



**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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# Disclosures for F Leebeek, MD

<b>CONFLICT</b>	<b>DISCLOSURE — IF CONFLICT OF INTEREST EXISTS</b>
<b>Employment</b>	- Erasmus University Medical Center, Rotterdam, the Netherlands
<b>Research support</b>	- CSL Behring, Baxalta/Shire
<b>Travel support</b>	
<b>Consultancy</b>	-uniQure, Shire, Novo Nordisk
<b>Major stockholder</b>	
<b>Speakers bureau</b>	
Honoraria	
Scientific advisory board	
Patents	
Other	

# Goal of gene therapy in hemophilia B: Transformation of disease severity

## Objectives

- **Control of bleeding** with effective protection against spontaneous bleeds
- **Elimination of the requirement** for continuous prophylaxis
- Establish **long term, multi-year benefit** from a one-time procedure
- Improvement in **quality of life**

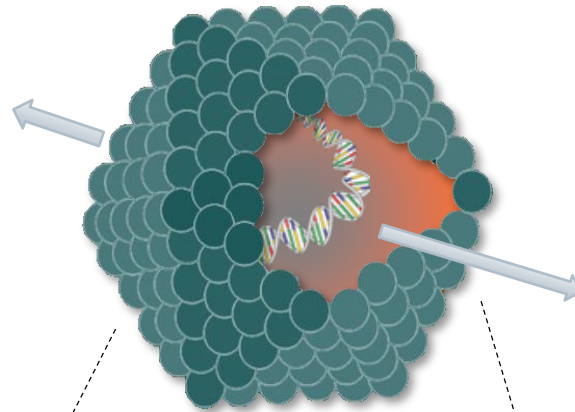
Phenotype	Spontaneous bleeding	Prophylaxis recommended	FIX activity
Severe	frequent	yes	<1%
Moderate	rare	variable	1-5%
Mild	very rare	no	5-40%

Adapted from: Srivastava A, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013

# AMT-060: AAV5 capsid with wildtype FIX cassette

## AAV5 Capsid

- **Low prevalence** of clinically-relevant pre-existing neutralizing antibodies<sup>1, 3</sup>
- Previously tested in human clinical trials with **no safety signals or detectable immune activation**<sup>2</sup>



