Clinical Outcomes in Patients With and Without Pre-existing Neutralizing Antibodies to the Vector: 6 Month Data from the Phase 3 HOPE-B Gene Therapy Trial of Etranacogene Dezaparvovec

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<table>
<thead>
<tr>
<th>Disclosures</th>
<th>Bayer, BioMarin, CSL Behring, Genentech, Grifols, Hema Biologics, LFB, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, Takeda, uniQure</th>
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</thead>
<tbody>
<tr>
<td>Research Funding to my employers:</td>
<td>Catalyst Biosciences, CSL Behring, Genentech, Hema Biologics, Kedrion, Novo Nordisk, Pfizer, Sanofi, Takeda, uniQure</td>
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<tr>
<td>Consulting/Advisory Boards:</td>
<td>Foundation for Women and Girls with Blood Disorders Partners in Bleeding Disorders</td>
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<td>Board of Directors:</td>
<td>American Thrombosis and Hemostasis Network Oregon Health &amp; Science University</td>
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HOPE-B: Etranacogene Dezaparvovec (AAV5-Padua hFIX)

- Ongoing Phase 3 study in hemophilia B
  - N=54
  - Mean FIX activity increased to near-normal levels at 6 months post-etranacogene dezaparvovec, meeting the first co-primary endpoint
  - Anti-AAV5 neutralizing antibodies (NABs) are assessed via luciferase assay but are not exclusionary

- Here we report safety and efficacy outcomes at 6 months post treatment by presence of pre-existing anti-AAV5 NABs at baseline

Pre-existing NAbs resulting from previous exposure to AAV may prevent efficient transduction of the therapeutic transgene due to the host’s immune response against the vector. However, prior clinical data have not shown pre-existing anti-AAV5 NAbs to have predictive value:

**Phase I/II (AMT-060): AAV5-WT hFIX (N=10)**
- Initial NAb analysis (GLP based) on screening did not detect NAbs
  - Retrospective NAb analysis (luciferase based) found 3/10 NAb positive
  - Subject with highest titer of 340 showed highest circulating FIX activity levels of this cohort
- Stable FIX activity over 4.5-5 years post dosing
- No new treatment-related AEs* observed during the last 12 months of observation post-treatment

**Ongoing Phase 2b (AMT-061-01): AAV5 with Padua FIX variant (N=3)**
- All patients NAb positive prior to treatment
  - 2 patients in this trial had been denied another gene therapy trial entry based on pre-existing anti-AAV NAbs
- Mean FIX activity at 2 years was 44.2% with no new treatment-related AEs.

* TRAE - treatment related adverse events

2. Leebeek FWG, et al, ASH 2020; Poster #33724
4. Leebeek FWG, et al, ASH 2020; Oral presentation #672
**HOPE-B (AMT-061): study design**

**Key inclusion criteria**
- Male adults ≥18 years
- FIX activity ≤2% of normal
- Continuous prophylaxis for ≥2 months

**Key exclusion criteria**
- Factors that might affect the evaluation of AMT-061 efficacy or safety, e.g.
  - FIX inhibitors
  - Active hepatitis B/C infection
  - Uncontrolled HIV infection

Pre-existing anti-NAbs were assessed, but not used as an exclusion criteria

No prophylactic immunosuppression

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HOPE-B: study endpoints and analyses

- **Primary endpoints**
  - FIX activity (central one stage aPTT) at 26 weeks after dosing\(^1\)
  - FIX activity 52 weeks after dosing\(^*\)
  - 52-week ABR compared to lead-in\(^*\)

- **Secondary endpoints**
  - Rates of total, spontaneous, traumatic, and treated/untreated bleeds
  - FIX consumption
  - Correlation of FIX activity levels and safety with pre-AMT-061 anti-AAV5 antibody titers over 26 weeks (6 months) follow up
  - Safety

- **Post-hoc analysis**
  - FIX activity (central one stage aPTT) and safety at 26 weeks after dosing in participants with and without pre-existing NAbs to AAV5

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*Planned co-primary endpoints; aPTT, activated partial thromboplastin time; ABR, annualized bleeding rate; AAV5, adeno-associated virus; NAbs, neutralizing antibodies.
54 patients were dosed and completed 26-weeks of follow up

75 patients screened

8 screen failures

67 entered lead-in phase

13 patients discontinued prior to dosing

54 patients dosed (FAS population)\textsuperscript{b,c}

Ineligible fibroscan\textsuperscript{a} score, concomitant medication, co-morbidities, withdrawn due to Covid-19 pandemic, or withdrawn consent

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\textsuperscript{1} Pipe S, et al. Oral presentation at the 62nd Virtual American Society of Hematology Annual Meeting & Exposition. Dec 5-8, 2020:

\textsuperscript{a} Or equivalent scan (magnetic resonance elastography, shear wave elastography).

\textsuperscript{b} FAS, full analysis set includes subjects who enrolled, entered the lead-in phase, were dosed with AMT-061 and provided ≥1 efficacy endpoint assessment.

