Phase 1 Safety and Pharmacokinetics of the Novel Enzyme Replacement Therapy neoGAA in Treatment-Naïve and Alglucosidase Alfa-Treated Late-Onset Pompe Disease Patients

INTRODUCTION

• Pompe disease is a progressive rare autosomal-recessive disorder caused by mutations in the gene that encodes acid α-glucosidase (GAA). Lysosomal GAA is required for the lysosomal degradation to glucose, and its deficiency leads to glycogen accumulation in lysosomes, with consequent muscle damage.1

• Alg glucosidase alfa (recombinant human GAA) therapy positively modifies the natural Pompe disease course,2,3 although a reduction in cardiac muscle, in skeletal muscle the effect is more variable4

• NeoGAA (recombinant human α-glucosidase conjugated with synthetic bis-mannose 6-phosphate-Mane glycan) is a second-generation, recombinant human GAA replacement therapy (Figure 1)

Figure 1. Enzyme replacement therapy in Pompe disease

OBJECTIVES

• To evaluate the safety, tolerability, and exploratory efficacy of neoGAA, and characterize its pharmacodynamic and pharmacokinetic (PK) profiles following repeat dose administrations in adults with late-onset Pompe disease

• Safety profiles and data were reported

Exploratory efficacy data are presented at the 12th Annual WORLDsymposium2016 as an oral presentation and poster

METHODS

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• Multicenter, multinational, open-label, ascending dose study (NCT0198364)

• Treatments: (Figure 2): S, 10, and 20 mg/kg neoGAA intravenous (IV) infusion every other week (step-wise increase in infusion rate: 1-7 ml/kg/h)

• 15 infusions over a 24-week treatment period

• Patients:

  • Adults aged 18+ years with late-onset Pompe disease (confirmed GAA enzyme deficiency from any tissue source and/or confirmed GAA gene mutation, and without known cardiac hypertrophy)

  • Ability to ambulate 50 m without stopping or using an assistive device

  • Upright forced vital capacity ≥50% predicted at baseline

  • 2 patient groups:

    • Naive Group: patients naïve to alglucosidase alfa therapy

    • Switch Group: patients previously treated with alglucosidase alfa for ≥9 months

  • Observation period: Up to a maximum of ~42 weeks (Figure 2): Screening (within 90 days); treatment period (24 weeks); post-treatment evaluation visit (6 weeks after the last infusion); Week 25; and end-of-study visit (4 weeks after the last infusion; Week 29)

  • Naive and Switch Groups were initiated simultaneously

Figure 2. Study design

Pharmacokinetic Assessments

• Blood samples collected for neoGAA PK before, during, and after neoGAA infusions on Days 1 (Day 1), 13, and 25

• Sampling times: pre-dose (prior to infusion); immediately before the infusion rate change from 1 to 3, 3 to 5, and 5 to 7 mg/kg/h; immediately before the end of the infusion, and at 1, 2, 4, 6, 12, 16, 20, 32, 40, and 48 h after the end of infusion

• Plasma concentrations of neoGAA after single and multiple doses using non-compartmental methods

• neoGAA plasma concentrations determined using a validated fluorometric assay using a 4-methylumbelliferyl-α-D-glucoside substrate to detect neoGAA activity (lower limit of quantification: 13 ng/mL)

RESULTS

Pharmacokinetic data (Figure 3)

• NeoGAA PK appeared to be generally similar between the Naive and Switch Groups

Figure 3. Patient disposition

Table 1. Demographic characteristics and Pompe disease history

Parameter
Naive Group
(n=10)
Switch Group
(n=14)
Age at study enrollment, years, mean ± SD
44.8 ± 20.2
46.7 ± 14.1
Female
7 (70)
9 (64)
Race
White
8 (80)
13 (93)
Black or African American
2 (20)
1 (7)
Asian
0 (0)
0 (0)
Multiple
1 (10)
0 (0)
Hispanic or non-Hispanic, n (%)
0 /10 (100)
0 /14 (100)
Body mass index, kg/m², mean ± SD
22.3 ± 4.14
24.6 ± 3.49
Age at Pompe disease diagnosis, years, mean ± SD
43.5 ± 23.79
36.5 ± 16.39
Pompe disease family history, yes/no, n (%)
4 /40 (100)
6 /68 (89)
0 /60 (0)
0 /60 (0)
0 /60 (0)
ACE genotype: ID/DD, n (%) 0 /11 (100) 9 /44 (20)
Assistance walking devices and orthoses, n (%)
1 /6 (17)
1 /6 (17)
None
8 /80 (101)
6 /63 (97)
Rolling walker
1 /10 (10)
1 /10 (10)
Straight cane
0 (0)
2 (14)
Two walking sticks (poles)
1 /10 (10)
0 (0)
ACE, angiotensin-converting enzyme

Table 2. Summary of treatment-emergent adverse events

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Naive Group</th>
<th>Switch Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated patients (n)</td>
<td>20</td>
<td>24</td>
</tr>
<tr>
<td>Events (n)</td>
<td>195</td>
<td>215</td>
</tr>
<tr>
<td>Percentage (%)</td>
<td>97.0</td>
<td>97.4</td>
</tr>
</tbody>
</table>

Table 3. Treatment-emergent adverse events related to study drug

<table>
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<tr>
<th>Preferred term</th>
<th>Naive Group</th>
<th>Switch Group</th>
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<tbody>
<tr>
<td>Pain</td>
<td>5 /15</td>
<td>7 /16</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 /15</td>
<td>3 /16</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>1 /15</td>
<td>1 /16</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 /15</td>
<td>2 /16</td>
</tr>
<tr>
<td>Headache</td>
<td>1 /15</td>
<td>2 /16</td>
</tr>
<tr>
<td>Myalgia</td>
<td>1 /15</td>
<td>2 /16</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>1 /15</td>
<td>1 /16</td>
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Table 4. Treatment-emergent adverse events assessed as infusion-associated reactions numbers of patients affected and events

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CONCLUSIONS

• NeoGAA had a well-tolerated safety profile in treatment-naïve and previously treated patients with late-onset Pompe disease

• The findings support further development of neoGAA in Pompe disease