**Subject Demographics in Study MT-1621-101**

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>No. Subjects</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 years</td>
<td>15 (40%)</td>
<td>3</td>
<td>12</td>
</tr>
<tr>
<td>2-12 years</td>
<td>14 (37%)</td>
<td>5</td>
<td>9</td>
</tr>
<tr>
<td>≥ 12 years</td>
<td>9 (24%)</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

**Median Age of Onset (Q1, Q3): 2.5 (1.1-4.7) years**

**Baseline Status**

- Ambulatory: 18 (47%)
- Ventilator Support Yes: 10 (26%)
- Feeding Tube Yes: 12 (31%)

**Study MT-1621-101 (RETRO)** is a retrospective, GCP-compliant, medical chart review study of pyrimidine nucleosides administered as oral solution in patients with TK2d.

The study comprises records from 38 pediatric and adult TK2d patients.

The primary objective of RETRO is to describe the safety and tolerability of pyrimidine nucleosides in patients with TK2d.

The secondary objective is the assessment of efficacy (including survival).

The responder analysis included a within-patient responder analysis that assessed changes observed by the same assessor during the study (Table 1).

**Analysis Methods**

- Clinical included endpoints (eg, EK, HFMS, 6MWT), motor milestones (eg, walking), respiratory status, pulmonary function tests, and feeding tube status.
- Each subject was scored in the MOTOR, RESPIRATORY, and FEEDING domains according to predefined response thresholds.
- The last timepoint was compared with pretreatment baseline to determine the subject status: improved/remained stable/worsened.

**Overall Response Analysis**

- In subjects administered pyrimidine nucleosides, most subjects (95%) either improved (68%) or remained stable (26%). A low percentage of subjects (5%) worsened (Figure 2).
- In each age of onset category, the majority of subjects improved or remained stable during the study (Table 2).
- As TK2d is a progressive disease, subjects who improved or remained stable may both be considered as demonstrating clinical benefit.

**Examples of Functional Improvement**

- 3 subjects who had lost ambulation prior to treatment regained ambulation; 1 subject who had never walked gained ambulation.

**Survival Analysis**

- Time to event for all subjects (Figure 1A).
- Time to event for ≤ 2 years at age of onset (Figure 1B).
- Time to event for ≥ 12 years at age of onset (Figure 1C).

**TABLE 1. MT-1621-101 Response Analysis**

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Overall Response</th>
<th>Motor Domain</th>
<th>Respiratory Domain</th>
<th>Feeding Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 years</td>
<td>Improved</td>
<td>Remained</td>
<td>Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved</td>
<td>Remained</td>
<td>Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remained</td>
<td>Stable</td>
<td>Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worsened</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusion**

No subjects treated with pyrimidine nucleosides in Study MT-1621-101 died.

Survival analysis compared treated subjects with untreated patient dataset that excluded subjects who died before age 1.3 years (youngest age of treated patient).

The statistical models applied utilized methods to correct for potential length biased sampling.

Comparing RETRO subjects to a dataset of all published untreated cases of TK2d (n=68), there was a statistically significant improvement in survival (p = 0.0006), using the Cox regression model and age of onset as a strata variable.

**TABLE 2. MT-1621-101 Response Analysis**

<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Overall Response</th>
<th>Motor Domain</th>
<th>Respiratory Domain</th>
<th>Feeding Domain</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 2 years</td>
<td>Improved</td>
<td>Remained</td>
<td>Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Improved</td>
<td>Remained</td>
<td>Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Remained</td>
<td>Stable</td>
<td>Worsened</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Worsened</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Responder Analysis**

**Analysis Methods**

- Clinical included endpoints (eg, EK, HFMS, 6MWT), motor milestones (eg, walking), respiratory status, pulmonary function tests, and feeding tube status.
- Each subject was scored in the MOTOR, RESPIRATORY, and FEEDING domains according to predefined response thresholds.
- The last timepoint was compared with pretreatment baseline to determine the subject status: improved/remained stable/worsened.

**Overall Response Analysis**

- In subjects administered pyrimidine nucleosides, most subjects (95%) either improved (68%) or remained stable (26%). A low percentage of subjects (5%) worsened (Figure 2).
- In each age of onset category, the majority of subjects improved or remained stable during the study (Table 1).
- As TK2d is a progressive disease, subjects who improved or remained stable may both be considered as demonstrating clinical benefit.

**Examples of Functional Improvement**

- 3 subjects who had lost ambulation prior to treatment regained ambulation; 1 subject who had never walked gained ambulation.

**Respiratory function:**

- 3 subjects who had lost ambulation prior to treatment regained ambulation; 1 subject who had never walked gained ambulation.

**Feeding Support:**

- 3 subjects had their feeding tubes removed, out of a total of 8 subjects on feeding tubes at study start.

**Summary**

- Treatment with pyrimidine nucleosides significantly improved survival in subjects with TK2d.
- Greater than 90% of subjects experienced improvement in response or no further decline overall.
- A number of subjects retained milestones that were previously lost. These regained milestones included 4 subjects that gained ambulation, 1 subject discontinuing respiratory support, and 3 subjects had feeding tubes removed.
- Pyrimidine nucleosides were generally safe and well tolerated. No deaths occurred in TK2d subjects treated with pyrimidine nucleosides.
- Pyrimidine nucleosides may provide an effective treatment option for patients with TK2d.
- Modis Therapeutics is developing MT1621, a GMP fixed dose combination of dC/dT for the treatment of TK2d.