Sustained factor IX levels at 5-years after etranacogene dezaparvovec – the exponential decay model may underestimate observed results

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Introduction

- Hemophilia B is a rare, X-linked congenital bleeding disorder caused by factor IX (FIX) deficiency[1]
- Despite routine prophylaxis, breakthrough bleeds and joint complications can still occur[2]
- Gene therapy aims to correct the underlying *F9* mutation in hemophilia B, negating the need for FIX prophylaxis[2]
- Etranacogene dezaparvovec is a one-time adeno-associated virus serotype-5 (AAV5) gene therapy for the treatment of adult patients with severe (<1 IU/dL) or moderately-severe (1 to ≤2 IU/dL) hemophilia B, which has demonstrated sustained endogenous FIX expression over 5 years post-treatment in the Phase 3 HOPE-B trial[2]
- To reduce uncertainty for clinicians, patients, and payors in the absence of longer-term durability data for sustained FIX activity levels, model-based predictions enable assessments of the long-term durability of gene therapy[3,4]
- A statistical model was previously developed to predict mean FIX levels over time, assuming the exponential decay of FIX activity, which demonstrated durable FIX activity at 2 years among 55 participants treated with etranacogene dezaparvovec, with >80% projected to remain free from prophylaxis (based on a FIX level ≥2% for a patient requiring prophylaxis) for up to 25.5 years post-infusion[4]
- As additional trial data, including up to 5 years of observed follow-up, are available for etranacogene dezaparvovec, it is now appropriate to validate the previous model and reassess its underlying assumptions

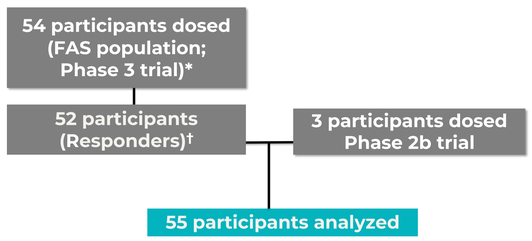
Objective

- **To validate predictions from the previously published exponential decay model using observed 5-year data from the Phase 2b trial and Phase 3 HOPE-B trial of etranacogene dezaparvovec**

Methods

- A combined dataset of 55 people with hemophilia B who were treated with and responded to etranacogene dezaparvovec was used to develop the model (**Figure 1**)
- These patients were pooled from the 2.5-year Phase 2b trial (n=3; NCT03489291) and the 2-year Phase 3 HOPE-B trial (n=52; NCT03569891)
- A Bayesian linear mixed-model framework was used to predict long-term FIX activity after etranacogene dezaparvovec infusion, based on FIX activity trends observed in the clinical trial population
- FIX activity levels, measured by a central laboratory one-stage aPTT assay, were log-transformed under the assumption that FIX activity follows a log-linear (exponential) trajectory over time, enabling long-term extrapolation from observed Phase 2b and Phase 3 trial data
- Long-term predictions were generated by applying estimated FIX activity trajectories from observed data to a synthetic population
- The predicted FIX activity levels post-infusion based on the 2-/2.5-year data were compared to the 5-year observations from the clinical trial data
- The model was then re-estimated, incorporating the combined Phase 2b/Phase 3 5-year data, and compared to the actual observations within the clinical trials

Figure 1. Analysis populations and evidence inputs for the exponential decay model



FAS, full analysis set.
*FAS included participants who enrolled in Phase 3 trial, entered the Lead-in Period, were dosed with etranacogene dezaparvovec and provided ≥1 efficacy endpoint assessment.
†Responders were defined as treated participants who achieved sustained endogenous FIX expression and discontinued prophylactic FIX replacement. Two participants who did not respond to treatment were excluded from the analysis.

Results

Original 2-year model

- Mean predicted FIX levels initially tracked the trajectory of FIX activity observed in the combined Phase 2b/Phase 3 HOPE-B trials, however, predictions were lower than the observed FIX levels over time (**Figure 2**)
- Mean predicted FIX levels at 5-years post-infusion (33.5%; 95% credible interval [CrI]: [6.5, 104.3]) were lower than observed 5-year FIX levels (36.7%) in the combined Phase 2b/Phase 3 clinical data (**Table 1**)

Updated 5-year model

- When the 5-year observed clinical data from the combined Phase 2b/Phase 3 trials were included, mean model-predicted FIX levels at 5 years post-infusion still underestimated the observed results (32.4% predicted versus 36.7% observed) (**Table 1; Figure 2**)

Underestimation of observed results

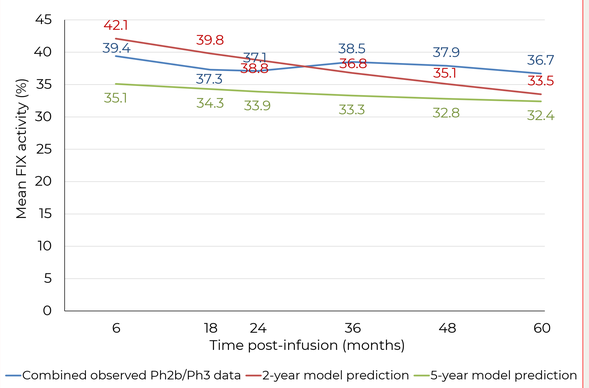
- The results suggest that the underestimation of the predicted values was driven by the underlying exponential decay assumption, rather than by the input data

Table 1. Observed mean FIX activity and model-predicted FIX levels for original 2-year and 5-year models

	Model-predicted mean FIX activity		Observed mean FIX activity
Time post-infusion, months	Original 2-year model, % (95% CrI)	Updated 5-year model, %* (95% CrI)	Combined Phase 2b/Phase 3, %
6	42.1 (10.6, 115.7)	35.1 (7.9, 100.8)	39.4
18	39.8 (9.6, 111.5)	34.3 (7.7, 98.3)	37.3
24	38.8 (9.2, 109.9)	33.9 (7.6, 97.4)	37.1
36	36.8 (8.2, 107.3)	33.3 (7.4, 96.4)	38.5
48	35.1 (7.4, 105.4)	32.8 (7.1, 96.5)	37.9
60	33.5 (6.5, 104.3)	32.4 (6.7, 97.4)	36.7

CrI, credible interval; FIX, factor IX.
*Updated 5-year model calibrated by integrating observed 5-year clinical data into Bayesian linear mixed model framework. Observed clinical data only available at scheduled visit months.

Figure 2. Observed mean FIX activity and model-predicted FIX levels for the original 2-year and 5-year models



FIX, Factor IX

Conclusions

- **While the exponential decay assumption appeared to align with the early 2-year combined Phase 2b/Phase 3 HOPE-B FIX trajectory, it may not fully capture the sustained FIX activity levels observed in the longer-term 5-year results**
- **Incorporating the 5-year clinical data did not improve the exponential decay model's accuracy of predictive modeling for liver-directed gene therapy, highlighting that exponential decay models may underestimate sustained FIX activity due to limitations in the underlying assumptions**
- **Using non-linear modeling methods that better reflect more recent clinical data may increase confidence in the durability of gene therapy**

References

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