Stable Expression of FIX and Maintained Reductions in Bleeding and Factor IX Consumption Following AMT-060 Gene Therapy with up to 3.5 Years of Follow Up in Adults with Severe or Moderate-Severe Hemophilia B

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Unmet needs in hemophilia B

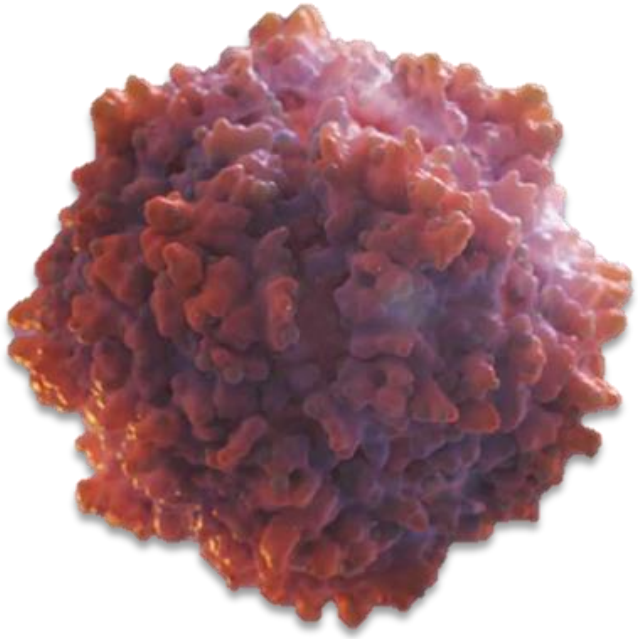
- *Significant unmet needs remain with the current standard of care factor IX (FIX) prophylaxis[1,2]:*
  - **Bleeding risk** *due to fluctuating levels of protection*
  - **Cumbersome treatment** *with frequent infusions and lifestyle restrictions*
  - **Treatment adherence issues** *and resulting suboptimal clinical outcomes*
  - **Quality of life** *and pain*
  - *Accrual of* **joint damage**

Steady state FIX levels in the mild to non-hemophilic ranges offer the potential to address these unmet needs

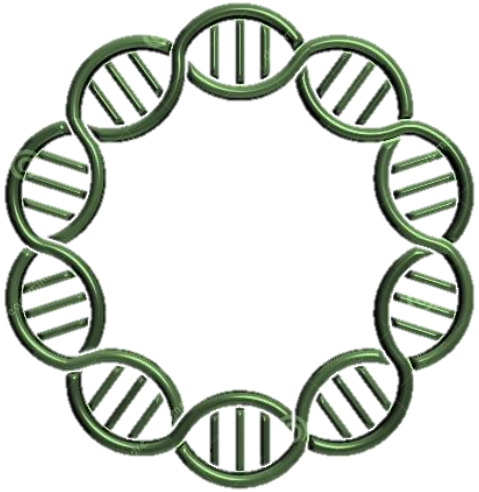
1. VandenDriessche T and Chuah MK. Hum Gene Ther. 2017;28(11):1013-1023; 2. Bauer KA. Am J Manag Care. 2015;21(6 Suppl):S112-22.

