

A novel Bayesian modeling approach increases precision of predicted long-term durability of etranacogene dezaparovec for the treatment of hemophilia B

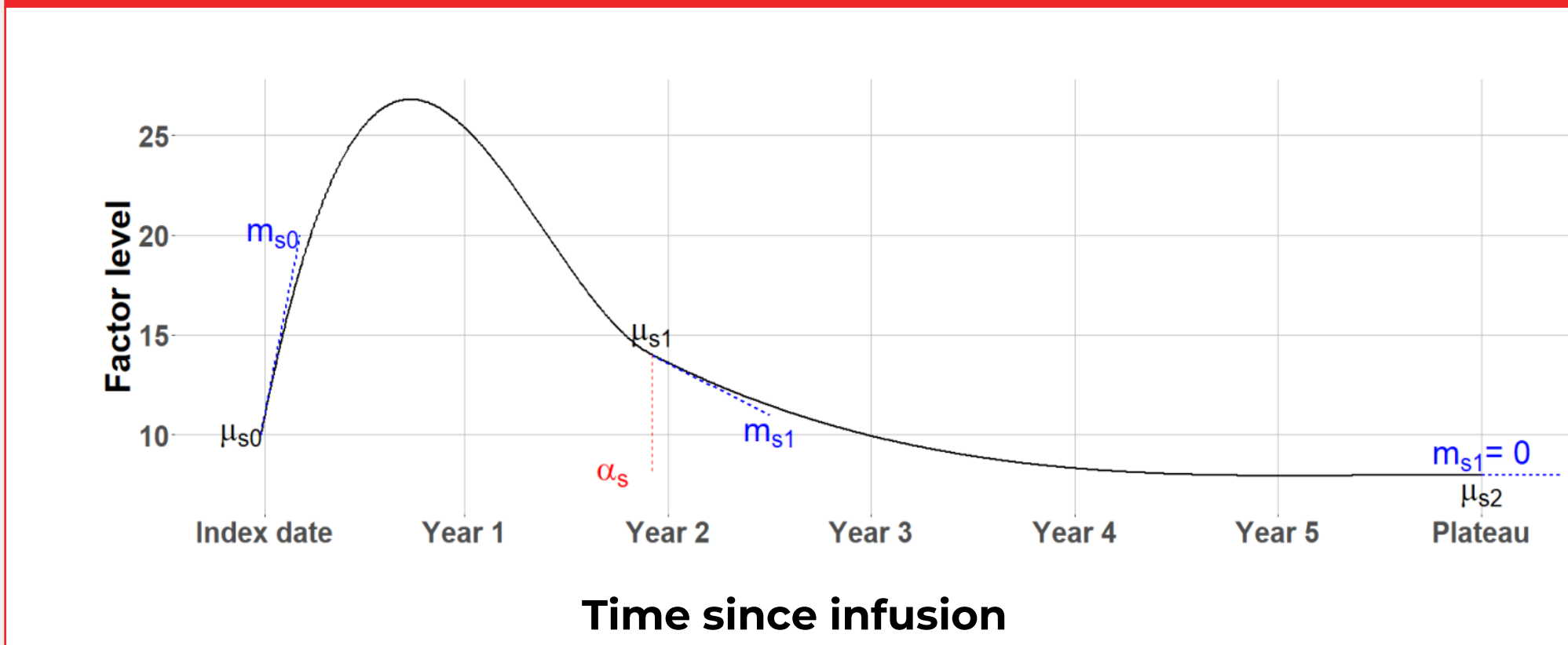
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Introduction

- Hemophilia B is a rare, X-linked congenital bleeding disorder caused by factor IX (FIX) deficiency¹
- Gene therapy offers treatment which can remove the need for exogenous FIX²
- In the Phase 3 HOPE-B trial, a single dose of etranacogene dezaparovec resulted in sustained FIX levels across 5 years of follow-up in participants with severe to moderately-severe hemophilia B²
- Evaluation of the long-term clinical and economic value of gene therapies is limited by the scarcity of long-term durability data³
- This evidence gap creates uncertainty for health technology assessment bodies and other decision makers, which may hinder the adoption of this innovation in clinical practice
- Modeling approaches, such as the exponential decay, QSP and BASE model⁴⁻⁶, have therefore been developed and/or applied to predict long-term durability of gene therapies in the absence of longer-term clinical data and can reduce such uncertainty

