Gait Improvement in Pegylarginase-treated Patients With Arginase 1 Deficiency: A Blinded Kinematic Analysis
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Background
- Arginase 1 Deficiency (ARG1-D) is a rare, progressive, inherited metabolic disorder and a distinct urea cycle disorder with debilitating manifestations driven by high plasma arginine.1,4
- The current standard of care (dietary protein restriction with essential amino acid supplementation and nitrogen scavengers) does not adequately lower plasma arginine or prevent progression of neurologic manifestations such as spasticity1,5
- Progressive muscle weakness, hypertonicity, and spasticity are associated with gait deviations and can result in difficulty walking or climbing stairs, need for bracing or assistive devices, and ultimately, functional immobility
- Pegylarginase is a human arginase 1 enzyme therapy in development as a potential treatment for ARG1-D. In a Phase 1/2 open-label study (101A/102A), pegylarginase led to a marked reduction in plasma arginine and clinically meaningful improvement in mobility assessments (6-minute walk test [6MWT], Gross Motor Function Measure [GMFM]-66, and GMFM-68) that were sustained through 48 weeks5
- Analyzing gait kinematics and spasticity in patients with ARG1-D would increase understanding of mobility impairments associated with this disorder and identify a potential foundation for the mobility improvements achieved with pegylarginase therapy

Objective
- To extend findings of the primary Phase 2 analysis by quantifying the impact of pegylarginase therapy on individual patient mobility changes (gait kinematics and lower-extremity spasticity) through 48 weeks of treatment

Mobility Assessment
- Of the 14 patients enrolled in the Phase 2 101A study, 7 had video recordings at baseline, Week 24, and Week 48 and were deemed appropriate for analysis
- Patients were video-captured while performing the 6MWT (with any needed bracing and/or assistive devices) and the GMFM (without bracing or assistive devices, Figure 1)
- Patients were stratified into low-functioning (LF) and high-functioning (HF) subgroups based on mobility level using the Gross Motor Function Classification System (GMFCS 1 and GMFCS=1, respectively)

Figure 1. Representative Performance of Mobility Assessments: Walking With Assistive Devices (left), Walking Without Assistive Devices (center), and Descending Stairs (right)

- Of the 7 patients included in the kinematics analysis, 3 were LF and 4 were HF
- Patients in the LF subgroup were older than those in the HF subgroup (mean age, 22 years vs 8 years)
- Impaired mobility in the LF subgroup was evident in the 6MWT, GMFM-66, and GMFM-68 assessments (Figure 2)

Figure 2. Impairment on Mobility Assessments Was Evident in the LF Subgroup Compared With the HF Subgroup

<table>
<thead>
<tr>
<th>Assessment</th>
<th>LF Subgroup</th>
<th>HF Subgroup</th>
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<tbody>
<tr>
<td>6MWT</td>
<td>281 ± 37.8</td>
<td>487 ± 90.5</td>
</tr>
<tr>
<td>GMFM-66</td>
<td>13.2 ± 2.8</td>
<td>16.5 ± 4.5</td>
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<tr>
<td>GMFM-68</td>
<td>88 ± 3.0</td>
<td>89 ± 1.9</td>
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6MWT, 6-minute walk test; GMFM-66, Gross Motor Function Measure (standing); GMFM-68, Gross Motor Function Measure (walking, running); HF, high functioning; LF, low-functioning. GMFM-68 uses a scale of potential scores of 25 to 30 and 0 to 72, respectively.