PO040

Analysis of elevated alanine transaminase in HOPE-B, a Phase 3 recombinant adeno-associated viral 5 gene therapy trial in people with haemophilia B

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Introduction

- Etranacogene dezaparvovec (formerly AMT-061), a gene therapy for haemophilia B, consists of an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimised, highly active factor IX (FIX) Padua R338L transgene under the control of a liver-specific promoter
- Etranacogene dezaparvovec is aiming to establish sustained FIX activity to protect against bleeding without FIX prophylactic treatment
- Based on the results of the HOPE-B clinical trial (NCT03569891), etranacogene dezaparvovec is the first gene therapy to obtain FDA approval for people with haemophilia B[1–4]
- As AAV5-based gene therapies are targeted to the liver, liver health and function are a key consideration

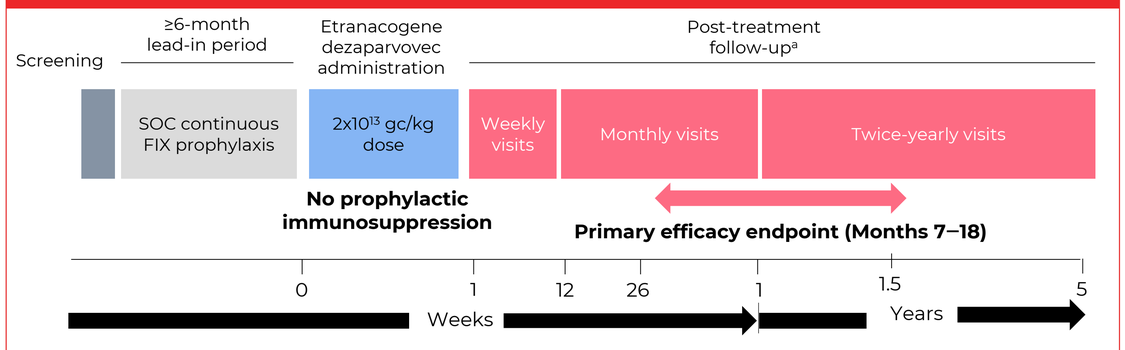
Aim

- Assess HOPE-B participants who had alanine transaminase (ALT) elevations

Methods

- HOPE B: Phase 3, open-label, single-dose, single-arm, international trial in adult males with severe or moderately severe haemophilia B (FIX activity ≤2% of normal) on routine FIX prophylaxis (for ≥2 months), with/without pre-existing AAV5 neutralising antibodies (**Figure 1**)[3]
- Participants were infused with a single dose of etranacogene dezaparvovec ($2x10^{13}$ gc/kg), following a ≥6-month lead-in period receiving FIX prophylaxis
- The key efficacy endpoints evaluated annualised bleeding rate (ABR) and FIX activity
- Liver function abnormalities were a principal safety outcome of the HOPE-B trial
  - Investigators reported adverse events of ALT elevations, which were defined per protocol as ALT increases of ≥2x the participant's baseline level or > laboratory upper limit of normal
  - Guidance for corticosteroid treatment in response to ALT elevations was provided in the protocol (**Table 1**)
- Here we discuss participants who had reported adverse events for ALT elevations

Figure 1. HOPE-B: Study design



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

Table 1. HOPE-B: Protocol recommendations for prednisolone administration for the treatment of ALT elevations

Timeline	Prednisone dose, mg/day
Week 1	60
Week 2	40
Week 3	30
Week 4	30
Maintenance until ALT level returns to baseline (pre-infusion)	20
After pre-infusion level of ALT has been reached	Reduce daily dose by 5 mg/week

ALT, alanine transaminase.

