A Single Infusion of AMT-061 (AAV5-Padua hFIX) is Safe and Effective in Adults with Hemophilia B: Interim Results from Dose-Confirmation Phase 2b Trial

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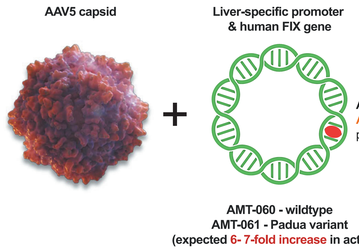
POSTER NO. 44

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)[3,5]
  - Mean FIX activity over 2 years was 7.4 IU/dL with the $2x10^{13}$ genome copies (gc)/kg dose of AMT-060
  - AMT-060 was safe and well tolerated:
    - All treatment-related adverse events (TRAEs) occurred in the first 3.5 months post treatment
    - No new TRAEs up to 2.5 years post treatment
- AMT-061 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]
  - AMT-061 (AAV5-Padua hFIX) is expected to result in 6- to 7-fold higher levels of FIX activity versus AMT-060[7]

Figure 1. Comparison of AMT-060 (AAV5-wild type hFIX) and AMT-061 (AAV5-Padua hFIX)



AIMS

- To confirm the efficacy and safety of AMT-061 (2 x 10^{13} genome copies (gc)/kg) for the Phase 3 study – **H**ealth **O**utcomes with **P**adua gene; **E**valuation in **H**emophilia **B** (**HOPE-B**, NCT03569891)[8]

Information on the ongoing HOPE-B clinical trial of AMT-061 is presented in poster number 30

METHODS

Trial design

- Phase 2b, open-label, single-dose, single-arm, multi-center trial (NCT03489291)[9]
- Single intravenous administration $2x10^{13}$ gc/kg of AMT-061

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 criteria

Outcomes

- Primary efficacy was assessed by FIX activity at 6 weeks (central one-stage clotting assay)
- Historical bleeds and FIX use were assessed from medical records
- From screening participants recorded bleeds and FIX use in their e-diary
- 52 week follow-up to assess FIX activity, bleeding rates and FIX replacement, and safety will be monitored for five years
- This poster includes 26-week data from an interim analysis

RESULTS

AMT-061 (AAV5-Padua hFIX): Changes to the vector-transgene construct result in improvements in FIX activity

Baseline demographics

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

Table 1. AMT-061 baseline demographics

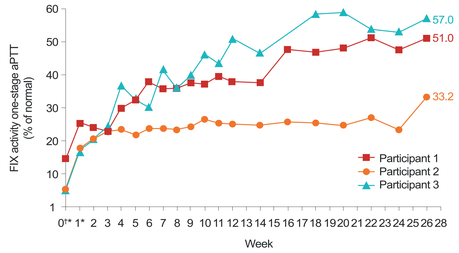
Characteristic	Participant		
	1	2	3
Age (years)	43	50	47
Weight (kg)	89	81	82
HIV Status	Negative	Positive, controlled	Positive, controlled
Hep B / Hep C	Hep C; resolved	Hep C; resolved	Hep C; resolved
Hemophilia B status	FIX <1%	FIX <1%	FIX <1%
Pre-screening FIX treatment	Prophylactic	Prophylactic	Prophylactic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

AAV; adeno-associated virus; FIX, Factor IX; Hep, hepatitis; HIV, human immunodeficiency virus. Participants 2 & 3 were excluded from another AAV-based gene therapy trial for hemophilia B based on neutralizing antibody activity

FIX activity with AMT-061

- The study achieved the primary endpoint of FIX activity >5% at 6 weeks (**Figure 3**):
  - Participant 1: 37.8%
  - Participant 2: 23.9%
  - Participant 3: 30.0%
- By week 26, mean FIX activity was 47.1%:

Figure 2. FIX activity post-AMT-061 treatment



*aPTT, activated partial thromboplastin time; FIX, Factor IX. No immunosuppression required. †The week 0 time point reflects FIX activity before AMT-061 treatment. *Samples that may include include activity from exogenous FIX replacement.*

Reduction in bleeds and FIX replacement with AMT-061

- In the year prior to screening and the screening period (approximately 4 weeks) the participants experienced a total of 10 bleeds (**Table 2**)
- During the 26-week interim analysis there have been no bleeds or requirement for FIX replacement following AMT-061

Table 2. Reduction in bleeds and FIX replacement

Participant	Bleeds	
	Pre-AMT-061	Post-AMT-061
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 screening but prior to dosing*

