Durability of Factor IX Activity and Bleeding Rate in People With Severe or Moderately Severe Hemophilia B After 5 Years of Follow-Up in the Phase 1/2 Study of AMT-060, and After 3 Years of Follow-Up in the Phase 2b and 2 Years of Follow-up in the Phase 3 Studies of Etranacogene Dezaparvovec (AMT-061)

Wolfgang Miesbach[1], Michael Recht[2], Nigel S. Key[3], Krupa Sivamurthy[4], Paul E. Monahan[4], Steven W. Pipe[5], on behalf of study investigators

[1]University Hospital Frankfurt, Frankfurt, Germany; [2]Yale University School of Medicine, New Haven, CT, USA; [3]University of North Carolina, Chapel Hill, NC, USA; [4]CSL Behring, King of Prussia, PA, USA; [5]University of Michigan, Ann Arbor, MI, USA

Introduction

- Previous studies have demonstrated a durable response to gene therapy for people with hemophilia B, with data presented over 5 and 8 years[1,2]
- AMT-060 and etranacogene dezaparvovec (formerly AMT-061) are investigational gene therapies for hemophilia B[3–5]
  - AMT-060: Precursor to etranacogene dezaparvovec; comprises an adeno-associated virus serotype 5 (AAV5) vector containing a transgene expressing wild-type factor IX (FIX)
  - Etranacogene dezaparvovec: Differs from AMT-060 by only one amino acid – transgene encodes the highly active Padua variant of FIX
- Etranacogene dezaparvovec aims to provide sustained FIX activity and hemostatic protection after a single infusion, to alleviate bleed risk and eliminate the need for continuous prophylaxis[4,5]
- Durability of response is expected to be similar for AMT-060 and etranacogene dezaparvovec due to the high similarity of the gene therapies

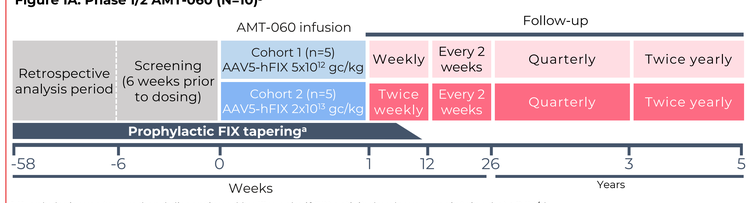
Aim

- To assess the observed durability of AMT-060 and etranacogene dezaparvovec in people with severe or moderately severe hemophilia B, defined by sustained FIX activity levels and hemostatic protection

Study designs

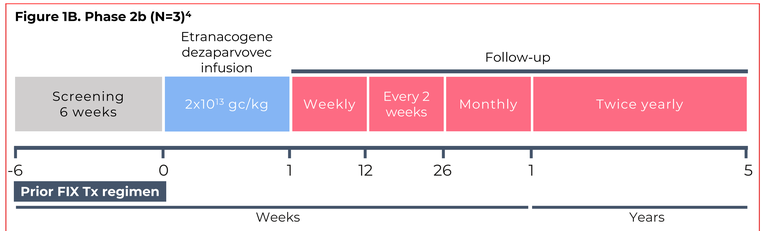
Figure 1. Study designs

Figure 1A. Phase 1/2 AMT-060 (N=10)[3]



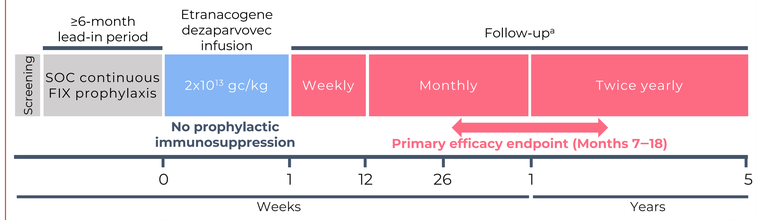
[a] Prophylaxis was tapered and discontinued by 12 weeks if FIX activity levels were maintained at ≥2 IU/dL.
AAV5, adeno-associated virus serotype 5; FIX, factor IX; gc/kg, genome copies/kilogram; hFIX, human factor IX.

