Follow-up on a Novel Adeno-Associated Virus (AAV) Gene Therapy (FLT180a) Achieving Normal FIX Activity Levels in Severe Haemophilia B (HB) Patients (B-AMAZE Study)

Pratima Chowdary,[1, 2] Susan Shapiro,[3] Mike Makris,[4] Gillian Evans,[5] Sara Boyce,[6] Kate Talks,[7] Gerry Dolan,[8] Ulrike Reiss,[9] Mark Phillips,[1, 2] Anne Riddell,[1] Maria Rita Peralta,[1] Michelle Quaye,[2] Ted Tuddenham,[1] Andrew Smith,[10] Alison Long,[10] Julie Krop,[10] Amit Nathwani[1, 2]

[1]Katharine Dormandy Haemophilia and Thrombosis Centre, Royal Free Hospital, London, UK; [2]University College London, London, UK; [3]Oxford University Hospitals, NIHR Oxford Biomedical Research Centre, Oxford University, UK, UK; [4]University of Sheffield, Sheffield, UK; [5]Kent and Canterbury Hospital, Canterbury, UK; [6]University Hospital Southampton, Southampton, UK; [7]Newcastle Haemophilia Comprehensive Care Centre, Newcastle, UK; [8]St Thomas' and Guy's Hospital, London, UK; [9]St Jude Children's Research Hospital, Memphis, TN, USA; [10]Freeline, Stevenage, UK

Disclosures: P. Chowdary Grant/Research support from: Bayer, CSL Behring, Novo Nordisk, Pfizer and Sobi; Consultant for: Baxter, Biogen, CSL Behring, Freeline, Novo Nordisk, Pfizer, Roche, Shire and Sobi.
S. Shapiro Grant/Research support from: Bayer, Novo Nordisk, Octapharma; Consultant for: Chugai/Roche, Novo Nordisk, Shire, Sobi; Speaker Bureau of: Bayer, Pfizer, and Roche. M. Makris Consultant for: CSL Behring, Novo Nordisk, Bioverativ, Spark and Catalyst; Speaker Bureau of: Pfizer. G. Evans: None Declared. S. Boyce: None Declared. K. Talks: None Declared. G. Dolan Grant/Research support from: Pfizer, Novo Nordisk, Bayer; Speaker Bureau of: Bayer, Biomarin, CSL, Novo Nordisk, Octapharma, Spark Therapeutics, Roche-Chugai, Takeda. U. Reiss: None Declared. M. Phillips: None Declared. A. Riddell: None Declared. M. R. Peralta: None Declared. M. Quaye: None Declared. T. Tuddenham Consultant for: Freeline. A. Smith Employee of: Freeline. A. Long Employee of: Freeline. J. Krop Employee of: Freeline. A. Nathwani Shareholder of: Freeline. Grant/Research support from: Freeline. The B-AMAZE study was sponsored by University College London and supported by Freeline

Acknowledgements: The authors would like to thank the study participants and their families, study investigators, coordinators, and site personnel.

Verbrinacogene setparvovec (FLT180a): Completed B-AMAZE Phase 1/2 study

Objectives To establish a safe and effective dose of FLT180a that normalises factor IX (FIX) activity levels between 50 and 150%, and to optimise an immune management regimen to preserve expression

