Interim results of an open-label, Phase 1/2 study of BMN 270, an AAV5-FVIII gene transfer in severe haemophilia A

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Rationale For Programme

FVIII Replacement Therapy

- Replacement products
  - an expensive and demanding treatment
  - must be given 3x or more times weekly iv
  - new EHLs still require 2x weekly iv
  - for optimal replacement therapy treatment burden is significant
- Factor levels not consistent
  - saw tooth response
  - microbleeding at low factor levels remains a concern

Gene Therapy

- Single gene disorder
  - clear cause and effect relationship
- Wide therapeutic window
  - low levels dramatically improve outcome
  - high levels welcome (up to a point)
- Efficacy easy to assess
  - clinical
  - laboratory
- BMN 270 (AAV5-hFVIII-SQ)
  - First in human study
  - adeno-associated virus(AAV) serotype 5
  - codon-optimized expression cassette
  - SQ variant B-domain-deleted human FVIII

Phase 1/2 Study- first-in-Human, dose escalation in patients with severe Haemophilia A

Design

- Subjects enrolled sequentially into one of up to four cohorts based on FVIII activity at 3 weeks:
    1. 6×10e12 vg/kg given as a single intravenous dose
    2. 2×10e13 vg/kg, iv
    3. 6×10e13 vg/kg, iv
    4. 4x10e13 vg/kg, iv
- Dose escalation occurred if the resulting FVIII activity at the Week 3 visit is < 5 IU/dL
- Subjects on prophylactic FVIII therapy switched to an “on-demand” schedule
- Out of abundance of caution, to ensure patient safety and to protect against loss of FVIII activity expression, cohorts 1-3 had prophylactic corticosteroids initiated after first subject had ALT elevation 1.5 fold above baseline
- No prophylactic corticosteroids in Cohort 4 at 4x10e13 vg/kg; trigger for corticosteroids set at ALT of 1.5x ULN

Endpoints

- Safety of a single intravenous administration of a recombinant AAV human-coagulation FVIII vector
- Change from baseline of FVIII expression level
- Impact on the frequency of FVIII replacement therapy and annualized bleeding rate

Key Eligibility Criteria

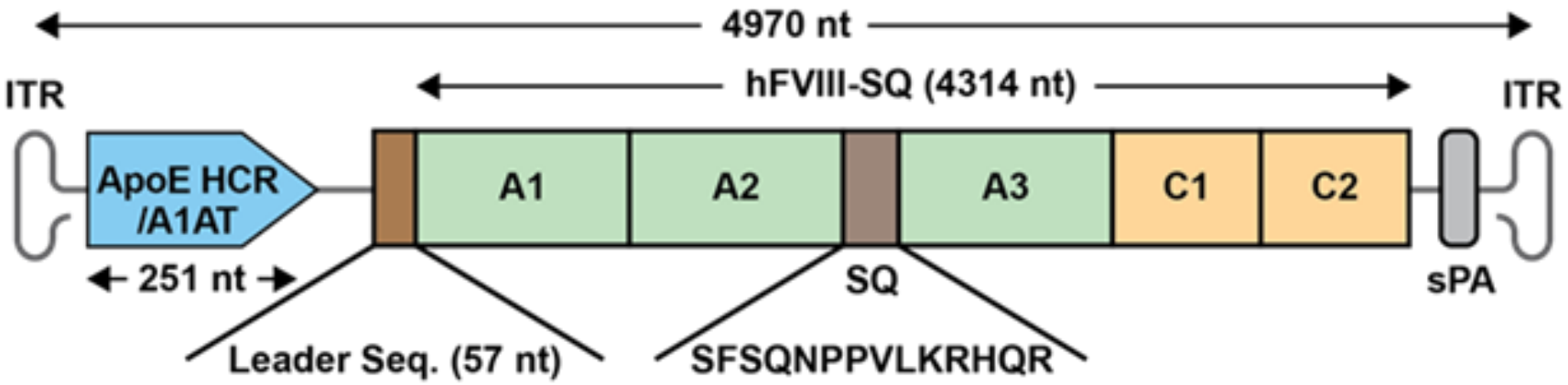
KEY INCLUSION CRITERIA

- Males that are 18 years or older with established severe haemophilia A (FVIII level ≤1 IU/dL)
- Treated/exposed to FVIII concentrates or cryoprecipitate for a minimum of 150 exposure days
- Greater or equal to 12 bleeding episodes therapy over the previous 12 months (on-demand subjects)
- Results from a modified Nijmegen Bethesda assay of <0.6 Bethesda Units

KEY EXCLUSION CRITERIA

- Detectable pre-existing immunity to the AAV5 capsid as measured by AAV5 transduction inhibition or AAV5 total antibodies
- HIV positive
- Significant liver dysfunction
  - ALT or TBili or ALP >3 fold ULN
  - INR ≥ 1.4
  - Liver fibrosis on biopsy if performed
  - Liver cirrhosis by US
- Hepatitis B if surface antigen positive
- Hepatitis C if RNA is positive

