Interim results of an open-label, Phase 1/2 study of BMN 270, an AAV5-FVIII gene transfer in severe haemophilia A

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Rationale For Programme

FVIII Replacement Therapy

- Replacement products
  - an expensive and demanding treatment
  - must be given 3x or more times weekly iv
  - new EHLs still require 2x weekly iv
  - for optimal replacement therapy treatment burden is significant

- Factor levels not consistent
  - saw tooth response
  - microbleeding at low factor levels remains a concern

Gene Therapy

- Single gene disorder
  - clear cause and effect relationship

- Wide therapeutic window
  - low levels dramatically improve outcome
  - high levels welcome (up to a point)

- Efficacy easy to assess
  - clinical
  - laboratory

- BMN 270 (AAV5-hFVIII-SQ)
  - First in human study
  - adeno-associated virus(AAV) serotype 5
  - codon-optimized expression cassette
  - SQ variant B-domain-deleted human FVIII
Design

• Subjects enrolled sequentially into one of up to four cohorts based on FVIII activity at 3 weeks:
  1. $6 \times 10^{12}$ vg/kg given as a single intravenous dose
  2. $2 \times 10^{13}$ vg/kg, iv
  3. $6 \times 10^{13}$ vg/kg, iv
  4. $4 \times 10^{13}$ vg/kg, iv
• Dose escalation occurred if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL
• Subjects on prophylactic FVIII therapy switched to an “on-demand” schedule
• Out of abundance of caution, to ensure patient safety and to protect against loss of FVIII activity expression, cohorts 1-3 had prophylactic corticosteroids initiated after first subject had ALT elevation 1.5 fold above baseline
• No prophylactic corticosteroids in Cohort 4 at $4 \times 10^{13}$ vg/kg; trigger for corticosteroids set at ALT of 1.5x ULN

Endpoints

• Safety of a single intravenous administration of a recombinant AAV human-coagulation FVIII vector
• Change from baseline of FVIII expression level
• Impact on the frequency of FVIII replacement therapy and annualized bleeding rate
# Key Eligibility Criteria

**KEY INCLUSION CRITERIA**

- Males that are 18 years or older with established severe haemophilia A (FVIII level ≤1 IU/dL)
- Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days
- Greater or equal to 12 bleeding episodes therapy over the previous 12 months (on-demand subjects)
- Results from a modified Nijmegen Bethesda assay of <0.6 Bethesda Units

**KEY EXCLUSION CRITERIA**

- Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- HIV positive
- Significant liver dysfunction
  - ALT or TBili or ALP >3 fold ULN
  - INR ≥ 1.4
  - Liver fibrosis on biopsy if performed
  - Liver cirrhosis by US
- Hepatitis B if surface antigen positive
- Hepatitis C if RNA is positive
AAV5 Seroprevalence/Humoral immunity
21 Screened; 2 were also positive by total antibody assay (TAb)
Baseline Demographics & Clinical Characteristics

15 subjects enrolled and dosed in 4 cohorts:
• 1 subject each at the $6 \times 10^{12}$ vg/kg and the $2 \times 10^{13}$ vg/kg dose cohort
• 7 subjects enrolled at the $6 \times 10^{13}$ vg/kg dose cohort
• 6 subjects enrolled at the $4 \times 10^{13}$ vg/kg dose cohort

<table>
<thead>
<tr>
<th></th>
<th>N=15</th>
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<tbody>
<tr>
<td>Age in years — mean (SD)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Race- no (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (7%)</td>
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<tr>
<td>White</td>
<td>12 (80%)</td>
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<tr>
<td>Treatment before enrollment — no (%)</td>
<td></td>
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<tr>
<td>FVIII prophylaxis</td>
<td>14 (93%)</td>
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<tr>
<td>On-demand treatment with FVIII</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Historical annualized bleeding rate — median</td>
<td></td>
</tr>
<tr>
<td>Prophylactic therapy n=14</td>
<td>6.5</td>
</tr>
<tr>
<td>On-demand treatment n=1</td>
<td>25</td>
</tr>
<tr>
<td><strong>6E13 cohort</strong></td>
<td></td>
</tr>
<tr>
<td>Prophylactic therapy n=6</td>
<td>16.5</td>
</tr>
<tr>
<td>On-demand treatment n=1</td>
<td>25</td>
</tr>
<tr>
<td><strong>4E13 cohort</strong></td>
<td></td>
</tr>
<tr>
<td>Prophylactic therapy n=6</td>
<td>8</td>
</tr>
<tr>
<td>Subjects with target joints — no. (%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>12 (80%)</td>
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<tr>
<td>Previous disease — no. (%)</td>
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<tr>
<td>Hepatitis B</td>
<td>1 (7%)</td>
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<tr>
<td>Hepatitis C</td>
<td>4 (27%)</td>
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</table>
Summary of Safety

• BMN 270 was well tolerated across all doses

• No subject developed inhibitors to FVIII

• No subject withdrew

• Most common AEs across all dose cohorts: ALT elevation (10 subjects, 67%), arthralgia (7 subjects, 47%) and back pain, fatigue, headache (5 subjects each, 33%)

• 2 Subjects reported SAE’s during the study:
  • Grade 2 pyrexia with myalgia and headache at time of infusion; observed in hospital overnight and resolved without sequelae
  • Planned total knee replacement for chronic arthropathy