General safety

- AMT-061 was well tolerated
- 1 participant experienced two adverse events (AE), possibly related to AMT-061, that resolved without intervention:
  - Transient, self-limiting headache and slightly elevated C-reactive protein
- No loss of FIX activity
- No FIX inhibitor development
- No serious AE

Liver-specific safety

- No clinically significant ALT elevations above upper limit of normal after dosing:
  - Participant 1 had an isolated, slight elevation in ALT at week 22 (44 U/L), which resolved without intervention or loss of efficacy
- 1 participant experienced two isolated elevations above the upper limit of normal in aspartate aminotransferase (AST):
  - 43 U/L (week 2) and 48 U/L (week 4)
  - Resolved quickly without treatment or impact on FIX activity
- No participants required immunosuppression

CONCLUSION

- AMT-061 resulted in increased FIX activity, with mean FIX of 47.1% at 26 weeks:
  - 2 of 3 participants had FIX activity in the non-hemophilic range
- AMT-061 was safe and well-tolerated, with no serious AEs
- Based on these favorable results, the efficacy and safety of AMT-061 will be further characterized in the pivotal HOPE-B study

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

References

1. White GC, et al. Thromb Haemost 2001;85:5602. Blanchette VS, et al. J Thromb Haemost 2014;12:1935-9; 3. Miesbach W, et al. Blood. 2018;131:1022-1031; 4. George LA, et al. N Engl J Med. 2017;377:2215-2227; 5. Leebeek F, et al. Blood 2018 132:3476; 6. Cantore A, et al. Blood 2012;120:4517-20; 7. Kao CY, et al. Thromb Haemost. 2013;110:244-56; 8. ClinicalTrials.gov. HOPE-B: Trial of AMT-061 in Severe or Moderately Severe Hemophilia B Patients. Accessed at: https://clinicaltrials.gov/ct2/show/NCT03569891 on 14 March 2019; 9. ClinicalTrials.gov. Dose Confirmation Trial of AAV5-hFIXco-Padua. Accessed at: https://clinicaltrials.gov/ct2/show/NCT03489291?term=AMT-061&rank=2 on 14 March 2019

DISCLOSURES

Steven W. Pipe reports fees paid to his institution from uniQure B.V. during the conduct of the study; consultant fees from Shire, Novo Nordisk, Bioverativ, CSL Behring, Pfizer, Genentech/Roche, Alnylam, Apcintex, Biomarin, uniQure, Bayer, Freeline, Spark Therapeutics, Catalyst Biosciences, HEMA Biologics; research grant from Shire. **Annette Von Drygalski** reports consultant fees from UniQure, Bayer, Bioverativ/Sanofi, Pfizer, Novo Nordisk, Biomarin, Shire, Spark and CSL Behring. **Adam Giermasz** reports fees paid to his institution from uniQure B.V. during the conduct of the study; consultant fees from Bioverativ, Genentech/Roche, Biomarin and uniQure; speaker's fees from Bioverativ and Genentech/Roche. **Giancarlo Castaman** reports a trial-related fee from UniQure B.V. during the conduct of the study; personal fees from Novo Nordisk, Shire, Sobi, CSL Behring, Pfizer, Bayer, Kedrion, Roche, and research grants to his institution from CSL Behring, Sobi and Pfizer outside the submitted work. **Nigel S. Key** reports consultant fees from uniQure B.V. for participation on the Steering Committee for this study. **Susan Lattimore** reports consultant fees from uniQure B.V. during the conduct of the study. **Wolfgang Miesbach** reports consultant fees from UniQure. B.V. during the conduct of the study; grants and personal fees from Novo-Nordisk, personal fees from Bayer, Shire, Biotest, Pfizer, Octapharma, LFB, CSL Behring, SOBI, Biogen, and BPL outside the submitted work. **Michael Recht** reports research support to his institution from Bioverativ, Genentech, NovoNordisk, and Shire. In addition, he reports consultant fees from Bioverativ, CSL Behring, Genentech, Kedrion, NovoNordisk, Pfizer, Shire, and uniQure. He is the immediate past chair, Board of Directors, American Thrombosis and Hemostasis Network. Alison Long and Robert Gut are uniQure employees. **Frank W.G. Leebeek** reports fees paid to his institution from UniQure B.V. during the conduct of the study; he has received research grants from CSL Behring and Baxalta/ Shire, outside the submitted work.

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