AAV5-hFVIII-SQ [BMN 270] Vector Genome Schematic



AAV5 Seroprevalence/Humoral immunity

21 Screened; 2 were also positive by total antibody assay (TAb)

Baseline Demographics & Clinical Characteristics

15 subjects enrolled and dosed in 4 cohorts:

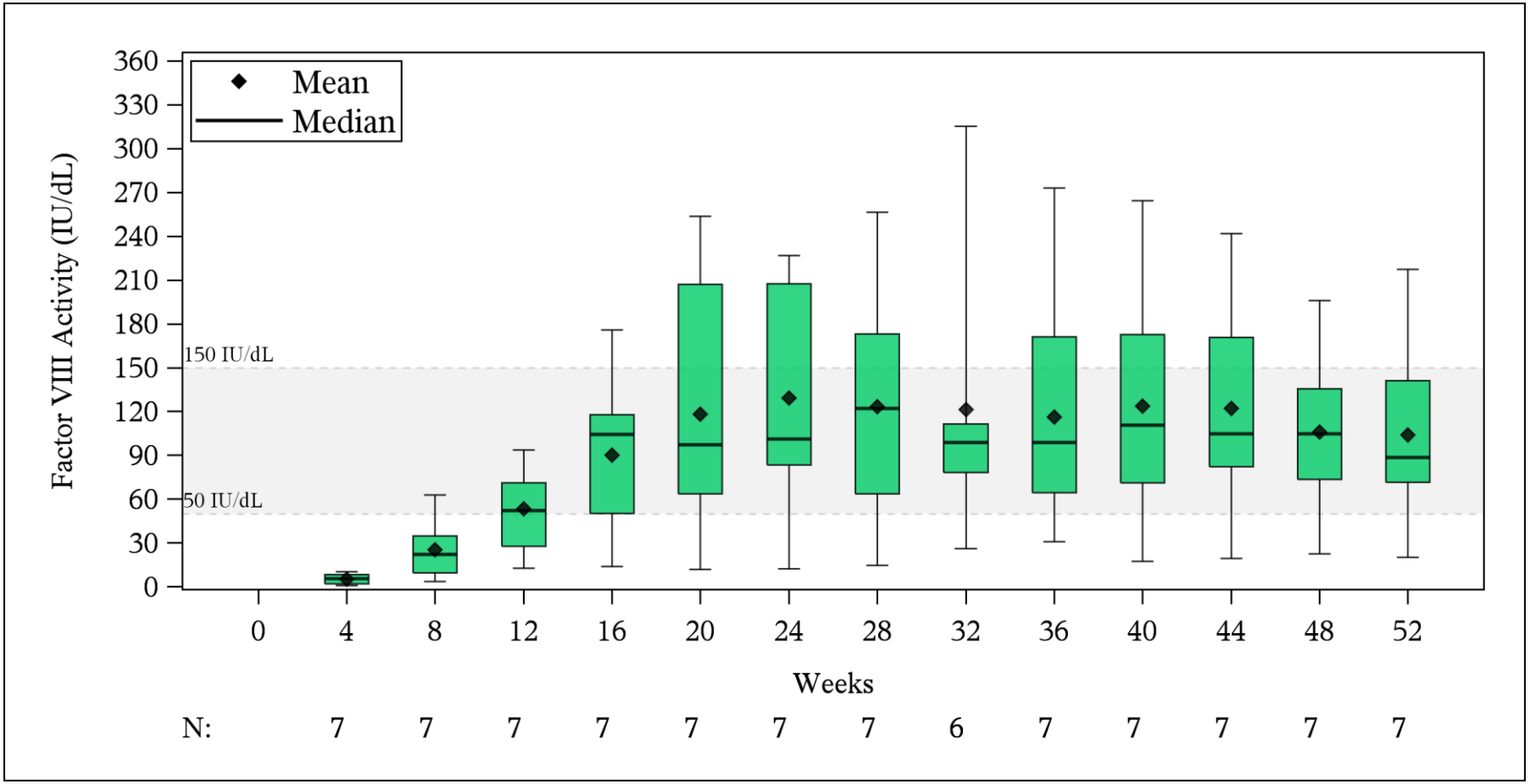
- 1 subject each at the 6 × 10e12 vg/kg and the 2 × 10e13 vg/kg dose cohort
- 7 subjects enrolled at the 6 × 10e13 vg/kg dose cohort
- 6 subjects enrolled at the 4 x 10e13 vg/kg dose cohort

	N=15
Age in years — mean (SD)	31 (8)
Race- no (%)	
Asian	2 (13%)
Black or African American	1 (7%)
White	12 (80%)
Treatment before enrollment — no (%)	
FVIII prophylaxis	14 (93%)
On-demand treatment with FVIII	1 (7%)
Historical annualized bleeding rate – median	
Prophylactic therapy n=14	6.5
On-demand treatment n=1	25
6E13 cohort	
Prophylactic therapy n=6	16.5
On-demand treatment n=1	25
4E13 cohort	
Prophylactic therapy n=6	8
Subjects with target joints — no. (%)	12 (80%)
Previous disease — no. (%)	
Hepatitis B	1 (7%)
Hepatitis C	4 (27%)

