Gene therapy with the Padua variant of a codon-optimized human factor IX gene, etranacogene dezaparvovec, in people with hemophilia B: effects on patient-oriented outcomes measured using the Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire in the HOPE-B study

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Background

- Hemophilia B is a rare disease that requires lifelong treatment, often resulting in reduced quality of life[1,2]
  - Chronic pain, functional limitations, and mental health problems such as depression or anxiety have been observed in patients with hemophilia B
- Etranacogene dezaparvovec (formerly AMT-061), the first approved gene therapy for hemophilia B in the EU and US, is an adeno-associated virus 5 (AAV5) vector expressing the Padua factor IX (FIX) variant[3–6]
- A single dose of etranacogene dezaparvovec aims to provide long-term circulating FIX activity, minimize severe bleeding, and eliminate the need for continuous prophylaxis[3,7,8]
- The HOPE-B trial was a pivotal Phase 3, open-label, single-dose, single-arm, international trial (NCT03569891) in adult males with severe or moderately severe hemophilia B whose FIX activity was ≤2% of normal[7,8]
  - Etranacogene dezaparvovec stably reduced annualized bleeding rate by 64% and demonstrated superiority to FIX prophylaxis for up to 3 years post treatment
  - 94.4% (51/54) of patients remained free of continuous prophylactic FIX infusions at 3 years post treatment
- The Patient Reported Outcomes, Burdens and Experiences (PROBE) questionnaire was created by patients and for patients with hemophilia to assess domains such as health status and health-related quality of life[9]

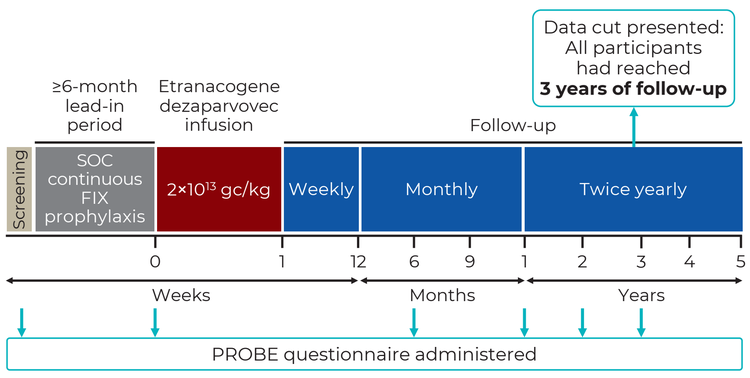
Objective

- **Determine the effect of a single dose of etranacogene dezaparvovec on participant quality of life and the burden of the disease as measured by the PROBE questionnaire after 3 years in the HOPE-B trial**

Methods

- In this Phase 3, open-label, single-arm trial, participants with severe to moderately severe hemophilia B received FIX prophylaxis for ≥6 months (lead-in period) followed by one infusion of etranacogene dezaparvovec (**Figure 1**)
- The PROBE questionnaire was administered at enrollment, during the lead-in period, and at 6 months and 1, 2, and 3 years after the treatment
  - Data collected at 6 months are not included in this analysis
  - PROBE assessments given within 2 weeks of an acute bleeding episode were excluded from this analysis

Figure 1: HOPE-B study design



FIX, factor IX; PROBE, Patient Reported Outcomes, Burdens and Experiences; SOC, standard of care.

- The outcomes provided are those reported directly by the participants and are not adjudicated with medical records or another objective dataset
- The PROBE score was calculated and ranged from 0 to 1 (worst to best health status possible)
- Baseline is considered the last available assessment before administration of etranacogene dezaparvovec
- The minimal clinically important difference in PROBE score is being confirmed in ongoing studies. The threshold for a change, set here as 0.1, is based on unpublished data (personal communication, F. Germini)

Results

- 54 adult males received etranacogene dezaparvovec
  - 48 participants consented to the PROBE substudy
    - 2 participants included in the PROBE substudy did not respond to treatment: 1 with the highest neutralizing antibody titer and 1 who received ~10% of the planned dose[7]
- The mean (standard deviation) PROBE score was 0.77 (0.16) at baseline (**Table 1**)
  - 81% (n=39) of participants had severe hemophilia B