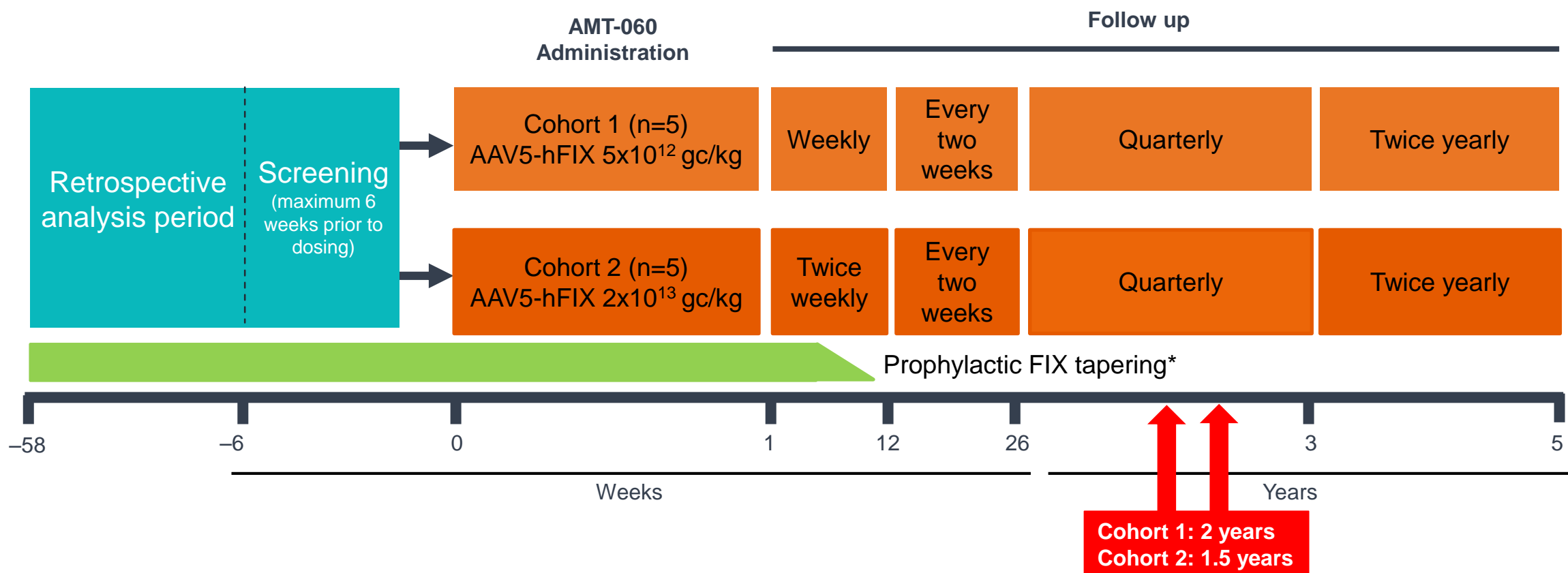
## Expression cassette

- Wildtype hFIX
- Clinically demonstrated **safe and durable** increases in FIX activity with meaningful improvement in clinical outcomes<sup>3,4</sup>

LP1  
(Liver-specific promoter) → Human wild type FIX  
(codon optimized)

# AMT-060 Phase I/II study: Study objective and trial design

*Multi-national, multi-center, open label, dose escalating Phase 1 / 2 study to investigate the safety and efficacy of AMT-060 at 2 dose levels in adults with moderate/severe or severe hemophilia B*



**\*Prophylaxis was tapered and discontinued by 12 weeks if FIX activity was maintained at ≥2%**

FIX, factor IX.

# Study population

- Male patients  $\geq 18$  years with severe or moderate-severe (FIX  $\leq 2\%$ ) hemophilia who required either:
  - Continuous exogenous FIX prophylaxis
  - On-demand exogenous FIX **AND** either  $\geq 4$  bleeds per year or chronic hemophilic arthropathy
- **Exclusion criteria** included:
  - Pre-existing neutralizing AAV5 antibodies measured by green fluorescent protein (GFP) bioassay
  - FIX inhibitors
  - Active Hepatitis B (s and e antigens & HBV DNA) and/or Hepatitis C (HCV RNA)
  - Uncontrolled HIV (CD4+  $\leq 200/\mu\text{L}$  or viral load  $> 200$  genome copies (gc)/mL)