Summary of Safety

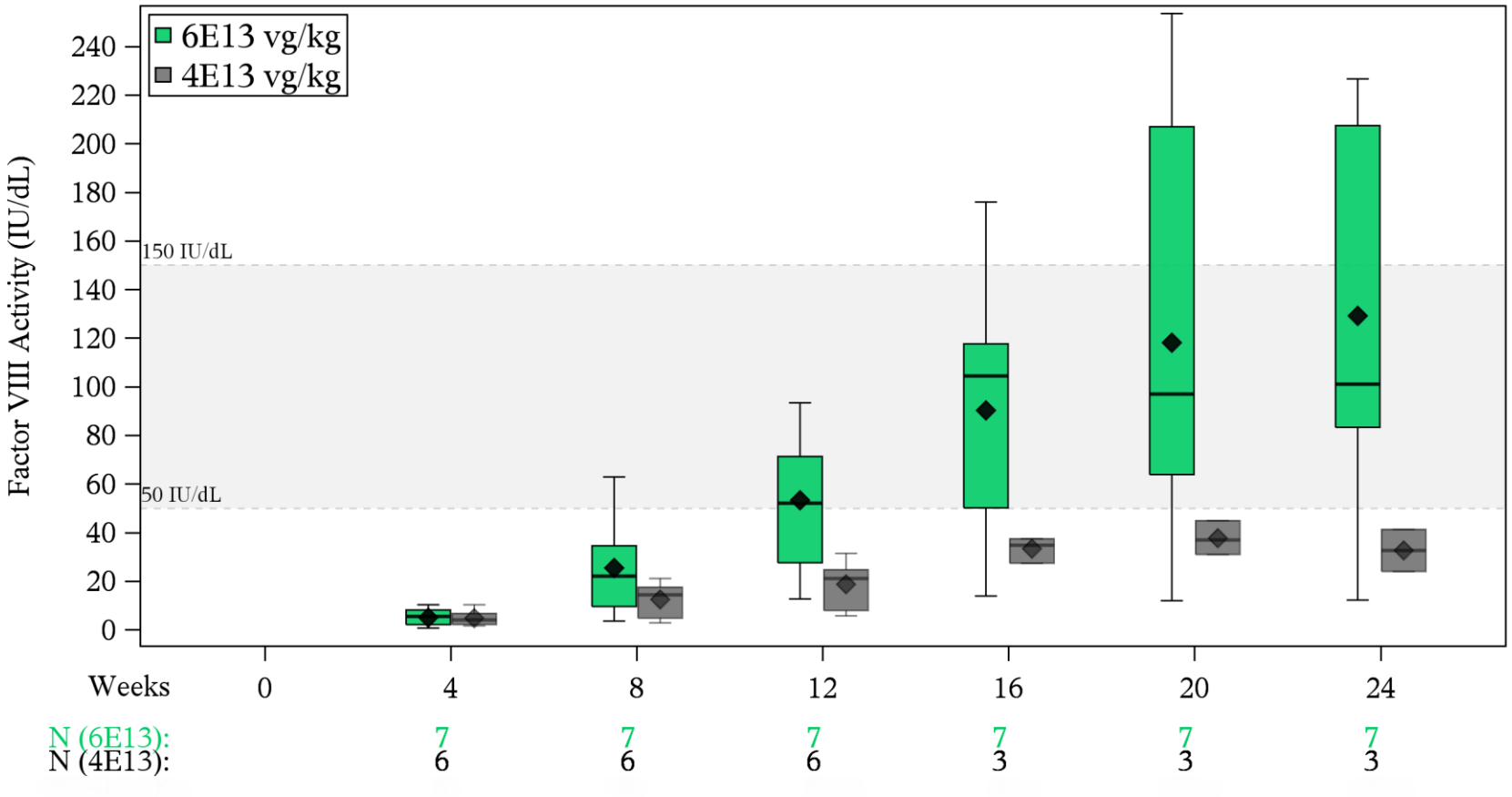
- BMN 270 was well tolerated across all doses
- No subject developed inhibitors to FVIII
- No subject withdrew
- Most common AEs across all dose cohorts: ALT elevation (10 subjects, 67%), arthralgia (7 subjects, 47%) and back pain, fatigue, headache (5 subjects each, 33%)
- 2 Subjects reported SAE's during the study:
  - Grade 2 pyrexia with myalgia and headache at time of infusion; observed in hospital overnight and resolved without sequelae
  - Planned total knee replacement for chronic arthropathy
- AE's of ALT elevation reported in 10/15 subjects:
  - 6E13 cohort peak ALT range 59-95 IU/L (60-95 among 6 reported ALT elevation)
  - 4E13 cohort peak ALT range 44-119 IU/L (70-119 among 3 reported ALT elevation)
  - All events of ALT increased non-serious, limited duration (0.4-7weeks) and Grade 1 severity (i.e. <3x ULN; ULN at 43 U/dL)
  - Treatment with corticosteroids well–tolerated in all subjects
  - All 6E13 subjects remain off steroids

