HOPE-B: Study design of a Phase 3 trial of an investigational gene therapy AMT-061 in subjects with severe or moderately severe hemophilia B

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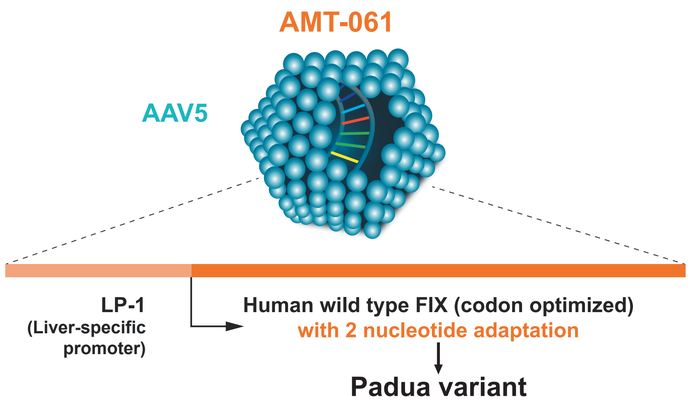
INTRODUCTION

- Gene therapy for hemophilia B aims to provide long-term Factor IX (FIX) production from a single intravenous (i.v.) administration, thereby reducing disease severity from severe or moderately severe to mild or non-hemophilic.
- AMT-061 is an investigational treatment that delivers the highly active Padua variant of FIX to the liver using an adeno-associated virus (AAV) serotype 5 vector (**Figure 1**).
- AMT-061 is a modified version of AMT-060, which encodes the wildtype FIX protein and was studied in 10 patients in Phase 1/2.
- A Phase 2b dose-confirmatory study of AMT-061 (NCT03489291) is ongoing.
- The Phase 3 AMT-061 study — **H**ealth **O**utcomes with **P**adua gene; **E**valuation in Hemophilia **B** (**HOPE-B**; NCT03569891) — is enrolling.

Figure 1. AMT-061 structure



BACKGROUND

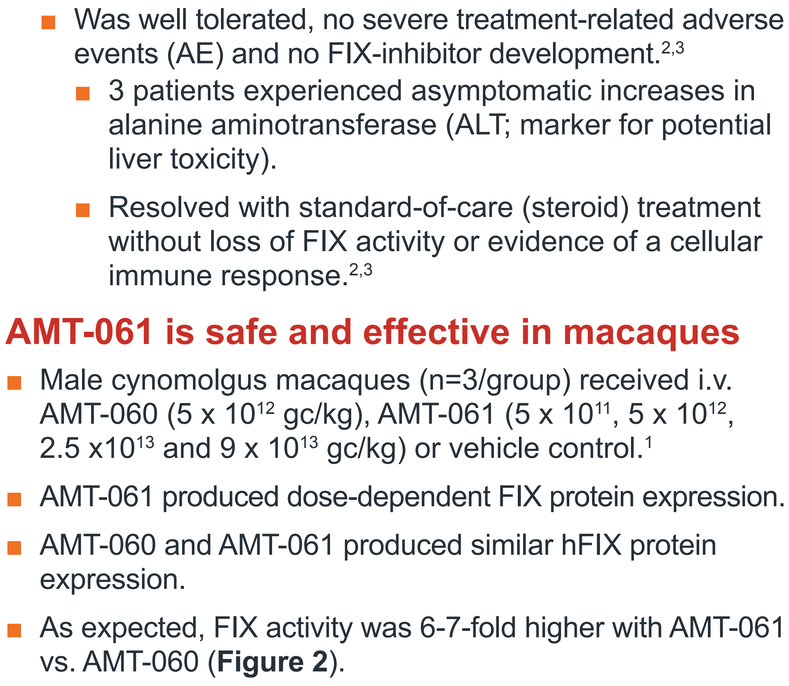
- A single i.v. administration of AMT-060 in 10 adults (n=5 each at 2 doses: $5x10^{12}$ or $5x10^{13}$ gc/kg) with severe or moderately-severe hemophilia B:
  - Stable FIX protein expression/activity for >1.5 years.[2]
  - Eliminated prophylaxis in 8/9 previously-dependent participants.[2,3]
  - Reduced annualized FIX consumption by 79%.[2,3]
  - Reduced the frequency of total+spontaneous bleeds.[2,3]
  - Was well tolerated, no severe treatment-related adverse events (AE) and no FIX-inhibitor development.[2,3]
    - 3 patients experienced asymptomatic increases in alanine aminotransferase (ALT; marker for potential liver toxicity).
    - Resolved with standard-of-care (steroid) treatment without loss of FIX activity or evidence of a cellular immune response.[2,3]