## Baseline characteristics

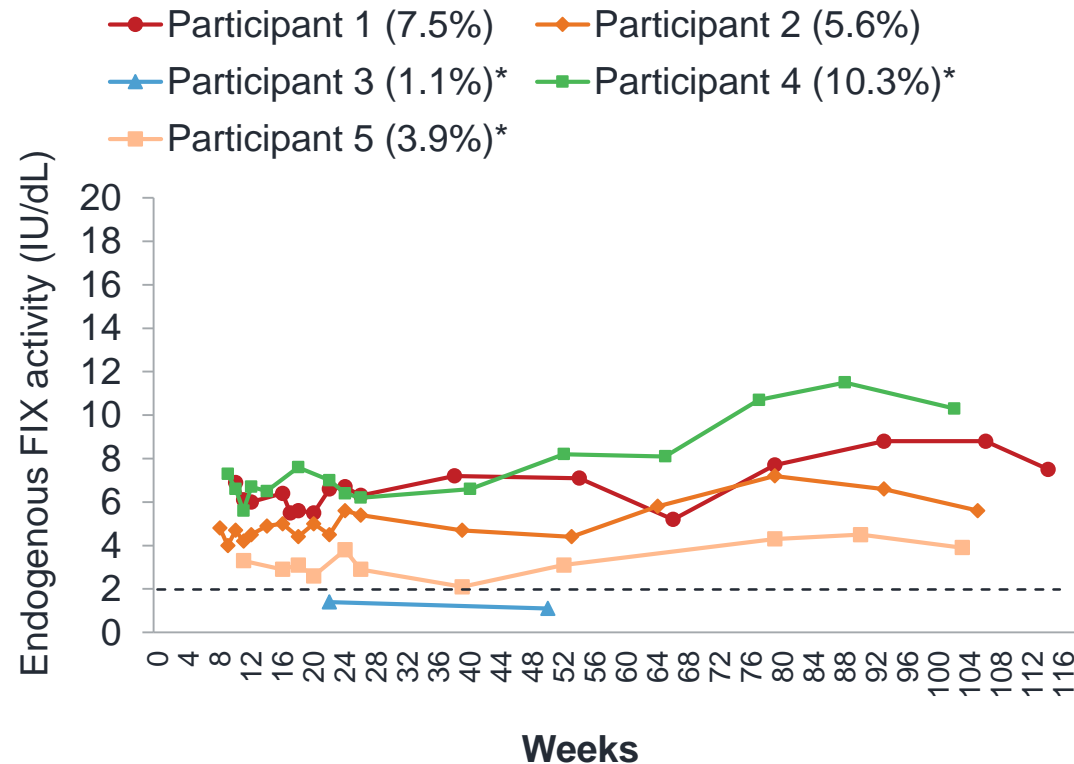
Variable	Cohort 1 (N=5)	Cohort 2 (N=5)
<b>Age (years)</b>	60.2 (35-72)	38.2 (33-46)
<b>Race</b>		
Black or African American	0	1
White	5	4
<b>FIX prophylaxis (IU/week)</b>	4800 (2000-8000)	5625 (4000-10500) <sup>a</sup>
<b>Bleeds (year prior to enrolment)</b>		
Total	14.4	4.0 <sup>b</sup>
Spontaneous	9.8	3.0
<b>Hemophilia joint health scores</b>	24.4 (2-49)	6.8 (0-17)
<b>HIV positive</b>	1	0
<b>Prior hepatitis C infection</b>	4	2
<b>AAV5 nAb+ by luciferase assay<sup>c</sup></b>	3	0

Values for quantitative results are given as mean (min-max) and n for qualitative results <sup>a</sup>, 1 patient received on-demand treatment and is therefore not included; <sup>b</sup>, 1 patient missing historical bleed data; <sup>c</sup>, measured using a luciferase-based assay; n, number of patients with the characteristic; N, total number of patients in the cohort; HIV, human immunodeficiency virus; FIX, factor IX; IU, international units; nAb, neutralizing antibodies.

