Stable FIX Expression and Durable Reductions in Bleeding and Factor IX Consumption for up to 4 Years Following AMT-060 Gene Therapy in Adults with Severe or Moderate-Severe Hemophilia B

Frank W.G. Leebeek[1], Karina Meijer[2], Michiel Coppens[3], Peter Kampmann[4], Robert Klamroth[5], Roger Schutgens[6], Giancarlo Castaman[7], Erhard Seifried[8] , Joachim Schwable[8], Halvard Bonig[9], Eileen K. Sawyer[10], Wolfgang Miesbach[9]

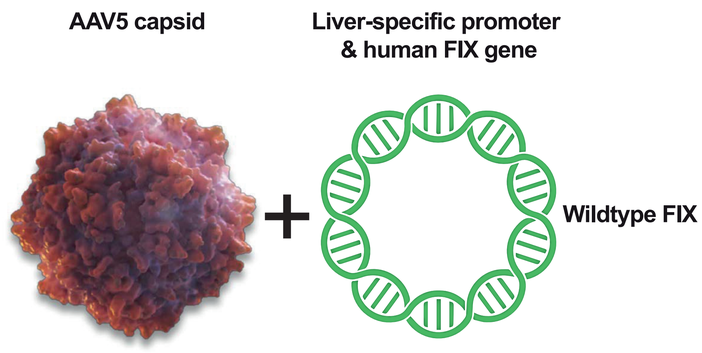
[1]Erasmus University Medical Center, Rotterdam, [2]University Medical Center Groningen, Groningen, [3]Academic Medical Center, Amsterdam, Netherlands, [4]Rigshospitalet, Copenhagen, Denmark, [5]Vivantes Klinikum, Berlin, Germany, [6]University Medical Center, Utrecht, Netherlands, [7]Azienda Ospedaliera Universitaria Careggi, Florence, Italy, [8]German Red Cross Blood Service Baden-Württemberg-Hessen, Institute Frankfurt, [9]Universitätsklinikum Frankfurt, Frankfurt, Germany, [10]uniQure B.V., Lexington, United States

Poster No. P100

INTRODUCTION

- Significant unmet needs with the current standard of care FIX prophylaxis.[1,2]
  - **Bleeding risk** due to fluctuating levels of protection.
  - **Inconvenient** frequent infusions and lifestyle restrictions.
  - **Treatment adherence issues** and suboptimal outcomes.
  - Accrual of **joint damage**.
  - **Poor quality of life** and pain.
- AMT-060:
  - **Adeno-associated virus serotype 5** (AAV5) vector.
  - Codon-optimized **wildtype human factor IX** (WT hFIX) gene.
  - **Liver-specific** promoter (**Figure 1**).

Figure 1. AMT-060: AAV5 capsid with wildtype FIX cassette

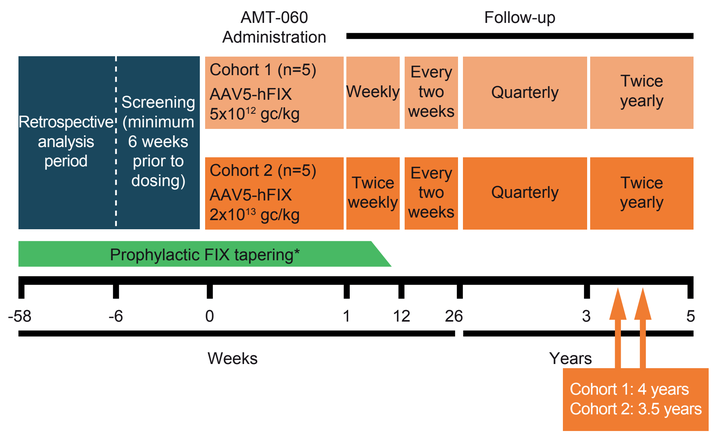


- AMT-060 phase I/II study results with up to **3.5-year follow-up** have been reported previously.[7,8]
  - Here we report **4-years post-treatment follow up**.

