52 Week Efficacy and Safety of Etranacogene Dezaparvovec in Adults with Severe or Moderate-Severe Hemophilia B: Data from the Phase 3 HOPE-B Gene Therapy Trial

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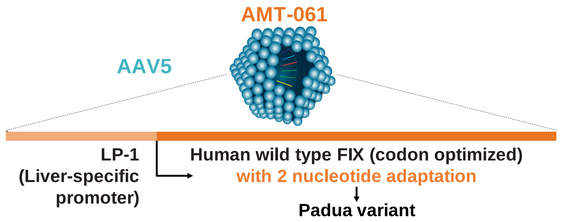
INTRODUCTION

- The investigational gene therapy for hemophilia B (HB) etranacogene dezaparvovec (AAV5-Padua hFIX; AMT-061) comprises an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized Padua variant human factor IX (FIX) transgene with a liver specific promoter (**Figure 1**).

Figure 1. Etranacogene dezaparvovec



AAV; adeno-associated virus; FIX, Factor IX.

- In the ongoing phase 3 **H**ealth **O**utcomes with **P**adua gene; **E**valuation in Hemophilia **B** (HOPE B, NCT03569891) study in 54 patients with HB:
  - Mean FIX activity increased to near-normal levels at 6 months post-etranacogene dezaparvovec.[1]
  - Bleeding was abolished in the majority of patients throughout the 26 weeks.[1]

AIMS

- To further assess efficacy and safety of etranacogene dezaparvovec in HOPE-B at 52 weeks (1 year).

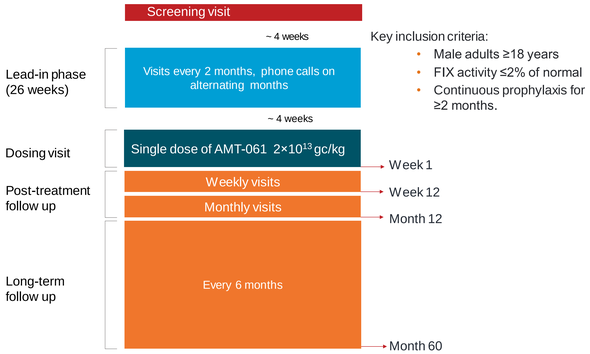
METHODS

Trial design

- Phase 3 open-label, single-dose, single-arm, international trial in adult males with severe or moderate-severe HB (FIX ≤ 2%) on routine FIX prophylaxis and with/without pre-existing neutralizing antibodies (NAbs) to AAV5 (**Figure 2**).
- A ≥6 month lead-in period preceded a single dose of etranacogene dezaparvovec ($2x10^{13}$gc/kg).
- Pre-existing anti-AAV NAbs were assessed, but not used as an exclusion criteria.
- No prophylactic immunosuppression was given.
- Participants were followed for a minimum of 52 weeks at the time of this analysis as part of a 5-year post-treatment follow-up period.

Study Design and participants

Figure 2. HOPE-B study design



For efficacy endpoints, the post-treatment period was considered to be the number of days of observation within the time interval reported (26 weeks, 52 weeks), excluding information prior to Day 21.

RESULTS

- Baseline demographics are shown in **Table 1**.
- 43% of participants had NAbs directed to the AAV5 capsid.

Table 1. Baseline demographics

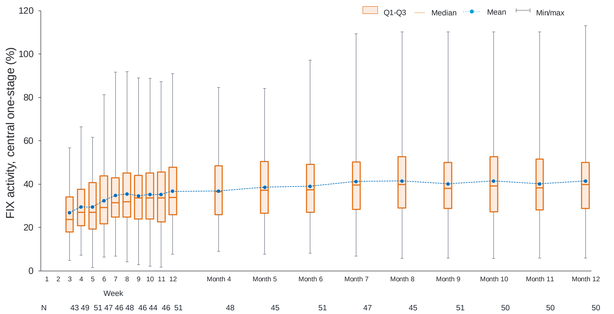
	Full analysis set (N = 54)
Age, mean (standard deviation, min-max), years	41.5 (15.8, 19-75)
Severity of HB at time of diagnosis, n (%) Severe (FIX <1%) Moderately severe (FIX ≥1% and ≤2%)	 44 (81.5) 10 (18.5)
Positive HIV status, n (%)	3 (5.6)
Prior hepatitis B infection, n (%)	9 (16.7)
Prior hepatitis C infection, n (%)	31 (57.4)
Pre-screening FIX treatment (n, %) Extended half-life Standard half-life	 31 (57.4) 23 (42.6)
Detectable NAbs at baseline, n (%)	23 (42.6)

HB, haemophilia B; HIV, human immunodeficiency virus; NAbs, neutralizing antibodies.

Stable and durable FIX activity post-etranacogene dezaparvovec treatment

- Following treatment, FIX activity increased rapidly to a mean of 39.0 (SD; min, max) IU/dL (±18.7; 8.2, 97.1) at Week 26 and 41.5 IU/dL (±21.7; 5.9, 113.0) at Week 52 (**Figure 3**).
- No clinically meaningful relationship was seen between pre-existing anti-AAV5 NABs and individual subject mean FIX between month 6 and 12.

