AMT-060 and etranacogene dezaparvovec in haemophilia B: duration of freedom from bleeding and prophylaxis

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Introduction

- Key questions in the field of gene therapy for haemophilia B (HB) concern the long-term durability and kinetics of factor IX (FIX) expression, and the haemostatic effect over time
- AMT-060 (expressing the wild-type *F9* gene) is the precursor of etranacogene dezaparvovec (formerly AMT-061; expressing Padua variant *F9*) and utilises the same adeno-associated virus serotype 5 (AAV5) vector as well as a near-identical gene expression cassette, having only a two-nucleotide difference in the *F9* complementary DNA[1-3]
  - Padua FIX is a FIX variant that results in ~6-fold increase in FIX activity compared with wild-type FIX
- Three open-label, multicentre clinical trials of AMT-060 or etranacogene dezaparvovec are ongoing in adults with severe or moderately severe HB[1–5]
  - The phase 2b trial of etranacogene dezaparvovec was a confirmatory trial that supported the transition from the phase 1/2 trial of AMT-060 to the phase 3 trial of etranacogene dezaparvovec[2]
  - Etranacogene dezaparvovec resulted in improved efficacy outcomes compared with prior continuous FIX prophylaxis and was well tolerated in the primary analysis of the HOPE-B study[3]

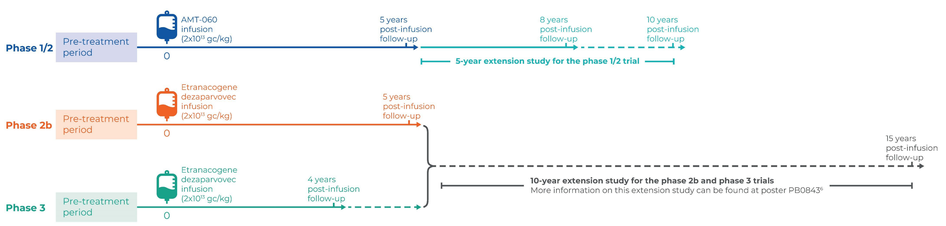
Objective

- **To determine durability, defined as sustained FIX activity and haemostatic protection, of AMT-060 and etranacogene dezaparvovec during extended surveillance of phase 1–3 clinical trial participants, all of whom were planned to receive a 2x10^{13} gc/kg vector dose**

Methods

- Long-term follow-up data from participants in three clinical trials of HB gene therapy were assessed, all of whom were planned to receive AMT-060 or etranacogene dezaparvovec at a dose of 2x10^{13} gc/kg (**Figure 1**)
  - Phase 1/2 trial (AMT-060; cohort 2 [N=5]; NCT02396342; 8-year follow-up)
  - Phase 2b trial of etranacogene dezaparvovec (N=3; NCT03489291; 5-year follow-up)
  - Phase 3 HOPE-B trial of etranacogene dezaparvovec (N=54; NCT03569891; 4-year follow-up)
- Study designs have been reported previously[1–3]
  - Informed consent was obtained from trial participants, and all trials were approved by medical ethics committees of the participating institutions
- For all three studies, endogenous FIX activity, freedom from bleeding, and freedom from continuous FIX prophylaxis were analysed; safety data were also analysed

Figure 1: Timelines for the phase 1/2 trial of AMT-060 (cohort 2)*, and the phase 2b and phase 3 trials of etranacogene dezaparvovec

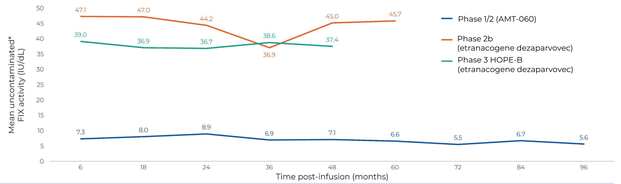


*Cohort 2 received AMT-060 at a dose of 2x10^{13} gc/kg.
gc, genome copies.

