Etranacogene dezaparvovec (AAV5-Padua hFIX variant), an Enhanced Vector for Gene Transfer in Adults with Severe or Moderate-Severe Hemophilia B: Two Year Data from a Phase 2b Trial

Annette von Drygalski,[1] Adam Giermasz,[2] Giancarlo Castaman,[3] Nigel S. Key,[4]
Susan U. Lattimore,[5] Frank W.G. Leebeek,[6] Wolfgang A. Miesbach,[7]
Michael Recht,[5] Esteban Gomez,[8] Robert Gut,[9] and Steven W. Pipe[10]

[1]University of California San Diego, La Jolla, CA, USA; [2]University of California Davis, Sacramento, CA, USA;
[3]Azienda Ospedaliera Universitaria Careggi, Florence, Italy; [4]University of North Carolina, Chapel Hill, USA;
[5]Oregon Health and Science University, Portland, USA; [6]Erasmus University Medical Center, Rotterdam, The Netherlands;
[7]University Hospital Frankfurt, Germany; [8]Phoenix Children's Hospital, Phoenix, USA;
[9]UniQure Inc, Lexington, MA, USA; [10]University of Michigan, Ann Arbor, MI, USA

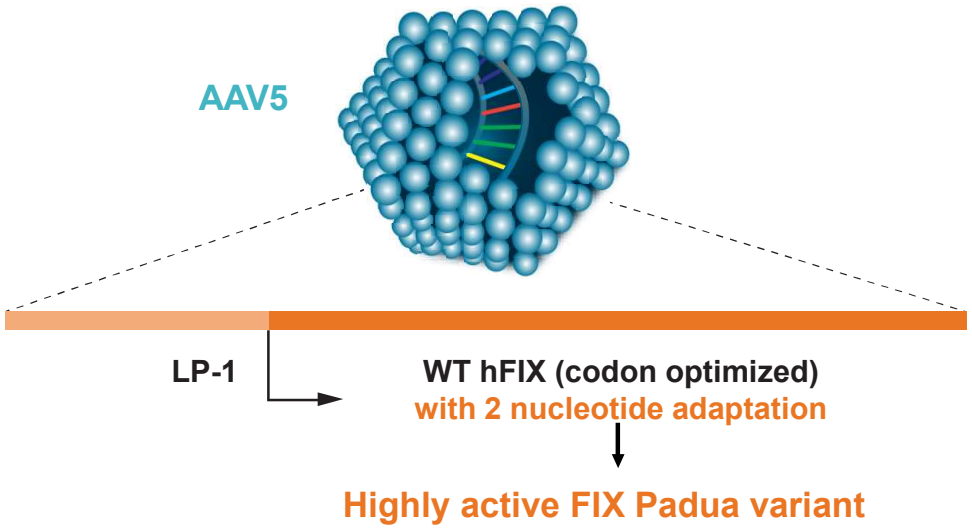
Disclosures

- **Presenter:** Dr. Annette von Drygalski
- Fees from Biomarin, Bioverativ/Sanofi-Genzyme, Genentech, Novo Nordisk, Pfizer, Takeda, and UniQure for participation in Industry sponsored Education events and Advisory Boards
- Co-Founder and a member of the Board of Directors of Hematherix Inc with a patent for super FVa
- Inventor for the Joint Activity and Damage Examination (JADE) Ultrasound measurement tool, copyrighted by the University of California

AAV5 gene therapy for hemophilia B

- **Etranacogene dezaparvovec** (AAV5-Padua hFIX):
  - Investigational treatment
  - AAV5 gene transfer to the liver
  - Enhanced version of **AMT-060** (AAV5-WT hFIX), which demonstrated safety and efficacy in a Phase 1/2 trial (N=10)[1-3]
    - **Stable expression of FIX** for up to 5 years
    - **Reductions in ABR** and **FIX replacement**
    - **No late-emergent safety signals**

Etranacogene dezaparvovec



A **Phase 2b** etranacogene dezaparvovec study (NCT03489291) is ongoing[4]

ABR, annual bleeding rate; AAV; adeno-associated virus; hFIX, human Factor IX; LP-1, liver-specific promotor; WT, wild type

[1]Miesbach W, et al. *Blood*. 2018;131:1022-1031; [2]Leebeek F, et al. *Res Pract Thromb Haemost* 2019;3(S1):81; [3]Leebeek F, et al. Presented at ASH 2020; [4]Von Drygalski A, et al. *Blood Adv*. 2019;3(21):3241-3247.

