Management of Infusion Reactions: Lessons from the Phase 3 HOPE-B Gene Therapy Trial of Etranacogene Dezaparvovec in Adults with Hemophilia B

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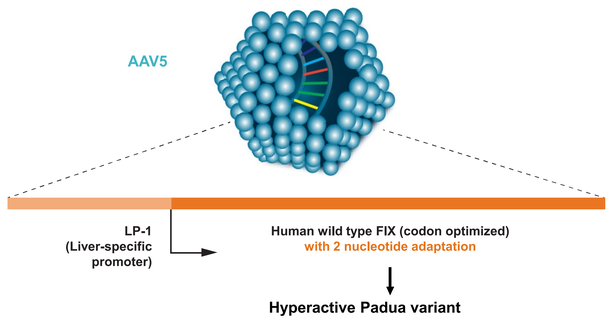
INTRODUCTION

- Etranacogene dezaparvovec (AMT-061) is an investigational gene therapy for hemophilia B (HB).
- AMT-060 (adeno-associated virus 5 [AAV5]-wildtype human FIX) has demonstrated efficacy and safety in an ongoing Phase 1/2 trial in HB.[1,2]
  - Stable expression of wildtype FIX was observed at 5 years follow up with no late-emergent safety signals.[2,3]
  - No infusion reactions were reported following AMT-060 treatment.
- Etranacogene dezaparvovec (AAV5-Padua hFIX) was developed by modifying the nucleotide transgene sequence of AMT-060, resulting in a highly active Padua FIX variant, which differs from the AMT-060 (wildtype hFIX) protein sequence by one amino acid **(Figure 1)**.
- 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.
- HOPE-B is the first Phase 3 study in HB and has the largest gene therapy cohort to date

Figure 1. Etranacogene dezaparvovec construct



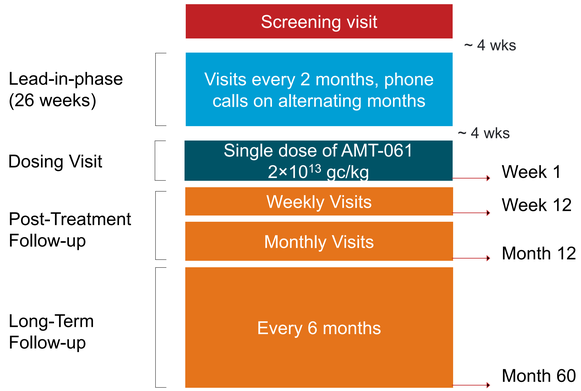
OBJECTIVES

- To detail infusion reactions, which occurred on the day of dosing.

METHODS

- HOPE-B (NCT03569891) is an ongoing open-label, single-dose, single-arm, multinational Phase 3 trial in adult males with severe or moderate HB (FIX≤2%) on routine FIX prophylaxis **(Figure 2)**. The presence of pre-existing AAV5 NAbs was not an exclusion criterion.
- A ≥6 month lead-in period preceded a single dose of etranacogene dezaparvovec ($2x10^{13}$gc/kg). The primary endpoint: 52-week annualized bleeding rate (ABR) after stable FIX expression has been achieved, compared to ABR in the lead-in period. Secondary endpoints include adverse events (AEs), FIX use compared with the lead-in period, FIX activity, and bleeding events **(Figure 2)**.

Figure 2. HOPE-B (AMT-061): study design[4]



RESULTS

- Participant baseline characteristics are described in **Table 1**.

	Full analysis set (N = 54)
Age, mean (SD, min-max), years	41.5 (15.8, 19-75)
Severity of hemophilia B at time of diagnosis, n (%)	
Severe (FIX <1%)	44 (81.5)
Moderately severe (FIX ≥1 and ≤2%)	10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior hepatitis B infection, n (%)	3 (5.6)
Prior hepatitis C infection, n (%)	27 (50.0)
Pre-screening FIX treatment (n, %)	
Extended half-life	31 (57.4)
Standard half-life	23 (42.6)
Detectable NAbs at baseline, n (%, max titer)	23 (42.6, 3212.3)
0 bleeds in lead-in, n (%)	16 (29.6)
Cumulative bleeds in lead-in, n	123

HIV, human immunodeficiency virus; NAb, neutralizing antibody; SD, standard deviation.

Safety: Infusion-related reactions (IRR)

- IRRs occurred in 7/54 participants (13%). Seven participants experienced 13 IRRs, which are detailed in **Table 2.**

Table 2. Infusion related reactions

Participant	NAb titer	Adverse event	Medication/Therapy	Severity	Action
1	189	Suspected hypersensitivity reaction	diphenhydramine IV methylprednisolone IV famotidine IV epinephrine IM lactated ringers bolus IV Demerol IV normal saline bolus (0.9%) IV	Moderate	Drug withdrawn
2	558.3	1. Infusion related reaction 2. Right eye itchiness 3. Hives behind the right ear 4. Headache 5. Dizziness	Diphenhydramine PO & IV hydrocortisone PO	Mild (all)	Drug interrupted
3	Negative	1. Light-headed 2. Chest tightness 3. Flushing	Benadryl IV	Moderate (all)	Drug interrupted
4	Negative	Fever	None	Mild	Dose not changed
5	481.9	Infusion related reaction: (facial flushing, feeling cold, shivers, rise in blood pressure)	Chlorophenamine IV hydrocortisone IV	Mild	Drug interrupted Infusion rate decreased to 250 mL/hr
6	3212.3	Epigastric pain	None	Mild	Dose not changed
7	23.3	Infusion related reaction: (itching, tightness of throat, and swelling right neck)	None	Mild	Dose not changed

Adverse events (AEs) are investigator categorized according to the following criteria. Mild AEs are usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living. Moderate AE is usually alleviated with specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the research subject. PO, oral; .IV, intravenous; IM, intramuscular.

- All events were reported on the day of infusion and most (12/13) resolved on the same day.
- The first occurrence (a moderate suspected hypersensitivity reaction) occurred after approximately 10% of the dose of etranacogene dezaparvovec was administered; the drug was withdrawn, and the participant received supportive treatment including, intravenous corticosteroids, and antihistamines.
- Subsequent IRRs were managed through a combination of temporarily interrupting or slowing the etranacogene dezaparvovec infusion and/or supportive treatment with steroids/antihistamines.
- Three mild reactions in 3 participants required no supportive treatment; this included 1 participant with a baseline AAV5 NAb titer of 3212.

Safety: Other treatment-related adverse events (AEs)

- No deaths and no inhibitors to FIX were reported.
- The most common treatment related AEs are listed in **Table 3**.
- Post 6-month data cut, a serious AE of hepatocellular carcinoma (HCC) in a subject with multiple pre-existing risk factors was reported. Integration analyses determined HCC was unlikely to be related to treatment with etranacogene dezaparvovec.[5]

Table 3. Most common treatment-related AEs

AE, preferred term	N = 54 n (%)
ALT increased	9 (16.7)
Headache	8 (14.8)
Influenza like illness	7 (13.0)
AST increased	5 (9.3)

n, Number of participants with events; (E), number of events

CONCLUSIONS

- Infusion-related reactions occurred in 7/54 participants (13%).
- The majority of IRRs were mild and resolved on the same day.
- Infusion reactions were successfully managed by:
  - Temporary infusion interruption
  - Decreasing infusion rate
  - Supportive treatment including antihistamines and steroids

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