Gene therapy in hemophilia A: The impact of valoctocogene roxaparvovec on patient outcomes – initial results from Patient Reported Outcomes, Burdens and Experiences (PROBE) from the GENEr8-1 trial

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Presentation learning objectives

- Understand application of a novel, hemophilia-specific, patient-reported outcome measure in a clinical trial involving a phase 3 gene therapy
- Understand the effect of a one-time infusion of valoctocogene roxaparvovec on health outcomes, burdens, and experiences identified as important by people living with hemophilia
- Understand the future direction for generation of real-world evidence using patient-centered outcomes with novel hemophilia treatments
Disclosures for Mark W. Skinner

I have the following potential conflict(s) of interest to report:

- **Research support:** Institution received research support for the PROBE study, an independent investigator-initiated research project

- **Director, officer, employee:** ICER, Institute for Policy Advancement Ltd., McMaster University, NORD, Patient Outcomes Research Group Ltd., and WFH USA

- **Honoraria:** Institution received honoraria or fees for attending advisory boards or educational presentations from Bayer, BioMarin Pharmaceutical Inc., Novo Nordisk, Roche/Genentech, Pfizer, and Takeda

- **Advisory committee:** Blue Cross Blue Shield, NHF MASAC, DSMB - Pfizer, Spark

- **Consultant:** NHF and Sanofi
Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence that enables endogenous FVIII production in people with severe hemophilia A (FVIII ≤1 IU/dL)\(^1\)\(^,\)\(^2\)
- In GENEr8-1, an open-label phase 3 trial, participants achieved FVIII activity providing improved protection from bleeding compared with prophylaxis for 52 and 104 weeks\(^1\)\(^,\)\(^2\)
- Here, we describe patient-reported changes from the PROBE questionnaire, a tertiary endpoint for the GENEr8-1 clinical trial
Phase 3 GENER8-1 study design

Eligible participants
- Adult men with severe hemophilia A (FVIII ≤1 IU/dL)
- Receiving routine FVIII prophylaxis at time of enrollment
- No history of FVIII inhibitors or anti-AAV5 antibodies
- No significant liver dysfunction, significant liver fibrosis, or cirrhosis

Endpoints
- Safety
- FVIII activity
- Change from baseline during post-prophylaxis
  - Annualized bleeding rate
  - Annualized FVIII utilization rate
- QoL

Screening
Year 1
Year 2
Year 3+

W0
W52
W104

6x10^{13} \text{ vg/kg}
valoctocogene
roxaparvovec infusion

AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; QoL, quality of life; W, week.
PROBE questionnaire

- Contains hemophilia-specific outcomes that assess health status and quality of life that are relevant to people with hemophilia\(^1\)
  - Pain, independence, education, employment, family life, and mobility
  - Developed by people with hemophilia
- Designed with the intent to collect data to improve treatment of hemophilia and assess outcomes beyond bleeding frequency
- Total score and item-specific changes from baseline were calculated at weeks 52 and 104 post valoctocogene roxaparvovec infusion
  - The total PROBE score ranges from 0 to 1 and the maximum score of 1 indicates the best HRQoL
Participant characteristics and disposition

Baseline characteristics\(^1\) ITT (N = 134)

<table>
<thead>
<tr>
<th>Age, years, mean ± SD</th>
<th>31.7 ± 10.3</th>
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</thead>
<tbody>
<tr>
<td>Race, n (%)</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>96 (71.6)</td>
</tr>
<tr>
<td>Asian</td>
<td>19 (14.2)</td>
</tr>
<tr>
<td>Black or African American</td>
<td>15 (11.2)</td>
</tr>
<tr>
<td>Hawaiian or Pacific Islander</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Not provided</td>
<td>3 (2.2)</td>
</tr>
<tr>
<td>Hispanic or Latino ethnicity, n (%)</td>
<td>7 (5.2)</td>
</tr>
<tr>
<td>BMI, kg/m(^2), mean ± SD</td>
<td>25.3 ± 4.6</td>
</tr>
<tr>
<td>Medical history, n (%)</td>
<td></td>
</tr>
<tr>
<td>Hepatitis B</td>
<td>20 (14.9)</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>41 (30.6)</td>
</tr>
<tr>
<td>HIV</td>
<td>2 (1.5)</td>
</tr>
<tr>
<td>Number of problem joints,(^a) n (%)</td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>97 (72.4)</td>
</tr>
<tr>
<td>1</td>
<td>17 (12.7)</td>
</tr>
<tr>
<td>2</td>
<td>9 (6.7)</td>
</tr>
<tr>
<td>3</td>
<td>8 (6.0)</td>
</tr>
<tr>
<td>&gt;3</td>
<td>3 (2.2)</td>
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</tbody>
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\(^a\)Problem joints were those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.