# Stable dose-dependent increases in FIX activity

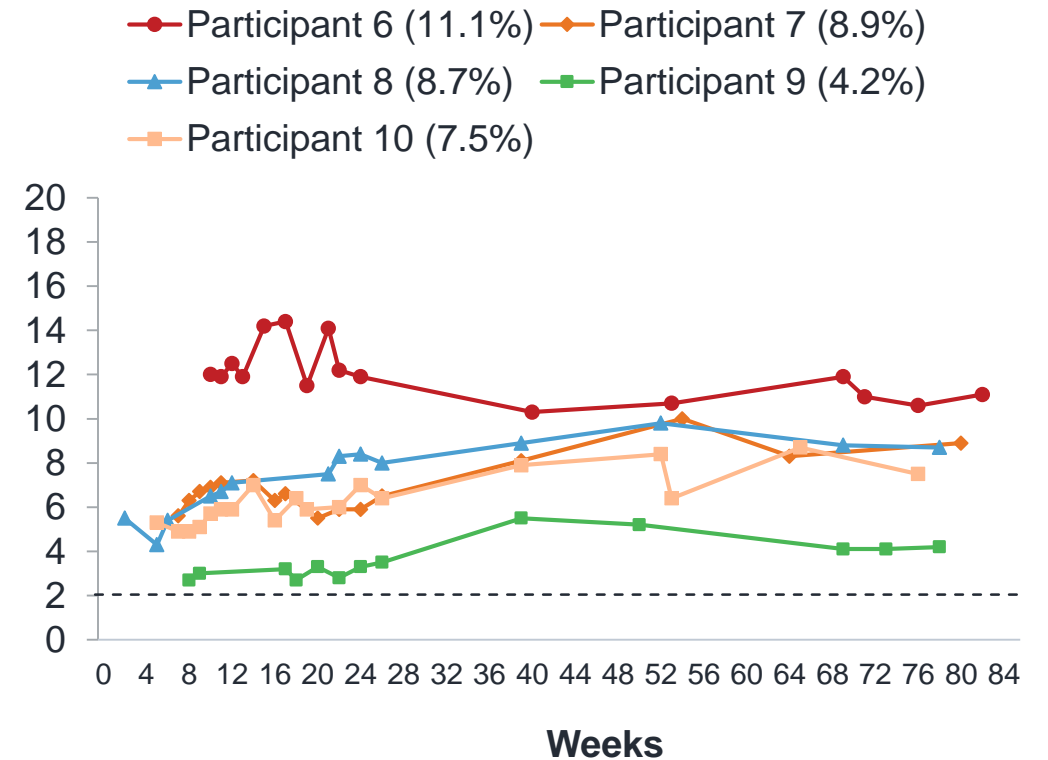
## Cohort 1

mean FIX activity 95%CI: 4.8 (1.6-8.0)



## Cohort 2

mean FIX activity 95%CI 7.2 (3.5-11.0)