Kinetics of FVIII Activity Levels In 4 Weekly Intervals
Subjects Administered BMN 270 at 6e13 vg/kg



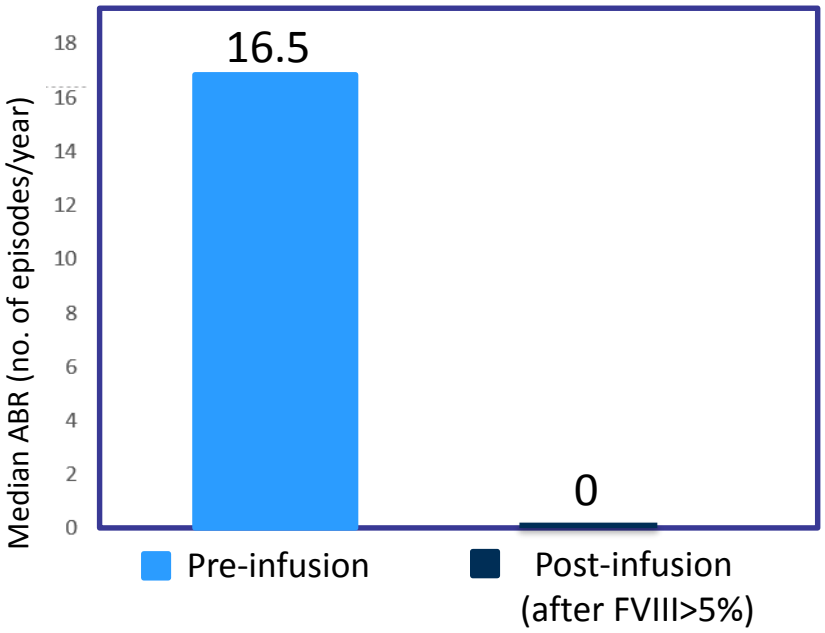
Median/Mean FVIII activity values were utilized within a visit window
Excludes FVIII values within 72 hours of exogenous FVIII administration

Kinetics of FVIII Activity Levels In 4 Weekly Intervals Subjects Administered BMN 270 at 4e13 vg/kg

