Multiple-year durability data from a Phase 2b trial of gene therapy with etranacogene dezaparvovec in people with hemophilia B

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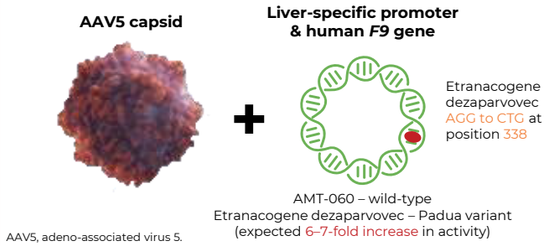
Introduction

- Etranacogene dezaparvovec: Investigational gene therapy for people with hemophilia B (HB)
- Recombinant adeno-associated virus 5 (AAV5) vector incorporating an expression cassette containing a codon-optimized Padua variant of factor IX (FIX) with a liver-specific promoter (**Figure 1**)[1]
- Similar to AMT-060,[2] an AAV-based gene therapy for HB with stable expression of wild-type FIX at 5 years,[3] differing only in a single amino acid substitution in the *F9* gene, encoding the highly active, naturally occurring Padua variant[4]

Figure 1. Etranacogene dezaparvovec



AAV5, adeno-associated virus 5.

- Aims to provide long-term circulating FIX activity after a single injection, adequate to ameliorate the severe bleeding phenotype of HB and eliminate the requirement for continuous prophylaxis[1]
- Currently being studied in the Phase 3 HOPE-B trial (NCT03569891)

Aims and methods

- Ongoing open-label, single-dose, single-arm Phase 2b study (NCT03489291) to confirm the efficacy and safety of etranacogene dezaparvovec
- Single intravenous dose of etranacogene dezaparvovec ($2x10^{13}$ gc/kg) in participants with severe or moderately severe HB (FIX activity ≤2%)
- Pre-existing neutralizing antibodies (NAbs) to AAV5 were evaluated but were not an exclusion criterion
- Primary efficacy endpoint was FIX activity at Week 6 (determined by one-stage clotting assay)

Results

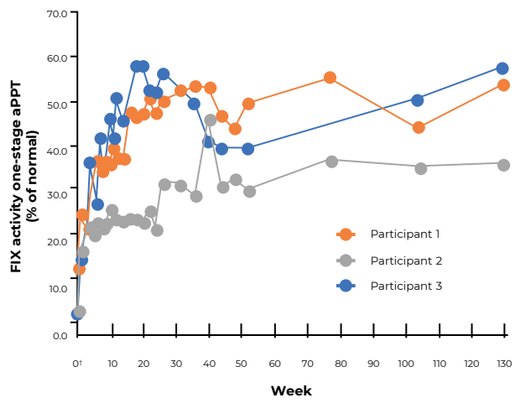
Baseline characteristics

- Three male participants aged 43–50 years were included
- All had resolved hepatitis C status and negative (n=1) or positive controlled (n=2) HIV status at baseline
- All received prophylactic extended half-life FIX treatment pre-screening, and had an annualized bleeding rate of 3, 1 and 5, respectively, 1 year prior to screening
- All participants had AAV5 NAbs at screening (titers: 25–48)

Stable and durable FIX activity

- The study achieved the primary endpoint of FIX activity ≥5% at Week 6 (**Figure 2**)[1]
- FIX activity in the three participants at 2.5 years was 58.6%, 54.4% and 37.1%, respectively. FIX activity continued to rise after 6 weeks, with a mean of 50% at 2.5 years (**Figure 2**)

Figure 2. FIX activity over time*



* Samples may include activity from exogenous FIX replacement.
† The Week 0 time point reflects FIX activity before etranacogene dezaparvovec treatment.

- Two participants maintained FIX activity in the non-hemophilic range (≥40%) after Week 16; one participant maintained FIX activity in the high–mild range (**Figure 2**)

Sustained reduction in bleeds and FIX replacement

- Post-treatment, there were no bleeds or FIX use in two out of three participants (**Table 1**)
- Participant 3 experienced two bleeds, which were treated with a single dose of FIX 2 days after the bleed started (**Table 1**)

Table 1. Number of bleeds

Participant	Bleeds	
	Pre-treatment	Post-treatment
1	3 spontaneous (severe)	0
2	1 spontaneous (moderate)	0
3	6 spontaneous* (moderate [n=2] and mild [n=4])	2 (traumatic [n=1] and spontaneous/mild [n=1])

* One bleed occurred after enrollment but prior to dosing.

- FIX use was also reported in Participant 3 for "other" instances, including protocol-specified use for perioperative surgical management
- All participants discontinued prophylaxis

Safety

- Previously reported for 6 months of follow-up[1]
  - Two treatment-related adverse events (TRAEs) in one participant; resolved without intervention (transient, self-limiting headache and slightly elevated C-reactive protein)
  - No clinically significant transaminase elevations or AAV5-specific T-cell response, no requirement for immunosuppression or loss of FIX activity
- Over the subsequent 24 months
  - No new TRAEs and no FIX inhibitor development
  - One serious adverse event unrelated to treatment (worsening of pre-existing avascular necrosis requiring two hip surgeries)
  - No clinically significant transaminase elevations or other findings
  - One participant with an additional isolated aspartate transaminase elevation at 18 months (62 U/L, upper limit of normal 34); resolved quickly without treatment or impact on FIX activity

Conclusions

- Substitution of wild-type FIX with FIX Padua leads to greatly increased circulating FIX activity, enabling the expression of near-normal FIX activity without increasing the dose exposure from that used in the Phase 1/2 trial of AMT-060[2]
  - This allowed for discontinuation of routine FIX prophylaxis whilst maintaining a sustained reduction in bleeds
- Durable expression of FIX Padua for at least 2.5 years is possible after a single dose of liver-targeted AAV gene therapy
- This was the first trial to show that presence of AAV5 NAbs did not interfere with the ability to express near-normal levels of FIX activity
- No treatment-related serious adverse event were reported

References

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Acknowledgments

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