AMT-061 is safe and effective in macaques

- Male cynomolgus macaques (n=3/group) received i.v. AMT-060 (5×10^{12} gc/kg), AMT-061 (5×10^{11}, 5×10^{12}, 2.5×10^{13} and 9×10^{13} gc/kg) or vehicle control.[1]
- AMT-061 produced dose-dependent FIX protein expression.
- AMT-060 and AMT-061 produced similar hFIX protein expression.
- As expected, FIX activity was 6-7-fold higher with AMT-061 vs. AMT-060 (**Figure 2**).
  - No adverse safety/toxicological findings or target organ defects with AMT-060 or AMT-061.

AMT-061 Phase 2B clinical data will be presented at EAHAD 2019:
Session 6 (SLAM): Friday 8th February, 08:30 – 10:00

Figure 2. AMT-061 shows similar protein expression in macaques, but a 6.5-fold increase in FIX activity after baseline correction.



Average of hFIX protein and FIX activity levels in plasma of the macaques that received AMT-060 and AMT-061 at 5×10^{12} gc/kg from Week 4 to Week 13 (+/- standard deviation).

Anti-AAV5 neutralizing antibodies (NAbs) do not impair AAV5-mediated gene transfer

- Most people are infected with naturally-occurring AAVs at some stage and have NAbs that prevent AAV-entry into cells.
  - Pre-existing anti-AAV NAbs may reduce the efficacy of AAV vector delivery; historically, those with NAbs have been excluded from studies.
  - Pre-existing anti-AAV5 NAb titers of ≤1,030 in macaques and ≤340 in humans did not impair AAV5-FIX (AMT-060) effcacy.[4]
  - The relationship between anti-AAV5 NAb and outcomes will be investigated in the AMT-061 Phase 3 study.

HOPE-B CLINICAL TRIAL

OBJECTIVE

- To determine the endogenous FIX activity, bleeding rate, and safety profile of AMT-061 in patients with severe or moderately severe hemophilia B.[5]

METHODS

- Open label Phase 3 study investigating the safety and efficacy of a one-time administration of a single dose of AMT-061 in adult patients with severe or moderately severe hemophilia B (**Table 1**).

Subject eligibility

Table 1. Inclusion/exclusion criteria

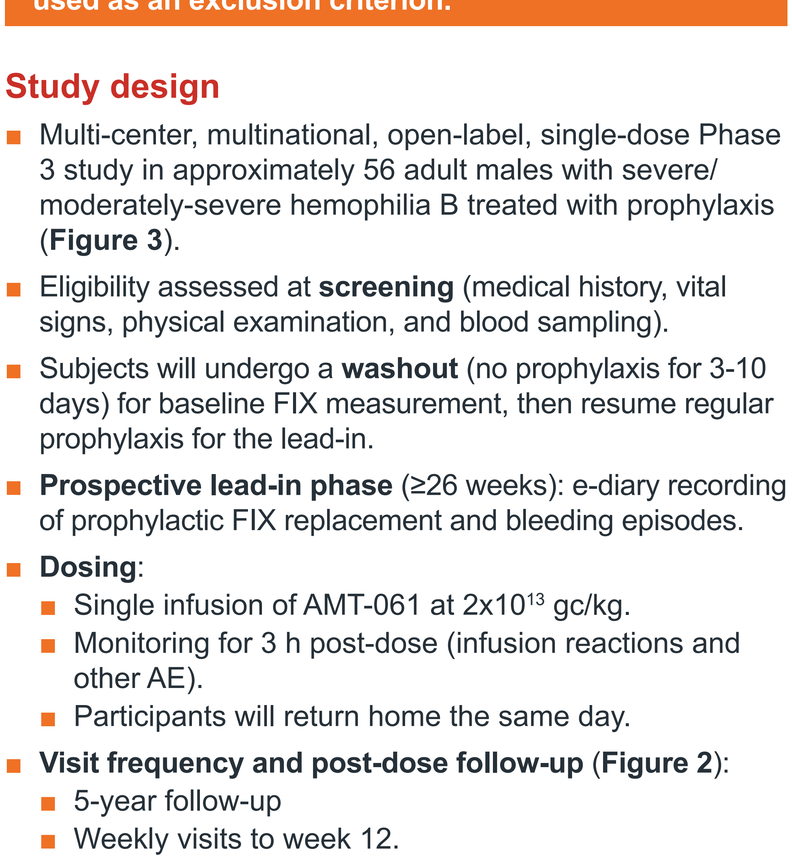
Inclusion criteria	Exclusion criteria
■ Male adults ≥18 years ■ FIX activity ≤ 2% of normal ■ Continuous prophylaxis for ≥2 months	Factors that might affect AMT-061 efficacy, e.g. ■ FIX inhibitors ■ Active hepatitis B/C infection ■ Uncontrolled HIV infection

