THREE-YEAR EFFICACY AND SAFETY RESULTS FROM A PHASE 1/2 CLINICAL STUDY FOR SEVERE HAEMOPHILIA A: CLINICAL OUTCOMES FOLLOWING GENE TRANSFER WITH VALOCTOCOGENE ROXAPARVOVEC

K. John Pasi, MB, ChB, PhD, FRCP, FRCPath, FRCPCH; Savita Rangarajan, MBBS, FRCP, FRCPath; Nina Mitchell, MB, BChir; Will Lester, MB, ChB, PhD, FRCP, FRCPath; Michael Laffan, DM, FRCP, FRCPath; Bella Madan, MD, FRCP, FRCPath; Emily Symington, BSc MBBS MRCP FRCPath; Benjamin Kim, MD; Xinquan Yang, PhD; Jennifer Quinn; Joshua Henshaw, PhD; Christian Vettermann, PhD; Glenn F. Pierce, MD, PhD; and Wing Y Jen Wong, MD

1Royal London Haemophilia Centre Barts Health NHS Trust London UK
2University Hospital Southampton, Southampton, UK
3BioMarin Pharmaceutical, Inc., Novato, CA, USA
4University Hospitals Birmingham NHS Foundation Trust, Birmingham, UK
5Hammersmith Hospital, Imperial College Healthcare NHS Trust, London, UK
6Guys & St Thomas’ NHS Foundation Trust, London, UK
7Cambridge University Hospitals NHS Foundation Trust, Cambridge, UK
8Consultant, La Jolla, CA, USA
Disclosures

• Grants and/or Research Support:
  – Alnylam Pharmaceuticals, BioMarin Pharmaceutical Inc, Bioverativ, UniQure

• Honoraria or Consultation Fees:
  – Alnylam Pharmaceuticals, ApcinteX, BioMarin Pharmaceutical Inc, Bioverativ, Catalyst BioSciences, Roche, Sanofi, and Sobi

• Company-Sponsored Speakers Bureau:
  – Bayer, Novo Nordisk, Octapharma, Pfizer, and Shire
Valoctocogene Roxaparvovec (AAV5-hFVIII-SQ) Expression Cassette

- Human factor VIII gene (hFVIII)
- B-domain-deleted (BDD) with SQ linker region
- Codon-optimized
- Human liver-specific promoter
- Synthetic polyadenylation signal (sPA)
- Flanked by inverted terminal repeats (ITRs)

A1AT = alpha-1-anti-trypsin promoter; ApoE = Apolipoprotein E; HCR = hepatic control region

BMN 270-201: Baseline Demographics & Clinical Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years, mean (SD)</td>
<td>31 (8)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>White</td>
<td>12 (80%)</td>
</tr>
<tr>
<td>Treatment before enrollment, n (%)</td>
<td></td>
</tr>
<tr>
<td>FVIII prophylaxis</td>
<td>14 (93%)</td>
</tr>
<tr>
<td>On-demand treatment with FVIII</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Proportion with zero bleeds</td>
<td>2 (13%)</td>
</tr>
<tr>
<td>Historical annualised bleeding rate, median</td>
<td></td>
</tr>
<tr>
<td>Prophylactic therapy (n=14)</td>
<td>6.5</td>
</tr>
<tr>
<td>6x10^{13} cohort (n=6)</td>
<td>16.5</td>
</tr>
<tr>
<td>4x10^{13} cohort (n=6)</td>
<td>8.0</td>
</tr>
<tr>
<td>On-demand treatment (n=1)</td>
<td>25</td>
</tr>
<tr>
<td>6x10^{13} cohort (n=1)</td>
<td>25</td>
</tr>
<tr>
<td>Subjects with target joints, n (%)</td>
<td></td>
</tr>
<tr>
<td>Previous disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>1 (7%)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>5 (33%)</td>
</tr>
</tbody>
</table>

