EFFECT OF APITEGROMAB ON MOTOR FUNCTION AND PEDICAT AND PROMIS AT 36-MONTHS IN PATIENTS WITH TYPE 2 AND NONAMBULATORY TYPE 3 SPINAL MUSCULAR ATROPHY: COMBINED PRESENTATION OF THE PHASE 2 TOPAZ STUDY

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On behalf of the entire TOPAZ Study Team
Dr Crawford is lead principal investigator of the TOPAZ trial.

Consulting/Ad Boards:
- AveXis/Novartis
- Biogen
- Pfizer
- Roche/Genentech
- Scholar Rock

Study Site Investigations:
- AveXis
- Biogen
- Catalyst
- Cytokinetics
- Parexel
- Scholar Rock

Patient Organizations:
- A-T Children’s Project®
- Cure SMA
- MDA
- SMA Foundation

A-T, ataxia telangiectasia; MDA, Muscular Dystrophy Association; SMA, spinal muscular atrophy.
Apitegromab is a fully human monoclonal antibody that targets muscle to improve motor function in SMA\(^1-3\)

**SMN1 gene**

- Decreased SMN activity
- Motor neuron degeneration
- Muscle atrophy
- Target of current SMA therapies

**TGFβ ligands through ActRIIB signaling\(^1-3\)**

- Promyostatin
- Pro-GDF-11
- Proactivin

Myostatin is a negative regulator of skeletal muscle growth. Pro- and latent myostatin are more divergent, thus inhibiting the activation of myostatin avoids unwanted off-target effects of ActRIIB signaling\(^1\).

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ActRIIB, activin receptor type 2b; GDF, growth differentiation factor; SMA, spinal muscular atrophy; SMN, survival motor neuron; TGF, transforming growth factor.

Apitegromab inhibits myostatin activation\(^1,2\)

- Apitegromab binds to both promyostatin and latent myostatin and inhibits activation of mature myostatin
- Apitegromab bound latent myostatin is proposed to be pulled from muscle into systemic circulation, and can be measured as part of total circulating myostatin\(^3\)

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Disease burden persists despite current SMA treatments

Mean improvement in HFMSE in Type 2 and nonambulatory Type 3 SMA in the Phase 3 CHERISH nusinersen trial

Limitations in mobility and daily activities continue

HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy.
TOPAZ Phase 2 trial design\textsuperscript{1,2}

Nonambulatory patients aged at least 2 years (Cohort 3)

\begin{itemize}
  \item Type 2; started SMN targeted therapy \textbf{before} age 5 years
  \item Apitegromab (2 or 20 mg/kg IV q4w) and nusinersen
\end{itemize}

Nonambulatory patients aged 5-21 years (Cohort 2)

\begin{itemize}
  \item Types 2 & 3; started SMN targeted therapy \textbf{at} or \textbf{after} age 5 years
  \item Apitegromab (20 mg/kg IV q4w) and nusinersen
\end{itemize}

Ambulatory patients aged 5-21 years (Cohort 1)

\begin{itemize}
  \item Type 3
  \item Apitegromab alone or apitegromab (20 mg/kg IV q4w) and nusinersen
\end{itemize}

Primary efficacy endpoint:
Mean HFMSE change from baseline at 12 months (Cohorts 2 and 3)
Mean RHS change from baseline at 12 months (Cohort 1)

Cohorts defined by age and present ambulatory status at time of enrollment.

HFMSE, Hammersmith Functional Motor Scale–Expanded; IV, intravenous; q4w, every 4 weeks; RHS, Revised Hammersmith Scale; SMA, spinal muscular atrophy; SMN, survival motor neuron.