Results

Study participants

- Of the 54 HOPE-B participants who received etranacogene dezaparvovec, 11 participants reported 12 adverse events of ALT elevation (six mild, five moderate, one severe)
  - Baseline demographics for participants with ALT elevations were comparable with those for participants without ALT elevations (**Table 2**)

Table 2. HOPE-B: Baseline demographics

	Participants with ALT elevations, n=11[a]	Participants without ALT elevations, n=42	Full analysis set, N=54
Age, mean (SD, minimum-maximum), years	33.9 (7.2, 22-49)	43.3 (17.0, 19-75)	41.5 (15.8, 19–75)
Race, n (%)			
Asian	0	2 (4.8)	2 (3.7)
Black/African American	0	1 (2.4)	1 (1.9)
White	9 (81.8)	30 (71.4)	40 (74.1)
Other	1 (9.1)	5 (11.9)	6 (11.1)
Missing	1 (9.1)	4 (9.5)	5 (9.3)
Ethnicity			
Hispanic or Latino	2 (18.2)	2 (4.8)	4 (7.4)
Not Hispanic or Latino	8 (72.7)	36 (85.7)	45 (83.3)
Not reported	1 (9.1)	4 (9.5)	5 (9.3)
Region			
US	7 (63.6)	12 (28.6)	20 (37.0)
Non-US	4 (36.4)	30 (71.4)	34 (63.0)
Severity of haemophilia B at diagnosis, n (%)			
Severe (FIX <1%)	9 (81.8)	34 (81.0)	44 (81.5)
Moderately severe (FIX ≥1% and ≤2%)	2 (18.2)	8 (19.0)	10 (18.5)
Positive HIV status, n (%)	1 (9.1)	1 (2.4)	3 (5.6)
Prior hepatitis B infection, n (%)	0	9 (21.4)	9 (16.7)
Prior hepatitis C infection, n (%)	5 (45.5)	25 (59.5)	31 (57.4)
Detectable AAV5 NAbs at baseline, n (%)	3 (27.3)	18 (42.98)	21 (38.9)
Detectable anti-FIX antibodies at baseline, n (%)	1 (9.1)	0	1 (1.9)

[a] One participant had an alcohol-related transaminase elevation that occurred on study day 740, and therefore was excluded from this analysis.
AAV5, adeno-associated virus 5; ALT, alanine transaminase; FIX, factor IX; HIV, human immunodeficiency virus; NAbs, neutralising antibodies; SD, standard deviation.

ALT elevations and corticosteroid use

- Mean (SD) time to first elevated ALT (per laboratory protocol definition) was 44.1 days (±28.6)
- Mean (SD) maximum duration of elevated ALT (per laboratory protocol definition) was 33.0 (±27.6)
- Nine participants received corticosteroids per protocol without reported serious adverse events
- Mean (SD) duration of corticosteroid use was 81.4 days (±28.6)
- Mean (SD) oral corticosteroid dose administrated was 27.6 mg/day (±5.35)
- Mean (SD) time from etranacogene dezaparvovec infusion to last corticosteroid treatment was 119.3 days (±31.2)
- All participants discontinued corticosteroid treatment between Days 85–170 after etranacogene dezaparvovec infusion (**Table 3**)
  - One subject (#10), initially steroid responsive, demonstrated an increase in ALT during initial taper, prompting a return to full dose, after which tapering proceeded without recurrent transaminitis. All others completed corticosteroid taper per protocol guidance without recurrent ALT increase

Table 3. HOPE-B: Corticosteroid use in participants experiencing ALT elevations after recieving etranacogene dezaparvovec infusion

Participant	Study day of first ALT lab (CL or LL) elevation	Maximum duration of ALT elevation, days	Time from infusion to first corticosteroid dose, days	Duration of corticosteroid use, days	Mean daily corticosteroid dose, mg/day	Time from infusion to last corticosteroid dose, days
1	22	15	22	64	25.8	85
2	24	42	24	83	23.9	106
3	30	21[a]	36	51	35.9	86
4	28	93[a]	49	101	33.2	149
5	120	8	-	-	-	-
6	28	17	31	117	27.3	147
7	71	52[a]	-	-	-	-
8	35	15	43	56	21.3	98
9	43	5	43	57	25.9	99
10	41	66[b]	41	130	33.4	170
11	43	29	61	74	21.7	134

[a] LL and CL elevations resolved at different days, therefore the longest duration is displayed.
[b] This subject had a recurrence of ALT increases therefore the duration is the sum across durations of ALTs.
ALT, alanine transaminase; CL central laboratory, LL local laboratory.