BMI, body mass index; HIV, human immunodeficiency virus; ITT, intent-to-treat; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.

PROBE total scores improved at weeks 52 and 104

***$P < 0.001$ compared to baseline using a linear mixed model. Data are mean ± SD or change from baseline (95% CI).

CI, confidence interval; PROBE, Patient Reported Outcomes, Burdens and Experiences; SD, standard deviation.
Outcomes for pain improved

*P <0.05, **P <0.01, ***P <0.001 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.

CI, confidence interval.
Outcomes for activities of daily living and mobility improved

**P < 0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.

CI, confidence interval.

**P < 0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.

CI, confidence interval.
Outcomes for work and school improved

*P < 0.05, **P < 0.01 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations.

CI, confidence interval.

Currently work full time

<table>
<thead>
<tr>
<th>Participants, %</th>
<th>Baseline</th>
<th>Week 52</th>
<th>Week 104</th>
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<tr>
<td>64.4</td>
<td>65.3</td>
<td>75.2</td>
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Made education/career decision due to health

<table>
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<tr>
<th>Participants, %</th>
<th>Baseline</th>
<th>Week 52</th>
<th>Week 104</th>
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<tr>
<td>57.5</td>
<td>47.0</td>
<td>48.2</td>
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Outcomes for number of missed work or school days per person-year due to health-related reasons improved

- Mean days of missed work or school in 12 months (95% CI)
- Rate ratio (95% CI) improvement
- Percentage of participants (95% CI)

*P < 0.05, **P < 0.01, ***P < 0.01 compared to baseline using negative-binomial regression models. Each person contributed 1 person-year. CI, confidence interval.
Outcomes for joint health improved

Currently have target joints
Experience chronic pain due to target joints
Have ≥3 spontaneous bleeds into any joint
Current reduced range of motion into any joints

Participants, %

Baseline | Week 52 | Week 104
---|---|---
Currently have target joints | 65.2 | 55.8 | 54.2
Experience chronic pain due to target joints | 65.9 | 62.2 | 72.0
Have ≥3 spontaneous bleeds into any joint | 21.8 | 5.7 | 7.6
Current reduced range of motion into any joints | 77.8 | 71.1 | 70.3

Change from baseline to week 52

- Experience chronic pain due to target joints
  - **P <0.01**

Have ≥3 spontaneous bleeds into any joint

- Current reduced range of motion into any joints
  - ***P <0.001***

% difference (95% CI)

- Change from baseline to week 52
- Change from baseline to week 104

*P <0.05, **P <0.01, ***P <0.001 compared to baseline using generalized estimating equations assuming Bernoulli variances with identity link and exchangeable outcome correlations. CI, confidence interval.
Conclusion

• Valoctocogene roxaparvovec led to quantifiable changes in patient-reported outcomes 2 years after a single infusion
  – Improvements were observed in health and quality of life outcomes

• PROBE score changes were generally consistent with EQ-5D-5L and Haemo-QoL-A results

• Further studies are needed to define a threshold for clinically meaningful changes in PROBE scores

• There are ongoing efforts to further interpret and identify underlying mechanisms for these results
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  - Alexandra Kucher
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- McMaster University
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  - Quazi Ibrahim
- Irish Haemophilia Society
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  - Mohit Jain

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