METHODS

- Multi-national, open-label, dose-escalating study (**NCT02396342**) (**Figure 2**).[7]
- 10 adult males with **severe or moderate-severe hemophilia B**.[7]

Figure 2. AMT-060 Phase I/II study design



**Prophylaxis was tapered and discontinued by 12 weeks if FIX activity was maintained at ≥2%; FIX, factor IX.*

RESULTS

Baseline characteristics

- Baseline characteristics described in **Table 1**.
- Exclusion criteria included pre-existing neutralizing antibodies (NAb) against AAV5 measured by green fluorescent protein (GFP) bioassay.
  - Retrospective screening with a more sensitive (luciferase-based) assay identified 3 participants with AAV5 NAb.

Endogenous FIX activity

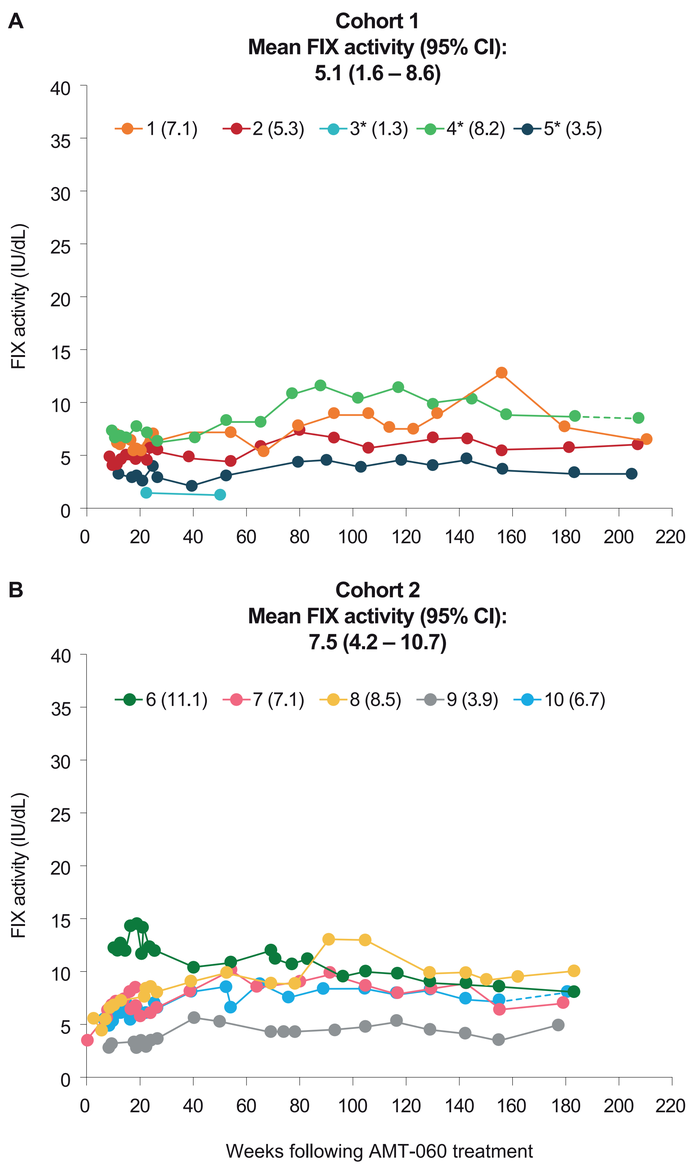
- Following AMT-060, mean endogenous FIX activity:
  - **5.1% (95% CI 1.6 – 8.6)** during 4 years of follow-up in the lower-dose cohort (Cohort 1).
  - **7.5% (95% CI 4.2 – 10.7)** during 3.5 years in the higher dose cohort (Cohort 2) (**Figure 3**).
- Stable FIX protein expression across both cohorts.
- No obvious relationship between presence of anti-AAV NAbs and response to AMT-060.