Introduction: gene therapy for hemophilia B: AMT-060

AAV5 capsid



Liver-specific promoter & human FIX gene



AMT-060 – wildtype

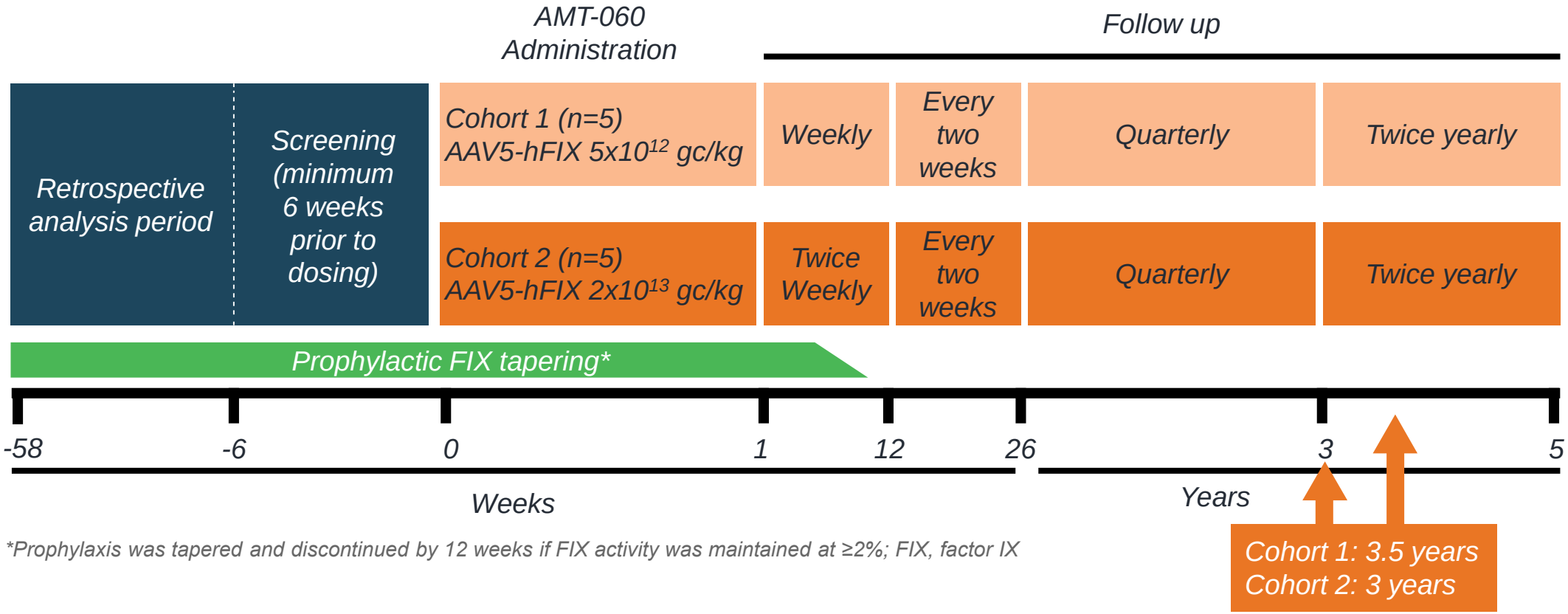
- *Low prevalence of pre-existing neutralizing antibodies able to impact clinical outcomes*[1,4]
- *Previously tested in humans without sign of cellular immune activation*[2]

- *WT hFIX (codon optimized)*
- *Clinically demonstrated* **safe and durable**[3] *increases in FIX activity with meaningful* **improvements in clinical outcomes**[3]

1. Boutin et al, Human Gen Ther 2010; 21(6):704-12. 2. D'Avola et al, Journal of Hepatology 2016; doi: http://dx.doi.org/10.1016/j.jhep.2016.05.012. 3. Nathwani et al. NEJM 2014; 371:1994-2004. 4. Majowicz et al. Mol Ther 2018; 26:458

AMT-060 Phase I/II study design

- *Multi-national, open-label, dose-escalating study (NCT02396342)[1,2]*
- *10 adult males with severe/moderately severe hemophilia B[1,2]*
- *Results previously reported to 2.5 years[2]*



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

1. Miesbach et al. Blood 2018;131:1022-31; 2. Leebeek et al. Poster presented at ASH, December 2018

Baseline characteristics[1]

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 in the year prior to enrollment, 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[d]		*27 (2-49)*	*6 (0-17)*
HIV positive status, n		*1*	*0*
Prior hepatitis C infection, n		*4*	*2*
AAV5 NAb⁺ *(luciferase assay)[2]*		**3**	**0**