FIX activity

- FIX activity levels for those with and without ALT elevations, and for those who received corticosteroids for ALT elevations are shown in **Table 4**
- Four of the nine participants receiving corticosteroids for ALT elevations had a FIX activity that was lower at 2 weeks post-corticosteroid treatment versus the FIX activity observed prior to corticosteroid treatment
- Five of the nine participants had a FIX activity that was higher at 2 weeks post-corticosteroid treatment versus the FIX activity observed prior to corticosteroid treatment

Table 4. HOPE-B: Effect of ALT elevations on FIX activity

	Participants who received corticosteroids, n=9	Participants with ALT elevations, n=11[a]	Participants without ALT elevations, n=42
Mean (±SD) peak FIX activity prior to corticosteroid treatment	22.2 (10.5)	-	-
Mean (±SD) FIX activity prior to corticosteroid treatment	17.1 (8.1)	-	-
Mean (±SD) FIX activity 2 weeks post-corticosteroid treatment	17.9 (10.6)	-	-
Mean (±SD) FIX level post-etranacogene dezaparvovec administration			
6 months	18.7 (11.1)	21.6 (11.8)	43.5 (17.6)
12 months	16.7 (9.7)	20.3 (11.5)	46.0 (20.1)
18 months	15.6 (7.9)	18.1 (9.1)	42.0 (21.2)
24 months	15.5 (7.7)	18.4 (9.6)	41.7 (18.0))

[a] One participant had an alcohol-related transaminase elevation that occurred on study day 740, and therefore was excluded from this analysis.
ALT, alanine transaminase; FIX, factor IX; SD, standard deviation.

ABR

- The mean (±SD) ABR at Months 7–24 post-treatment was 0.8 (1.0) and 1.1 (2.0) in the participants with and without ALT elevations, respectively
- No participant returned to continuous FIX prophylaxis (defined as receiving exogenous FIX >80% of the time during a 3-month period on or subsequent to post-infusion Day 21) (**Table 5**)

Table 5. HOPE-B: ABR in participants experiencing ALT elevations after receiving etranacogene dezaparvovec infusion

Participant	FIX prophylactic regimen during lead-in period	ABR: Lead-in period	ABR: Months 7–24 post-infusion	Return to continuous FIX prophylaxis
1	EHL 47.6 IU/kg Q3W	5.1	0	No
2	EHL 97.5 IU/kg QW	5.1	2.2	No
3	EHL 101.7 IU/kg Q2W	7.9	3.0	No
4	SHL 76.9 IU/kg QW	0	0.7	No
5	EHL 39.1 IU/kg QW	0	0	No
6	EHL 51.7 IU/kg QW	0	1.4	No
7	SHL 75.9 IU/kg Q2W	7.9	0	No
8	EHL 86.0 IU/kg Q2W	7.0	0.7	No
9	SHL 20.2 IU/kg Q2W	1.9	0	No
10	SHL 10.1 IU/kg Q2W	5.2	0.8	No
11	SHL 34.9 IU/kg Q2W	2.9	0	No

ABR, annualised bleeding rate; ALT, alanine transaminase; EHL, extended half life; FIX, factor IX; QW, once weekly; Q2W, once every 2 weeks; Q3W, once every 3 weeks; SD, standard deviation; SHL, standard half life.

Conclusions

- During the HOPE-B study, increased liver transaminases triggered supportive care with corticosteroids, which was associated with normalization of transaminase levels
- Participants who received corticosteroids maintained pre-steroid levels of FIX activity
- No participants who had ALT elevations returned to continuous FIX prophylaxis over 24 months of follow-up

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Disclosures

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