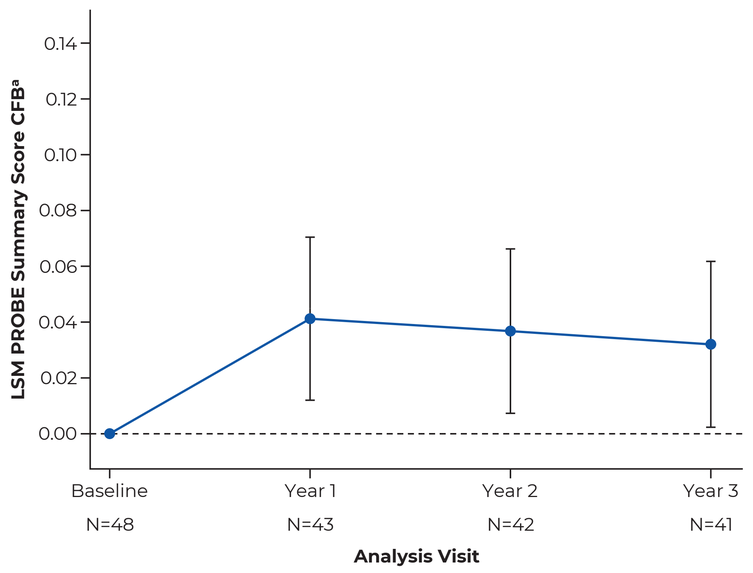
Table 1: Baseline characteristics of the study population

Characteristics	N=48
Age, mean (SD), years	42.8 (16.1)
Weight, mean (SD), kg	86.1 (19.8)
Body mass index, mean (SD), kg/m²	27.5 (5.1)
Hemophilia severity, n (%)[a]	
Moderately severe (FIX level 1% to ≤2%)	9 (18.8)
Severe (FIX level <1%)	39 (81.3)
Baseline PROBE summary score, mean (SD)[b]	0.77 (0.16)

[a]Hemophilia severity category is defined as the historical FIX level category at the time of diagnosis collected at the screening visit.
[b]Baseline value is the last value before administration of etranacogene dezaparvovec.
FIX, factor IX.

- Using the baseline as a reference, there was a least-squares mean change (95% CI) in the PROBE score of 0.04 (0.01, 0.07) at 1 year (**Figure 2**), which persisted at 2 years, 0.04 (0.007, 0.07), and 3 years, 0.03 (0.002, 0.06)
- At 3 years, 9 (22.0%) of 41 participants with PROBE scores had an improvement of at least 0.1 in the PROBE score, and 5 (12.2%) had a worsening of at least 0.1
  - Of the 5 participants who experienced a worsening, 4 participants had near-maximal baseline PROBE scores (mean=0.94)
  - 1 participant who experienced a worsening underwent liver transplant following diagnosis of hepatocellular carcinoma, which was deemed unrelated to treatment[10]

Figure 2: Change in PROBE score over time



[a]Changes in PROBE scores were analyzed using a linear mixed model with random intercept, adjusted for baseline PROBE score.
Error bars show 95% CI.
CFB, change from baseline; LSM, least-squares mean.

- At 3 years, there was a 24.5% (95% CI, –42.2, –6.9) reduction in the prevalence of participants having experienced acute pain in the previous 12 months (**Table 2**)
- Participants' responses to questions on problem joints joints indicated that relative clinical stability was maintained over 3 years (**Table 3**)
- There was a trend toward reduction in the proportion of participants experiencing difficulties with activities of daily living reported by the subgroup who had at least one self-reported problem joint at baseline

Table 2: PROBE participant self-report on pain

Study visit	Use of pain medication[a]	Experience acute pain[b]	Experience chronic pain[c]
Proportion of participants reporting selected outcome, n/N (%)			
Baseline	39/48 (81.3)	35/48 (72.9)	33/48 (68.8)
Year 1	33/44 (75.0)	19/44 (43.2)	30/44 (68.2)
Year 2	33/43 (76.7)	20/43 (46.5)	31/43 (72.1)
Year 3	32/45 (71.1)	22/45 (48.9)	33/45 (73.3)
Change from baseline, % (95% CI[d])			
Year 1	–7.5 (–17.6, 2.7)	–28.8 (–43.9, –13.7)	0.0 (–9.9, 10.0)
Year 2	–6.5 (–22.0, 9.0)	–24.8 (–42.4, –7.2)	6.0 (–6.0, 18.1)
Year 3	–11.3 (–24.3, 1.7)	–24.5 (–42.2, –6.9)	5.1 (–5.0, 15.1)