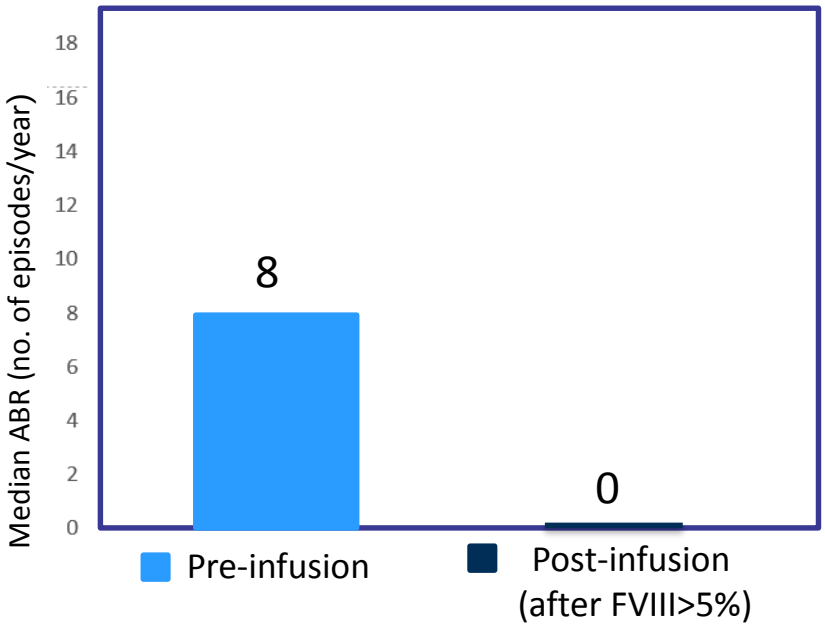


ABRs Post BMN 270: Bleeding Stopped After FVIII Expression >5%

ABRs Pre and Post BMN 270 6e13 dose



ABRs Pre and Post BMN 270 4e13 dose



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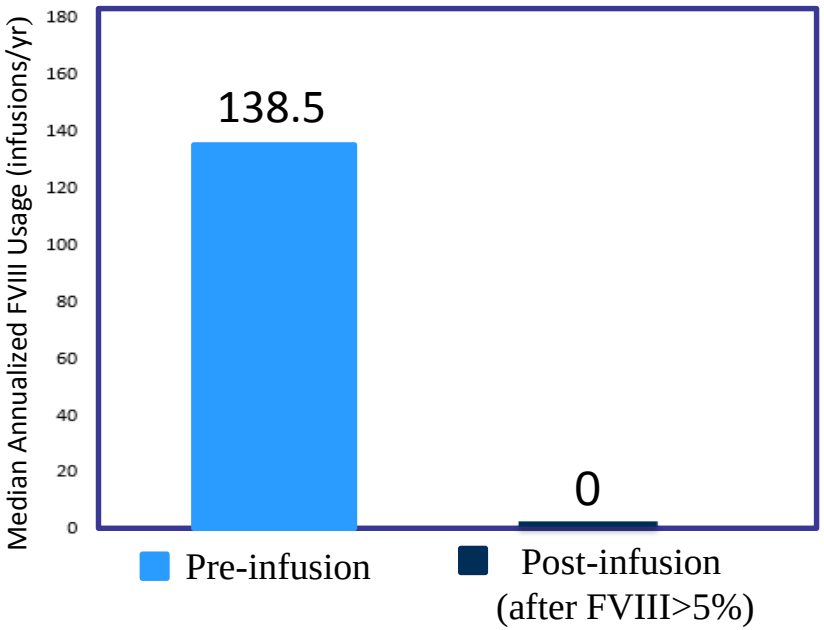
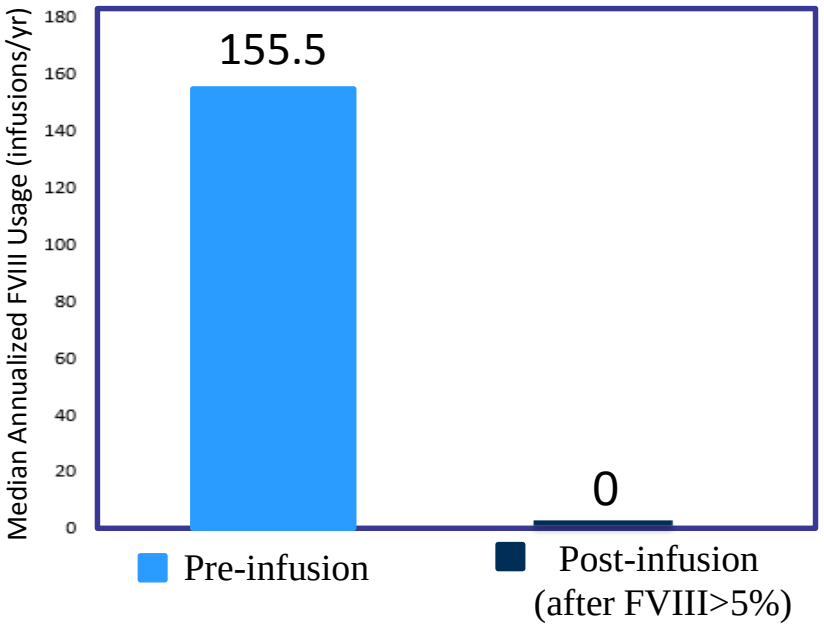
ABR is calculated as (the number of bleeding episodes/total number of days during the calculation period) x 365.25. Note that the figure includes only the 6 subjects in Cohort 3 who were receiving prophylactic exogenous FVIII replacement therapy prior to study enrollment.

Annualized FVIII Usage Reduced To Zero Post BMN 270

FVIII use Pre and Post BMN 270 6e13 dose



FVIII use Pre and Post BMN 270 4e13 dose

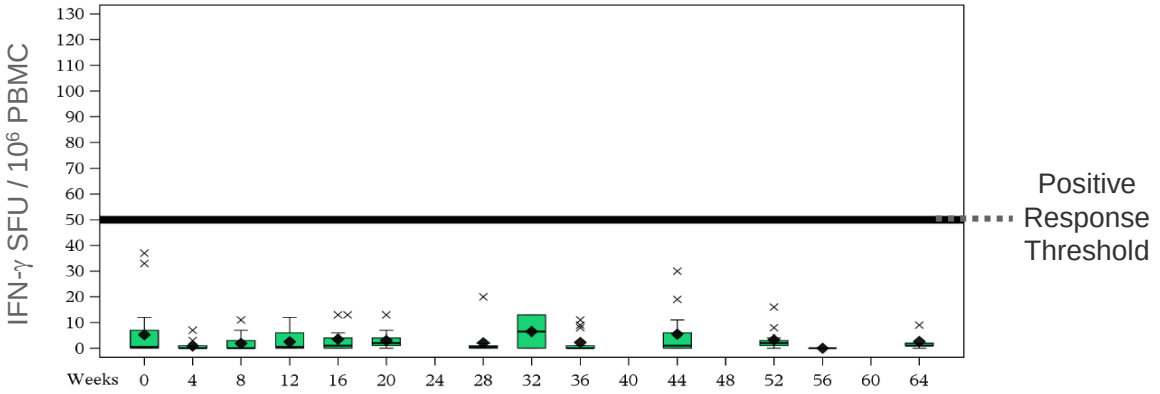


The annualized Factor VIII usage is calculated as (the number of infusions of exogenous FVIII replacement therapy/total number of days during the calculation period) x 365.25

