Long-term safety and efficacy of velmanase alfa (VA) treatment in children under 6 years of age with alpha-mannosidosis (AM)

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**BACKGROUND**

**Alpha-mannosidosis (AM):**
A rare, inherited, lysosomal storage disease caused by a deficiency of the alpha mannosidase enzyme and characterized by the accumulation of mannose-rich oligosaccharides with highly variable clinical symptom severity and progression.\textsuperscript{1,2}

**Velmanase alfa (VA):**
A recombinant human lysosomal alpha-mannosidase product developed to treat non-neurological symptoms of AM.\textsuperscript{3}

Previous studies show VA may produce greater clinical benefit when administered early over the course of disease,\textsuperscript{2} but long-term studies in children are limited.

- **Objective:** To evaluate the safety and efficacy of long-term VA treatment in young children with AM for at least 24 months.
- **Study design:** Phase 2, multicenter, open-label study in 5 children under 6 years of age with AM (NCT02998879\textsuperscript{4}).

**Screening visit**

Weekly intravenous infusion of VA (1 mg/kg) for 24\textsuperscript{a} months

**End-of-trial visit**

Safety assessments (weekly) and efficacy assessments (every 6 months)

\textsuperscript{a}One child received treatment for 40 months until VA was approved for market access in the country of residence

**Note:** Multiple efficacy assessments were investigated as secondary endpoints and a select group are presented here.
**RESULTS**

Baseline Demographics (N = 5)

<table>
<thead>
<tr>
<th>Median age, years (range), N = 5</th>
<th>Male, %</th>
<th>Race (%), N = 4a</th>
<th>Median BMI (range), N = 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.3 (3.7, 5.9)</td>
<td>60</td>
<td>White (100)</td>
<td>17.91 kg/m² (15.7, 18.3)</td>
</tr>
</tbody>
</table>

- Adverse events and immunogenicity status of children treated with VA over a 24-monthb treatment period were well-managed or resolved and all children completed the study.

### Adverse Events (N = 5)

<table>
<thead>
<tr>
<th>Pretreatment adverse eventsc</th>
<th>Children, n (%)</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4 (80.0)</td>
<td>10</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment-emergent adverse eventsd</th>
<th>Children, n (%)</th>
<th>Number of events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious TEAEsd</td>
<td>5 (100.0)</td>
<td>184</td>
</tr>
<tr>
<td>Severe Intensity TEAEsd</td>
<td>1 (20.0)</td>
<td>1</td>
</tr>
<tr>
<td>TEAEs leading to discontinuation or death</td>
<td>0 (0.0)</td>
<td>0</td>
</tr>
</tbody>
</table>

**Most frequent TEAEs (> 50% patients)**

- Vomiting: 5 (100.0) events, 11 occurrences
- Pyrexia: 4 (80.0) events, 20 occurrences
- Cough: 4 (80.0) events, 10 occurrences
- Otitis media: 4 (80.0) events, 9 occurrences
- Nasopharyngitis: 3 (60.0) events, 10 occurrences
- Rhinitis: 3 (60.0) events, 10 occurrences
- Diarrhea: 3 (60.0) events, 4 occurrences

**Infusion-related reactione**

- 2 (40.0) events, 12 occurrences

**Adverse-drug reactionf**

- 4 (80.0) events, 16 occurrences
  - Chills: 1 (20.0) events, 3 occurrences
  - Hyperthermia: 1 (20.0) events, 2 occurrences
  - Pyrexia: 1 (20.0) events, 1 occurrence
  - Cyanosis: 1 (20.0) events, 2 occurrences
  - Anal pruritus: 1 (20.0) events, 3 occurrences
  - Urticaria: 1 (20.0) events, 5 occurrences

### Immunogenicity Status (N = 5)

<table>
<thead>
<tr>
<th>ADA positive at baseline</th>
<th>Children, n</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>ADA positive during VA treatment</td>
<td>4</td>
</tr>
<tr>
<td>Neutralizing antibodies</td>
<td>3</td>
</tr>
</tbody>
</table>

Note: A child who had multiple occurrences of an adverse event is presented only once in the respective child count. 

