, and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, a desensitization procedure to XENPOZYME may be considered.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
CLINICAL TRIAL IN ADULT PATIENTS
A MULTICENTER, RANDOMIZED, DOUBLE-BLINDED TRIAL

31 ADULT PATIENTS
WITH ASMD TYPE B OR A/B

A MULTICENTER, RANDOMIZED, DOUBLE-BLINDED TRIAL

XENPOZYME IV INFUSION
ONCE EVERY 2 WEEKS* (n=13)

PLACEBO IV INFUSION
ONCE EVERY 2 WEEKS (n=18)

XENPOZYME (n=30)†
(PLACEBO PATIENTS CROSSED OVER
to ACTIVE THERAPY)

17 out of 18 patients previously receiving placebo and 13 out of 13 patients previously treated with XENPOZYME in the primary analysis period started or continued treatment with XENPOZYME, respectively, for up to 4 years.

KEY EFFICACY ENDPOINTS AT WEEK 52:
MEAN PERCENT CHANGE FROM BASELINE (VS PLACEBO)*

- DLco (% predicted)
- Liver volume (MN)
- Spleen volume (MN)
- Platelet count (10^9/L)

*Patients received XENPOZYME via a dose escalation regimen over a minimum period of 14 weeks from 0.1 mg/kg to a target dose of 3 mg/kg.
DLco=diffusing capacity of the lungs for carbon monoxide; MN=multiples of normal.

IMPORTANT SAFETY INFORMATION
WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis

Prior to XENPOZYME administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during XENPOZYME administration.

- If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue XENPOZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering XENPOZYME following severe hypersensitivity reactions (including anaphylaxis).
- If a mild or moderate hypersensitivity reaction occurs, the infusion rate may be slowed or temporarily withheld, and/or the XENPOZYME dose reduced.

Hypersensitivity reactions, including anaphylaxis, have been reported in olipudase alfa-treated patients.

- Hypersensitivity reactions in adults included urticaria, pruritus, erythema, rash, rash erythematous, eczema, angioedema, and erythema nodosum.
- Hypersensitivity reactions in pediatric patients included urticaria, pruritus, rash, erythema and localized edema.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
IN ADULT PATIENTS

**XENPOZYME DEMONSTRATED SIGNIFICANT MULTISYSTEMIC IMPROVEMENTS AT WEEK 52 AND SUSTAINED IMPROVEMENTS AT WEEK 104**: 

**DATA ARE NOMINALLY STATISTICALLY SIGNIFICANT**

**21% (P=0.0003)***

**SIGNIFICANT IMPROVEMENT IN LUNG FUNCTION AS MEASURED BY DLco**

- 24% mean increase in % predicted DLco (n=12) vs 3% mean increase with placebo (n=17)
  - Mean values
    - XENPOZYME—Baseline: 49.1%, Week 52: 59.4%, Placebo—Baseline: 48.5%, Week 52: 49.9%

**39% (P<0.0001)***

**SIGNIFICANT REDUCTION IN SpleEN VOLUME**

- 39% mean reduction in spleen volume (n=13) vs 0.5% mean increase with placebo (n=17)
  - Mean values
    - XENPOZYME—Baseline: 11.5 MN, Week 52: 7.2 MN, Placebo—Baseline: 11.2 MN, Week 52: 11.2 MN

**25% (P<0.0001)***

**SIGNIFICANT REDUCTION IN LIVER VOLUME**

- 27% mean reduction in liver volume (n=12) vs 2% mean reduction with placebo (n=17)
  - Mean values
    - XENPOZYME—Baseline: 1.4 MN, Week 52: 1.0 MN, Placebo—Baseline: 1.6 MN, Week 52: 1.6 MN

**16% (P=0.0280)***

**SIGNIFICANT INCREASE IN PLATELET COUNT**

- 18.3% mean increase in platelet count (n=13) vs 2.7% mean increase with placebo (n=16)
  - Mean values
    - XENPOZYME—Baseline: 109.3 × 10^9/L, Week 52: 126.4 × 10^9/L, Placebo—Baseline: 115.6 × 10^9/L, Week 52: 120.2 × 10^9/L

**SUSTAINED IMPROVEMENTS IN MULTIPLE ORGANS AT 104 WEEKS**

Patients previously in the XENPOZYME arm continued experiencing sustained improvements in all key endpoints compared to baseline:

- 34% improvement in lung function (n=5)
- 48% reduction in spleen volume (n=9)
- 32% reduction in liver volume (n=9)
- 24% increase in platelet count (n=9)

*P value is nominal (without a prespecified multiplicity adjustment).