Figure 1. Hypothesized FIX trajectory of the BASE model

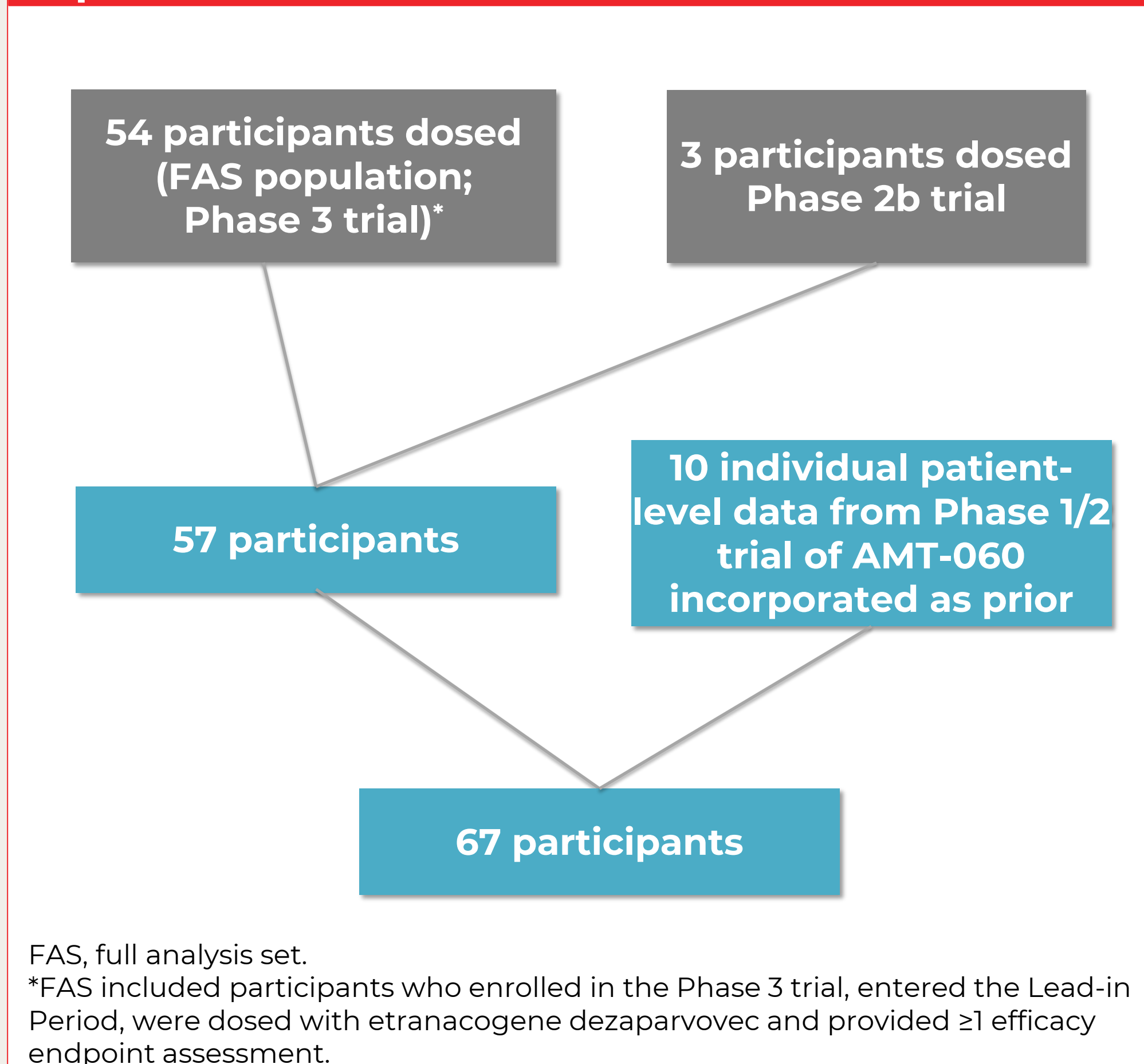


Note: This figure is intended to illustrate the functional form and non-linear shape of the BASE model over time. The y-axis is schematic and not intended to represent absolute values; quantitative predictions are reported in Table 1 and Figure 3.

