AMT-061 (AAV5-Padua hFIX variant) an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B: Follow-up up to 9 Months in a Phase 2b trial

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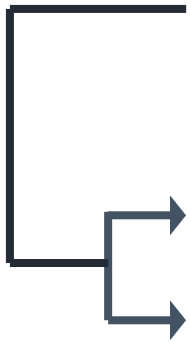
Goal of gene therapy for hemophilia B: Transformation of disease severity

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

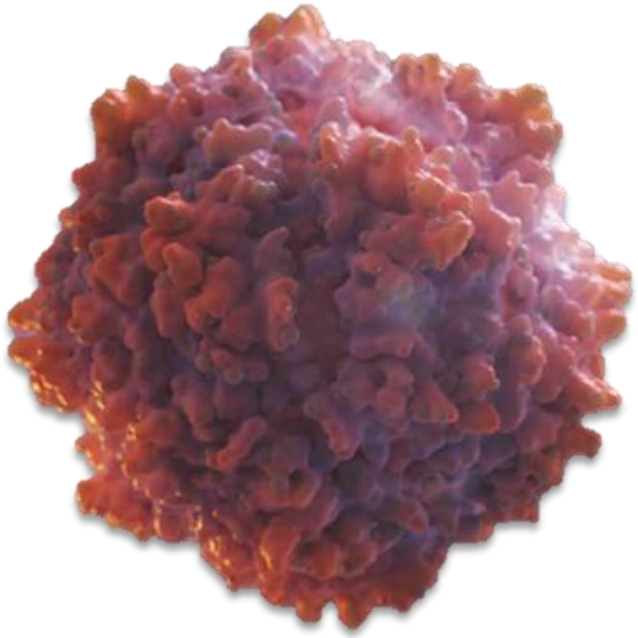


Phenotype	Spontaneous bleeding	Prophylaxis recommended	FIX activity
Severe	*frequent*	*yes*	*<1%*
Moderate	**rare**	*variable*	*1-5%*
Mild	**very rare**	**no**	*5-40%*
Normative	**no**	**no**	*>40%*

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

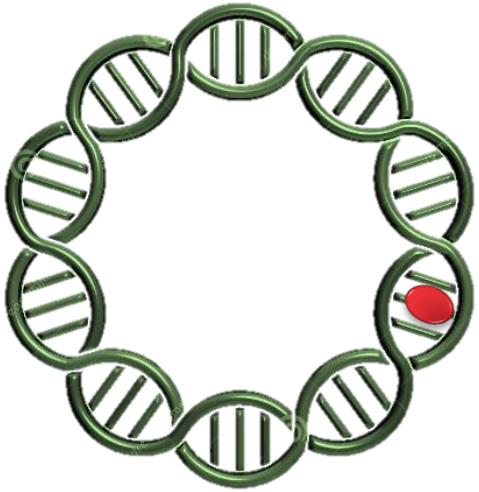
Introduction: gene therapy for hemophilia B: AMT-060/AMT-061

AAV5 capsid



- *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]

Liver-specific promoter & human FIX gene



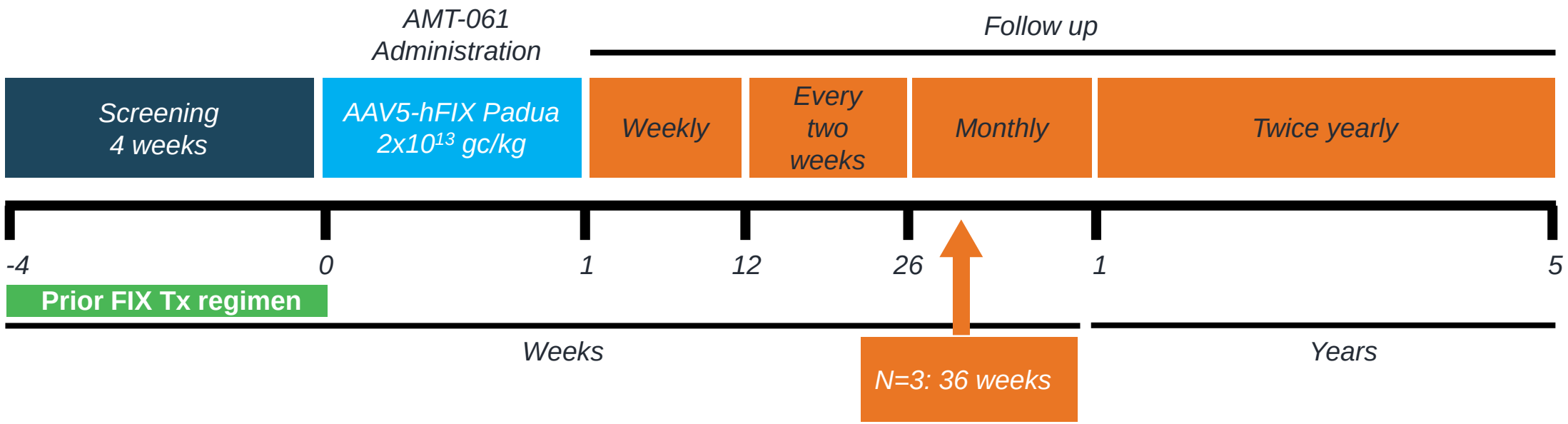
AMT-061
AGG to CTG *in gene resulting in* **R338L** *in protein*