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONTINUED)**

**Infusion–Associated Reactions**

Antithiamines, antipyretics, and/or corticosteroids may be given prior to XENPOZYME administration to reduce the risk of infusion–associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment.

- If severe IARs occur, discontinue XENPOZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering XENPOZYME following severe IARs.
- If a mild or moderate IAR occurs, the infusion rate may be slowed or temporarily withheld, and/or the XENPOZYME dosage may be reduced.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
IN ADULT PATIENTS

XENPOZYME DEMONSTRATED SIGNIFICANT IMPROVEMENT IN LUNG FUNCTION AS MEASURED BY DLCO\(^1\)

DATA ARE NOMINALLY STATISTICALLY SIGNIFICANT

**KEY ENDPOINT: MEAN PERCENT CHANGE IN % PREDICTED DLco**

**EARLY IMPROVEMENT\(^*\)**
AT WEEK 26 VS BASELINE

**SIGNIFICANT 21% IMPROVEMENT\(^1\)**
AT WEEK 52 VS PLACEBO \((P=0.0003)\)

**SUSTAINED IMPROVEMENT**
AT WEEK 104 VS BASELINE

<table>
<thead>
<tr>
<th>Analysis visit (week)</th>
<th>Placebo</th>
<th>XENPOZYME</th>
<th>Patients who transferred from placebo to XENPOZYME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Week 26</td>
<td>-10</td>
<td>+3%</td>
<td>+5%</td>
</tr>
<tr>
<td>Week 52</td>
<td>+24%</td>
<td>+3%</td>
<td>+21%</td>
</tr>
<tr>
<td>Week 80</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Week 104</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Number of patients

<table>
<thead>
<tr>
<th>Visit/Treatment</th>
<th>Placebo/XENPOZYME</th>
<th>XENPOZYME/XENPOZYME</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>Week 26</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Week 52</td>
<td>17</td>
<td>12</td>
</tr>
<tr>
<td>Week 80</td>
<td>15</td>
<td>11</td>
</tr>
<tr>
<td>Week 104</td>
<td>10</td>
<td>5</td>
</tr>
</tbody>
</table>

After Week 52, all patients received XENPOZYME. Vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week 104.\(^1\)

\(^{1}\)\(P\) value is nominal (without a prespecified multiplicity adjustment).\(^1\)

CI=confidence interval; LS=least squares.

Patients previously in the XENPOZYME arm continued experiencing improvement in lung function at Week 104 vs baseline, with a mean percent increase of 34% predicted DLco.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONTINUED)**

**Infusion-Associated Reactions (continued)**

The most frequent IARs in:

- adult patients were headache, pruritus, vomiting and urticaria;
- pediatric patients were urticaria, erythema, headache, nausea, pyrexia, and vomiting.

Please see **Important Safety Information** and full **Prescribing Information**, including Boxed WARNING, for complete details.
IN ADULT PATIENTS

XENPOZYME DEMONSTRATED SIGNIFICANT REDUCTION IN SPLEEN VOLUME

DATA ARE NOMINALLY STATISTICALLY SIGNIFICANT

KEY ENDPOINT: MEAN PERCENT CHANGE IN SPLEEN VOLUME

EARLY REDUCTION* AT WEEK 26 VS BASELINE

SIGNIFICANT 39% REDUCTION AT WEEK 52 VS PLACEBO (P<0.0001)†

SUSTAINED REDUCTION AT WEEK 104 VS BASELINE

After Week 52, all patients received XENPOZYME. Vertical bars represent the 95% CIs for the LS means. The LS means and 95% CIs are based on a mixed model for repeated measures approach, using data up to Week 104.†

†P value is nominal (without a prespecified multiplicity adjustment).†

Patients previously in the XENPOZYME arm continued experiencing reduction in spleen volume (MN) at Week 104 vs baseline, with a mean percent reduction of 48%.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONTINUED)

Infusion-Associated Reactions (continued)

An acute phase reaction (APR), an acute inflammatory response accompanied by elevations in inflammatory serum protein concentrations, was observed.