Methods (cont'd)

- The accuracy and precision of model simulations were assessed by comparing predicted 5-year model outcomes with observed 5-year follow-up data from the Phase 2b/Phase 3 trials
- The BASE model also incorporated 9.5-year data from the Phase 1/2 trial of AMT-060, and was applied to the 5-year Phase 2b/Phase 3 clinical data of etranacogene dezaparovec (**Figure 2**)
- The model outputs were used to estimate the proportion of PwHB predicted to maintain FIX activity $\geq 5\%$ up to 30 years post-infusion

Figure 2. Analysis populations and evidence inputs for the BASE model



FAS, full analysis set.
*FAS included participants who enrolled in the Phase 3 trial, entered the Lead-in Period, were dosed with etranacogene dezaparovec and provided ≥ 1 efficacy endpoint assessment.

Results

Model validation

- Mean observed FIX values from the combined Phase 2b/Phase 3 trials and the Phase 3 trial alone were within the 95% credible intervals (CrI) of the corresponding model-predicted means in years 3, 4, and 5 post-infusion of etranacogene dezaparovec (**Table 1**)
- The observed 5-year FIX activity from the combined Phase 2b/Phase 3 data was 36.7% and the BASE model prediction was 33.6% (95% CrI: 24.7, 39.5)
- Importantly, the CrI around the model predictions exhibited low variability, which reduce uncertainty around the predictions

Table 1. Observed mean FIX activity and model-predicted FIX levels through 5 years

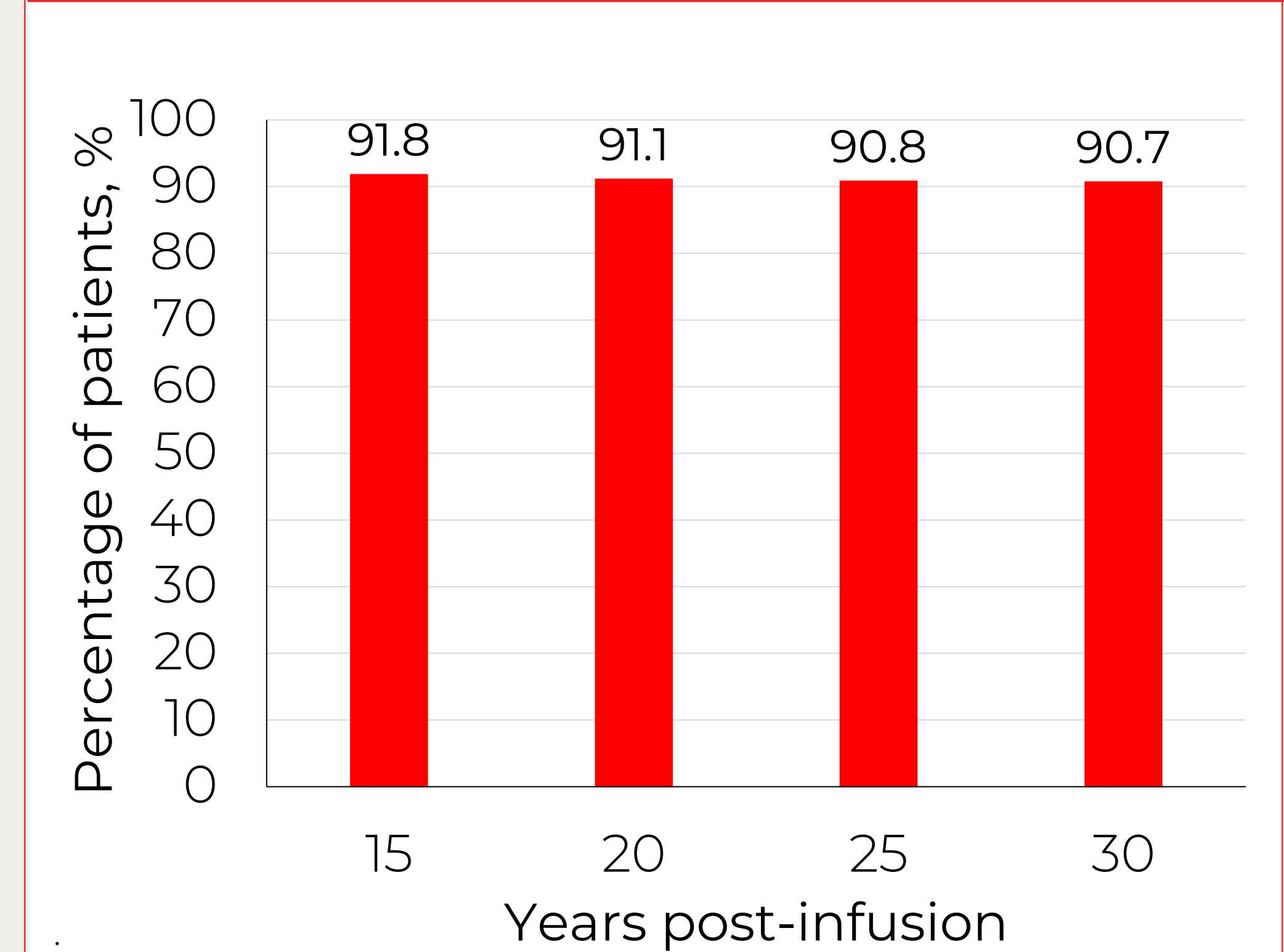
Time post-infusion, years	Model-predicted mean FIX activity, % (95% CrI)	Observed mean FIX activity	
		Phase 3, %	Combined Phase 2b/Phase 3, %
3	35.3 (30.7, 39.5)	38.6	38.5
4	34.2 (27.6, 39.3)	37.4	37.9
5	33.6 (24.7, 39.5)	36.1	36.7

