Stable Expression of FIX and Maintained Reductions in Bleeding and Factor IX Consumption Following AMT-060 Gene Therapy with up to 3.5 Years of Follow Up in Adults with Severe or Moderate-Severe Hemophilia B

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Unmet needs in hemophilia B

- Significant unmet needs remain with the current standard of care factor IX (FIX) prophylaxis\(^1,2\):
  - **Bleeding risk** due to fluctuating levels of protection
  - **Cumbersome treatment** with frequent infusions and lifestyle restrictions
  - **Treatment adherence issues** and resulting suboptimal clinical outcomes
  - **Quality of life** and **pain**
  - **Accrual of joint damage**

Steady state FIX levels in the mild to non-hemophilic ranges offer the potential to address these unmet needs

Introduction: gene therapy for hemophilia B: AMT-060

AAV5 capsid + Liver-specific promoter & human FIX gene

- Low prevalence of pre-existing neutralizing antibodies able to impact clinical outcomes\(^1,^4\)
- Previously tested in humans without sign of cellular immune activation\(^2\)

- WT hFIX (codon optimized)
- Clinically demonstrated safe and durable\(^3\) increases in FIX activity with meaningful improvements in clinical outcomes\(^3\)

AMT-060 Phase I/II study design

- Multi-national, open-label, dose-escalating study (NCT02396342)¹,²
- 10 adult males with severe/moderately severe hemophilia B¹,²
- Results previously reported to 2.5 years²

AMT-060

<table>
<thead>
<tr>
<th>Administration</th>
<th>Follow up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohort 1 (n=5) AAV5-hFIX 5x10¹² gc/kg</td>
<td>Weekly</td>
</tr>
<tr>
<td>Cohort 2 (n=5) AAV5-hFIX 2x10¹³ gc/kg</td>
<td>Twice Weekly</td>
</tr>
</tbody>
</table>

Retrospective analysis period

- Screening (minimum 6 weeks prior to dosing)

Weeks

-58 -6 0 1 12 26

Prophylactic FIX tapering*

-58 -6 0 1 12 26 36 5

Years

Cohort 1: 3.5 years
Cohort 2: 3 years

*Prophylaxis was tapered and discontinued by 12 weeks if FIX activity was maintained at ≥2%; FIX, factor IX

## Baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cohort 1 (N=5)</th>
<th>Cohort 2 (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>69 (35-72)</td>
<td>35 (33-46)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>85 (71-89)</td>
<td>84 (71-96)</td>
</tr>
<tr>
<td><strong>FIX use</strong></td>
<td>Prophylaxis, IU/week</td>
<td>4000 (2000–8000)</td>
</tr>
<tr>
<td></td>
<td>Annualized mean, IU/year</td>
<td>354,800</td>
</tr>
<tr>
<td><strong>Mean bleeds in the year prior to enrollment, n</strong></td>
<td>Total</td>
<td>14.4</td>
</tr>
<tr>
<td></td>
<td>Spontaneous</td>
<td>9.8</td>
</tr>
<tr>
<td></td>
<td>Traumatic</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Unknown</td>
<td>1.8</td>
</tr>
<tr>
<td><strong>Hemophilia joint health scores(^d)</strong></td>
<td></td>
<td>27 (2-49)</td>
</tr>
<tr>
<td><strong>HIV positive status, n</strong></td>
<td></td>
<td>1</td>
</tr>
<tr>
<td><strong>Prior hepatitis C infection, n</strong></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td><strong>AAV5 NAb(^+) (luciferase assay)(^2)</strong></td>
<td></td>
<td>3</td>
</tr>
</tbody>
</table>

Values are median (min-max) unless otherwise stated. N=number. \(^a\)QOD used as 3.5 x per week for calculations. \(^b\)1 participant in Cohort 2 received on-demand treatment and is therefore not included; \(^c\)Historical bleed data missing for 1 participant in Cohort 2 who is therefore not included; \(^d\)Joint status was assessed using the Haemophilia Joint Health Score version 2.1.6 FIX, factor IX; n, number of participants; HIV, human immunodeficiency virus; NAb, neutralizing antibody

Sustained dose-dependent increases in FIX activity

Cohort 1

Steady state mean FIX activity (95%CI):
5.1 (1.7 – 8.5)

Values in parentheses represent mean FIX activity over time. Only values at least 10 days after last FIX concentrate administration are included. FIX prophylaxis was continued after AMT-060 and tapered between Weeks 6 and 12. *Patient retrospectively tested positive for AAV5 neutralizing antibodies using the luciferase-based assay. 3 patients were presumed cross-reactive matter positive. FIX, factor IX; CI, confidence interval; IU, international units.