### TOPAZ Phase 2 trial baseline characteristics\(^1,2\)

<table>
<thead>
<tr>
<th></th>
<th>Nonambulatory, Aged at least 2 years (Cohort 3)</th>
<th>Nonambulatory, Aged 5-21 years (Cohort 2)</th>
<th>Ambulatory, Aged 5-21 years (Cohort 1)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>20 mg/kg with nusinersen</td>
<td>2 mg/kg with nusinersen</td>
<td>Pooled</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>10</td>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>Mean age (min, max)</td>
<td>4 (2, 6)</td>
<td>4 (2, 6)</td>
<td>4 (2, 6)</td>
</tr>
<tr>
<td>Mean RHS (min, max)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean HFMSE (min, max)</td>
<td>24 (14, 42)</td>
<td>26 (12, 44)</td>
<td>25 (12, 44)</td>
</tr>
<tr>
<td>Prior nusinersen, months</td>
<td>24 (10, 34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (min, max)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients with 2, 3, or 4 SMN2 copies*</td>
<td>1, 8, 0</td>
<td>1, 8, 1</td>
<td>2, 16, 1</td>
</tr>
</tbody>
</table>

*SMN2 copy numbers were not available for all patients. All discontinuations were for reasons unrelated to study drug.

HFMSE, Hammersmith Functional Motor Scale–Expanded; max, maximum; min, minimum; RHS, Revised Hammersmith Scale; SMN, survival motor neuron.

Motor function with SMN therapies appear to plateau after initial gains

Change in HFMSE over four years with nusinersen
Overall population aged 2-12 years

<table>
<thead>
<tr>
<th>Analysis Visit, days</th>
<th>Nusinersen</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 84 82 84 83 76</td>
<td>42 41 41 42 39</td>
</tr>
<tr>
<td></td>
<td>83 83 79 61 20</td>
<td></td>
</tr>
</tbody>
</table>

Mean (+SE) Change in HFMSE Total Score From Baseline

Change in MFM over four years with risdiplam
Overall population aged 2-25 years

<table>
<thead>
<tr>
<th>Visit (months)</th>
<th>Risdiplam</th>
<th>Placebo (months 0-12)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n= 115 113 113 112 107 103 85 100 101 98</td>
<td>59 57 58 58</td>
</tr>
</tbody>
</table>

Mean change from baseline in MFM32 total score

HFMSE, Hammersmith Functional Motor Scale–Expanded; MFM, motor function measure; SE, standard error; SMN, survival motor neuron.

**Improved HFMSE at 12 months in Phase 2 TOPAZ study**

*Post hoc analysis of nonambulatory groups*

### Type 2 & nonambulatory Type 3 SMA
(Apitegromab 20 mg/kg)

<table>
<thead>
<tr>
<th>Primary efficacy endpoint at 12 months:</th>
<th>Aged 2-12 years (n=16*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean HFMSE change from baseline, (95% CI)</td>
<td>+4.4 (1.3, 7.4)</td>
</tr>
</tbody>
</table>

- **Participants with ≥1-point increase in HFMSE, n (%):** 13 (81%)
- **Participants with ≥3-point increase in HFMSE, n (%):** 9 (56%)

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HFMSE gains also notable in individuals who started nusinersen at ≥5 years old:
- 75% (6/8) with ≥1-point increase
- 50% (4/8) with ≥3-point increase

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*For 12-month endpoint, if participants skipped 3 consecutive doses due to site restrictions caused by COVID-19, records after dose skipping were excluded from analysis. The last observation carried forward was used for other missing data.*

CI, confidence interval; COVID-19, coronavirus disease 2019; HFMSE, Hammersmith Functional Motor Scale–Expanded; SMA, spinal muscular atrophy.

TOPAZ Phase 2 study patient disposition

- Patients stratified based on previous treatment with approved SMN therapy.
- COVID-19, coronavirus 2019; SMA, spinal muscular atrophy; SMN, survival motor neuron.