CrI, credible interval; FIX, factor IX.

Long-term predictions

- After applying the BASE model to the 5-year observed combined Phase 2b/Phase 3 data of etranacogene dezaparovec and the 9.5-year Phase 1/2 data of AMT-060, the model predicted that 91% of PwHB receiving etranacogene dezaparovec would maintain FIX levels $\geq 5\%$ at 30 years post-infusion (**Figure 3**)

Figure 3. Predicted percentage of PwHB maintaining FIX $\geq 5\%$ after receiving etranacogene dezaparovec



Objective

- To assess the accuracy and precision of a novel, non-linear Bayesian (BASE) model by comparing the 5-year predictions of FIX activity with observed 5-year clinical data for etranacogene dezaparovec
- To predict long-term FIX activity levels by incorporating the most recently available clinical data into the BASE model

Methods

- A non-linear Bayesian (BASE) model was developed (**Figure 1**) which incorporated FIX activity data from people with hemophilia B (PwHB) treated with etranacogene dezaparovec, 2.5-year Phase 2b data (n=3; NCT03489291), and 2-year Phase 3 data (n=54; NCT03569891)
- The model also incorporated 5-year Phase 1/2 trial data of AMT-060 (n=10; NCT02396342), a predecessor to etranacogene dezaparovec
- Initial model outputs were used to generate 5-year post-infusion predictions

Conclusions

- The BASE model generated statistically unbiased estimates with low variability and was validated from long-term data of relevant clinical trials, including the pivotal Phase 3 HOPE-B trial
- This reduces uncertainty around long-term predictions on FIX levels following etranacogene dezaparovec infusion, reflecting the durability induced by gene therapy
- The low variability observed in the CrI's around the predictions compared with other predictive models (please see poster MSR98 for further details on the exponential decay model)⁴, indicate greater precision in long-term FIX durability predictions from the BASE model
- These findings support long-term durability of etranacogene dezaparovec in sustaining FIX levels, with >90% of treated PwHB predicted to maintain FIX levels $\geq 5\%$ over 30 years, thus predicting a low percentage of patients may return to prophylaxis

Disclosures

YS and WS have nothing to disclose.
XZ and DD are employees of CSL Behring.

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