• AE’s of ALT elevation reported in 10/15 subjects:
  • 6E13 cohort peak ALT range 59-95 IU/L (60-95 among 6 reported ALT elevation)
  • 4E13 cohort peak ALT range 44-119 IU/L (70-119 among 3 reported ALT elevation)
  • All events of ALT increased non-serious, limited duration (0.4-7weeks) and Grade 1 severity (i.e. <3x ULN; ULN at 43 U/dL)
  • Treatment with corticosteroids well–tolerated in all subjects
  • All 6E13 subjects remain off steroids
Kinetics of FVIII Activity Levels In 4 Weekly Intervals
Subjects Administered BMN 270 at 6e13 vg/kg

Median/Mean FVIII activity values were utilized within a visit window
Excludes FVIII values within 72 hours of exogenous FVIII administration
Kinetics of FVIII Activity Levels In 4 Weekly Intervals
Subjects Administered BMN 270 at 4e13 vg/kg
ABRs Post BMN 270: Bleeding Stopped After FVIII Expression >5%

ABRs Pre and Post BMN 270 6e13 dose

**ABRs Pre and Post BMN 270 4e13 dose**

ABR is calculated as (the number of bleeding episodes/total number of days during the calculation period) x 365.25. Note that the figure includes only the 6 subjects in Cohort 3 who were receiving prophylactic exogenous FVIII replacement therapy prior to study enrollment.
The annualized Factor VIII usage is calculated as (the number of infusions of exogenous FVIII replacement therapy/total number of days during the calculation period) x 365.25

Note that the figure includes only the 6 subjects in Cohort 3 that were receiving prophylactic exogenous FVIII replacement therapy prior to study enrollment.
No significant CTL response detected by IFN-γ ELISpot

**AAV5 Capsid Peptide Stimulation**

**FVIII Peptide Stimulation**

*Positive controls: PMA/Ionomycin stimulates polyclonal T-cell activation and cytokine secretion. CEF pool is a mix of CMV, EBV and Influenza virus peptides.*
Consistent Correlation of One-stage With Chromogenic FVIII Activity Assay

![Graph showing correlation between Factor VIII Activity One-stage (IU/dL) and Chromogenic FVIII Activity (IU/dL). The graph includes data points for different subjects, with a linear regression line indicating a strong positive correlation. The R-square value is 0.957 and the slope is 1.654.]
Western Blot Analysis of hFVIII-SQ Transgene Products

Lanes 1-5: Subject plasma (Lane 1: Subject #3, Week 15; Lane 2: Subject #5, Week 12; Lane 3: Subject #8, Week 10; Lane 4: Subject #9, Week 6; Lane 5: Subject #6, Week 13); Lane 6: Molecular Weight Marker (SeeBlue® Plus 2); Lane 7: 100 ng/mL Xyntha® in congenital FVIII-deficient plasma; Lane 8: Congenital FVIII-deficient plasma; Lane 9: Pooled normal human plasma.

kDa, kilo Daltons; FVIII BDD-HC, B-domain deleted FVIII heavy chain; FVIII LC, FVIII light chain; FVIII BDD-SCP, B-domain deleted FVIII single chain precursor; asterisks (*) mark the position of non-specific bands also detected in congenital FVIII-deficient plasma.
Haem-A-QOL Evaluations in 6E13 COHORT

Mean total score change from baseline to week 52 = 9.6, 95%CI (-2.13, 21.42)

- Data encompasses all 6E13 subjects
- Mean total score change observed by week 16 and maintained over 52 weeks
- QOL improvement observed in all 6 domains; i.e. Consequences of Bleeding, Emotional Impact, Physical Functioning, Role Functioning, Treatment Concern, Worry

Week 16: 13.4
Week 28: 12.9
Week 52: 9.6

*Std. Dev take from high, low and medium dose patients at baseline (n=9)
**Distribution based MCID
------- MCID upper & lower thresholds

Pocoski J et al., 2014 Spinart trial 3-year results: improved quality of life in adults using prophylaxis with Bayer’s sucrose-formulated recombinant factor VIII. International Society on Thrombosis and Haemostasis 12 (Suppl. 1) (2014) 1–10620 ABSTRACTS
At 6E13/kg, AAV5-FVIII produced sustained mean and median FVIII levels of 104% and 89% respectively over 1 year of observation

- This dose eliminates occurrence of spontaneous bleeds
- Provides FVIII coverage, eliminating the need for FVIII even in cases of major trauma or surgery except for 1 patient who required peri-operative FVIII infusions at endogenous FVIII level of \( \approx 20 \text{ IU/dL} \)

AAV5-FVIII gene therapy was well-tolerated

- Mild elevations in liver enzymes were transient
- No sequelae related to transient steroid use
- No inhibitors detected

Dose response established

- 4E13 dose level resulted in lower FVIII expression levels than 6E13 dose level with lower correction of FVIII activity

**NEXT STEPS** – Initiate Phase 3 studies utilizing 6E13 dose to achieve normal levels of FVIII in subjects with hemophilia A
THANK YOU

All patients, teams and PIs

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Basingstoke, United Kingdom

Barts Health NHS Trust
London, United Kingdom

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Cambridge, United Kingdom

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