Reduction in Annualized Bleeding and Factor IX Consumption for up to 2.5 Years in Adults with Severe or Moderate-Severe Hemophilia B Treated with AMT-060 (AAV5-hFIX) Gene Therapy

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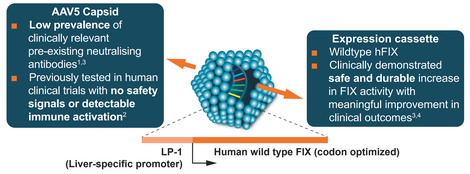
INTRODUCTION

- AMT-060:
  - Adeno-associated virus serotype 5 (**AAV5**) vector
  - Codon-optimized wildtype human factor IX (**hFIX**) gene
  - Liver-specific promoter (**Figure 1**)

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



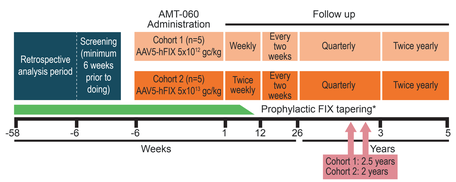
AAV, adeno-associated virus; FIX, Factor IX; hFIX, human FIX

- Phase I/II study safety and efficacy results with AMT-060 up to **1-year follow-up** in 10 adults with moderate-severe or severe hemophilia B has been previously reported[5]
- This poster examines the clinical course of these patients for **up to 2.5 years** post-treatment

METHODS

- Multi-national, open-label, dose-escalating study in participants with FIX activity ≤2% of normal, and a severe bleeding phenotype (NCT02396342) (**Figure 2**):
  - FIX activity ≤2% of normal, receiving either prophylactic or on-demand FIX with ≥4 bleeds per year or hemophilic arthropathy

Figure 2. Study objective and trial design



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

- Key outcome measures are shown in **Table 1**

Table 1. Key outcome measures

Endpoints	Outcomes
Primary safety	■ Adverse events
Secondary safety	■ Vector DNA in body fluids ■ Neutralizing antibodies to AAV5 ■ Total (IgM and IgG) antibodies to AAV5 ■ AAV5 capsid-specific T cells ■ FIX inhibitors ■ Inflammatory markers: IL-1β, IL-2, IL-6, IFN-γ, MCP-1
Confirmatory secondary efficacy	■ FIX activity (measured ≥10 days after last exogenous FIX use)
Supportive secondary efficacy	■ Bleeding rate ■ Total consumption of FIX replacement therapy (excluding use for surgeries/procedures) ■ Quality of life

IL-1β, interleukin-1β; IL-2, interleukin-2; IL-6, interleukin-6; IFN-γ, interferon-γ; MCP-1, monocyte chemotactic protein-1

- As of May 15, 2018, Cohort 1 had 2.5 years and Cohort 2 had 2 years of follow-up post-administration of AMT-060
  - Data are presented by year of follow-up after discontinuation of prophylaxis
  - Where applicable, efficacy outcomes for Cohort 1 were annualized for the partial year of follow-up

RESULTS

Demographics

- Patient demographics are described in **Table 2**

Table 2. Demographics and baseline characteristics

Variable		Cohort 1 (N=5)	Cohort 2 (N=5)
Age, years		69 (35–72)	35 (33–46)
Weight, kg		85.0 (71 - 89)	84.0 (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
Haemophilia joint health scores[d]		27 (2–49)	6 (0–17)
HIV positive status, n		1	0
Prior hepatitis C infection, n		4	2

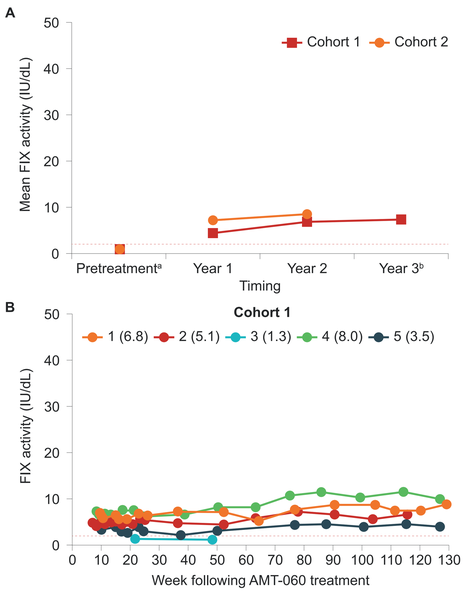
Values are median (min-max) unless otherwise stated. N=number
[a]QOD used as 3.5 x per week for calculations. [b]1 participant in Cohort 2 received on-demand treatment and is therefore not included; [c]Historical bleed data missing for 1 participant in Cohort 2 who is therefore not included; [d]Joint status was assessed using the Haemophilia Joint Health Score version 2·1.[6] FIX, factor IX; n, number of participants with the characteristic; HIV, human immunodeficiency virus