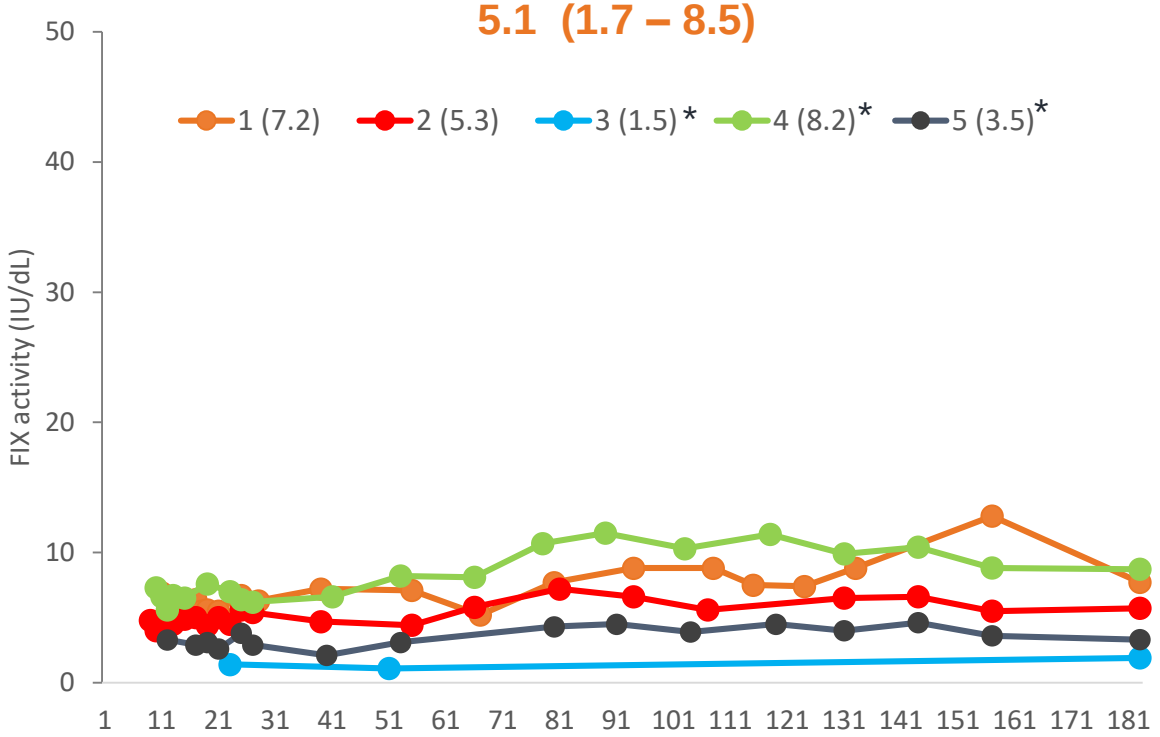
Values are median (min-max) unless otherwise stated. N=number. [a]QOD used as 3.5 x per week for calculations. [b]1 participant in Cohort 2 received on-demand treatment and is therefore not included; [c]Historical bleed data missing for 1 participant in Cohort 2 who is therefore not included; [d]Joint status was assessed using the Haemophilia Joint Health Score version 2·1.6 FIX, factor IX; n, number of participants; HIV, human immunodeficiency virus; NAb, neutralizing antibody