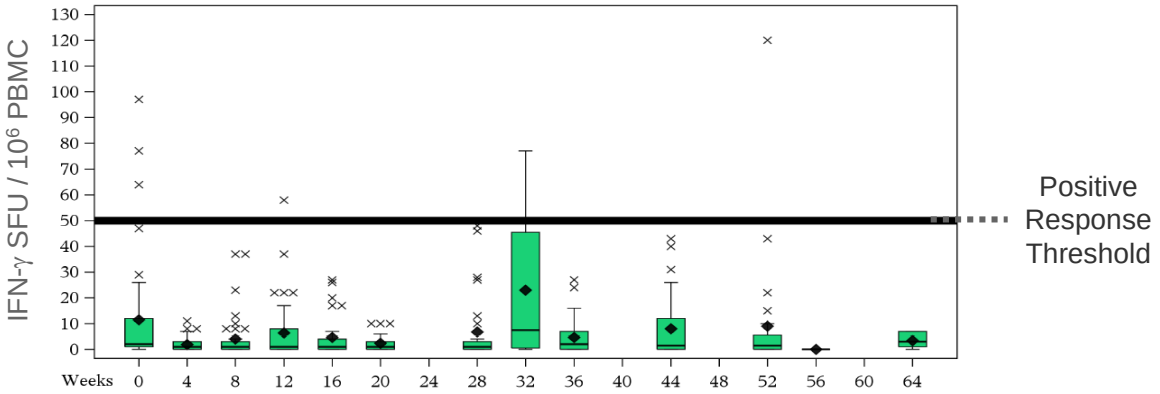
Note that the figure includes only the 6 subjects in Cohort 3 that were receiving prophylactic exogenous FVIII replacement therapy prior to study enrollment