\textsuperscript{c} Per-Protocol population \((N = 53)\), which included all subjects from the FAS who adhered to a stable and adequate prophylaxis use during the lead-in phase, completed assessments through the 6 month visit, and had no major protocol deviations that impacted the interpretation of efficacy.
## HOPE-B: Baseline demographics

<table>
<thead>
<tr>
<th></th>
<th>Full analysis set (N = 54)</th>
<th>antiAAV5 NAb +ve (n=23)</th>
<th>antiAAV5 NAb –ve (n=31)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, mean (SD, min-max), years</strong></td>
<td>41.5 (15.8, 19-75)</td>
<td>43.1 (17.4, 19-75)</td>
<td>40.3 (14.6, 21-73)</td>
</tr>
<tr>
<td><strong>Severity of hemophilia B at time of diagnosis, n (%)</strong></td>
<td></td>
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<tr>
<td>Severe (FIX &lt;1%)</td>
<td>44 (81.5)</td>
<td>17 (73.9)</td>
<td>27 (87.1)</td>
</tr>
<tr>
<td>Moderately severe (FIX ≥1% and ≤2%)</td>
<td>10 (18.5)</td>
<td>6 (26.1)</td>
<td>4 (12.9)</td>
</tr>
<tr>
<td><strong>Positive HIV status, n (%)</strong></td>
<td>3 (5.6)</td>
<td>1 (4.3)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td><strong>Prior hepatitis B infection, n (%)</strong></td>
<td>3 (5.6)</td>
<td>2 (8.7)</td>
<td>1 (3.2)</td>
</tr>
<tr>
<td><strong>Prior hepatitis C infection, n (%)</strong></td>
<td>31 (57.4)</td>
<td>15 (65.2)</td>
<td>16 (51.6)</td>
</tr>
<tr>
<td><strong>Pre-screening FIX treatment (n, %)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extended half-life</td>
<td>31 (57.4)</td>
<td>15 (65.2)</td>
<td>16 (51.6)</td>
</tr>
<tr>
<td>Standard half-life</td>
<td>23 (42.6)</td>
<td>8 (34.8)</td>
<td>-</td>
</tr>
<tr>
<td><strong>Detectable NAbs at baseline, n (%)</strong></td>
<td>23 (42.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Maximum titer</strong></td>
<td></td>
<td>3212.3</td>
<td>-</td>
</tr>
<tr>
<td><strong>Median titer (1st quartile, 3rd quartile)</strong></td>
<td></td>
<td>56.9 (23.8, 282.5)</td>
<td>-</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; NAb, neutralizing antibody; SD, standard deviation.
HOPE-B: FIX activity\textsuperscript{a}: Up to 26 weeks (month 6)\textsuperscript{1}

- Mean (SD) FIX activity at Month 6: 37.2% (19.6); change from baseline +36.01% (19.693), p<0.0001

\textsuperscript{1} Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subject's historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level \(\geq\)1% and \(\leq\) 2%), their baseline factor IX activity level was imputed as 2%. SD, standard deviation.

HOPE-B: FIX activity by BL NAb status: Up to 26 weeks

Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value. Baseline factor IX was imputed based on subject’s historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤ 2%), their baseline factor IX activity level was imputed as 2%. SD, standard deviation.

NAb + (n=23)

NAb - (n=31)
Mean FIX activity at 26 weeks was 41.3 IU/dL in participants without NAbs and 32.7 IU/dL in those with NAbs.

Uncontaminated central laboratory data (the visit did not occur within 10 days of exogeneous FIX use). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value.

Baseline factor IX was imputed based on subject’s historical hemophilia B severity documented on the case record form. If the patient had documented severe factor IX deficiency (FIX plasma level < 1%), their baseline factor IX activity level is imputed as 1%. If the subject had documented moderately severe factor IX deficiency (factor IX plasma level ≥1% and ≤ 2%), their baseline factor IX activity level was imputed as 2%. NAbs, neutralizing antibody; SD, standard deviation.
No clinical significant correlation of pre-existing NABs with FIX activity identified up to a titer of 678

One patient with a titer of 3212.3 did not respond (data not shown)
For subjects with bleeds, no clinically significant difference in individual patterns of post treatment bleeds in subjects with and without baseline NAbs.
### HOPE-B: Most common treatment-related AEs

<table>
<thead>
<tr>
<th>AE, preferred term</th>
<th>Participants with NAbs</th>
<th>Participants without NAbs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 23</td>
<td>N = 31</td>
</tr>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Transient transaminitis, requiring corticosteroids</td>
<td>2 (8.7)</td>
<td>7 (22.6)</td>
</tr>
<tr>
<td>Infusion-related reactions&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5 (21.7)</td>
<td>2 (6.5)</td>
</tr>
<tr>
<td>Headache</td>
<td>2 (8.7)</td>
<td>5 (16.1)</td>
</tr>
<tr>
<td>Influenza-like illness</td>
<td>4 (17.4)</td>
<td>3 (9.7)</td>
</tr>
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- No deaths and no inhibitors to FIX were reported.
- Post 6 month data cut, an SAE of HCC in a subject with multiple pre-existing risk factors was reported. Integration analyses determined HCC was unlikely to be related to treatment with etranacogene dezaparvovec<sup>1</sup>

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<sup>a</sup>The set of IRRs here is broader than just the preferred term ‘infusion related reactions’.
HOPE-B: Conclusions

- FIX activity was similar in participants without and with pre-existing NAbs to AAV5 up to a titer of 678
- Insufficient data to assess a relationship with higher titer NAbs (n=1, 3213.5)
- No relationship between AAV5 NAbs and safety was observed
- This study demonstrates for the first time, successful treatment of patients with pre-existing NAbs at generally prevalent levels with an AAV5 construct, supporting broad eligibility for AAV5-based therapies