Figure 1B. Phase 2b (N=3)[4]



FIX, factor IX; gc/kg, genome copies/kilogram; Tx, treatment.

Figure 1C. Phase 3 HOPE-B (N=54)[5]



[a] At least quarterly contact (±2 weeks) between site staff and subjects to monitor occurrence of adverse events. Last subject visit planned Q1 2025. FIX, factor IX; gc/kg, genome copies/kilogram; SOC, standard of care.

Methods

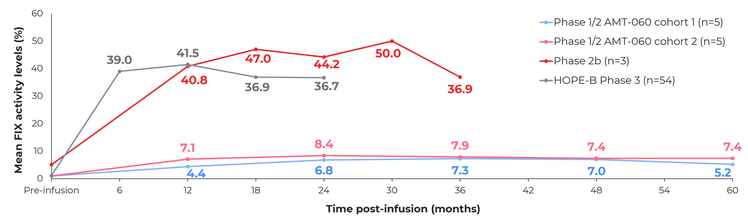
- Three open-label, multicenter clinical trials are ongoing in adults with severe or moderately severe hemophilia B
  - Phase 1/2 assessing AMT-060 (5-year follow-up; NCT02396342; **Figure 1A**)[3]
  - Phase 2b assessing etranacogene dezaparvovec (3-year follow-up; NCT03489291; **Figure 1B**)[4]
  - Phase 3 HOPE-B assessing etranacogene dezaparvovec (2-year follow-up; NCT03569891; **Figure 1C**)[5]
- In the HOPE-B Phase 3 trial, two non-responders were excluded from the full analysis set (N=54) to form the modified intent-to-treat population (n=52)
  - One had the highest AAV5 neutralizing antibody titer (3212) and one received only a partial dose
  - There were no uncontaminated FIX activity-level data for the two non-responders
- Study designs have been reported previously[3–5]
- For all three studies, FIX activity levels and bleeding events were evaluated

Results

Sustained FIX activity

- In the Phase 1/2 AMT-060 study, FIX activity levels remained stable in both cohorts over 5 years (**Figure 2**)
  - Cohort 1: Mean FIX activity was 4.4% at 52 weeks and 5.2% at 5 years
  - Cohort 2: Mean FIX activity was 6.9% at 26 weeks and increased to 7.4% at 5 years
- Greater FIX activity was achieved with etranacogene dezaparvovec versus AMT-060 (**Figure 2; Table 1**)
- In the Phase 2b study of etranacogene dezaparvovec, mean FIX activity increased from 23.4% (n=3) at Week 3 to 36.9% (n=2) at Year 3 (**Figure 2**)
- Similarly, in the Phase 3 HOPE-B study, mean FIX activity was sustained from 38.95% (n=51) at Month 6 to 36.66% (n=50) at Year 2 in both the full analysis set and the modified intent-to-treat population (**Figure 2; Table 1**)

Figure 2. Mean FIX activity levels over time in the clinical trials of AMT-060 and etranacogene dezaparvovec[a]



[a] Phase 1/2 AMT-060 and Phase 2b had no lead-in period; Phase 3 HOPE-B had a ≥ 6 month lead-in period where participants received prophylaxis. For Phase 2b, baseline FIX expression was 0–2%, but no washout of infused FIX was required prior to day 1; n=3 for all timepoints except pre-infusion (n=1), 18 months (n=2), and 36 months (n=2). For HOPE-B Phase 3, n=54 at pre-infusion, n=51 at 6 months, and n=50 at 12, 18 and 24 months. FIX, factor IX.