No significant CTL response detected by IFN-γ ELISpot

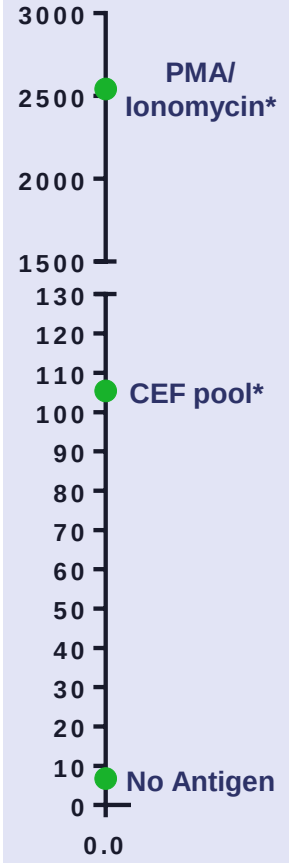
AAV5 Capsid Peptide Stimulation



FVIII Peptide Stimulation

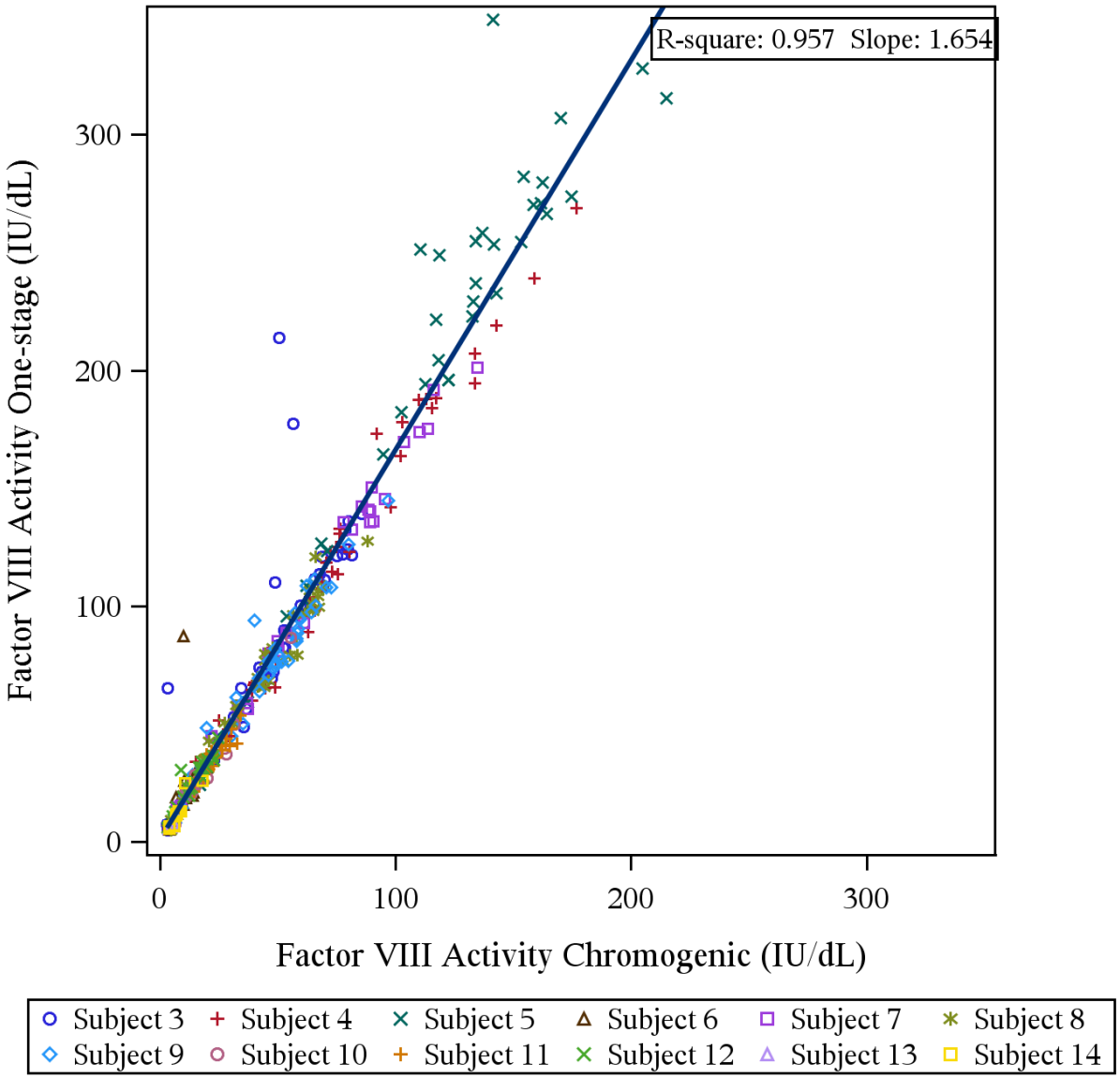


Control Mean at Baseline

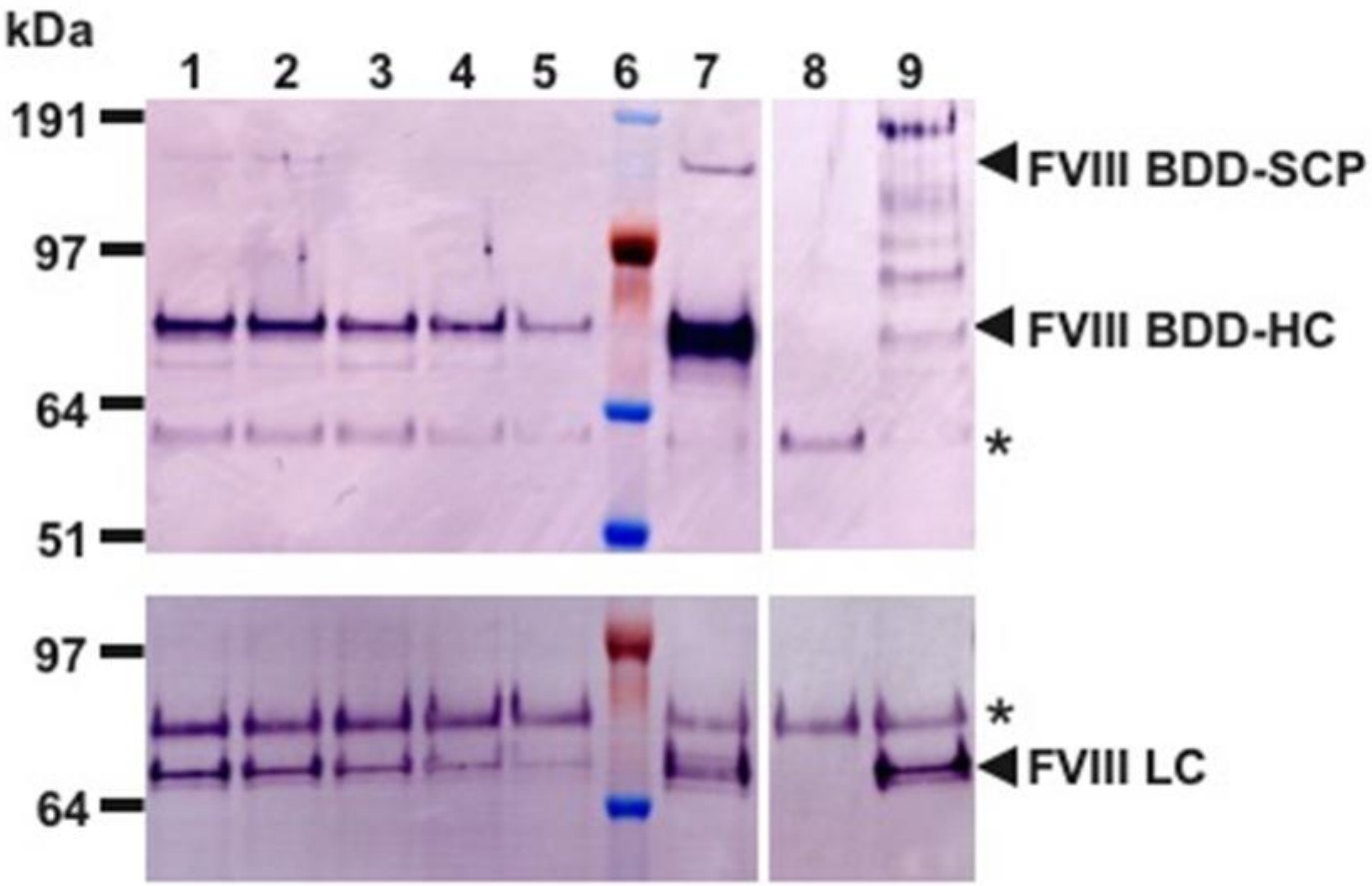


*Positive controls: PMA/Ionomycin stimulates polyclonal T-cell activation and cytokine secretion. CEF pool is a mix of CMV, EBV and Influenza virus peptides.

