One Year Data from a Phase 2b Trial of AMT-061 (AAV5-Padua hFIX variant), an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B

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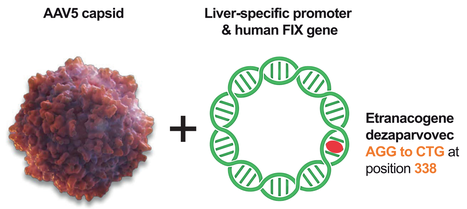
INTRODUCTION

- Gene transfer for severe hemophilia B can shift the disease phenotype to moderate (Factor IX [FIX] 1%–5% of normal), mild (FIX >5% to <40%) or normal (FIX ≥40%)[1,2] and significantly reduce or abrogate bleed risk.[3,4]
- AMT-060 (adeno-associated virus 5 [AAV5]-wildtype [wt] human FIX) has demonstrated efficacy and safety in an ongoing Phase 1/2 trial in hemophilia B (CT-AMT-060-01, see poster 2059).[3,5]
  - Stable expression of wildtype FIX observed at 3.5-4 years follow up with no late-emergent safety signals.
- Etranacogene dezaparvovec (AAV5-Padua hFIX) was developed by introducing a 2-nucleotide change into the transgene coding sequence of AMT-060, resulting in the naturally occurring highly active Padua FIX variant (**Figure 1**).[6]
- The phase 3 **H**ealth **O**utcomes with **P**adua gene; **E**valuation in Hemophilia **B** (HOPE B, NCT03569891) etranacogene dezaparvovec study is currently ongoing.[7]

Figure 1. Comparison of AMT-060 and etranacogene dezaparvovec



AIMS

- To confirm the 1-year efficacy and safety of etranacogene dezaparvovec in the phase 2b study.

METHODS

Trial design

- Phase 2b, open-label, single-dose, single-arm, multicenter trial (NCT03489291).[8]
- Single intravenous administration $2x10^{13}$ gc/kg of etranacogene dezaparvovec.

Study participants

- Three adult hemophilia B participants with FIX activity ≤2%.
- Controlled HIV, cleared hepatitis B/C, and no FIX inhibitors.
- Pre-existing neutralizing antibodies (NAbs) to AAV5 were evaluated but were not an exclusion criterion.

Outcomes

- Primary efficacy was assessed by FIX activity at 6 weeks (central one-stage clotting assay).
- Historical bleeds and FIX use for the year prior to study entry were assessed from medical records.
- Participants recorded bleeds and FIX use in their e-diary from screening to 1 year post treatment.
- FIX activity, bleeding rates and FIX replacement, and safety will be monitored for five years.
- This poster includes 1-year data from an interim analysis.

RESULTS

- Baseline demographics are shown in **Table 1**.
- Notably, all 3 had low titers of NAbs to AAV5 at baseline.

Table 1. Etranacogene dezaparvovec baseline demographics

Characteristic	Participant 1	Participant 2	Participant 3
Age (years)	43	50	47
Weight (kg)	89	81	82
HIV Status	Negative	Positive, controlled	Positive, controlled
Hep B / Hep C	Hep C; resolved	Hep C; resolved	Hep C; resolved
Hemophilia B status	FIX = 1%	FIX <1%	FIX <1%
Pre-screening FIX treatment	Prophylaxis (EHL FIX)	Prophylaxis (EHL FIX)	Prophylaxis (EHL FIX)
Annualized bleed rate 1-year prior to screening[a]	3	1	5
Neutralizing antibody activity (AAV5) (Luciferase assay)[b]	Positive 48	Positive 44	Positive 25

AAV, adeno-associated virus; EHL, extended half-life; FIX, Factor IX; Hep, hepatitis; HIV, human immunodeficiency virus; NAb, neutralizing antibody. Participants 2 and 3 were excluded from another AAV-based gene therapy trial for hemophilia B based on anti-AAV NAb titer. [a]Total bleeds (treated + untreated). [b]AAV5 NAb data from screening visit, considered positive if titer is ≥2.