15 subjects enrolled and dosed in 4 cohorts
- 1 subject in the 6x10^{12} vg/kg dose cohort
- 1 subject in the 2x10^{13} vg/kg cohort
- 7 subjects in the 6x10^{13} vg/kg dose cohort
- 6 subjects in the 4x10^{13} vg/kg dose cohort
Substantial Reduction in Treated Annualised Bleed Rate in Both Cohorts

6×10^{13} vg/kg dose cohort at Years 1, 2 & 3; N=6*

<table>
<thead>
<tr>
<th>Treated Annualised Bleed Rate (episodes/year)</th>
<th>Pre-Infusion</th>
<th>Y1 post</th>
<th>Y2 post</th>
<th>Y3 post</th>
</tr>
</thead>
<tbody>
<tr>
<td>median</td>
<td>16.5</td>
<td>0.9</td>
<td>0.2</td>
<td>0.7</td>
</tr>
<tr>
<td>mean</td>
<td>16.3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

96% reduction in mean ABR

% Patients Bleed Free**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>14%</td>
<td>71%</td>
<td>86%</td>
<td>86%</td>
</tr>
</tbody>
</table>

All patients off prophylaxis; 100% resolution in target joints

4×10^{13} vg/kg dose cohort at Years 1 & 2; N=6

<table>
<thead>
<tr>
<th>Treated Annualised Bleed Rate (episodes/year)</th>
<th>Pre-Infusion</th>
<th>Y1 post</th>
<th>Y2 post</th>
</tr>
</thead>
<tbody>
<tr>
<td>median</td>
<td>8</td>
<td>0.9</td>
<td>1.2</td>
</tr>
<tr>
<td>mean</td>
<td>12.2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

92% reduction in mean ABR

% Patients Bleed Free

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>17%</td>
<td>83%</td>
<td>67%</td>
</tr>
</tbody>
</table>

All patients off prophylaxis

* n=6; excludes the one participant treated with on demand FVIII pre-infusion

** n=7; includes the one participant treated with on demand FVIII pre-infusion
Continued Reduction in Annualised FVIII Usage

6x10^{13} \text{ vg/kg} \text{ Cohort in years 1, 2 & 3; N=6*}

- Pre-infusion: 138.5
- Y1 post: 2.1
- Y2 post: 8.8
- Y3 post: 5.5

96% reduction in mean FVIII usage

4x10^{13} \text{ vg/kg} \text{ Cohort in years 1 & 2; N=6}

- Pre-infusion: 155.5
- Y1 post: 2
- Y2 post: 0.5

97% reduction in mean FVIII usage

<table>
<thead>
<tr>
<th>Reduction in FVIII usage post-administration ((6\times10^{13} \text{ vg/kg}))</th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>98%</td>
<td>94%</td>
<td>96%</td>
</tr>
<tr>
<td>Median</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reduction in FVIII usage post-administration ((4\times10^{13} \text{ vg/kg}))</th>
<th>Year 1</th>
<th>Year 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>99%</td>
<td>95%</td>
</tr>
<tr>
<td>Median</td>
<td>100%</td>
<td>99.7%</td>
</tr>
</tbody>
</table>

*n=6; excludes the one participant treated with on demand FVIII pre-infusion*
Haemo-QoL-A Mean Total Score Change from Baseline Through Year 3

Haemo-QoL-A Mean Total Score Change From Baseline in $6 \times 10^{13}$ vg/kg Cohort

QOL improvement observed in all 6 domains:
- Consequences of bleeding
- Emotional impact
- Physical functioning
- Role functioning
- Treatment concern
- Worry

Mean Total Score

<table>
<thead>
<tr>
<th>Week</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>12.9</td>
</tr>
<tr>
<td>52</td>
<td>9.6</td>
</tr>
<tr>
<td>104</td>
<td>19.1</td>
</tr>
<tr>
<td>156</td>
<td>11.9</td>
</tr>
</tbody>
</table>

Week
270-201: Durable FVIII Activity Expression with Plateau Forming in Years 2-3

- FVIII activity levels reported here were measured using the chromogenic assay.

- FVIII levels were previously reported in terms of the less-conservative, one-stage assay. One-stage assay results continue to be ~1.6x higher than chromogenic.