AMT-060 – wildtype
Clinically demonstrated **safe and durable**[3] *increases in FIX activity with meaningful* **improvements in clinical outcomes**[3]

AMT-061 – Padua variant
(expected 6- to 7-fold increase in activity)

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, ASGCT 2018

AMT-061 gene therapy for hemophilia B



- *This* **Phase 2b study** *of AMT-061 is* **currently ongoing**[1]
  - *Data cut off: 28 May 2019*

- **Phase 3 AMT-061 study is ongoing**[2]
  - **Health Outcomes with Padua gene; Evaluation in Hemophilia B (HOPE-B)**

[1] NCT03489291 [2] NCT03569891

AAV; adeno-associated virus; FIX, Factor IX; gc, genome copies; wt, wildtype

AMT-061: Baseline characteristics

Characteristic	Participant		
	1	2	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	FIX = 1%	FIX <1%	FIX <1%
Pre-screening FIX treatment	Prophylaxis (EHL FIX)	Prophylaxis (EHL FIX)	Prophylaxis (EHL FIX)
Annualized bleed rate 1-year prior to screening[a]	3	1	5
Neutralizing antibody activity (AAV5) (Luciferase assay)[b]	Positive 48	Positive 44	Positive 25

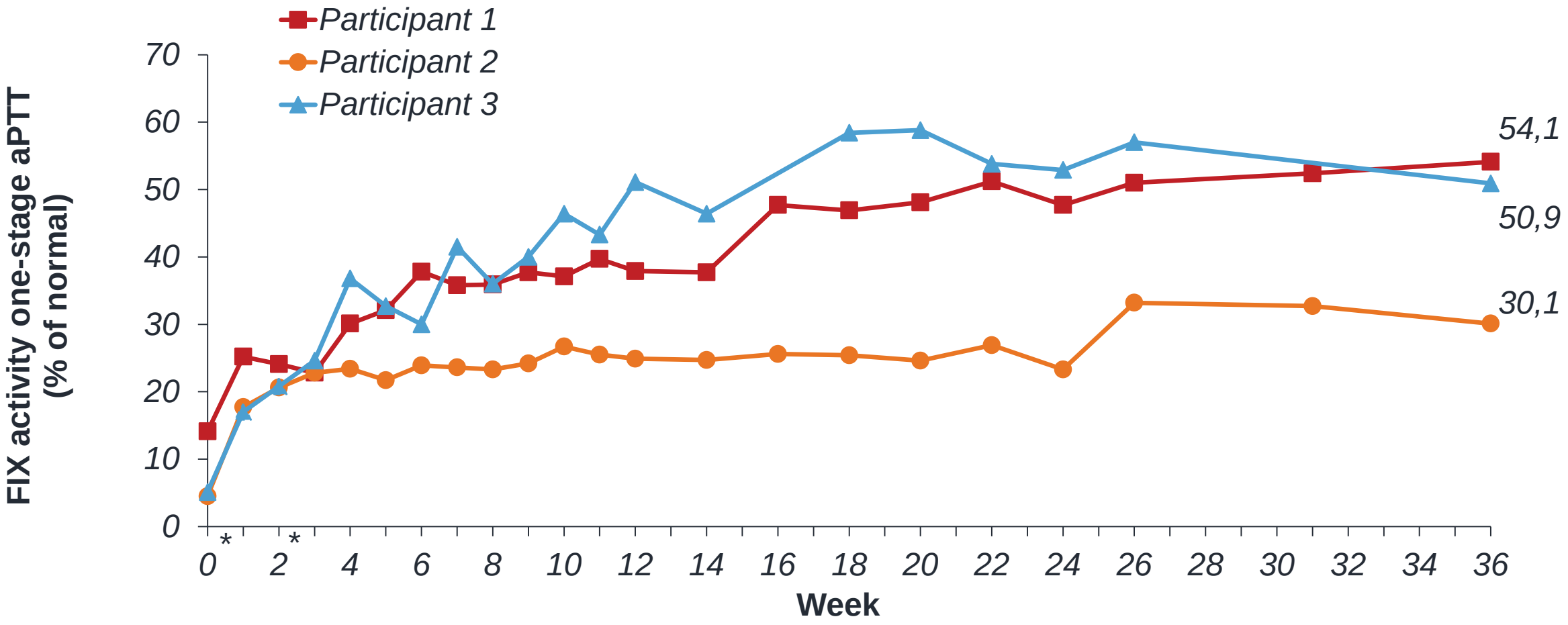
AAV, adeno-associated virus; EHL, extended half-life; FIX, Factor IX; Hep, hepatitis; HIV, human immunodeficiency virus; NAb, neutralizing antibody. Participants 2 and 3 were excluded from another AAV-based gene therapy trial for hemophilia B based on anti-AAV NAb titer.