[a]PROBE question 10: During the past 12 months did you use any medication for pain?
[b]PROBE question 11: "Acute pain" is defined as pain that arises in response to an event (like an injury or bleeding episode). "Acute pain" does not include "chronic pain." "Chronic pain" is defined as pain from a persistent cause; it can vary in frequency and intensity (like back pain, pain from sore joints, or arthropathy). During the past 12 months, have you experienced acute pain?
[c]PROBE question 12: "Chronic pain" is defined as pain from a persistent cause; it can vary in frequency and intensity (like backpain, pain from sore joints, or arthropathy). "Chronic pain" does not include "acute pain." "Acute pain" is defined as pain that arises in response to an event (like an injury or bleeding episode). During the past 12 months, have you experienced chronic pain?
[d]The 95% CIs about percent change from baseline were calculated using standard errors derived using the delta method.
PROBE, Patient Reported Outcomes, Burdens and Experiences.

Table 3: PROBE participant self-report on problem joints

Study visit	Currently have problem joints[a]	Experience chronic pain due to problem joints[b]	Current reduced range of motion in any joints[c]
Proportion of participants reporting selected outcome, n/N (%)			
Baseline	36/48 (75.0)	28/46 (60.9)	36/48 (75.0)
Year 1	34/43 (79.1)	24/38 (63.2)	29/42 (69.0)
Year 2	30/41 (73.2)	25/39 (64.1)	28/42 (66.7)
Year 3	27/41 (65.9)	20/32 (62.5)	29/42 (69.0)
Change from baseline, % (95% CI[d])			
Year 1	4.5 (–7.6, 16.6)	–4.5 (–13.0, 4.0)	–4.1 (–9.8, 1.5)
Year 2	–0.9 (–8.7, 7.0)	7.9 (–3.1, 18.9)	–4.9 (–13.2, 3.4)
Year 3	–10.5 (–23.1, 2.0)	4.2 (–10.2, 18.6)	–5.2 (–13.1, 2.8)

[a]PROBE question 24: Do you currently have any problem joints*? (Please check all that apply.)
(A "problem joint"* is defined as having chronic joint pain and/or limited range of movement due to compromised joint integrity (e.g., chronic synovitis and/or hemophilic arthropathy), with or without persistent bleeding). *The term "target joints" was used in the questionnaire administered during the HOPE-B study. This term has since been updated to "problem joints."
[b]PROBE question 24a: Are any of these joints causing you "chronic pain"?
[c]PROBE question 26: Is the range of motion of any joint currently reduced because of your having hemophilia? (Please check all that apply.)
[d]The 95% CIs about percent change from baseline were calculated using standard errors derived using the delta method.
PROBE, Patient Reported Outcomes, Burdens and Experiences.

Conclusions

- **Administering a single dose of etranacogene dezaparvovec to participants with hemophilia B led to an improvement in PROBE score through 3 years**
- **The majority of participants experienced an improvement or no change in PROBE score at 3 years despite discontinuing FIX prophylaxis**
- **Improvements in PROBE scores suggest that etranacogene dezaparvovec may reduce the burden associated with hemophilia and FIX prophylaxis treatment**

References

1. Burke T, et al. *Orphanet J Rare Dis* 2021;16(1):143.
2. Buckner TW, et al. *Eur J Haematol* 2018;100(6):592–602.
3. US Food & Drug Administration. Etranacogene dezaparvovec (HEMGENIX®) US Prescribing Information. Updated November 2022.
4. US Food & Drug Administration. https://web.archive.org/web/20221130102341/https://www.fda.gov/news-events/press-announcements/fda-approves-first-gene-therapy-treat-adults-hemophilia-b. Accessed February 14, 2024.
5. European Medicines Agency. https://www.ema.europa.eu/en/news/first-gene-therapy-treat-haemophilia-b#:~:text=Hemgenix%20is%20the%20first%20gene,not%20cause%20disease%20in%20humans. Accessed February 14, 2024.
6. Von Drygalski A, et al. *Blood Adv* 2019;3(21):3241–7.
7. Pipe SW, et al. ASH 2023. Oral presentation. Abstract 1055.
8. Pipe SW, et al. *N Engl J Med* 2023;388(8):706-718.
9. Chai-Adisaksopha C, et al. *BMJ Open* 2018;8(8):e021900.
10. Schmidt M, et al. *Blood Adv* 2023;7(17):4966–9.

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Learn more about the PROBE Questionnaire

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