Pre-existing anti-AAV5 NAbs will be assessed but not used as an exclusion criterion.

Study design

- Multi-center, multinational, open-label, single-dose Phase 3 study in approximately 56 adult males with severe/moderately-severe hemophilia B treated with prophylaxis (**Figure 3**).
- Eligibility assessed at **screening** (medical history, vital signs, physical examination, and blood sampling).
- Subjects will undergo a **washout** (no prophylaxis for 3-10 days) for baseline FIX measurement, then resume regular prophylaxis for the lead-in.
- **Prospective lead-in phase** (≥26 weeks): e-diary recording of prophylactic FIX replacement and bleeding episodes.
- **Dosing**:
  - Single infusion of AMT-061 at $2x10^{13}$ gc/kg.
  - Monitoring for 3 h post-dose (infusion reactions and other AE).
  - Participants will return home the same day.
- **Visit frequency and post-dose follow-up** (**Figure 2**):
  - 5-year follow-up
  - Weekly visits to week 12.
  - Monthly visits: month 4 to 1 year.
  - Bi-annual visits: 4 years ("long-term follow-up").
    - e-diary recording of FIX use and bleeding episodes during the lead-in and year 1.

Figure 3. Study design



Post-treatment study outcomes

Table 2. Key efficacy/safety outcomes

Efficacy outcomes	■ FIX activity ■ Bleeding events during the lead-in period vs. after AMT-061 administration ■ Use of FIX replacement ■ Hemophilia joint health score (HJHS) ■ Patient-reported outcomes (PRO) questionnaires ■ Routine laboratory parameters
Safety outcomes	■ Adverse events ■ Infusion site reactions ■ Anti-AAV capsid-specific T-cells ■ Liver enzymes ■ Anti-FIX antibodies ■ FIX inhibitor formation ■ Vector DNA in blood and semen ■ Inflammatory markers ■ Vital signs

Study locations

- Approximately 30-40 sites across Europe (**Figure 4**), South Africa, and North America.

Figure 4. Study centers across Europe

CONCLUSION

- The Phase 3 HOPE-B trial will examine the safety and efficacy of AMT-061 in severe hemophilia B.
- Modification of AMT-060 to AMT-061 via replacement of the wildtype FIX gene with the highly active FIX ('Padua') variant provides greater FIX activity, whilst preserving the safety profile observed with AMT-060.
- Inclusion of subjects with pre-existing NAbs allows evaluation in a broader population.
  - Study data will be used to seek regulatory approval of AMT-061 for adults with hemophilia B.

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

References

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DISCLOSURES

S Zelenkofske was a uniQure B.V. employee at the time of contributing; all other authors are members of the study steering committee and either they or their institution received consulting fees from uniQure B.V. Writing support, funded by uniQure B.V., was provided by Jackie Read of GK Pharmacomm Ltd.

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