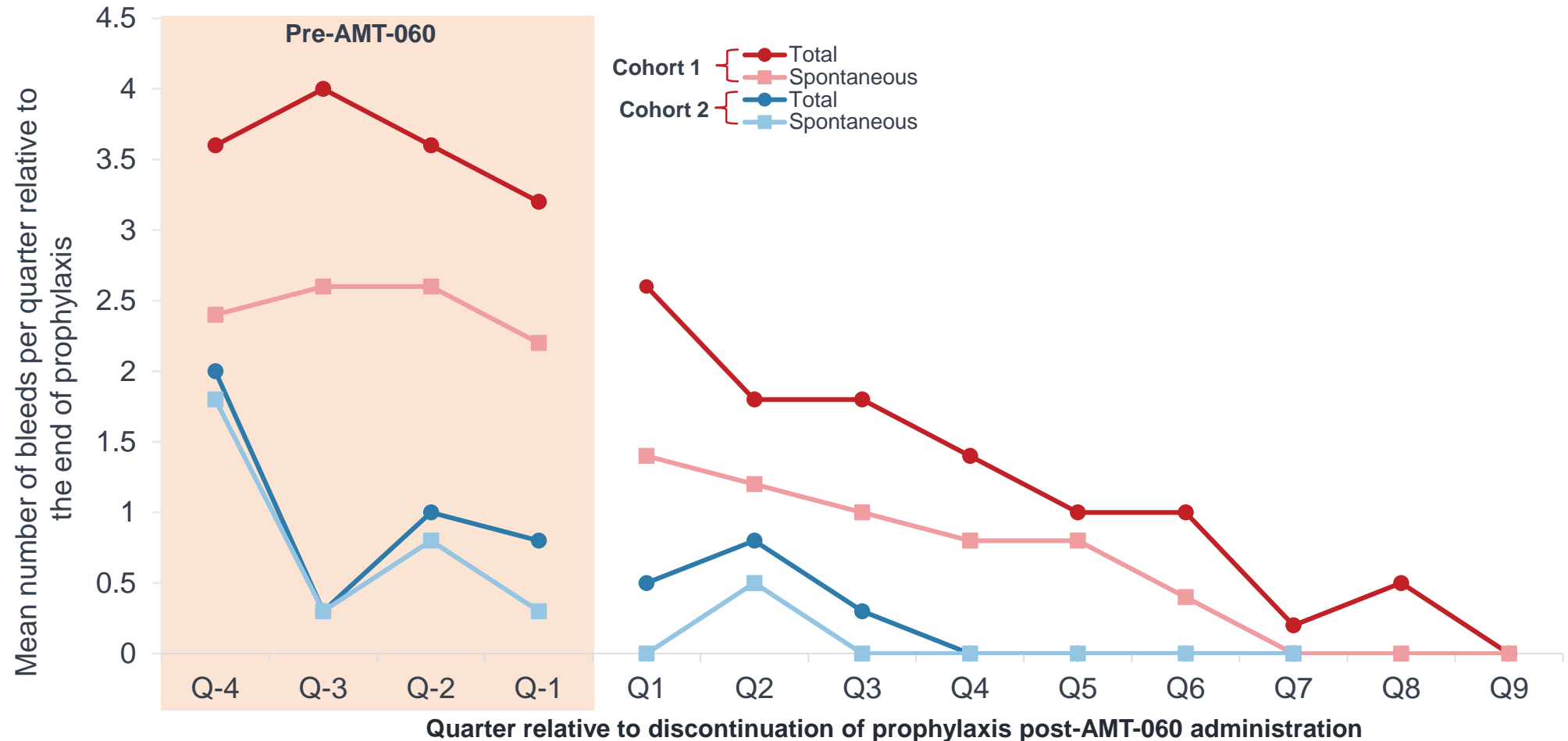


## FIX activity levels correlated at an approximate 1:1 ratio with FIX protein expression

Values in parentheses represent FIX activity at last clean measurement. Only values at least 10 days after last FIX concentrate administration are included. The dotted line at FIX activity of 2 IU/dL indicates the threshold required for ceasing prophylaxis per protocol. FIX prophylaxis was continued after AMT-060 and tapered between Week 6 and Week 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; IU, international units. Post treatment period=after end of tapering



# Sustained reductions in bleeding episodes over time



Cohort 1 (n)	5	5	5	5	5	5	5	5	5	5	5	4	1
Cohort 2 (n)	4	4	4	4	4	4	4	4	4	3	2		

Cohort 2: results presented on 4 participants due to missing historical data from one participant (Participant 10; experienced 1 traumatic bleed in Q3 post-prophylaxis and no spontaneous bleeds). Bleed data were recorded by study participants using an electronic diary and reviewed by the physician at study visits. FIX, factor IX; IU, International units; Q, quarter pre- or post-AMT-060 administration

## Marked reductions in FIX consumption

**84% reduction in cumulative FIX consumption  
across all 10 patients**

	Cohort 1	Cohort 2
Pre-AMT-060 (IU)	1,774,000	866,000
Post-AMT-060 (IU)	235,062	193,492
% decrease	87	78

# Safety: Treatment Emergent Adverse Events classified as possibly / probably related to treatment (TRAE)

TRAE	n (E) Cohort 1 (N=5)	n (E) Cohort 2 (N=5)
<b>Any TRAE</b>	<b>3 (4)</b>	<b>3 (11)</b>
Liver enzyme increased	1 (1)	2 (3 <sup>a</sup> )
Pyrexia	1 (1)	2 (2)
Anxiety	1 (1)	1 (1)
Drug ineffective	1 (1)	0
Palpitations	0	1 (1)
Headache	0	1 (1)
Prostatitis	0	1 (1)
Rash	0	1 (1)

*n, Number of patients with events; (E), Number of events;  
<sup>a</sup>2 events reported in the same patient*

## Treatment Related Serious Adverse Events

- 1 patient: short, self-limiting fever in first 24 hours post-AMT-060
- 2 patients (1 in each cohort): mild, asymptomatic elevations in liver enzymes

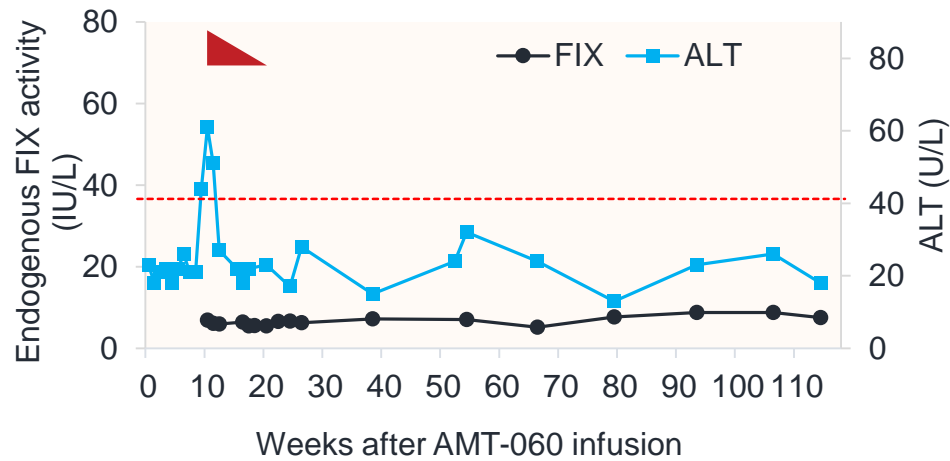
## Overall...