1. Table modified from Miesbach et al. Blood 2018;131:1022-31; 2. Majowicz et al. Mol Ther 2018; 26:458

Sustained dose-dependent increases in FIX activity

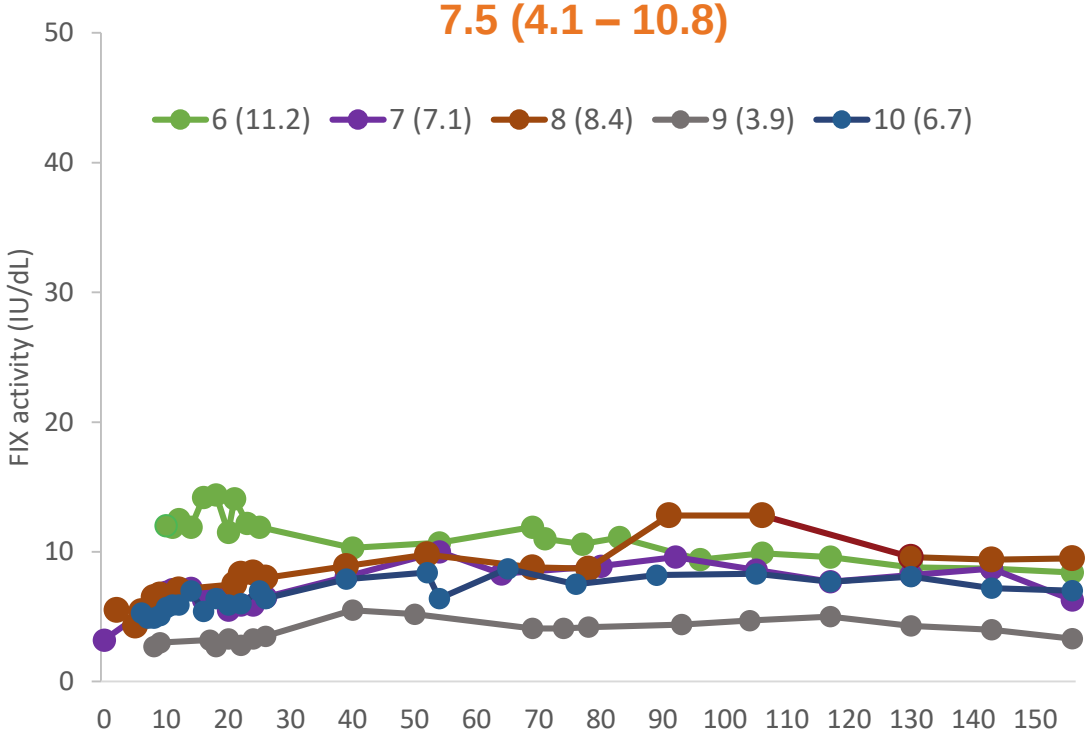
Cohort 1

Steady state mean FIX activity (95%CI): 5.1 (1.7 – 8.5)



Cohort 2

Steady state mean FIX activity (95%CI): 7.5 (4.1 – 10.8)