• Most of the APRs occurred at 48 hours post infusion during the dose escalation period.
• Elevations of C-reactive protein, calcitonin, and IL-6, and reduction of serum iron were observed.
• The most common clinical symptoms associated with APRs were pyrexia, vomiting, and diarrhea. APRs can be managed as other IARs.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
IN ADULT PATIENTS

**XENPOZYME DEMONSTRATED SIGNIFICANT REDUCTION IN LIVER VOLUME**

**DATA ARE NOMINALLY STATISTICALLY SIGNIFICANT**

**KEY ENDPOINT: MEAN PERCENT CHANGE IN LIVER VOLUME**

**SIGNIFICANT 25% REDUCTION AT WEEK 52 VS PLACEBO (P<0.0001)**

**SUSTAINED REDUCTION AT WEEK 104 VS BASELINE**

After Week 52, all patients received XENPOZYME. Vertical bars represent the standard errors (SE) for the LS means.\(^1\)

\(^*\)P value is nominal (without a prespecified multiplicity adjustment).\(^1\)

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONTINUED)**

**Elevated Transaminases Levels**

XENPOZYME may be associated with elevated transaminases (ALT, AST, or both) within 24 to 48 hours after infusion.

- Elevated transaminase levels were reported in patients during the XENPOZYME dose escalation phase in clinical trials.
- At the time of the next scheduled infusion, these elevated transaminase levels generally returned to levels observed prior to the XENPOZYME infusion.

Please see [Important Safety Information](#) and full [Prescribing Information](#), including Boxed WARNING, for complete details.
IN ADULT PATIENTS
XENPOZYME DEMONSTRATED SIGNIFICANT INCREASE IN PLATELET COUNT\textsuperscript{1,3}

DATA ARE NOMINALLY STATISTICALLY SIGNIFICANT

KEY ENDPOINT: MEAN PERCENT CHANGE IN PLATELET COUNT

**SIGNIFICANT 16% INCREASE**
AT WEEK 52 VS PLACEBO (\(P=0.0280\))*

**SUSTAINED INCREASE**
AT WEEK 104 VS BASELINE

After Week 52, all patients received XENPOZYME. Vertical bars represent the standard errors (SE) for the LS means.\textsuperscript{1}

\*\textit{P} value is nominal (without a prespecified multiplicity adjustment).\textsuperscript{1}

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONTINUED)

Elevated Transaminases Levels (continued)

To manage the risk of elevated transaminase levels, assess ALT and AST:

\begin{itemize}
  \item within one month prior to initiation of XENPOZYME,
  \item within 72 hours prior to any infusion during dose escalation, which includes the first 3 mg/kg dose, or prior to the next scheduled XENPOZYME infusion upon resuming treatment following a missed dose.
  \item See full Prescribing Information for additional information on assessment and management of elevated transaminases.
\end{itemize}

Upon reaching the recommended maintenance dose, transaminase testing is recommended to be continued as part of routine clinical management of ASMD.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
SAFETY PROFILE IN ADULT PATIENTS

ADVERSE REACTIONS OCCURRING AT >7% IN ADULT PATIENTS WITH ASMD DURING THE 52-WEEK PRIMARY ANALYSIS PERIOD

<table>
<thead>
<tr>
<th>ADVERSE REACTION</th>
<th>XENPOZYMEN = 13</th>
<th>PLACEBON = 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>7 (54%)</td>
<td>8 (44%)</td>
</tr>
<tr>
<td>Cough</td>
<td>4 (31%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2 (15%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>2 (15%)</td>
<td>2 (11%)</td>
</tr>
<tr>
<td>Ocular hyperemia</td>
<td>2 (15%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (8%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Asthenia</td>
<td>1 (8%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>1 (8%)</td>
<td>1 (6%)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Urticaria</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Papule</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>Throat irritation</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
<tr>
<td>C-reactive protein abnormal</td>
<td>1 (8%)</td>
<td>0</td>
</tr>
</tbody>
</table>
CLINICAL TRIALS IN PEDIATRIC PATIENTS

**A MULTICENTER, OPEN-LABEL, REPEATED-DOSE TRIAL**

The trial population included pediatric patients in the following age ranges:

- 7 patients, 2 to <12 years old
- 1 patient, <2 years old

Eight pediatric patients from this trial continued in a long-term, open-label extension trial and were treated for 2.5 to 3.2 years.