- No new TRAEs were observed during the last 6 months of observation post-treatment
- No inhibitors were detected in any patient

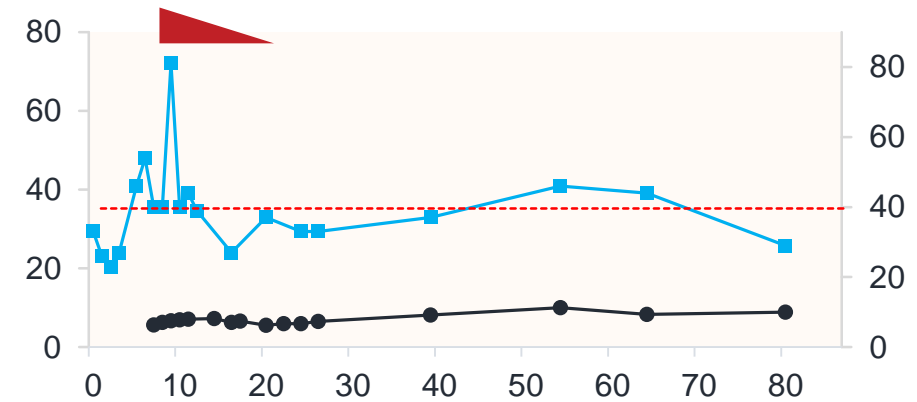
# ALT elevations resolved without activation of capsid-specific T-cells or loss of FIX activity

Cohort 1 Participant 1

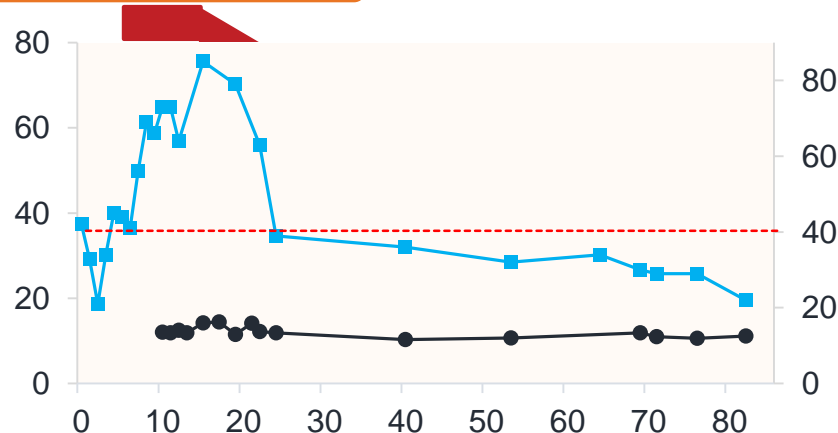
 Prednisone course



Cohort 2 Participant 7



Cohort 2 Participant 6



- ALT elevations were present in 3/10 patients:
  - ALT elevations resolved without recurrence following a tapering course of prednisolone
  - FIX activity remained stable
- No cellular immune response detected by ELISPOT
- No liver enzyme abnormalities in patients with AAV5 nAbs at baseline as measured by the luciferase-based assay

Participant 7 received concomitant treatment with ciprofloxacin and reported alcohol intake at week 9 and 52.