Table 1. Baseline characteristics[7]

Variable		Cohort 1 (N=5)	Cohort 2 (N=5)
Age (years)		69 (35-72)	35 (33-46)
Weight (kg)		85 (71-89)	84 (71-96)
FIX use[a]	Prophylaxis, IU/week	4000 (2000–8000)	4000 (4000–10,500)[b]
	Annualized mean, IU/year	354,800	173,200
Mean bleeds (year prior to enrolment), n	Total	14.4	4.0[c]
	Spontaneous	9.8	3.0
	Traumatic	2.8	1.0
	Unknown	1.8	0.0
Hemophilia joint health scores		27 (2-49)	6 (0-17)
HIV positive, n		1	0
Prior hep C infection, n		4	2
AAV5 NAb+ (luciferase assay)[6]		3	0
Presumed cross-reactive matter +ve		2	1

Values are median (min-max) unless otherwise stated. N=number. [a]Every other day dosing defined as 3.5 x per week for calculations. [b]1 participant in Cohort 2 received on-demand treatment and is therefore not included; [c]Historical bleed data missing for 1 participant in Cohort 2 who is therefore not included; [d]Joint status was assessed using the Haemophilia Joint Health Score version 2.1. FIX, factor IX; n, number of participants; hep C, hepatitis C; HIV, human immunodeficiency virus; IU, international units; NAb, neutralizing antibody.

Figure 3. Sustained dose-dependent increases in FIX activity

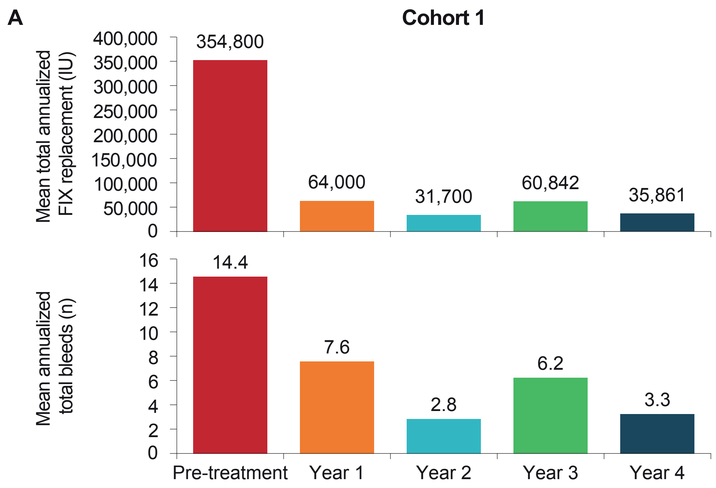


*Values in parentheses represent mean FIX activity over time. Only values at least 10 days after last FIX concentrate administration are included. FIX prophylaxis was continued after AMT-060 and tapered between Weeks 6 and 12. *Patients 3, 4 and 5 retrospectively tested positive for AAV5 neutralizing antibodies using the luciferase-based assay. Dashed line indicates sample collection occurred after the data cut (09Oct2019). Values after the data cut (Patient 4, year 3.5; Patient 10, year 4) are not included in calculations of mean FIX activity. FIX, factor IX; CI, confidence interval; IU, international units.*

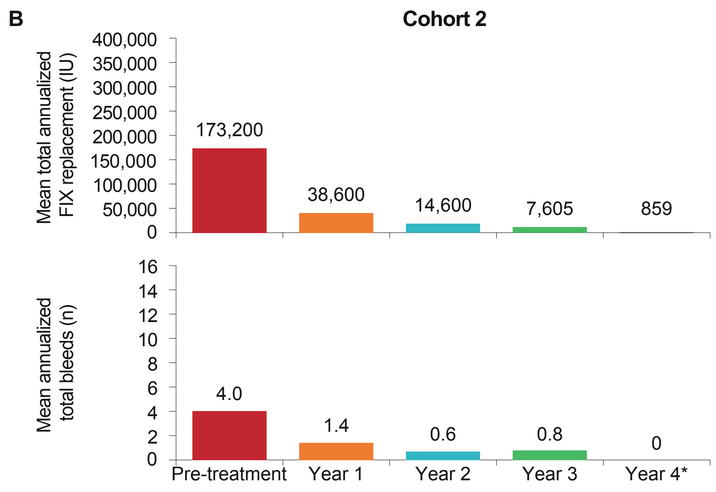
Sustained reductions in FIX use and bleeds

- Cohort 1: By year 4, FIX use was reduced relative to pre-AMT-060 up to 90% and bleeds by 77% (**Figure 4A**).
- Cohort 2: By year 3.5, FIX use and bleeds were both reduced relative to pre-AMT-060 by 100% (**Figure 4B**).

