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ASH abstract category: **801. Gene Therapy and Transfer**
Includes basic studies of gene transfer techniques, including vector design, target cell physiology, and investigations of gene transfer efficiency. Also includes studies of marker gene insertion, vector-target cell interactions, and investigation of determinants of marker gene expression/regulation. Also includes preclinical and clinical applications of gene transfer and gene therapy in human disorders, in vivo animal models, and related settings.

Title: 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-hFIX) gene therapy

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Background: Gene transfer for hemophilia offers the potential to convert the disease from a severe to mild phenotype with a single treatment. AMT-060 consists of an adeno-associated virus serotype 5 (AAV5) vector containing a codon-optimized wildtype human factor IX (FIX) gene under control of a liver-specific promoter.

Aim: This phase 1/2 study investigates the safety and efficacy of AMT-060 at 2 dose levels in adults with moderate-severe or severe hemophilia B. Updated data with up to 2 years follow up will be presented.

Methods: Multi-national, open-label, dose-escalating study in patients (pts) with FIX activity ≤2 IU/dL of normal, and a severe bleeding phenotype (prophylactic exogenous FIX; or on-demand exogenous FIX, plus ≥4 bleeds/year or hemophilic arthropathy). Pts received either $5x10^{12}$ gc/kg (Cohort 1, n=5) or $2×10^{13}$ gc/kg (Cohort 2, n=5) of AMT-060 iv. Efficacy assessments include FIX activity (measured ≥10 days after use of exogenous FIX); reduction of FIX use; and annualized spontaneous bleeding rates. Safety assessments include treatment related adverse events, immunological and inflammatory biomarkers.

Results: Nine pts with severe (FIX <1%) and 1 with moderate-severe (FIX 1.5%) hemophilia B were enrolled and received AMT-060. At study entry, 9 pts were on FIX prophylaxis, and 1 pt with severe

hemophilia B in Cohort 2 used FIX on demand. Following AMT-060, mean FIX activity in the lower dose cohort was 4.6 IU/dL (95% CI 1.6-7.6) during 1.5 year of follow-up, and 7.1% (95% CI 3.2-11.1) in the higher dose cohort during 1 year of follow-up with stable FIX protein expression across both cohorts. Disease severity improved in all pts: severe to mild (n=5), severe to moderate (n=4), and from moderate to mild (n=1). Eight of 9 pts on FIX prophylaxis at study entry discontinued use after AMT-060 infusion. Across all pts, the total annualized reduction of exogenous FIX use post-AMT-060 and discontinuation of prophylaxis was 79% (85% in Cohort 1 and 68% in Cohort 2). Mean annualized spontaneous bleeds were reduced from 9.8 in the year prior to AMT-060 to 4.2 in the 1.5 years after treatment for pts in Cohort 1 (58% reduction), compared with a 54% reduction at the previously-reported 1-year follow up, while total bleeds were reduced by 54%. In 4 pts in Cohort 2, annualized spontaneous bleeds were reduced from a mean of 3.0 to 0.5 (84% reduction), compared with a 70% reduction at the previously-reported 6-month follow up, with no spontaneous bleeds reported in the last 6 months of follow up. Total bleeds were reduced by 64%. One pt in Cohort 2 was not included in the calculation as historical bleed data was not available; he experienced 1 traumatic bleed after discontinuation of prophylaxis. No pts developed inhibitors to FIX and there were no detectable signs of sustained AAV5 capsid-specific T-cell activation. Six pts (3 in each cohort) experienced a total of 14 treatment-emergent adverse events classified as possibly/probably related to treatment, most of which were classified as mild (n=11) and some as moderate (n=3). Mild, temporary elevations in ALT not associated with changes in FIX activity or capsid-specific T-cell responses were observed in 3 pts with higher mean FIX activity (6.4-12.7 IU/dL; 1 in the lower- and 2 in the higher-dose cohort). Each received a tapering course of prednisolone. ALT elevations have not recurred. Additional efficacy and safety data will be presented up to 2- and 1.5-years of follow-up for Cohorts 1 and 2, respectively.

Conclusions: Longer-term outcomes for up to 1.5 years following a single infusion of AMT-060 continue to indicate a positive safety profile coupled with stable and clinically meaningful elevations in FIX protein expression and activity without evidence of capsid-specific immune responses. Bleeding rates declined over time, with a near cessation of spontaneous bleeds in the high dose cohort.

Conflict of interest statements

ASH abides by rules formulated by the Accreditation Council for Continuing Medical Education (ACCME) that require that you disclose any relevant financial relationship you or your spouse/partner have had within the past 24 months. For this purpose, “relevant financial relationships” are those from which you have received or may receive financial benefit and which are related to the CME content.

F. 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, grants and Baxalta/Shire, outside the submitted work.

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E. Seifried, J. Schwäble and H. Bonig declare no conflicts of interest.

E. Sawyer is a uniQure employee.