Participants and design

Primary endpoint[1;2]

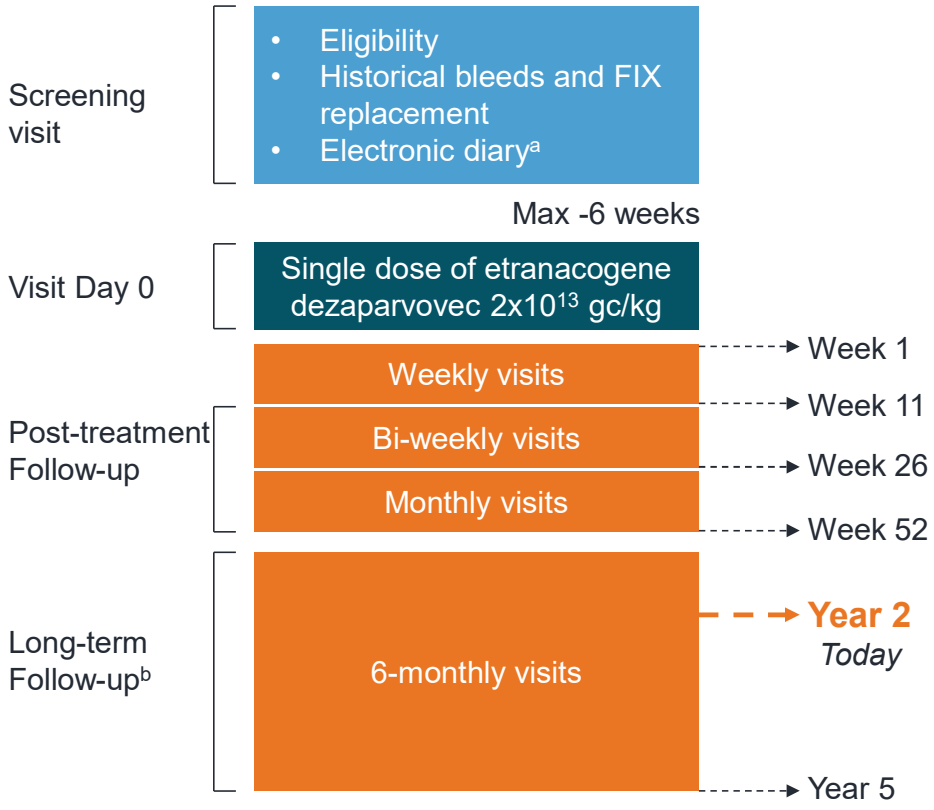
- FIX activity at 6 weeks (one-stage aPTT clotting assay)

Secondary endpoints[1;2]

- FIX activity at other time points (aPTT and chromogenic assay)
- Bleeds and FIX use
- Safety

Participants[1;2]

- 3 adults with **severe or moderate-severe hemophilia B**
- Controlled HIV, cleared hepatitis B/C, and no FIX inhibitors
- Participants with **pre-existing NAbs to AAV5 were not excluded**



[a]Recording of bleeds and FIX replacement prior to, and following, AMT-061 treatment. Assessment of bleeds and FIX replacement prior to screening were based on medical records. [b]No e-diary recording during long-term follow-up.
aPTT, activated partial thromboplastin time; FIX, factor IX; gc, genome copies; HIV, human immunodeficiency virus; NAbs, neutralizing antibodies
[1]NCT03489291; [2]Von Drygalski A, et al. *Blood Adv*. 2019;3(21):3241-3247.