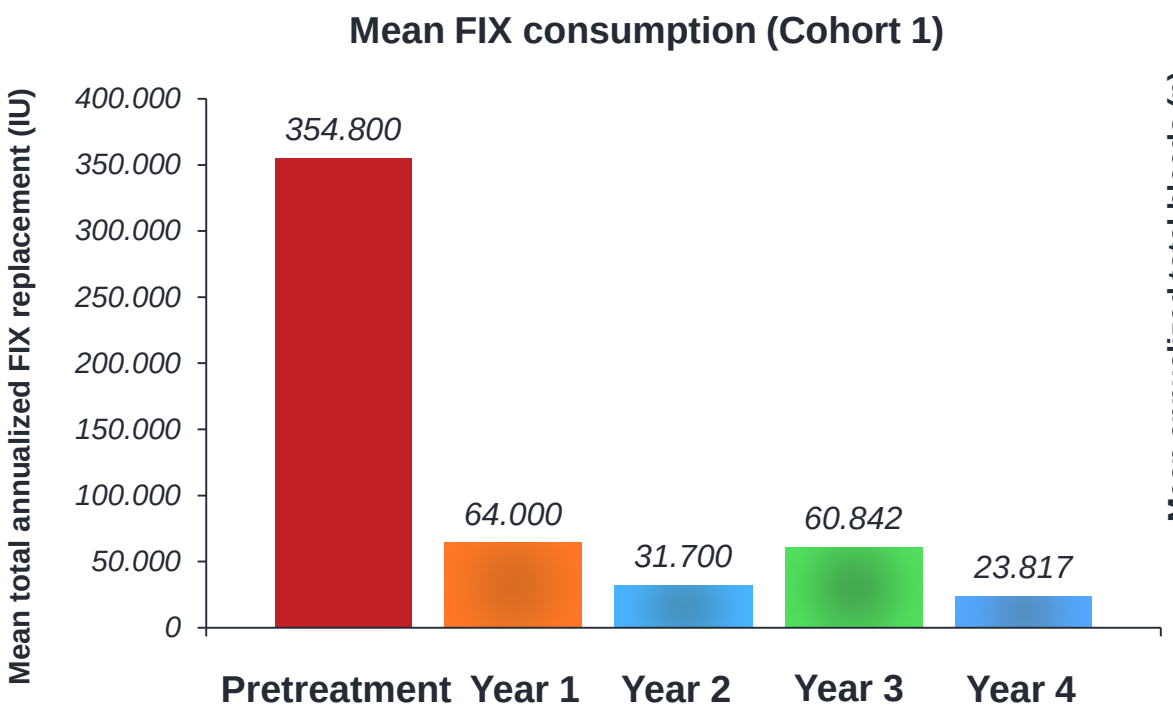


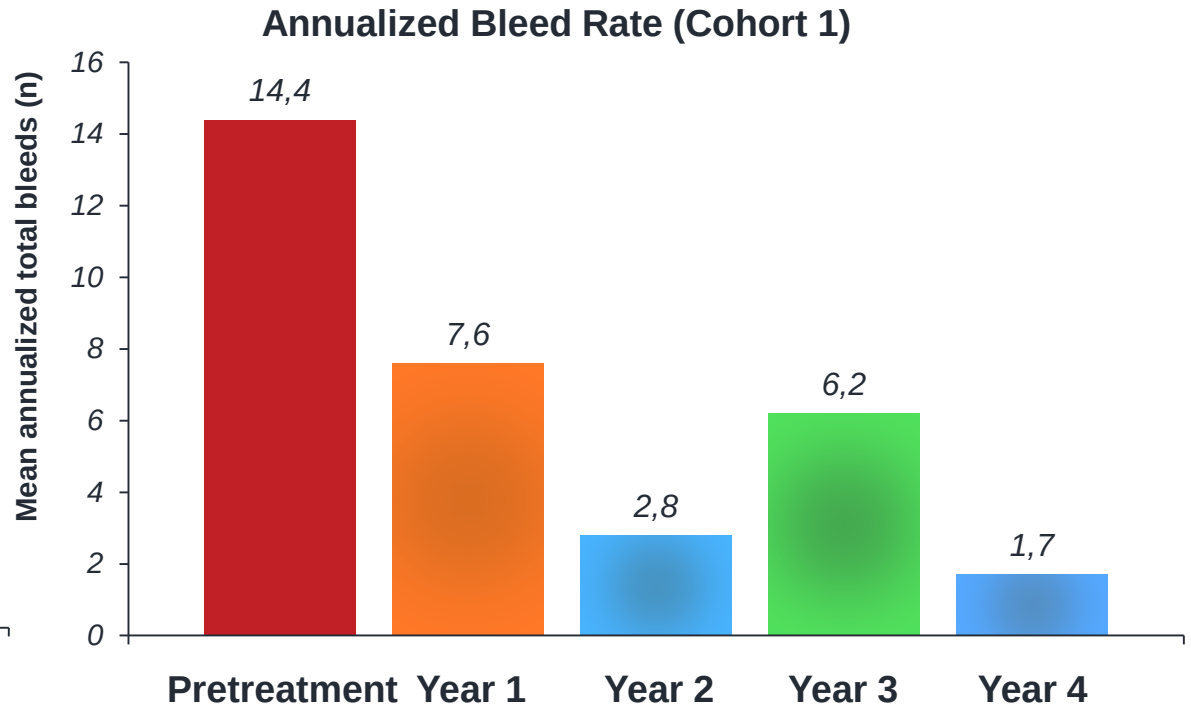
Weeks following AMT-060 treatment

FIX activity levels correlated approximately 1:1 with FIX protein expression

*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 *Patient retrospectively tested positive for AAV5 neutralizing antibodies using the luciferase-based assay. 3 patients were presumed cross-reactive matter positive. FIX, factor IX; CI, confidence interval; IU, international units*

Reductions in FIX use and bleeds sustained over long term follow up (Cohort 1)