- Race was not recorded for 1 patient.
- Child received VA treatment for 40 months until VA was approved for market access in the country of residence.
- Pretreatment AEs were those that began prior to first VA administration.
- TEAEs were those that began after first VA administration and were related to the infusion process.
- Infusion-related reactions were any AEs related to the infusion process.
- Adverse-drug reactions were any AEs related to VA.
- Hyperthermia was classified as an infusion-related reaction and an adverse-drug reaction.
- "Classified as an adverse-drug reaction."
• Over the VA treatment period, serum GlcNac(Man)2 oligosaccharide levels decreased in all children.

*The rise in serum GlcNac(Man)2 concentration corresponded with the patient being positive for ADAs and nAbs at the 24-month time point

• Over the VA treatment period, serum IgG concentrations increased in all children.
Over the VA treatment period, hearing impairment improved numerically in each child, with clinically significant improvements in 2 children.

- **Patient 2**
  - **Right ear**
  - **Left ear**
  - Change in A-ABR audiometry from BL by patient

- **Patient 3**
  - **Right ear**
  - **Left ear**
  - Abnormal, CS at all timepoints

- **Patient 4**
  - **Right ear**
  - **Left ear**
  - Abnormality in hearing

- **Patient 5**
  - **Right ear**
  - **Left ear**
  - Abnormality in hearing

A-ABR, automated auditory brainstem response; BL, baseline; CS, clinically significant; VA, velemase alfa.

*Auditory assessment at baseline were not performed. Assessments were performed at unscheduled visits at approximately 9, 21, and 24 months after beginning VA treatment. After 24 months of treatment an improvement in V wave thresholds was observed in both ears.*

• Clinically significant improvements seen in patient 3 and 5.
CONCLUSIONS

• Over the 24-month\(^a\) VA treatment period, all children:
  – Demonstrated a favorable safety and tolerability profile.
  – Demonstrated a reduction in serum oligosaccharides, increase in serum IgG concentrations, and an improvement in hearing impairment.
• Overall, these findings suggest that long-term VA treatment may provide clinical benefits to patients with AM who are under 6 years of age; additional studies are warranted.

REFERENCES


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DISCLOSURES

N.G. has received hospital grants as a PI for this study and rhLAMAN 07 and has received fees for participating as an expert into lysosomal disease management with Chiesi, Sanofi Genzyme, Takeda, Ultragenyx, and BioMarin; V.K. has received hospital grants as PI for this study and travel support from Chiesi and has received honoraria from Sanofi Genzyme and Takeda; J.B.H received consulting fees and/or honoraria/travel support from Amicus, Chiesi, Sanofi Genzyme, and Shire/Takeda; N.M. has received consulting fees and/or honoraria/travel support from Actelion, Amicus, BioMarin, Chiesi, JCR Pharmaceuticals, Lysogene, Sanofi Genzyme, Shire/Takeda and Sobi as well as received grant/research support from BioMarin, Sanofi Genzyme and Shire/Takeda; I.B. has no disclosures to be declared; A.T. has no disclosures to be declared; F.C. was an employee of Chiesi Farmaceutici, the sponsor of the study; G.Z. is a consultant for Chiesi Farmaceutici, the sponsor of the study; A.M.L has received consulting fees and/or honoraria/travel support from Amicus, BioMarin, Chiesi, Sanofi Genzyme, Shire/Takeda, Recordati and Sobi as well as grant/research support from Sanofi Genzyme and Shire/Takeda.

AM, alpha-mannosidosis; IgG, immunoglobulin G; VA, velmanase alfa.

\(^a\) Child received VA treatment for 40 months until VA was approved for market access in the country of residence.