Cohort 2

Steady state mean FIX activity (95%CI):
7.5 (4.1 – 10.8)

FIX activity levels correlated approximately 1:1 with FIX protein expression.
Reductions in FIX use and bleeds sustained over long term follow up (Cohort 1)

Mean FIX consumption (Cohort 1)

- Pretreatment: 354,800 IU
- Year 1: 64,000 IU
- Year 2: 31,700 IU
- Year 3: 60,842 IU
- Year 4: 23,817 IU

Mean total annualized FIX replacement (IU)

- Pretreatment: 354,800 IU
- Year 1: 64,000 IU
- Year 2: 31,700 IU
- Year 3: 60,842 IU
- Year 4: 23,817 IU

Annualized Bleed Rate (Cohort 1)

- Pretreatment: 14.4 bleeds
- Year 1: 7.6 bleeds
- Year 2: 2.8 bleeds
- Year 3: 6.2 bleeds
- Year 4: 1.7 bleeds

Reduction relative to pre-AMT-060

<table>
<thead>
<tr>
<th>Year</th>
<th>FIX use</th>
<th>Bleeds</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year 1</td>
<td>82%</td>
<td>47%</td>
</tr>
<tr>
<td>Year 2</td>
<td>91%</td>
<td>81%</td>
</tr>
<tr>
<td>Year 3</td>
<td>83%</td>
<td>57%</td>
</tr>
<tr>
<td>Year 4</td>
<td>93%</td>
<td>88%</td>
</tr>
</tbody>
</table>

Mean FIX consumption excludes surgical procedures
Reductions in FIX use and bleeds sustained over long term follow up (Cohort 2)

Reduction relative to pre-AMT-060 | FIX use | Bleeds
--- | --- | ---
Year 1 | 78% | 65%
Year 2 | 92% | 85%
Year 3 | 96% | 83%

Mean FIX consumption excludes surgical procedures
## Treatment Emergent Adverse Events considered possibly / probably related to treatment (TRAE)

<table>
<thead>
<tr>
<th>TRAE</th>
<th>n (E) Cohort 1 (N=5)</th>
<th>n (E) Cohort 2 (N=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any TRAE</td>
<td>4 (5)</td>
<td>5 (10)</td>
</tr>
<tr>
<td>Liver enzyme increased</td>
<td>1 (1)</td>
<td>2 (3&lt;sup&gt;a&lt;/sup&gt;)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>1 (1)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Anxiety</td>
<td>1 (1)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Drug ineffective</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Joint swelling&lt;sup&gt;*&lt;/sup&gt;</td>
<td>1 (1)</td>
<td>0</td>
</tr>
<tr>
<td>Palpitations</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Headache</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Prostatitis</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Rash</td>
<td>0</td>
<td>1 (1)</td>
</tr>
</tbody>
</table>

TRAE, treatment emergent adverse event reported as possibly/probably related to treatment by the investigator; FIX, factor IX; n, Number of participants with events; (E), number of events; <sup>a</sup>2 events reported in the same participant; <sup>*</sup>TRAE reported in last 12 months

### Serious AE
- 1 participant: short, self-limiting fever in first 24 hours post-AMT-060
- 2 participants (1 in Cohort 1, 1 in Cohort 2): mild, asymptomatic elevations in liver enzymes

### Overall
- 1 new TRAE<sup>*</sup> was observed during the last 12 months of observation post-treatment
- No participants developed FIX inhibitors
Conclusions

- **The safety profile of AMT-060 remains positive**
  - No development of FIX inhibitors
  - No new clinically significant AEs, ALT elevation or capsid-specific T-cell activation since last report

- Stable, durable FIX activity over 3.5 years

- **Long-term clinical benefit in all participants**
  - Reductions in bleeds sustained over time in both cohorts
  - All participants who discontinued prophylaxis remain prophylaxis-free
  - Annualized FIX consumption decreased by 87% across the duration of follow up (78-96% per year) compared to pre-treatment
Next steps: Phase IIb and Phase III with AMT-061

- **The Phase IIb AMT-061 study** (NCT03489291) in 3 participants with FIX activity ≤1% and anti-AAV5 NAbs showed at 36 weeks post treatment:\(^1\)
  - AMT-061 was well-tolerated with no serious AEs
  - Sustained FIX activity up to 54.1%
    - Mean FIX activity 45.0% at 36 weeks (n=3)
    - Suggests anti-AAV5 NAbs may not be a barrier for AAV5 gene therapy\(^2\)
  - No bleeds or associated use of factor replacement therapy
  - No loss of FIX activity or requirement for immunosuppression

- **The Phase 3 HOPE-B AMT-061 study** (NCT03569891) is enrolling
  - First patient treated early 2019
  - Expected to enroll approximately 55 participants with severe hemophilia B
  - Those with pre-existing AAV5 NAbs will not be excluded

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