Figure 3. Endogenous FIX activity over 52 weeks[a]



[a]Uncontaminated central laboratory data (the visit did not occur within 5X half life). FIX levels beginning with the Week 3 assessment were used in the analysis. Subjects with 0 uncontaminated central-laboratory post-AMT-061 values had change from baseline assigned to zero for this analysis and had their post-baseline values set equal to their baseline value.

Sustained reduction in bleeds and FIX replacement post-etranacogene dezaparvovec treatment

- The adjusted annualized bleeding rate (ABR) reduced on treatment compared with the lead-in period (**Table 2**).

Table 2. Adjusted annualized bleeding rates in the first 12 months post-treatment

All subjects (N=54)	Lead-in ABR	Year 0-1 ABR	Ratio (% Reduction)	P-value
All bleeds[a]	3.98	1.33	0.34 (66.6)	p<0.0001
All bleeds treated with FIX	3.39	0.68	0.20 (80.0)	p<0.0001
Spontaneous bleeds treated with FIX	1.16	0.18	0.15 (84.5)	p<0.0001
Traumatic bleeds treated with FIX	1.75	0.30	0.17 (82.9)	p<0.0001
Joint bleeds treated with FIX	1.92	0.30	0.16 (84.4)	p<0.0001

[a]All bleeds are reported regardless of whether the investigator adjudicated them as non-bleeds or continuing bleeds.
ABR, annualized bleeding rate.

- The majority of participants did not report any bleeding during 52 weeks after dosing; spontaneous bleeding was uncommon and decreased over time (**Table 3**).

Table 3. Bleeding[a] events in the first 12 months post-treatment

All subjects (N=54)	Lead-in[b]		Months 0-6[c]		Months 7-12	
	Subjects N (%)	Bleeds N	Subjects N (%)	Bleeds N	Subjects N (%)	Bleeds N
All bleeds	40 (74.1)	136	18 (33.3)	29	14 (25.9)	26
All bleeds treated with FIX	37 (68.5)	118	10 (18.5)	15	9 (16.7)	14
Spontaneous bleeds treated with FIX	22 (40.7)	44	4 (7.4)	6	2 (3.7)	2
Traumatic bleeds treated with FIX	26 (48.1)	58	7 (13.0)	7	6 (11.1)	7
Joint bleeds treated with FIX	31 (57.4)	70	5 (9.3)	8	5 (9.3)	6

[a]All bleeds are reported regardless of whether the investigator adjudicated them as non-bleeds or continuing bleeds; [b]Includes mean bleeding events at 32 weeks; [c]Excludes data prior to Day 21.

- Substantial reductions in FIX replacement and use of prophylaxis occurred compared with lead-in (**Table 4**).
- 96% of subjects discontinued prophylaxis and remain prophylaxis free (**Table 4**).
- There was a 96% reduction in FIX adjusted infusion rate from 72.5 to 3.04 infusions/year.

Table 4. FIX use in the first 12 months post-treatment

FIX replacement therapy usage	Lead-in N = 54	Month 0-6 N = 54	Month 7-12 N = 54
Patients on prophylaxis[a], n (%)	54 (100%)	2 (4%)	2 (4%)
FIX usage (IU/year/patient), mean (SD)	257,070 (149,181.7)	12,913 (37,093.1)	8,401 (29,721.1)

[a]Two participants remain on prophylaxis (1 patient received a partial infusion and FIX expression remained <2% in 1 patient). These two patients had no bleeds in the lead in phase and two untreated bleeds (1 traumatic/1 spontaneous) post-treatment, and five treated bleeds (3 spontaneous/2 unknown) in lead in and none post-treatment, respectively.

General safety

- Fifty-three participants had 408 adverse events post-treatment, of which 39 participants had a total of 91 treatment-related adverse events (TRAEs). The most common TRAEs are shown in **Table 5.**
- 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.[2]

Table 5. Treatment related[a]-adverse events with an incidence of ≥5% in the safety population in the post-treatment period

AE, preferred term	N = 54 n (%)
At least one related incident[b] AE	39 (72.2)
ALT increased	9 (16.7)
Headache	8 (14.8)
Influenza like illness	7 (13.0)
AST increased	5 (9.3)
Fatigue	4 (7.4)
Blood creatine phosphokinase increased	4 (7.4)
Nausea	4 (7.4)
Dizziness	4 (7.4)
Infusion-related reactions	3 (5.6)
Arthralgia	3 (5.6)

[a]Related = possibly related or related; [b]an incident AE is an adverse event that began or worsened within the period.
AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase.

CONCLUSIONS

- Following a single dose of etranacogene dezaparvovec, FIX activity increased, without the need for prophylactic immunosuppression, into the mild-to-normal range at 52 weeks in patients with severe/moderately severe HB.

REFERENCES

1. Pipe S, et al. Oral presentation at the 62nd Virtual American Society of Hematology Annual Meeting & Exposition, Dec 5–8, 2020. Abstract LBA-6.
2. Schmidt M, et al. Oral presentation at the ISTH 2021 Virtual Congress, July 17–21, 2021. Abstract OC 67.4.