Key inclusion criteria

- Severe or moderate Haemophilia B ≤ 2%
- Adults ≥18 years

Key exclusion criteria

- Neutralising antibodies to AAVS3
- Liver disease

Endpoints at 6 months

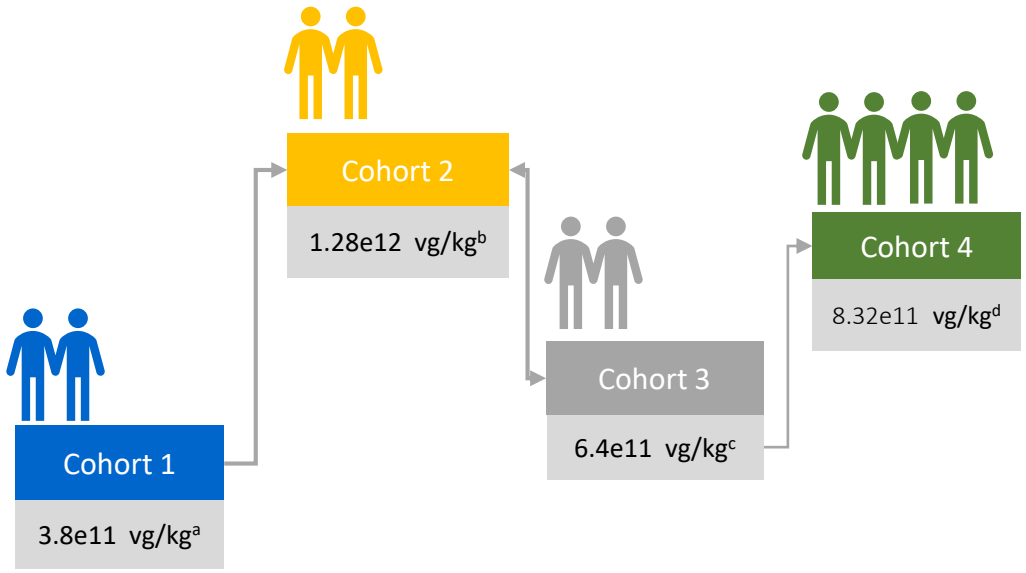
- Safety
- FIX activity level

Target range for dose finding

- 50 to 150%

Verbrinacogene setparvovec (FLT180a): novel, potent, engineered capsid (AAVS3) and expression cassette encoding FIX protein variant with gain-of-function 'Padua' mutation

Adaptive dose escalation design



Immune management strategy

- Prophylactic/reactive immunosuppression with Corticosteroids +/- Tacrolimus
- Intensive monitoring

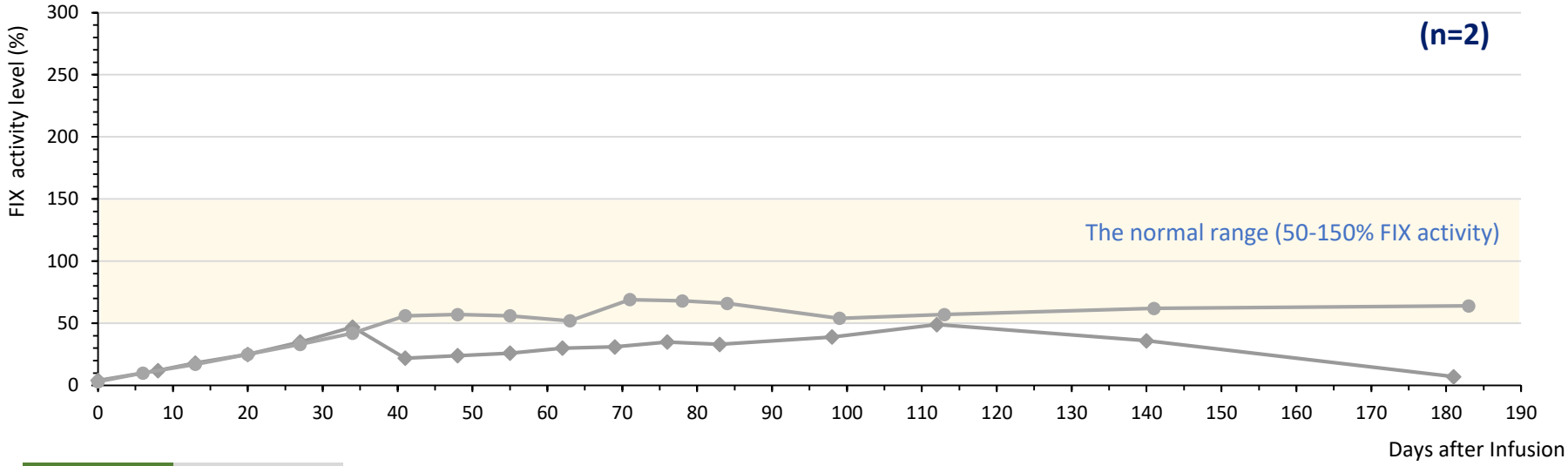
Assessments: Safety; FIX activity level (one-stage clotting assay); Exogenous FIX concentrate usage; Bleeding frequency

Enrolment criteria: Haemophilia B patients aged ≥18 years with FIX activity levels <2%; Lack of neutralising antibodies to AAVS3; >150 exposure days to FIX and no history of inhibitors; Normal liver function; No evidence of active Hepatitis B, C, or HIV infection