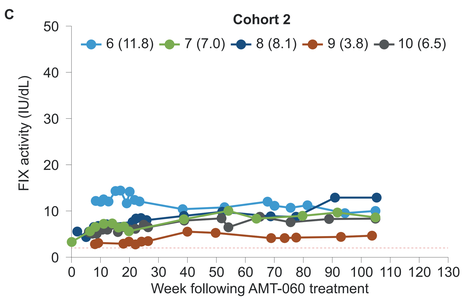
Efficacy Outcomes

Endogenous FIX activity

- Mean **annualized FIX activity was higher in Cohort 2 versus 1** and was **stable** in both cohorts (**Figure 3A**)
  - Modest dose-response effect sustained over time
- **Sustained** and stable individual FIX activity (**Figure 3B and 3C**)

Figure 3. Sustained elevation of endogenous FIX activity following AMT-060 gene transfer. Mean FIX activities by cohort (A) and individual values for Cohorts 1 (B) and 2 (C) are shown





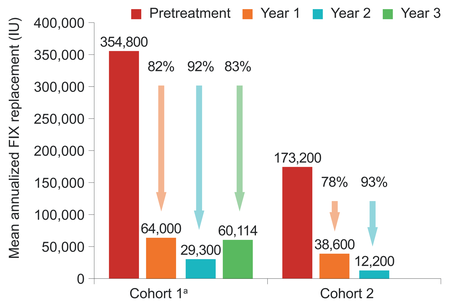
[a]Pretreatment values are historical baseline FIX activities; for Cohort 1: FIX activity <1 IU/dL (n=5); Cohort 2: FIX activity <1 IU/dL (n=4), FIX activity 1.5 IU/dL (n=1). Pretreatment values plotted as 1 IU/dL for both cohorts. [b]Data for Cohort 1 annualized based on partial follow-up available for Year 3. Dotted line indicates protocol-defined threshold for discontinuation of prophylaxis (2 IU/dL)

- Following treatment overall disease severity improved in all pts: severe to mild (n=6), severe to moderate (n=3), moderate to mild (n=1)

FIX replacement

- Eight of the nine participants on FIX prophylaxis at study entry discontinued use after AMT-060
- Cohort 1: ≥82% decrease in annualized exogenous FIX use each year compared to pre-treatment (**Figure 4**)
  - ≥85% in 4 participants who discontinued prophylaxis
- Cohort 2: ≥78% decrease in exogenous FIX use each year compared to pre-treatment (**Figure 4**)
- Decreases in consumption were sustained across the course of follow-up

Figure 4. Reduction relative to pretreatment in mean replacement FIX use

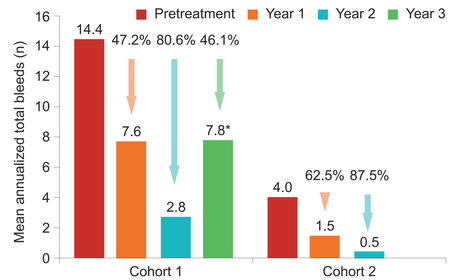


[a]Data for Cohort 1 annualized based on partial follow-up available for Year 3. One participant in Cohort 2 was not included in the calculation as historical bleed data was not available; he experienced one bleed in quarter 3 of Year 1 after the discontinuation of prophylaxis.