**EXPLORATORY EFFICACY ENDPOINTS AT WEEK 52 (CHANGE FROM BASELINE)**

- DLco (% predicted)
- Spleen volume (MN)
- Liver volume (MN)
- Platelet count (10⁹/L)
- Height Z-scores

*Patients received XENPOZYME via a dose escalation regimen over a minimum period of 16 weeks from 0.03 mg/kg to a target dose of 3 mg/kg. All but one patient completed the dose escalation up to the maintenance dose of 3 mg/kg within 22 weeks.¹

**PEDIATRIC PATIENTS IN A LONG-TERM TRIAL**

**TRIAL DESIGN**

- 8 pediatric patients from the open-label pediatric trial continued treatment in an open-label, Long-Term Trial.
  - Patients ranged from 2 to <12 years of age and were treated for 2.5 to 3.2 years.
  - XENPOZYME was administered at 3 mg/kg once every 2 weeks by IV infusion.

**IMPORTANT SAFETY INFORMATION**

**WARNINGS AND PRECAUTIONS (CONTINUED)**

**Risk of Fetal Malformations During Dosage Initiation or Escalation in Pregnancy**

XENPOZYME dosage initiation or escalation, at any time during pregnancy, is not recommended as it may lead to elevated sphingomyelin metabolite levels that may increase the risk of fetal malformations. The decision to continue or discontinue XENPOZYME maintenance dosing in pregnancy should consider the female’s need for XENPOZYME, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal ASMD disease. Verify pregnancy status in females of reproductive potential prior to initiating XENPOZYME treatment. Advise females of reproductive potential to use effective contraception during XENPOZYME treatment and for 14 days after the last dose if XENPOZYME is discontinued.

*Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.*


## EXPLORATORY EFFICACY ENDPOINTS

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Baseline Mean</th>
<th>Week 52 Mean</th>
<th>LS Mean Change</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lung function</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n=3</td>
<td>n=3</td>
<td>45.9%</td>
</tr>
<tr>
<td></td>
<td>48.5%</td>
<td>70.9%</td>
<td>Change in % predicted DLco</td>
</tr>
<tr>
<td><strong>Spleen volume</strong></td>
<td></td>
<td></td>
<td>-46.7%</td>
</tr>
<tr>
<td></td>
<td>n=8</td>
<td>n=8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>18.3 MN</td>
<td>9.5 MN</td>
<td>Change in spleen volume (MN)</td>
</tr>
<tr>
<td><strong>Liver volume</strong></td>
<td></td>
<td></td>
<td>-38.1%</td>
</tr>
<tr>
<td></td>
<td>n=8</td>
<td>n=8</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2.5 MN</td>
<td>1.6 MN</td>
<td>Change in liver volume (MN)</td>
</tr>
<tr>
<td><strong>Platelet count</strong></td>
<td></td>
<td></td>
<td>37.6%</td>
</tr>
<tr>
<td></td>
<td>n=8</td>
<td>n=7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>136.7 x 10^9/L</td>
<td>184.5 x 10^9/L</td>
<td>Change in platelet count (10^9/L)</td>
</tr>
<tr>
<td><strong>Height Z-scores</strong></td>
<td></td>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>n=8</td>
<td>n=7</td>
<td></td>
</tr>
<tr>
<td></td>
<td>-1.9</td>
<td>-1.5</td>
<td>mean improvement in height Z-score</td>
</tr>
</tbody>
</table>

The use of XENPOZYME in pediatric patients is supported by evidence from an adequate and well-controlled trial in adults with supportive efficacy, safety, and tolerability data in pediatric patients.

## IMPROVEMENTS IN THE LONG-TERM TRIAL

- Improvements in % predicted DLco (n=3), spleen volume (n=8), liver volume (n=8), and platelet count (n=6) compared to baseline, were noted in pediatric patients over the course of the trial.
- Height Z-score increased by 1.3 from baseline when evaluated through 24 months of treatment with XENPOZYME, and bone age (as assessed by hand x-ray), which was delayed by a mean of 26.4 months at baseline, improved to within a mean of 12 months of chronological age when assessed at 24 months (n=7).

## IMPORTANT SAFETY INFORMATION

### ADVERSE REACTIONS

- Most frequently reported adverse drug reactions in adults (incidence ≥10%) were headache, cough, diarrhea, hypotension, and ocular hyperemia.
- Most frequently reported adverse drug reactions in pediatric patients (incidence ≥20%) were pyrexia, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, rash, arthralgia, pruritus, fatigue, and pharyngitis.

