Phase 2b trial of AMT-061 (AAV5-Padua hFIX variant): Translation into Humans of an Enhanced Gene Transfer Vector for Adults with Severe or Moderately-Severe Hemophilia B

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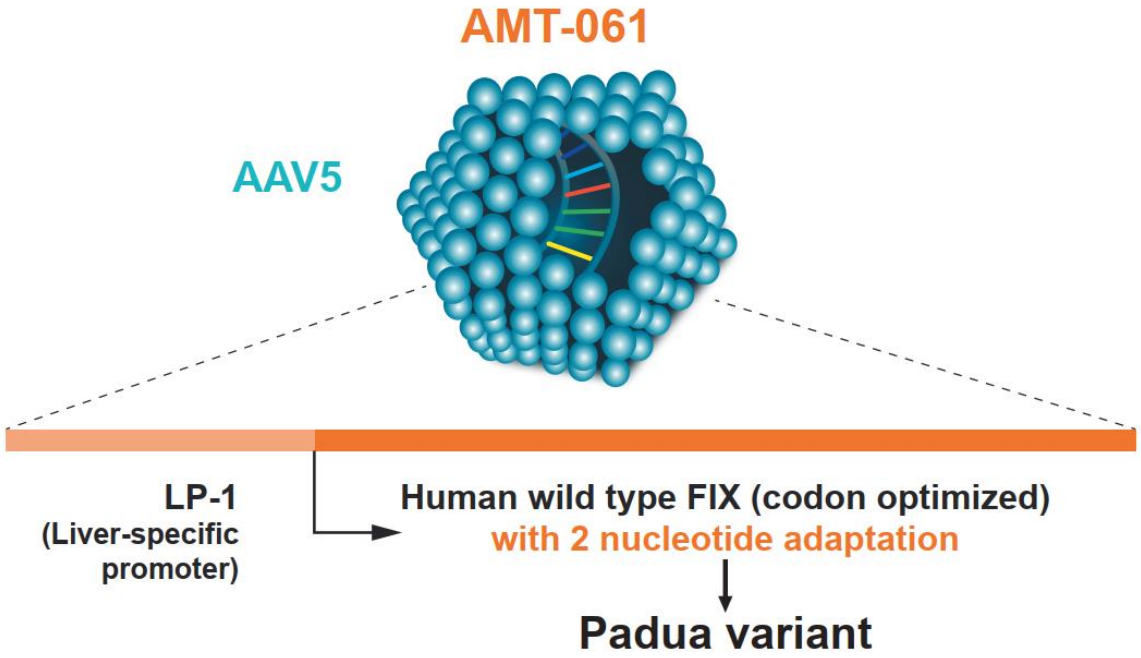
Introduction: gene therapy for hemophilia B

- **AMT-061**:
  - *Investigational treatment*
  - *AAV5 gene transfer to the liver*
  - *Encodes F9 gene,* **Padua variant**
  - **Enhanced version of AMT-060 which** *was studied in 10 patients in a Phase 1/2 trial*

- *This* **Phase 2b study** *of AMT-061 is* **currently ongoing** [1]
  - *One time dose of $2x10^{13}$ gc/kg*
  - *Data cut off: 13 December 2018*