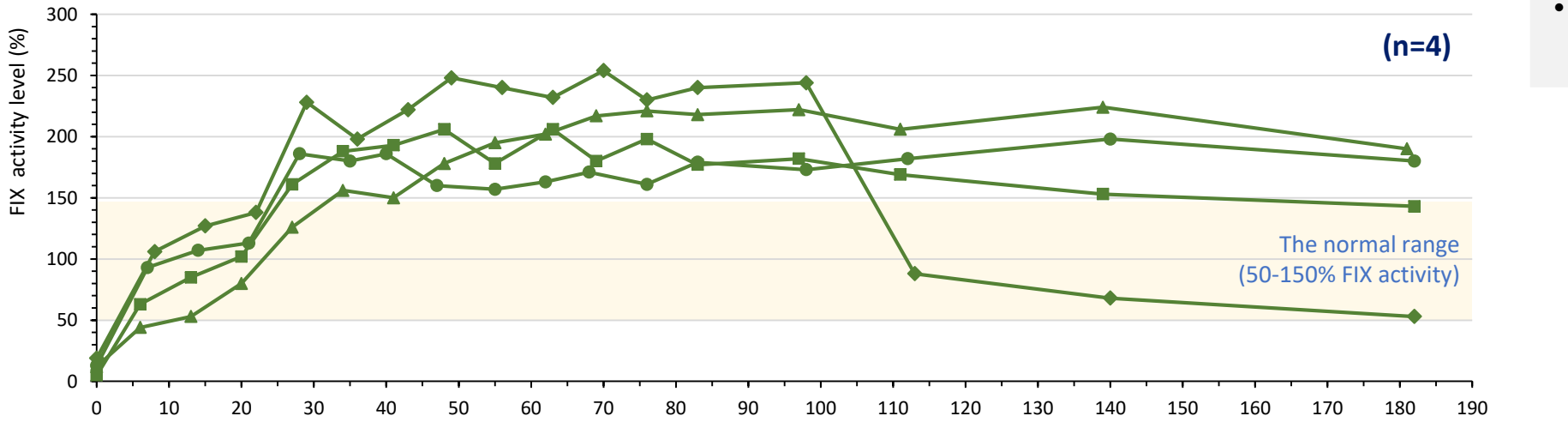
[a]previously reported as 4.5e11vg/kg; [b]previously reported as 1.5e12vg/kg; [c]previously reported as 7.5e11vg/kg; [d]previously reported as 9.75e11vg/kg

Verbrinacogene setparvovec (FLT180a): potential to provide a functional cure by normalizing FIX activity

Cohort 3 | 6.4e11 vg/kg[a]



Cohort 4 | 8.32e11 vg/kg[b]



Cohort 1 (n=2) 3.8e11 vg/kg

- Continue to see consistent FIX activity levels in the range of 40% for ~3 years of follow-up

Cohort 2 (n=2) 1.28e12 vg/kg

- One patient showed supraphysiological FIX levels and the other patient achieved FIX activity levels within the normal range
- FIX activity has stabilised in both patients

No bleeds required FIX supplementation

[a]previously reported as 7.5e11vg/kg; [b]previously reported as 9.75e11vg/kg. ALT = alanine aminotransferase. One-stage assay, central laboratory measurement. Data as of 21st August 2020.

Verbrinacogene setparvovec (FLT180a): favourable safety profile and well tolerated

Key Safety Results

- No infusion reactions and no discontinuations of infusion
- No other allergic reactions to date
- Most common drug related SAE was transient transaminitis. Manifests as an elevation in ALT, with or without a decrease in expression
- A single patient in the highest dose cohort developed thrombosis of AV fistula in the context of supraphysiological FIX levels

Conclusions

- Stable and durable FIX response up to ~3 years (Cohort 1)
- No bleeds requiring FIX supplementation
- Immune management evolved during the study as transaminitis has a significant impact on predictability of long-term expression
- A Phase 2b/3 clinical trial to be initiated in 2021
  - Dose with potential to achieve FIX activity in the normal range is expected to be between 6.4e11 and 8.32e11 vg/kg[a]

[a]previously reported as 7.5e11vg/kg and 9.75e11vg/kg, respectively. ALT = alanine aminotransferase; SAE = serious adverse event.