FIX activity with etranacogene dezaparvovec

- The study achieved the primary endpoint of FIX activity ≥5% at 6 weeks 23.9-37.8%, n=3 (**Figure 2**):
- FIX activity continued to rise after week 6, stabilizing with a mean of 41.0% at week 52:
  - 2 participants maintain FIX activity in the nonhemophilic range (≥40%).
  - 1 participant maintains FIX activity in the high-mild range

Reduction in bleeds and FIX replacement with etranacogene dezaparvovec

- In the year prior to screening and the screening period (approximately 4 weeks) the participants experienced a total of 10 bleeds (**Table 2**).
- There have been no bleeds post-treatment, during the 52-week interim analysis.
- 97.6-100% reduction in FIX use post-treatment (excluding major surgery):
  - No FIX use in 2 participants.
  - 1 infusion of FIX self-administered by participant 3 for suspicion of a bleed (later confirmed to not be a bleed).
  - Protocol-specified use for perioperative management.

Table 2. Reduction in bleeds

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

*Table includes all bleeds (treated and untreated). *1 bleed occurred after enrollment but prior to dosing.*

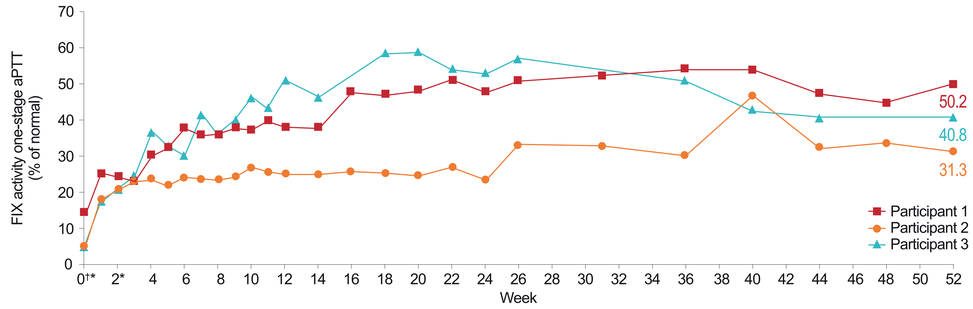
General safety

- Etranacogene dezaparvovec was well tolerated.
- 1 participant experienced two adverse events (AE), possibly related to etranacogene dezaparvovec, that resolved without intervention:
  - Transient, self-limiting headache and slightly elevated C-reactive protein.
- No loss of FIX activity.
- No FIX inhibitor development.
- 1 serious adverse event, deemed unrelated to treatment:
  - Participant 3: hip surgery due to worsening of pre-existing condition (avascular necrosis).

Liver-specific safety

- No clinically significant alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevations above upper limit of normal after dosing:
  - Participant 1 had isolated, slight elevations in ALT at week 22 (44 U/L) and week 44 (44 U/L).
  - Participant 2 experienced 3 isolated elevations in AST of 43 U/L (week 2), 48 U/L (week 4) and 90 U/L (week 31).

Figure 2. FIX activity post-etranacogene dezaparvovec treatment



*aPTT, activated partial thromboplastin time; FIX, Factor IX. No immunosuppression required. †The week 0 time point reflects FIX activity before etranacogene dezaparvovec treatment.*Samples may include activity from exogenous FIX replacement.*

- All incidences resolved quickly without treatment or impact on FIX activity.
- A single, isolated, positive AAV5-capsid specific T cell assay result (17 spot-forming units (SFU)/300,000 peripheral blood mononuclear cells (PBMC); threshold for positivity 5 SFU/300,000 PBMC) was reported in participant 2 at week 48.
- No participants required immunosuppression.

CONCLUSION

- Sustained FIX activity in the functionally curative range was observed after a single administration of etranacogene dezaparvovec with mean FIX activity of 41.0% at 52 weeks.
  - No bleeds post-treatment.
  - All subjects discontinued FIX prophylaxis.
- Etranacogene dezaparvovec was generally safe and well-tolerated.
- Efficacy and safety of etranacogene dezaparvovec is being further characterized in the ongoing pivotal HOPE-B study.

For more information, please visit www.ClinicalTrials.gov NCT03569891 or contact uniQure at uniQureHOPE-B@uniqure.com

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