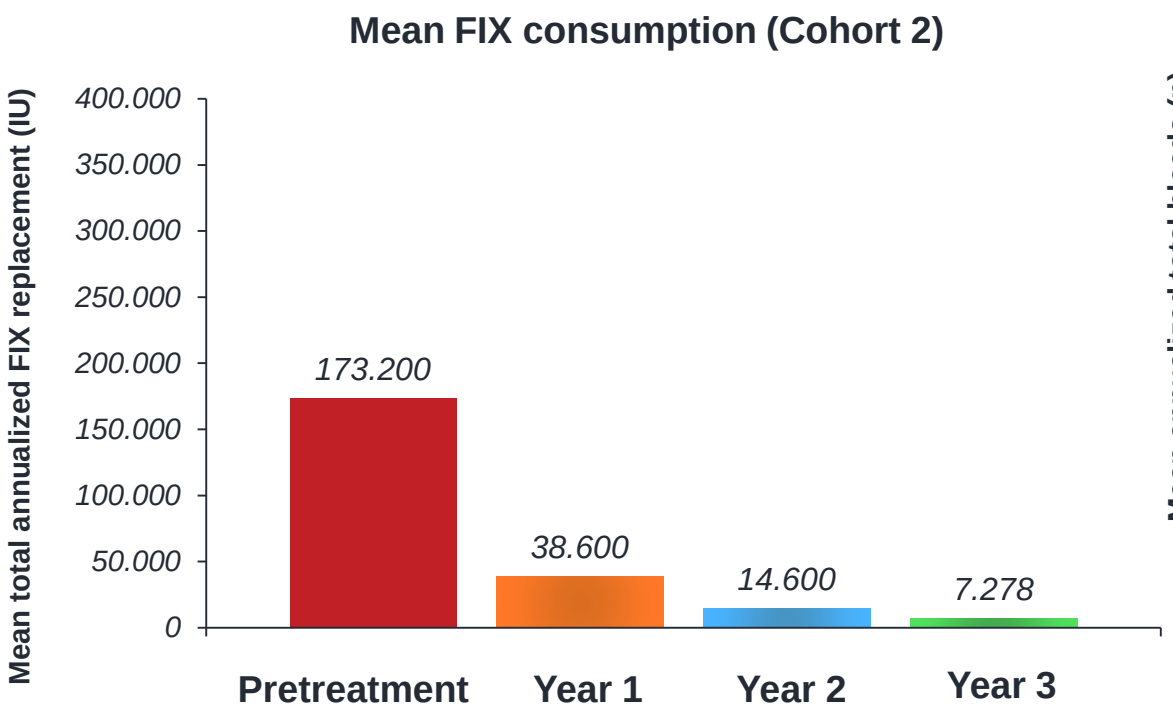


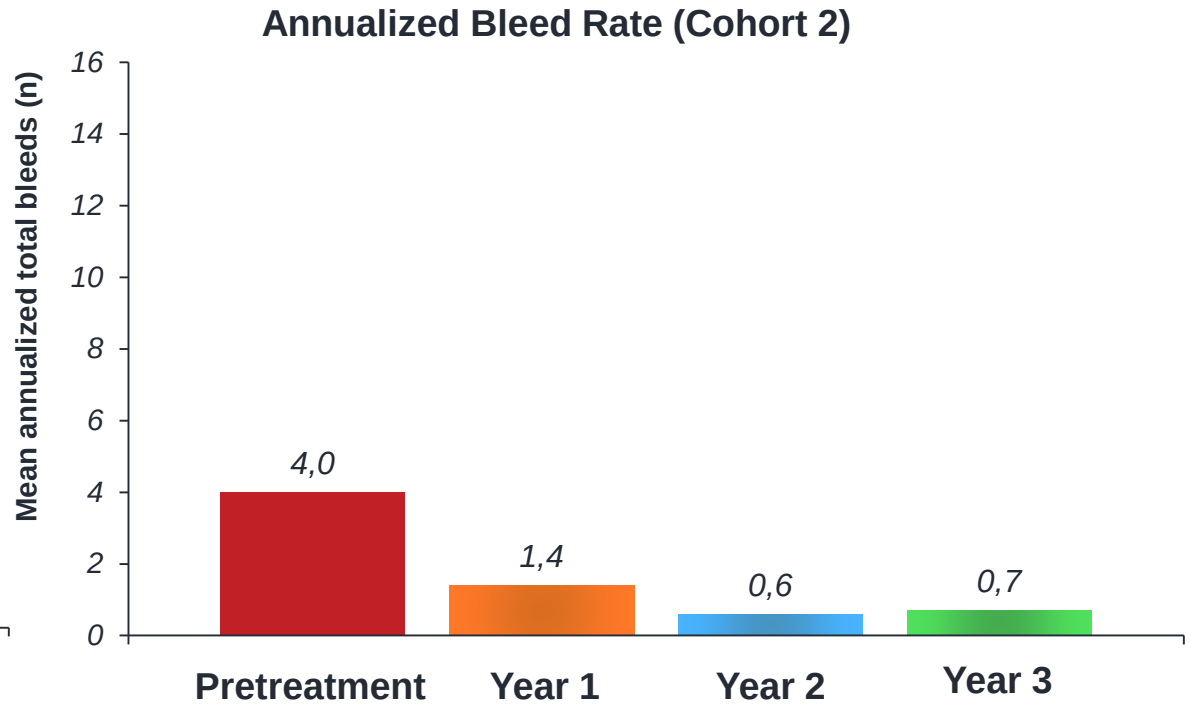


Reduction relative to pre-AMT-060	FIX use	Bleeds
Year 1	*82%*	*47%*
Year 2	*91%*	*81%*
Year 3	*83%*	*57%*
Year 4	*93%*	*88%*

Mean FIX consumption excludes surgical procedures

Reductions in FIX use and bleeds sustained over long term follow up (Cohort 2)





Reduction relative to pre-AMT-060	FIX use	Bleeds
Year 1	*78%*	*65%*
Year 2	*92%*	*85%*
Year 3	*96%*	*83%*

Mean FIX consumption excludes surgical procedures

Treatment Emergent Adverse Events considered possibly / probably related to treatment (TRAE)

TRAE	n (E) Cohort 1 (N=5)	n (E) Cohort 2 (N=5)
Any TRAE	**4 (5)**	**5 (10)**
Liver enzyme increased	*1 (1)*	*2 (3[a])*
Pyrexia	*1 (1)*	*2 (2)*
Anxiety	*1 (1)*	*1 (1)*
Drug ineffective	*1 (1)*	*0*
Joint swelling[*]	*1 (1)*	*0*
Palpitations	*0*	*1 (1)*
Headache	*0*	*1 (1)*
Prostatitis	*0*	*1 (1)*
Rash	*0*	*1 (1)*

TRAE, treatment emergent adverse event reported as possibly/probably related to treatment by the investigator; FIX, factor IX; n, Number of participants with events; (E), number of events; [a]2 events reported in the same participant; [*]TRAE reported in last 12 months

Serious AE

- *1 participant: short, self-limiting fever in first 24 hours post-AMT-060*
- *2 participants (1 in Cohort 1, 1 in Cohort 2): mild, asymptomatic elevations in liver enzymes*

Overall

- *1 new TRAE[*] was observed during the last 12 months of observation post-treatment*
- *No participants developed FIX inhibitors*

Conclusions

- *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 since last report*