Results

- Of 62 participants treated with 2x10^{13} gc/kg AMT-060 or etranacogene dezaparvovec, 60 expressed transgene-derived FIX/FIX Padua
  - Two participants in HOPE-B did not express FIX Padua (high AAV5 neutralising antibody titre of 1:3212, n=1; received 10% of the planned dose, n=1)
- Endogenous mean FIX activity remained stable over 8 years in the phase 1/2 study of AMT-060 and over 5 and 4 years in the phase 2b and phase 3 HOPE-B studies, respectively (**Figure 2**)
- Proportions of participants free from bleeds ranged from 20–80% over 8 years post-AMT-060 infusion (wild-type FIX expression) and 57–100% over 4 or 5 years post-etranacogene dezaparvovec infusion (FIX Padua expression) (**Figure 3A–C**)
- All (100%) participants treated with 2x10^{13} gc/kg vector from the phase 1/2 and phase 2b studies remained free of continuous FIX concentrate prophylaxis up to their respective data cut-off (8- and 5-years post-infusion, respectively) (**Figure 3A–B**)
  - Of the 60 participants across the three studies who expressed endogenous FIX, 59/60 (98.3%) remained free of continuous prophylaxis during the reported follow-up periods
- Of the subjects who expressed endogenous FIX in the HOPE-B trial (n=52), 98% of participants remained free from continuous prophylaxis over a 4-year period
- Across the time periods analysed for all three trials, only one participant returned to continuous prophylaxis
- Throughout the three trials, no AAV5-associated genotoxicity has been confirmed, and no persistent late hepatotoxicity events were observed
- In HOPE-B, 96 treatment-related adverse events occurred up to 4 years post-infusion, 92 of which (95.8%) occurred in the first 6 months

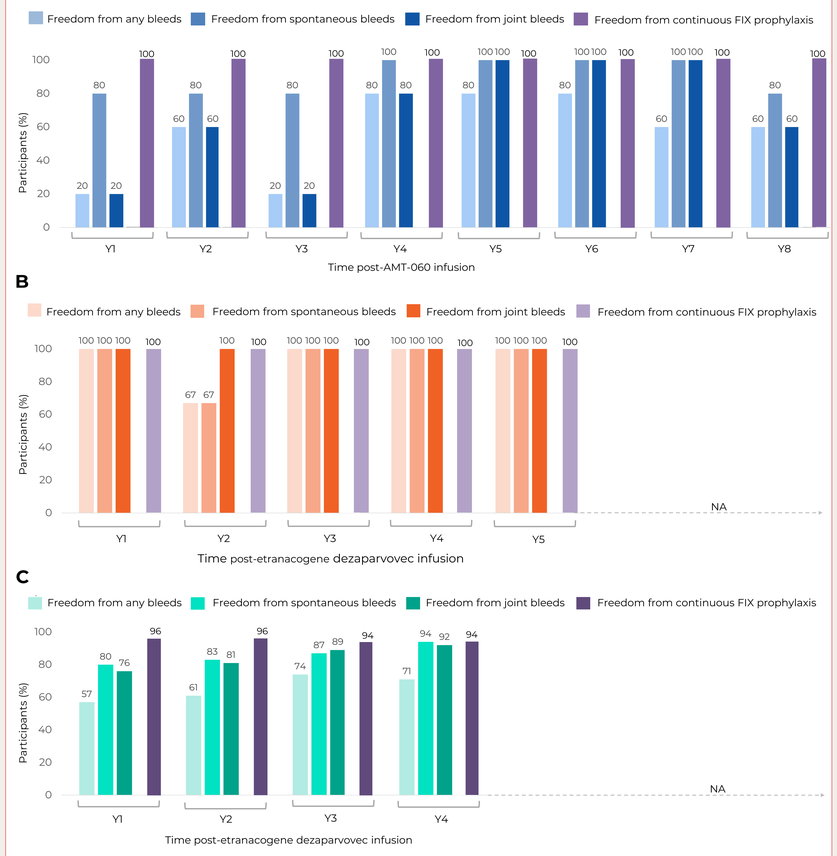
Figure 2: Mean endogenous FIX activity from Month 6 post-infusion for AMT-060 ≤8 years and etranacogene dezaparvovec ≤5 years



	6	18	24	36	48	60	72	84	96
Phase 1/2 study (AMT-060)	n=5	n=5	n=5	n=5	n=5	n=4	n=5	n=5	n=5
Phase 2b study (etranacogene dezaparvovec)	n=3	n=2	n=3	n=2	n=3	n=3			
Phase 3 HOPE-B study (etranacogene dezaparvovec)	n=51	n=50	n=50	n=48	n=47				

*FIX activity (from the OSA) is shown only for blood sampling that did not occur within five half-lives of exogenous FIX use (i.e., "uncontaminated" data).
FIX, factor IX; OSA, one-stage assay.

Figure 3: Freedom from bleed outcomes and freedom from continuous FIX prophylaxis in the phase 1/2 trial of AMT-060 (A; N=5), and the phase 2b (B; N=3) and phase 3 HOPE-B (C; N=54*) trials



*Includes two participants who were not responders.
FIX, factor IX; NA, not available; Y, year.

Conclusions

HB gene therapy with AMT-060 and etranacogene dezaparvovec resulted in durable endogenous FIX activity over 8 and 5 years, respectively

AMT-060 and etranacogene dezaparvovec provided long-term haemostatic protection, with freedom from continuous exogenous FIX prophylaxis and freedom from bleeds

No AAV5-associated genotoxicity has been confirmed, and no persistent late hepatotoxicity events were observed in the clinical trials reported here

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