AMT-061 (AAV5-Padua hFIX variant) an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B: Follow-up up to 9 Months in a Phase 2b trial

Adam Giermasz¹, Annette Von Drygalski², Giancarlo Castaman³, Nigel S. Key⁴, Susan Lattimore⁵, Frank W.G. Leebeek⁶, Wolfgang Miesbach⁷, Michael Recht⁵, Alison Long⁸, Robert Gut⁸, Steven W. Pipe⁹

Goal of gene therapy for hemophilia B: Transformation of disease severity

- Establish long term benefit with sustained FIX activity from a one-time procedure
- Control of bleeding with effective protection against bleeds
- Elimination of the requirement for continuous prophylaxis
- Improvement in quality of life

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Spontaneous bleeding</th>
<th>Prophylaxis recommended</th>
<th>FIX activity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>frequent</td>
<td>yes</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Moderate</td>
<td>rare</td>
<td>variable</td>
<td>1-5%</td>
</tr>
<tr>
<td>Mild</td>
<td>very rare</td>
<td>no</td>
<td>5-40%</td>
</tr>
<tr>
<td>Normative</td>
<td>no</td>
<td>no</td>
<td>&gt;40%</td>
</tr>
</tbody>
</table>

Introduction: gene therapy for hemophilia B: AMT-060/AMT-061

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\(^2\)

**AMT-060 – wildtype**

Clinically demonstrated **safe and durable**\(^3\) increases in FIX activity with meaningful improvements in clinical outcomes\(^3\)

**AMT-061 – Padua variant**

(expected **6- to 7-fold increase** in activity)

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This Phase 2b study of AMT-061 is currently ongoing\(^1\)
- Data cut off: 28 May 2019

Phase 3 AMT-061 study is ongoing\(^2\)
- Health Outcomes with Padua gene; Evaluation in Hemophilia B (HOPE-B)

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\(^1\) NCT03489291  \(^2\) NCT03569891

AAV; adeno-associated virus; FIX, Factor IX; gc, genome copies; wt, wildtype
### AMT-061: Baseline characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Participant</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1</td>
</tr>
<tr>
<td>Age (years)</td>
<td>43</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>89</td>
</tr>
<tr>
<td>HIV Status</td>
<td>Negative</td>
</tr>
<tr>
<td>Hep B / Hep C</td>
<td>Hep C; resolved</td>
</tr>
<tr>
<td>Hemophilia B status</td>
<td>FIX = 1%</td>
</tr>
<tr>
<td>Pre-screening FIX treatment</td>
<td>Prophylaxis (EHL FIX)</td>
</tr>
<tr>
<td>Annualized bleed rate 1-year prior to screening(^a)</td>
<td>3</td>
</tr>
<tr>
<td>Neutralizing antibody activity (AAV5) (Luciferase assay)(^b)</td>
<td>Positive</td>
</tr>
<tr>
<td></td>
<td>48</td>
</tr>
</tbody>
</table>

AAV, adeno-associated virus; EHL, extended half-life; FIX, Factor IX; Hep, hepatitis; HIV, human immunodeficiency virus; NAb, neutralizing antibody. Participants 2 and 3 were excluded from another AAV-based gene therapy trial for hemophilia B based on anti-AAV NAb titer.

\(^a\)Total bleeds (treated + untreated).

\(^b\)AAV5 NAb data from screening visit, considered positive if titer is ≥2.
AMT-061 Efficacy: FIX activity at 36 weeks post-treatment

Mean FIX activity at 36 weeks: 45.0%

aPTT, activated partial thromboplastin time; FIX, Factor IX. No immunosuppression required. *May include activity from exogenous FIX replacement.
**Reduction in bleeds and FIX replacement**

<table>
<thead>
<tr>
<th>Participant</th>
<th>Pre-AMT-061</th>
<th>Post-AMT-061</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3 spontaneous (severe)</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>1 spontaneous (moderate)</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>6 spontaneous* (moderate [n=2] and mild [n=4])</td>
<td>0</td>
</tr>
</tbody>
</table>

*1 bleed occurred after enrollment but prior to dosing

- **No requirement for FIX replacement after treatment***

* Pt 3, received a total of 5 infusions of short acting FIX, associated with hip surgery: 1 infusion pre-operatively and a total of 4 infusions (once per day for 4 days) post-operatively
Safety summary

General

▪ AMT-061 was well tolerated
  ▪ 1 patient experienced two AE, possibly related to AMT-061, that resolved without intervention
  ▪ Transient, self-limiting headache and slightly elevated CRP

▪ No loss of FIX activity

▪ No FIX inhibitor development

▪ Participant 3 had hip surgery due to worsening of pre-existing condition (avascular necrosis)
  ▪ Reported as SAE deemed unrelated to AMT-061 by Investigator

Liver Specific

▪ No clinically significant ALT elevations above upper limit of normal after dosing
  ▪ Participant 1 had an isolated, slightly elevation at Week 22 (44 U/L) which resolved without intervention or loss of efficacy

▪ 1 participant experienced three isolated elevations above the upper limit of normal in aspartate aminotransferase (AST)
  ▪ 43 U/L (week 2), 48 U/L (week 4), 90 U/L (week 31)
  ▪ Resolved quickly without treatment or impact on FIX activity

▪ No participants required immunosuppression

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CRP, C-reactive protein; FIX, Factor IX; SAE, serious adverse event
AMT-061 Phase 2b: Conclusions and next steps

- **AMT-061 was generally well-tolerated with no serious AEs related to treatment**
- **All participants achieved clinically meaningful FIX activity:**
  - FIX activity increased by week 1-2
  - Mean 45% of normal at week 36
  - FIX activity in the normal range for two of the three participants
- **No bleeds or associated use of factor replacement therapy**
- **No clinically significant liver enzyme elevations**
- **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

AE, adverse event; FIX, Factor IX; NAbs, neutralizing antibodies.
The authors would like to thank the study participants & their families, staff at the three sites and the uniQure AMT-061 team.

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- University of California San Diego: A. Von Drygalski
- University of Michigan: S. Pipe