Figure 4. Sustained reductions in FIX use and bleeds (A: Cohort 1, B: Cohort 2)



Reduction relative to pre-AMT-060	FIX use	Bleeds
Year 1	82%	47%
Year 2	91%	81%
Year 3	83%	57%
Year 4	90%	77%



Reduction relative to pre-AMT-060	FIX use	Bleeds
Year 1	78%	65%
Year 2	92%	85%
Year 3	96%	80%
Year 4*	100%	100%

**In cohort 2, year 4 results reflect 6 months of data. Annualized bleeding rates are calculated for years since the cessation of prophylaxis.*

Safety

- Previously reported in Miesbach et al 2018 (1 year follow up).[7]
  - Majority of treatment-related AEs (TRAE) occurred in first 3.5 months of follow up.
- 1 TRAE since 1 year of follow up:[7]
  - 1 joint swelling post exercise.

CONCLUSION

- The safety profile of AMT-060 remains positive.
  - No development of FIX inhibitors.
  - No new clinically significant AEs, ALT elevation or capsid-specific T-cell activation.
- Stable, durable FIX activity over 4 years.
  - 2nd longest follow up reported in a gene therapy trial in hemophilia B
- Long-term clinical benefit in all participants.
- Data support the ongoing etranacogene dezaparvovec development program.

REFERENCES

1. VandenDriessche and Chuah. Hum Gene Ther. 2017;28(11):1013-1023; 2. Bauer et al. Am J Manag Care. 2015; 21(6 Suppl):S112-22; 3. Boutin et al, Human Gen Ther 2010; 21(6):704-12; 4. D'Avola et al, Journal of Hepatology 2016;65(4):776-783; 5. Nathwani et al. NEJM 2014; 371:1994-2004; 371:1994-2004; 6. Majowicz et al. Mol Ther Methods Clin Dev. 2019;14:27-36; 7. Miesbach et al. Blood 2018;131:1022-31; 8. Leebeek et al. Res Pract Thromb Haemost 2019;3(S1):81; 9. Simioni, et al. N Engl J Med 2009;361(17):1671-1675; 10. Von Drygalski et al. Blood Advances 2019;3(21):3241-3247.

DISCLOSURES

Frank W.G. Leebeek: CSL Behring: Research Funding; Unique: Consultancy, of which fees go to the University; Baxalta/Shire: Research Funding; **Karina Meijer**: BMS: Honoraria; Aspen: Honoraria; Boehringer Ingelheim: Honoraria; Pfizer: Research Funding; Sanquin: Honoraria, Research Funding; Bayer: Honoraria, Other: Travel support, Research Funding; UniQure: Research Funding. **Michiel Coppens**: Bayer: Honoraria, Other: Non-financial support, Research Funding; CSL Behring: Honoraria, Other: non-financial support, Research Funding; Uniqure BV: Research Funding; **Peter Kampmann**: Uniqure BV: Research Funding; Robert Klamroth: Baxalta (Shire), Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Shire, and SOBI: Consultancy; Baxalta (Shire), Bayer, CSL Behring, Novo Nordisk, Octapharma, Pfizer, Shire, and SOBI: Research Funding. **Roger Schutgens**: Baxalta/Shire: Research Funding; Novo Nordisk: Research Funding; Bayer: Research Funding; CSL Behring: Research Funding; Pfizer: Research Funding; Uniqure BV: Research Funding; **Giancarlo Castaman**: umiQure: Advisory Board; Bayer, Shire/Takeda, CSL Behring, Sobi, Novo Nordisk, Roche, Werfen, Ablynx, Kedrion: speaker fees/Advisory Board; Pfizer, Sobi and CSLBehring: Research Funding; **Erhard Seifried**: Medac: Other: BSD owns IP and is contract manufacturer; Uniqure BV: Research Funding; **Joachim Schwäble**; UniQure BV: Research Funding; **Halvard Bonig**: Kiadis Pharma: Consultancy; Eileen K Sawyer is an employee of uniQure; **Wolfgang Miesbach**: Bayer, Shire, Biotest, pfizer, Octapharma, LFB, CSL Behring, SOBI, Biogen, BPL: Consultancy; UniQure BV: Research Funding; Novo Nordisk: Consultancy, Research Funding;

Presented at The 13th Annual Congress of the European Association for Haemophilia and Allied Disorders, EAHAD 2020, The Hague, 5-7 February 2020