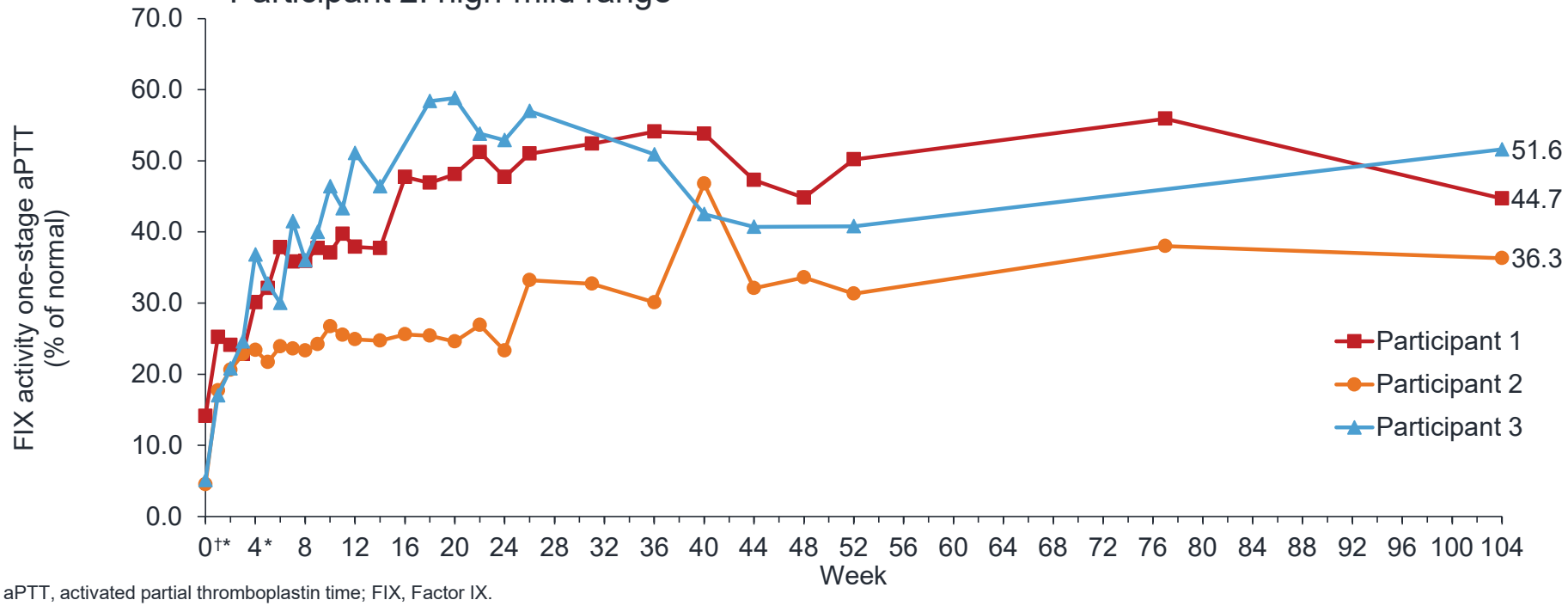
Baseline characteristics

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. aTotal bleeds (treated + untreated). bAAV5 NAb data from screening visit, considered positive if titer is ≥2.

FIX activity sustained at 2yrs post-treatment

- The primary endpoint (FIX activity ≥5% at 6 weeks) was achieved in all 3 participants
  - **Mean FIX activity at 2 years: 44.2%**
  - All participants maintain factor activity at levels comparable to those at 1 year
    - Participant 1 and 3: non-hemophilic range (≥40%)
    - Participant 2: high-mild range



aPTT, activated partial thromboplastin time; FIX, Factor IX.
No immunosuppression required. †The week 0 time point reflects FIX activity before etranacogene dezaparvovec treatment.
*Samples may include activity from exogenous FIX replacement.

Sustained reduction in bleeds and FIX replacement

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

*1 bleed occurred after enrollment but prior to dosing

- **All participants remain prophylaxis-free through 2 years post-treatment**
  - No FIX use or bleeds in 2/3 participants
  - Over 2 years, 1 participant has used a total of 2 infusions of FIX replacement therapy (1 suspected and 1 confirmed bleed) on separate occasions (excluding surgery)

FIX, Factor IX.

Safety summary

General safety

- **Previously reported for first year of follow up[1]:**
  - 2 treatment-related* AEs in 1 participant, that resolved without intervention (transient, self-limiting headache and slightly elevated CRP)
  - 1 serious AE deemed unrelated to treatment:
    - Participant 3: worsening of avascular necrosis resulting in hip surgery
- **Over the second year of follow-up:**
  - No new AEs deemed related to treatment
  - No FIX inhibitor development
  - 1 serious AE deemed unrelated to treatment:
    - Participant 3: worsening of avascular necrosis resulting in hip surgery

Liver specific

- **Previously reported for first year of follow up[1]:**
  - No clinically significant ALT or AST elevations or AAV5-specific T-cell responses
  - No requirement for immunosuppression
  - No loss of FIX activity
- **Over the second year of follow-up:**
  - No clinically significant transaminase elevations or other findings
    - 1 participant had an additional isolated AST elevation at 18 months (62 U/L; ULN 34)
    - Resolved quickly without treatment or impact on FIX activity
  - No requirements for immunosuppression or loss of FIX activity

AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransaminase; CRP, C-reactive protein; FIX, Factor IX; ULN, upper limit of normal; *assessed as possibly, probably, or definitely related by investigator

[1]Von Drygalski A, et al. *Blood Adv*. 2019;3(21):3241-3247

Conclusions and next steps

- **Etranacogene dezaparvovec** was **well-tolerated** in these 3 pts with **no new treatment-related adverse events in year 2**
- **All participants** achieved **sustained FIX activity** in the functionally curative range after a single administration
  - Mean FIX activity at 2 years was **44.2%**
- Over 2 years, 2 participants remain **free from bleeds and use of FIX replacement therapy**
  - A single bleed has been reported in 1 participant, who has used 2 FIX infusions total (excluding surgery)
- **No loss of FIX activity** and **no requirement for immunosuppression**
- Participants will be followed for a further 3 years[1]
- The efficacy and safety of **etranacogene dezaparvovec** is being further characterized in the ongoing Phase 3 **HOPE-B study** (NCT03569891)[2]
  - Data to be presented on Tuesday, December 8, 2020 at 8:45 AM

AAV, adeno-associated virus; AE, adverse event; FIX, Factor IX; NAbs, neutralizing antibodies.

[1]Von Drygalski A, et al. *Blood Adv*. 2019;3(21):3241-3247; [2]Pipe S, et al. ASH 2020: Late Breaker Abstract.