- **Stable, durable FIX activity over 3.5 years**

- **Long-term clinical benefit** *in all participants*
  - *Reductions in bleeds sustained over time in both cohorts*
  - *All participants who discontinued prophylaxis remain prophylaxis-free*
  - *Annualized FIX consumption decreased by 87% across the duration of follow up (78-96% per year) compared to pre-treatment*

ALT, alanine aminotransferase; AE, adverse event; FIX, factor IX;

Next steps: Phase IIb and Phase III with AMT-061

- *The **Phase IIb AMT-061 study** (NCT03489291) in 3 participants with FIX activity ≤1% and anti-AAV5 NAbs showed at 36 weeks post treatment:[1]*
  - *AMT-061 was **well-tolerated** with no serious AEs*
  - ***Sustained FIX activity** up to 54.1%*
    - *Mean FIX activity 45.0% at 36 weeks (n=3)*
    - *Suggests **anti-AAV5 NAbs** may not be a barrier for AAV5 gene therapy[2]*
  - ***No bleeds** or associated use of factor replacement therapy*
  - ***No loss of FIX activity** or requirement for immunosuppression*
- *The **Phase 3 HOPE-B AMT-061 study** (NCT03569891) is enrolling*
  - ***First patient treated early 2019***
  - *Expected to enroll approximately 55 participants with severe hemophilia B*
  - *Those with pre-existing AAV5 NAbs will not be excluded*

hFIX, human Factor IX; Nab, neutralizing antibodies; HOPE B, Health Outcomes with Padua gene: Evaluation in Hemophilia B

1. Giermasz et al. Oral presentation at ISTH on July 6th 2019. 2. Majowicz et al. Mol Ther - Methods Clin Develop 2019. DOI : 10.1016/j.omtm.2019.05.009.

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