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



[1] NCT03489291
[2] NCT03569891

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

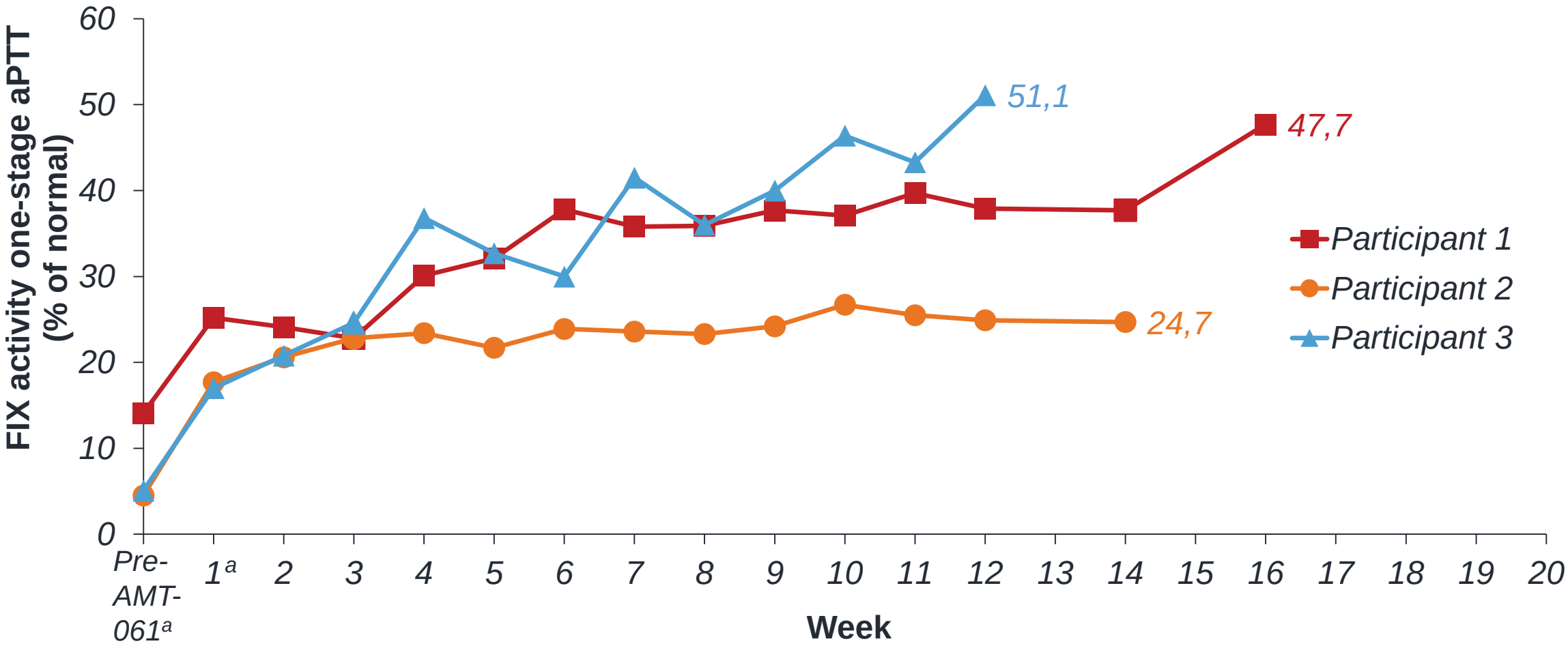
Baseline characteristics

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	*Severe FIX deficiency**	*Severe FIX deficiency**	*Severe FIX deficiency**
Pre-screening FIX treatment	*Prophylactic*	*Prophylactic*	*Prophylactic*
Annualized bleed rate 1-year prior to screening	*3*	*1*	*5*
Anti-AAV5 antibodies *IgG* *IgM*	 *-ve* *+ve*	 *-ve* *-ve*	 *-ve* *-ve*
Neutralizing antibody activity (AAV5)	*+ve (1:48)*	*+ve (1:44)*	*+ve (1:25)*

*AAV; adeno-associated virus; FIX, Factor IX; Hep, hepatitis; HIV, human immunodeficiency virus. *<1% of normal FIX activity.*

Efficacy:
FIX activity up to 16 weeks post-treatment

Mean FIX activity at 12 weeks: 38.0%



aPTT, activated partial thromboplastin time; FIX, Factor IX. No immunosuppression required. [a] 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*

Safety Summary

General Safety

- *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 material loss of FIX activity*
- *No FIX inhibitor development*
- *No serious AE*

Liver Specific

- *No ALT elevations above ULN after dosing*
- *1 patient experienced a mild, asymptomatic, transient increase in AST:*
  - *43 U/L (week 2) and 48 U/L (week 4)*
  - *Resolved quickly without additional treatment*
- *No requirement for immunosuppression*

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CRP, C-reactive protein; FIX, Factor IX; ULN, upper limit of normal

AMT-061 Phase 2b: Conclusions and next steps

- *AMT-061 was* **generally well-tolerated** *with no serious AEs*
- *All participants achieved* **clinically meaningful FIX activity***:*
  - *FIX activity increased by week 1-2*
  - *Mean 38% of normal by week 12*
- **No bleeds** *or requirement for factor replacement therapy*
- **No loss of FIX activity** *or requirement for immunosuppression*

- *Phase 3 HOPE-B AMT-061 study is enrolling*
  - **First patient treated**
  - *Expected to enroll approximately 50 participants with severe hemophilia B*
  - *Those with pre-existing AAV5 NAbs will not be excluded*
  - *For more information about the trial see* **Poster P108**

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

Acknowledgements

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