Please see [Important Safety Information](#) and full [Prescribing Information](#), including Boxed WARNING, for complete details.
**SAFETY PROFILE IN PEDIATRIC PATIENTS\(^1\)**

**ADVERSE REACTIONS OCCURRING AT ≥13% IN XENPOZYME–TREATED PEDIATRIC PATIENTS WITH ASMD IN THE OPEN-LABEL PEDIATRIC TRIAL* AND A LONG-TERM TRIAL FOR AN OVERALL OBSERVATION PERIOD OF 2.5 TO 3.2 YEARS**

<table>
<thead>
<tr>
<th>ADVERSE REACTION</th>
<th>XENPOZYME n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrexia</td>
<td>8 (100%)</td>
</tr>
<tr>
<td>Cough</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>6 (75%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>5 (63%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Headache</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Urticaria</td>
<td>4 (50%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Rash</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>3 (38%)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>2 (25%)</td>
</tr>
<tr>
<td>C-reactive protein increased</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Hypotension</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Anaphylactic reaction</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Hypersensitivity</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Infusion site swelling</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1 (13%)</td>
</tr>
<tr>
<td>Pharyngeal swelling</td>
<td>1 (13%)</td>
</tr>
</tbody>
</table>

*Duration of treatment in the open-label trial was 64 weeks. All patients continued into the Long-Term Trial.*  
*Abdominal pain includes abdominal pain and abdominal pain upper. Fatigue includes fatigue and asthenia. Rash includes rash and erythema.*

- Treatment-related serious adverse reactions, hypersensitivity reactions including anaphylaxis, and infusion-associated reactions (IARs) occurred within 24 hours of infusion and were observed in a higher percentage of pediatric patients than in adult patients.
- Serious adverse reactions of anaphylactic reaction were reported in 2 (25%) pediatric patients treated with XENPOZYME.
DOSING AND PRETREATMENT

XENPOZYME REQUIRES 2 DOSING PHASES: DOSE ESCALATION AND MAINTENANCE

- The recommended starting dose is 0.1 mg/kg for adult patients and 0.03 mg/kg for pediatric patients (under age 18).
- The maintenance dose of 3 mg/kg is reached gradually, according to the biweekly dose escalation regimen in a clinical setting, over at least 14 weeks for adult patients and at least 16 weeks for pediatric patients.
  - In the clinical trial in pediatric patients, all but one patient completed the dose escalation up to the maintenance dose of 3 mg/kg within 22 weeks.
- If doses are missed, re-escalation may be necessary.
- Please see the full Prescribing Information for complete details on the dose escalation and maintenance phases.

XENPOZYME is administered every 2 weeks, with an option for home infusion during the maintenance phase, if recommended by the treating physician.

STEPS TO TAKE PRIOR TO TREATMENT INITIATION

- Verify pregnancy status in females of reproductive potential.
  - XENPOZYME dosage initiation or escalation, at any time during pregnancy, is not recommended.
  - Based on findings from animal reproduction studies, treatment with XENPOZYME may cause embryo-fetal harm. (See Warnings & Precautions, Section 5.4 of the Prescribing Information.)
  - Advise female patients of reproductive potential to use effective contraception during treatment with XENPOZYME and for 14 days after the last dose if XENPOZYME is discontinued.
- The decision to continue or discontinue XENPOZYME maintenance dosing in pregnancy should be made based on considerations with regard to both the fetus and the female patient.
- Consider administering pretreatment medication.
  - Antihistamines, antipyretics, and/or corticosteroids may be given prior to XENPOZYME administration to reduce the risk of IARs. However, IARs may still occur in patients after receiving pretreatment.
- Assess baseline transaminase (ALT and AST) levels in all patients within 1 month prior to treatment initiation.

ALT=alanine aminotransferase; AST=aspartate aminotransferase.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis
Prior to XENPOZYME administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during XENPOZYME administration.

- If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue XENPOZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering XENPOZYME following severe hypersensitivity reactions (including anaphylaxis).
- If a mild or moderate hypersensitivity reaction occurs, the infusion rate may be slowed or temporarily withheld, and/or the XENPOZYME dose reduced.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
PATIENT MONITORING

MONITORING TRANSAMINASE (ALT AND AST) LEVELS

XENPOZYME may be associated with elevated transaminases within 24 to 48 hours after infusion. In clinical trials, elevated transaminase levels were reported in 4 (13%) adult patients and 1 (13%) pediatric patient during the dose escalation phase with XENPOZYME. Transaminase levels generally returned to pre-infusion levels at the time of the next scheduled infusion.