[a]*Total bleeds (treated + untreated).*

[b]*AAV5 NAb data from screening visit, considered positive if titer is ≥2.*

AMT-061 Efficacy: FIX activity at 36 weeks post-treatment

Mean FIX activity at 36 weeks: 45.0%



*aPTT, activated partial thromboplastin time; FIX, Factor IX. No immunosuppression required. *May include activity from exogenous FIX replacement.*

Reduction in bleeds and FIX replacement

Participant	Bleeds	
	Pre-AMT-061	Post-AMT-061
1	*3 spontaneous (severe)*	*0*
2	*1 spontaneous (moderate)*	*0*
3	*6 spontaneous* (moderate [n=2] and mild [n=4])*	*0*

**1 bleed occurred after enrollment but prior to dosing*

- *No requirement for FIX replacement after treatment**

** Pt 3, received a total of 5 infusions of short acting FIX, associated with hip surgery: 1 infusion pre-operatively and a total of 4 infusions (once per day for 4 days) post-operatively*

Safety summary

General

- *AMT-061 was well tolerated*
  - *1 patient experienced two AE, possibly related to AMT-061, that resolved without intervention*
  - *Transient, self-limiting headache and slightly elevated CRP*
- *No loss of FIX activity*
- *No FIX inhibitor development*
- *Participant 3 had hip surgery due to worsening of pre-existing condition (avascular necrosis)*
  - *Reported as SAE deemed unrelated to AMT-061 by Investigator*

Liver Specific

- *No clinically significant ALT elevations above upper limit of normal after dosing*
  - *Participant 1 had an isolated, slightly elevation at Week 22 (44 U/L) which resolved without intervention or loss of efficacy*
- *1 participant experienced three isolated elevations above the upper limit of normal in aspartate aminotransferase (AST)*
  - *43 U/L (week 2), 48 U/L (week 4), 90 U/L (week 31)*
  - *Resolved quickly without treatment or impact on FIX activity*
- *No participants required immunosuppression*

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CRP, C-reactive protein FIX, Factor IX; SAE, serious adverse event

AMT-061 Phase 2b: Conclusions and next steps

- *AMT-061 was* **generally well-tolerated** *with no serious AEs related to treatment*
- *All participants achieved* **clinically meaningful FIX activity***:*
  - *FIX activity increased by week 1-2*
  - *Mean 45% of normal at week 36*
  - *FIX activity in the normal range for two of the three participants*
- **No bleeds** *or associated use of factor replacement therapy*
- **No clinically significant liver enzyme elevations**
- **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*

AE, adverse event; FIX, Factor IX; NAbs, neutralizing antibodies.

uniQure

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