Cohort 3 (N = 20)
- Type 2 SMA
- Aged ≥2 years; SMN <5
  - N = 10
    - apitegromab 2 mg/kg & nusinersen

Cohort 2 (N = 15)
- Type 2 & Nonambulatory Type 3 SMA
- Aged 5-21 years; SMN ≥5
  - N = 10
    - apitegromab 20 mg/kg & nusinersen
  - N = 15
    - apitegromab 20 mg/kg & nusinersen

Cohort 1* (N = 23)
- Ambulatory Type 3 SMA
- Aged 5-21 years; SMN ≥5
  - No SMN Therapy
  - SMN Therapy
    - N = 11
      - apitegromab 20 mg/kg & nusinersen
      - 1 withdrew consent (COVID concern)
      - 1 withdrew consent (lack of benefit)
    - N = 12
      - apitegromab 20 mg/kg & nusinersen
      - 1 withdrew consent (fatigue/weight gain)

Year 1
- N = 10 apitegromab 2 mg/kg & nusinersen
- N = 10 apitegromab 20 mg/kg & nusinersen
- N = 15 apitegromab 20 mg/kg & nusinersen

Year 2 & 3 (Extension Period)
- N = 20 apitegromab 20 mg/kg & nusinersen
  - 1 withdrew consent (COVID concern)
- N = 15 apitegromab 20 mg/kg & nusinersen
  - 4 withdrew consent (lack of benefit)
  - 1 withdrew consent (lack of benefit)
- N = 11 apitegromab 20 mg/kg & nusinersen
  - 1 withdrew consent (COVID concern)

Year 4 and ONYX

*Patients stratified based on previous treatment with approved SMN therapy.
COVID-19, coronavirus 2019; SMA, spinal muscular atrophy; SMN, survival motor neuron.
EFFECT OF APITEGROMAB ON MOTOR FUNCTION AT 36-MONTHS IN PATIENTS WITH TYPE 2 AND NONAMBULATORY TYPE 3 SPINAL MUSCULAR ATROPHY
Improvements in motor function outcomes by HFMSE scores are sustained over 36 Months

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). This analysis excludes data post scoliosis surgery from six patients. Error bars represent SE. RULM, Revised Upper Limb Module; SE, standard error.
Improvements in motor function outcomes by RULM scores are sustained over 36 months

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). This analysis excludes data post scoliosis surgery from six patients. Error bars represent SE.

RULM, Revised Upper Limb Module; SE, standard error.
New WHO development milestones achieved

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Hands &amp; knees crawling</th>
<th>Standing with assistance</th>
<th>Walking with assistance</th>
<th>Standing alone</th>
<th>Walking alone</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>X</td>
<td></td>
<td>X</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>X</td>
<td>X</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>2</td>
<td>X</td>
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<td>5</td>
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<tr>
<td>8</td>
<td></td>
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<tr>
<td>9</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Proportion of patients gaining new milestones

**Cohort 2:** 12 months (20%), 24 months (7%), 36 months (0%)
**Cohort 3:** All doses: 12 months (24%), 24 months (26%), 36 months (30%)
**Cohort 3:** Randomized to 20mg/kg dose: 12 months (25%), 24 months (33%), 36 months (40%)

BL, baseline; M, month; WHO, World Health Organization
EFFECT OF APITEGROMAB ON PEDI-CAT AND PROMIS-FATIGUE QUESTIONNAIRE AT 36-MONTHS IN PATIENTS WITH TYPE 2 AND NONAMBULATORY TYPE 3 SPINAL MUSCULAR ATROPHY
The PEDI-CAT assesses four domains of function:
1. **Daily Activities**
2. **Mobility**
3. **Social/Cognitive**
4. **Responsibility**

Possible daily activities questions:
- “Tucks in shirt or blouse”
- “Dries hair with a towel”

PEDI-CAT, Pediatric Evaluation Of Disability Inventory-computer Adaptive Test; SE, standard error.
Mean changes in PEDI-CAT daily activities and mobility scaled scores over 36 months in patients aged 2-21 years

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). Error bars represent SE.
PEDI-CAT, Pediatric Evaluation of Disability Inventory-computer Adaptive Test; SE, standard error.
Mean changes in PEDI-CAT daily activities and mobility scaled scores over 36 months in patients aged 2-12 years

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2). Error bars represent SE.

