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-hemorrhagic.

AMT-061 is an investigational treatment that delivers the highly active Padua variant of FIX to the liver using an aden-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-confirmation study of AMT-061 (NCT03406921) is ongoing.

The Phase 3 AMT-061 study — Health Outcomes with Padua gene; Evaluation in Hemophilia B (HOPE-B: NCT03569891) — is enrolling.

BACKGROUND
AMT-061 produced dose-dependent FIX protein expression.

■ AMT-061 is an investigational treatment that delivers the highly active Padua variant of FIX to the liver using an aden-associated virus (AAV) serotype 5 vector.

■ As expected, FIX activity was 6-7-fold higher with AMT-061 vs. AMT-060 (Figure 2).

The Phase 3 AMT-061 study — Health Outcomes with Padua gene; Evaluation in Hemophilia B (HOPE-B: NCT03569891) — is enrolling.

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.

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

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 or moderately-severe hemophilia B treated with prophylaxis (Figure 3).

■ Eligibility assessed at screening (medical history, vital signs, physical examination, and blood sampling).

■ Participants will return home the same day.

■ Weekly visits to week 12.

■ Bi-annual visits: years 4 (“long-term follow-up”).

■ e-diary recording of FIX use and bleeding episodes during the lead-in and year 1.

■ Safety outcomes

■ 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

Stability of Fix expression in macaques

Male cynomolgus macaques (m=3/group) received i.v. AMT-060 (5 x 1012 gc/kg), AMT-061 (5 x 1012, 5 x 1011, 2.5 x 1011 and 9 x 1011 gc/kg) or vehicle control.

■ Resolved with standard-of-care (steroid) treatment

■ No FIX-inhibitor development

■ Reduced the frequency of total+spontaneous bleeds

■ Eliminated prophylaxis in 8/9 previously-dependent

■ No pre-existing anti-AAV5 NAbs will be assessed

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-AAV5 NAbs may reduce the efficacy of AAV vector delivery; historically, those with NAbs have been excluded from studies.

■ Pre-existing anti-AAV5 NAbs titers of ≤0.1,300 in macaques and ≤340 in humans did not impair AAV5-FIX (AMT-060) efficacy.

■ The relationship between anti-AAV5 NAb and outcomes will be investigated in the AMT-061 Phase 3 study.

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.

Figure 3. Study design

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 patient population.

■ Study data will be used to seek regulatory approval of AMT-061 for adults with hemophilia B.

DISCLOSURES
S Zelenkofske was a uniQure B.V. employee at the time of contributing; 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 Pharmaco Ltd. For more information, please visit www.ClinicalTrials.gov NCT03569891 or contact uniQure at uniQureHOPE@uniQure.com.

References

2. Leebeek FWG, Meijer K, Coppens M, et al. Stable Elevations in FIX Activity and Reductions in Annualized Bleeding Rate over up to 2 Years of Follow-Up of Adults With Severe or Moderate-Severe Hemophilia B Treated With AMT-060 (AAV5-FIX) Gene Therapy. Blood 2017 130:602.