TRANSAMINASE TESTING MUST OCCUR TO MANAGE THE RISK OF ELEVATED TRANSAMINASE LEVELS PRIOR TO AND DURING DOSE ESCALATION, OR UPON RESUMING TREATMENT FOLLOWING A MISSED DOSE

- Baseline transaminase levels must be assessed within 1 month prior to treatment initiation to manage the risk of elevated transaminase levels and assess ALT and AST levels.
- Assess transaminase levels within 72 hours prior to any infusion during dose escalation, or prior to the next scheduled XENPOZYME infusion upon resuming treatment following a missed dose.
  - If transaminase levels are elevated above baseline and >2 times the ULN, the XENPOZYME dose can be adjusted (prior dose repeated or reduced) or treatment can be temporarily withheld until the liver transaminases return to the patient’s baseline value.
  - If either the baseline or pre-infusion transaminase level (during the dose escalation phase) is >2 times the ULN, repeat transaminase levels within 72 hours after the end of the infusion to monitor trends in liver transaminase elevations.
- Transaminase testing is recommended to be continued as part of routine clinical management.

MONITORING INFUSION-ASSOCIATED REACTIONS (IARs) AND HYPERSENSITIVITY

Patients must be observed closely during and for an appropriate period of time after the infusion, based on clinical judgment.

- In the event of a severe hypersensitivity reaction (e.g., anaphylaxis) or a severe IAR, immediately discontinue XENPOZYME administration and initiate appropriate medical treatment.
- In the event of a mild to moderate hypersensitivity reaction or a mild to moderate IAR, consider temporarily holding or slowing the infusion rate, and/or reducing the XENPOZYME dose. If dose is reduced, re-escalate according to the dose escalation regimens for adult and pediatric patients, as applicable.

Ensure appropriate medical support measures, including cardiopulmonary resuscitation equipment, are readily available during XENPOZYME administration.

ULN=upper limit of normal.

IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONTINUED)

Hypersensitivity Reactions Including Anaphylaxis (continued)

Hypersensitivity reactions, including anaphylaxis, have been reported in olipudase alfa-treated patients.

- Hypersensitivity reactions in adults included urticaria, pruritus, erythema, rash, rash erythematous, eczema, angioedema, and erythema nodosum.
- Hypersensitivity reactions in pediatric patients included urticaria, pruritus, rash, erythema and localized edema.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.
WARNINGS AND PRECAUTIONS

Hypersensitivity Reactions Including Anaphylaxis

Prior to XENPOZYME administration, consider pretreating with antihistamines, antipyretics, and/or corticosteroids. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during XENPOZYME administration.

- If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, discontinue XENPOZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering XENPOZYME following severe hypersensitivity reactions (including anaphylaxis).

- If a mild or moderate hypersensitivity reaction occurs, the infusion rate may be slowed or temporarily withheld, and/or the XENPOZYME dose reduced.

Hypersensitivity reactions, including anaphylaxis, have been reported in olipudase alfa-treated patients.

- Hypersensitivity reactions in adults included urticaria, pruritus, erythema, rash, rash erythematous, eczema, angioedema, and erythema nodosum.

- Hypersensitivity reactions in pediatric patients included urticaria, pruritus, rash, erythema and localized edema.

Infusion-Associated Reactions

Antihistamines, antipyretics, and/or corticosteroids may be given prior to XENPOZYME administration to reduce the risk of infusion-associated reactions (IARs). However, IARs may still occur in patients after receiving pretreatment.

- If severe IARs occur, discontinue XENPOZYME immediately and initiate appropriate medical treatment. Consider the risks and benefits of re-administering XENPOZYME following severe IARs.

- If a mild or moderate IAR occurs, the infusion rate may be slowed or temporarily withheld, and/or the XENPOZYME dosage may be reduced.

The most frequent IARs in:

- adult patients were headache, pruritus, vomiting and urticaria;
- pediatric patients were urticaria, erythema, headache, nausea, pyrexia, and vomiting.

An acute phase reaction (APR), an acute inflammatory response accompanied by elevations in inflammatory serum protein concentrations, was observed.

- Most of the APRs occurred at 48 hours post infusion during the dose escalation period.
- Elevations of C-reactive protein, calcitonin, and IL-6, and reduction of serum iron were observed.
- The most common clinical symptoms associated with APRs were pyrexia, vomiting, and diarrhea. APRs can be managed as other IARs.