PEDI-CAT, Pediatric Evaluation of Disability Inventory-computer Adaptive Test; SE, standard error.
Improvement in PROMIS fatigue scores (caregiver proxy) over 36 months

Aged 2-21 years, apitegromab: all doses

Aged 2-12 years, apitegromab: all doses

This analysis population included patients receiving either low dose (2 mg/kg) or high dose (20 mg/kg) apitegromab (inclusive of patients in Cohort 3 who transitioned from 2 mg/kg to 20 mg/kg in Year 2).

Error bars represent SE.

PROMIS, Patient-reported Outcomes Measurement Information System; SE, standard error.
Patient-reported outcomes and motor function measures over 36 months in patients aged 2-21 years

TOPAZ safety summary over 36 months

<table>
<thead>
<tr>
<th>TEAEs*</th>
<th>Apitegromab 2 mg/kg</th>
<th>Apitegromab 20 mg/kg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=10</td>
<td>N=48</td>
<td>N=58</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any TEAE</td>
<td>10 (100)</td>
<td>46 (95.8)</td>
<td>56 (96.6)</td>
</tr>
<tr>
<td>Any serious TEAE</td>
<td>5 (50)</td>
<td>16 (33.3)</td>
<td>21 (36.2)</td>
</tr>
<tr>
<td>Any TEAE leading to study drug discontinuation</td>
<td>0</td>
<td>1 (2.1)</td>
<td>1 (1.7)</td>
</tr>
<tr>
<td>Any grade 3 (severe) or higher TEAE</td>
<td>4 (40)</td>
<td>16 (33.3)</td>
<td>20 (34.5)</td>
</tr>
</tbody>
</table>

- TEAEs were consistent with previous reports with no new findings after 198 patient-years of exposure
  - Most frequently reported TEAEs*: headache (38%), pyrexia (38%), COVID-19 (36%), nasopharyngitis (36%), and upper respiratory tract infection (33%)
  - TEAEs were mostly mild to moderate in severity and generally consistent with the underlying patient population and nusinersen therapy
- No deaths or suspected unexpected serious adverse reactions or hypersensitivity reactions to apitegromab were reported
- Three patients tested positive for the presence of anti-apitegromab antibodies (ADA), but confirmatory test showed titers were below the level of sensitivity, therefore interpreted as negative

*Defined as AEs that start after the first dose of study drug or start prior to the administration of study drug and worsen in severity/grade or relationship to investigational medication after the administration of study drug. % = 100 x n/N; % at 12 months.

ADA, anti-drug antibody; TEAE, treatment emergent adverse event; COVID-19, coronavirus disease 2019.
Summary

- Improvements in motor function outcomes are sustained over 36 months with apitegromab treatment in Type 2 and nonambulatory Type 3 SMA.
- Results on caregiver-reported outcomes are consistent with improvements in motor function as assessed by the HFMSE and RULM.
- New WHO development milestones were achieved in patients from both nonambulatory groups and maintained in patients receiving prior SMN treatment before 5 years old.
- The safety profile was consistent with previous reports.
- A randomized, double-blind, placebo-controlled, phase 3 clinical trial, assessing the efficacy and safety of apitegromab is ongoing.

HFMSE, Hammersmith Functional Motor Scale–Expanded; RULM, Revised Upper Limb Module; SMA, spinal muscular atrophy.
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- ChilliPharm
- BBK
- CRECare
- Immunologix
- Charles River Labs
- Sephirus Inc.

**Scientific Advisors:**
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Scholar Rock Research and Development Team

TOPAZ sponsorship and funding provided by Scholar Rock, Inc.

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CRO, contract research organization; PI, principal investigator.

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