Durable FVIII Activity Expression in Years 2-3

LOESS (LOcally Estimated Scatterplot Smoother) Curves of FVIII Activity Level Over Time in $6\times10^{13}$ and $4\times10^{13}$ vg/kg Cohorts
Persistence of Stable, Circularized DNA Supports Long-Term Expression
PBMCs Model the Fate of Transgene DNA in Long-Lived Cells

- PBMCs represent a relatively long-lived, nucleated cell that is easily accessible

- As a proxy for hepatocytes, whole blood and PBMC fractions were analyzed
  - Linear forms of FVIII DNA associated with RBCs predominate for 4-6 months
  - ITR-fused (presumed circular) FVIII DNA persists in longer-lived PBMCs

- Formation of durable, circularized vectors promotes FVIII expression for durations governed by host cell turnover rates
Ongoing Development Based on Phase 2 Results

- Product manufactured using final process at full-scale in dedicated gene therapy facility
- Prospective run-in study fully enrolled
- Ongoing Phase 3 trial
  - Completed planned interim data analysis (n=22) at six months to support initial registration
  - Larger cohort (n~110) to evaluate superiority of valoctocogene roxaparvovec to FVIII prophylactic therapy
  - 52-week analysis to assess ABR primary endpoint; study ongoing
GENEr8-1 Interim Analysis: Substantial Reduction in ABR and FVIII Usage

85% reduction in mean ABR from baseline levels where all patients were on standard of care prophylaxis.

95% reduction in mean FVIII usage annualized after week 5.

6×10^{13} \text{ vg/kg dose Interim Analysis Cohort (mITT; n=16)}

- Pre-infusion: Median 0.9, Mean 1.5
- Post-infusion: Median 0, Mean 1.5

6×10^{13} \text{ vg/kg dose Interim Analysis Cohort (mITT; n=16)}

- Pre-infusion: Median 132.7, Mean 146.1
- Post-infusion: Median 1.2, Mean 6.8

BMB 270-301 Clinicaltrials.gov identifier NCT03370913; EudraCT number 2017-003215-19
Successful Treatment in Phase 3 at Planned Interim Analysis
Confirms Activity of Product Manufactured at Full-Scale
Favourable and Consistent Safety Profile Across Phases 2 and 3

- Accumulated data have shown valoctocogene roxaparvovec to have a favorable safety and tolerability profile
- Liver biomarker abnormalities and infusion-associated reactions have been the most important treatment-related adverse events, with no emergence of delayed AEs
  - Transient, asymptomatic, mild to moderate ALT elevations were observed ~8-16 weeks after dosing in most subjects
  - No clinical sequelae to corticosteroid use
  - No evidence of clinically significant impact on liver function
  - No correlation between ELISPOT reactivity and ALT elevations
- Two participants experienced mild infusion reactions
  - Events were mitigated by managing infusion rates
  - All resolved without clinical sequelae within 48 hours following routine medical management
- No subjects have developed thrombotic events or inhibitors to FVIII
Summary

- Durable efficacy demonstrated for up to at least three years following administration of valoctocogene roxaparvovec in 270-201
- Clinically meaningful increases in FVIII activity significantly above the threshold required for haemostatic efficacy
  - Demonstrated by profound effects on bleeding and factor VIII usage
- Favourable safety profile with no unexpected events across studies
- Based on observed durability and biological mechanism of stabilization in 270-201, clinically transformative results observed in 270-301 expected to be sustained
THANK YOU
To all study participants, advisors, teams, and principal investigators

Hampshire Hospitals NHS Foundation Trust
Basingstoke, United Kingdom

Barts Health NHS Trust
London, United Kingdom

Cambridge University Hospitals NHS Foundation Trust
Cambridge, United Kingdom

Guy’s & St. Thomas’ NHS Foundation Trust
London, United Kingdom

Queen Elizabeth Hospital Birmingham
Birmingham, United Kingdom

Imperial College Healthcare NHS Trust
London, United Kingdom

Thank you to the BioMarin team