Bleedings

- **Mean annualized total bleeds decreased** over follow-up versus pretreatment particularly in Cohort 2 (**Figure 5**)
- In Cohort 2, there were 16 bleeds pretreatment, compared with 6 bleeds (4 traumatic and 2 spontaneous) in Year 1 and 2 bleeds (1 traumatic and 1 spontaneous) in Year 2 post-AMT-060

Figure 5. Mean reduction in annualized total bleeds



**Data for Cohort 1 annualized based on partial follow-up available for Year 3 One participant in Cohort 2 was not included in the calculation as historical bleed data was not available; he experienced one bleed in quarter 3 of Year 1 after the discontinuation of prophylaxis.*

Safety

- As previously reported:[5]
  - 6 pts (3 in each cohort) experienced a total of 14 mild (n=11) or moderate (n=3) TRAE (**Table 3**)
  - **All occurred within first 3.5 months** post-treatment
  - 3 treatment-related serious adverse events (TRAE) elevation of liver enzymes (n=1), febrile episode (n=1) and elevation of alanine aminotransferase (ALT) (n=1)
- In this longer-term follow up to 2.5 years, **no new TRAE occurred**
- **As previously reported, mild, temporary elevations in ALT observed in 3 patients in the 3-6 months** post-administration were not associated with changes in FIX activity or capsid-specific T-cell responses:
  - Resolved with a tapering course of prednisolone
  - No recurrence
- No participants developed FIX inhibitors
- No deaths during the study

Table 3. Previously-reported treatment-related adverse events

Parameter	Cohort 1 (N=5)		Cohort 2 (N=5)	
	No. participants affected (%)	No. events	No. participants affected (%)	No. events
Any TRAE	3 (60)	4	3 (60)	10
Drug ineffective	1 (20)	1	0	0
Pyrexia	1 (20)	1	2 (40.0)	2
Hepatic enzyme increased	1 (20)	1	1 (20)	1
Anxiety	1 (20)	1	1 (20)	1
Alanine aminotransferase Increased	0	0	1 (20)	1
Transaminases increased	0	0	1 (20)	1
Palpitations	0	0	1 (20)	1
Headache	0	0	1 (20)	1
Prostatitis	0	0	1 (20)	1
Rash	0	0	1 (20)	1

TRAE, treatment-related adverse event

NEXT STEPS

- Transgene cassette of AMT-060 prospectively modified with a two-nucleotide substitution to encode hyperactive Padua variant of FIX AMT-061
- A phase 2b, open-label, single-dose, single-arm, multi-center trial is in progress to confirm the FIX activity level following AMT-061 administration to three adults with FIX <2%

- Here we report interim data for three participants at 6 weeks:
  - No exclusion based on neutralizing antibody (NAb) activity
  - Two participants had previously failed screening for another gene therapy due to pre-existing NAb
  - Baseline characteristics are shown in **Table 4**

Table 4. Baseline characteristics

Parameter	Participant 1	Participant 2	Participant 3
Age (years)	43	50	47
Weight (kg)	89	81	82
HIV Status	Negative	Positive, controlled	Positive, controlled
Hep B / Hep C	Hep C; resolved	Hep C; resolved	Hep C; resolved
Hemophilia B status	Severe FIX Deficiency (<1%)	Severe FIX Deficiency (<1%)	Severe FIX Deficiency (<1%)
Pre-screening FIX treatment	Prophylactic	Prophylactic	Prophylactic
Annualized bleed rate 1 year prior to screening	3	1	5

Efficacy at 6 weeks

- Efficacy at 6 weeks after the administration of AMT-061:
  - All patients achieved and sustained therapeutic FIX activity levels
  - Mean FIX activity was 31% of normal at six weeks after infusion
  - No reported bleeding events, no infusion of FIX therapy and no immunosuppression required

Safety at 6 weeks

- AMT-061 was generally well-tolerated with no serious AE
  - One patient experienced two AE, reported as possibly related to treatment, that resolved without any intervention
    - Transient, self-limiting headache shortly after vector administration
    - Slightly elevated C-Reactive Protein (CRP) during weeks 1 and 2 post-administration
  - One patient experienced a mild, asymptomatic and transient increase in liver enzymes
    - Resolved quickly without additional treatment

CONCLUSION

- **Clinically meaningful reductions in bleeds and exogenous FIX use** were sustained in each subsequent year of follow-up post- AMT-060 treatment:
  - Trend towards annualized bleed rates reducing with longer length of follow up particularly in Cohort 2
- **Endogenous FIX activity remained stable** over the duration of follow-up
- The **safety profile of AMT-060 remained positive** over the longer follow up
- Initial Phase 2b data show AMT-061 is well tolerated and all pts achieved therapeutic factor IX activity levels

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