Please see full Prescribing Information, including Boxed WARNING, for complete details.
IMPORTANT SAFETY INFORMATION

WARNINGS AND PRECAUTIONS (CONTINUED)

Elevated Transaminases Levels

XENPOZYME may be associated with elevated transaminases (ALT, AST, or both) within 24 to 48 hours after infusion.

• Elevated transaminase levels were reported in patients during the XENPOZYME dose escalation phase in clinical trials.

• At the time of the next scheduled infusion, these elevated transaminase levels generally returned to levels observed prior to the XENPOZYME infusion.

To manage the risk of elevated transaminase levels, assess ALT and AST:

• within one month prior to initiation of XENPOZYME,

• within 72 hours prior to any infusion during dose escalation, which includes the first 3 mg/kg dose, or prior to the next scheduled XENPOZYME infusion upon resuming treatment following a missed dose.

• See full Prescribing Information for additional information on assessment and management of elevated transaminases.

Upon reaching the recommended maintenance dose, transaminase testing is recommended to be continued as part of routine clinical management of ASMD.

Risk of Fetal Malformations During Dosage Initiation or Escalation in Pregnancy

XENPOZYME dosage initiation or escalation, at any time during pregnancy, is not recommended as it may lead to elevated sphingomyelin metabolite levels that may increase the risk of fetal malformations. The decision to continue or discontinue XENPOZYME maintenance dosing in pregnancy should consider the female’s need for XENPOZYME, the potential drug-related risks to the fetus, and the potential adverse outcomes from untreated maternal ASMD disease.

Verify pregnancy status in females of reproductive potential prior to initiating XENPOZYME treatment. Advise females of reproductive potential to use effective contraception during XENPOZYME treatment and for 14 days after the last dose if XENPOZYME is discontinued.

ADVERSE REACTIONS

• Most frequently reported adverse drug reactions in adults (incidence ≥10%) were headache, cough, diarrhea, hypotension, and ocular hyperemia.

• Most frequently reported adverse drug reactions in pediatric patients (incidence ≥20%) were pyrexia, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, rash, arthralgia, pruritus, fatigue, and pharyngitis.

Please see full Prescribing Information, including Boxed WARNING, for complete details.
XENPOZYME: THE FIRST AND ONLY DISEASE-SPECIFIC TREATMENT FOR ASMD (NON–CNS MANIFESTATIONS)¹

IN ADULT PATIENTS

XENPOZYME was evaluated in key efficacy endpoints that were assessed at Week 52 and Week 104, including lung function as measured by DLco, spleen volume, liver volume, and platelet count.

IN PEDIATRIC PATIENTS

The use of XENPOZYME in pediatric patients is supported by evidence from an adequate and well-controlled trial in adult patients with supportive efficacy, safety, and tolerability data in pediatric patients.

Most frequently reported adverse drug reactions in adult patients (incidence ≥10%) were headache, cough, diarrhea, hypotension, and ocular hyperemia.

Most frequently reported adverse drug reactions in pediatric patients (incidence ≥20%) were pyrexia, cough, diarrhea, rhinitis, abdominal pain, vomiting, headache, urticaria, nausea, rash, arthralgia, pruritus, fatigue, and pharyngitis.

PATIENT SUPPORT THROUGH CARECONNECTPSS®

CareConnectPSS can help patients with starting treatment, insurance changes, transition of care, and can provide resource connections.

INDICATIONS AND USAGE

XENPOZYMETM (olipudase alfa-rpcp) is indicated for treatment of non–central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) in adult and pediatric patients.

IMPORTANT SAFETY INFORMATION

WARNING: SEVERE HYPERSENSITIVITY REACTIONS

Hypersensitivity Reactions Including Anaphylaxis

Patients treated with XENPOZYME have experienced hypersensitivity reactions, including anaphylaxis. Appropriate medical support measures, including cardiopulmonary resuscitation equipment, should be readily available during XENPOZYME administration. If a severe hypersensitivity reaction (e.g., anaphylaxis) occurs, XENPOZYME should be discontinued immediately, and appropriate medical treatment should be initiated. In patients with severe hypersensitivity reaction, a desensitization procedure to XENPOZYME may be considered.

Please see Important Safety Information and full Prescribing Information, including Boxed WARNING, for complete details.