----- ALT upper limit of normal (40 U/L); ALT, alanine aminotransferase; nAb, neutralizing antibody

# Exploratory quality of life and clinical outcomes

## SF-36v2

- At baseline, Cohort 1 generally scored lower than Cohort 2 on domains related to physical health (physical functioning, role physical, pain, and general health)
  - Mean physical component score<sup>a</sup> (norm = 50; SD = 10)
    - Cohort 1: 43.7 (baseline) to 44.1 (at 2 years)
    - Cohort 2: 53.1 (baseline) to 47.0 (at 1 year)
- Interpret with caution due to small study size
- Need for more specific quality of life measurements targeted to patients with hemophilia

## Hemophilia Joint Health Score (HJHS)

- Cohort 1: Mean score of 24.4 at baseline and 20.0 at 2 years
- Cohort 2: Mean score of 6.8 at baseline and 9.0 at 1 year

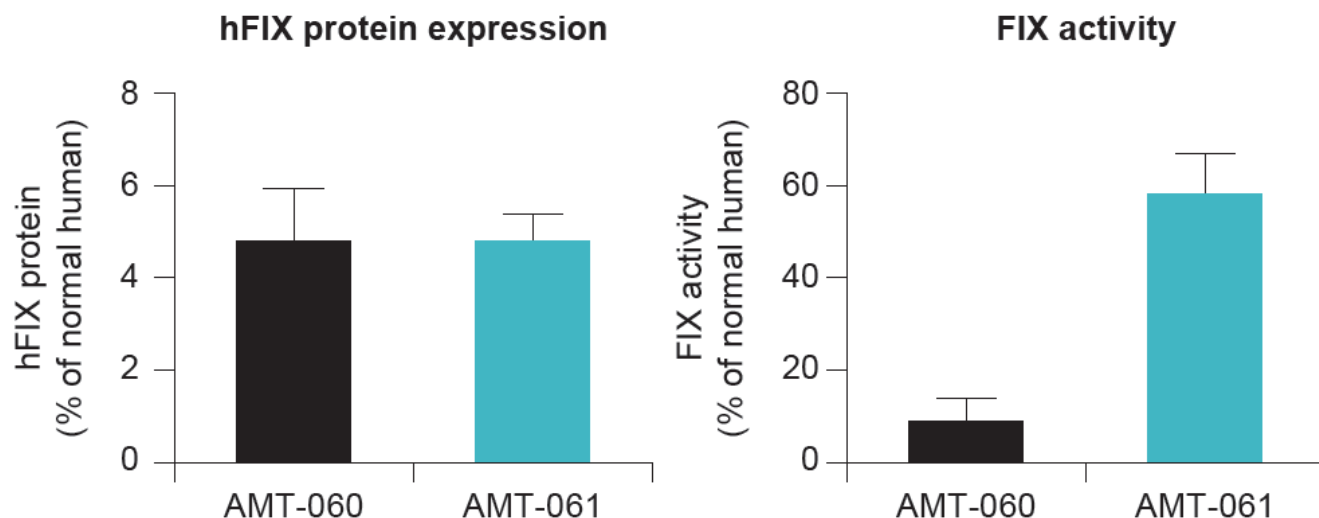
a. The Physical Component Score is calculated using weighted scores across 8 domains.

# Conclusions

- **AMT-060 continued to be generally well tolerated throughout the trial**
  - No development of FIX inhibitors
  - No new adverse events of ALT elevation or capsid-specific T-cell activation observed since last report
- **Clinical benefit endured in all patients**
  - Clinically relevant FIX activity persisted for the duration (up to 2 years) of follow up
  - Continued reductions in bleeds over time in both cohorts
    - No bleeds in Cohort 2 in last 9 months
  - All patients who discontinued prophylaxis remain prophylaxis-free (8/8)
    - Annualized FIX consumption decreased by 84% (2.64 million IU to 428,554 IU)
  - Patient's health status perception generally improved or remained stable
    - Effects on QoL will be further explored in subsequent trials

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

### Nonhuman primates



**Poster #2058**

Ying Poi Liu, Dec 9, 5.30-7.30pm

- AMT-061 includes a **single point mutation** in the *FIX* gene in the AMT-060 gene cassette resulting in R338L switch in the final protein (Padua mutation)
  - Padua mutation previously reported to increase specific activity 8-9 fold<sup>1</sup>
- Initial studies in cynomolgus macaques demonstrate:
  - **Similar safety profiles**
  - Approximate **6-7 fold increase** in baseline-corrected clotting activity
- A pivotal **Phase III** study investigating the safety and efficacy of AMT-061 in humans is scheduled for 2018

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