Table 1. Mean uncontaminated FIX activity levels and ABR after etranacogene dezaparvovec in the Phase 3 HOPE-B trial

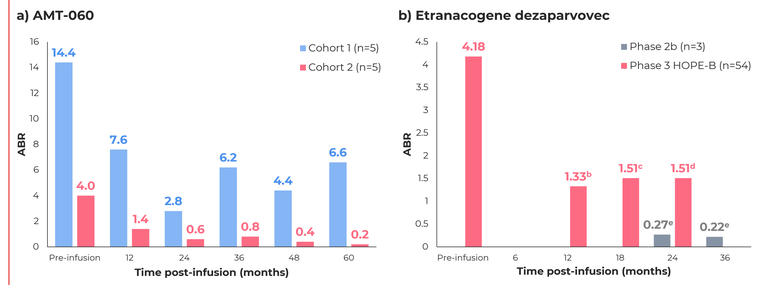
		Month			
	Lead-in period[a]	6	12	18	24
Phase 3, full analysis set					
Mean FIX activity level (%)	n=54 1.19	n=51 38.95	n=50 41.48	n=50 36.90	n=50 36.66
Mean ABR (all bleeds)	n=54 4.18	-	0–12 months n=54 1.33	7–18 months n=54 1.51	7–24 months n=54 1.51
Phase 3, modified intent-to-treat population[b]					
Mean FIX activity level (%)	n=52 1.19	n=51 38.95	n=50 41.48	n=50 36.90	n=50 36.66
Mean ABR (all bleeds)	n=52 4.00	-	0–12 months n=52 1.10	7–18 months n=52 1.01	7–24 months n=52 0.95

[a] Phase 3 had a ≥6-month lead-in period, where participants received FIX prophylaxis.
[b] The modified intent-to-treat population excludes two non-responders (one with the highest AAV5 NAb titer of 3212; one who received only partial dose); there were no uncontaminated FIX activity-level data for the two non-responders.
AAV5, adeno-associated virus 5; ABR, annualized bleeding rate; FIX, factor IX; NAb, neutralizing antibody.

Hemostatic protection

- In the Phase 1/2 AMT-060 study, mean ABRs in both cohorts decreased at Year 5 versus Year 1 (**Figure 3**)
  - Cohort 1: Mean ABR was 7.6 at Year 1 and 6.6 at Year 5
  - Cohort 2: Mean ABR was 1.4 at Year 1 and 0.2 at Year 5
- Similar low bleeding rates were observed in the Phase 2b and Phase 3 HOPE-B etranacogene dezaparvovec studies (**Figure 3; Table 1**)
  - Phase 2b: ABR at 3 years was 0.22 and no bleeding episodes occurred between 2.5–3 years
    - One participant experienced two lower leg muscle bleeding episodes (one spontaneous; one traumatic) and received 1700 IU FIX product replacement therapy for each
  - Phase 3 HOPE-B: ABR (all bleeds) was reduced at Months 7–18 post-dose (1.51) versus baseline (4.18), and maintained at Months 7–24 in the full analysis set (**Figure 3; Table 1**)
    - A similar reduction was observed in the modified intent-to-treat population: ABR (all bleeds) reduced from 4.00 at baseline to 0.95 at Months 7–24
    - Reductions in ABR for spontaneous, joint and traumatic bleeds were also maintained at Months 7–24

Figure 3. Mean ABR over time with (a) AMT-060 or (b) etranacogene dezaparvovec[a]



[a] Phase 1/2 AMT-060 and Phase 2b had no lead-in period; Phase 3 HOPE-B had a ≥6-month lead-in period where participants received prophylaxis. ABR calculated for [b] 0–12 months; [c] 7–18 months; [d] 7–24 months. [e] ABR not calculated for previous years. ABR, annualized bleeding rate.

Conclusions

- Gene therapy for hemophilia B appears to have a durable response
- FIX activity levels were sustained throughout the observation period across the Phase 1/2 study of AMT-060 and the Phase 2b and Phase 3 studies of etranacogene dezaparvovec
- Reductions in bleeding events remained stable across the course of the three studies
- Similar durable responses have been observed in published literature for hemophilia B gene therapies[1,2]

Acknowledgments

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