Consistent Correlation of One-stage With Chromogenic FVIII Activity Assay



Western Blot Analysis of hFVIII-SQ Transgene Products

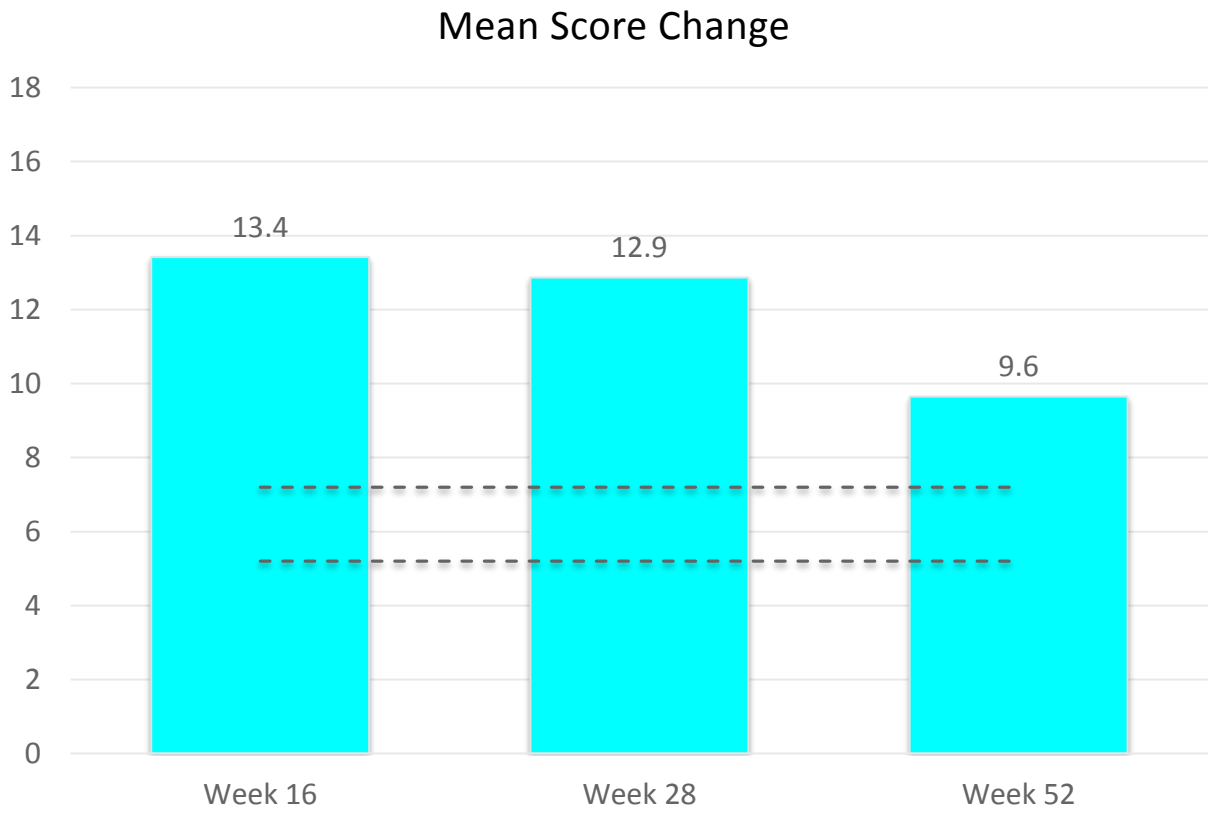


Lanes 1-5: **Subject plasma** (Lane 1: Subject #3, Week 15; Lane 2: Subject #5, Week 12; Lane 3: Subject #8, Week 10; Lane 4: Subject #9, Week 6; Lane 5: Subject #6, Week 13); **Lane 6: Molecular Weight Marker** (SeeBlue® Plus 2); **Lane 7: 100 ng/mL Xyntha® in congenital FVIII-deficient plasma**; **Lane 8: Congenital FVIII-deficient plasma**; **Lane 9: Pooled normal human plasma.**

kDa, kilo Daltons; FVIII BDD-HC, B-domain deleted FVIII heavy chain; FVIII LC, FVIII light chain; FVIII BDD-SCP, B-domain deleted FVIII single chain precursor; asterisks (*) mark the position of non-specific bands also detected in congenital FVIII-deficient plasma

Haem-A-QOL Evaluations in 6E13 COHORT

Mean total score change from baseline to week 52 = 9.6, 95%CI (-2.13, 21.42)



- Data encompasses all 6E13 subjects
- Mean total score change observed by week 16 and maintained over 52 weeks
- QOL improvement observed in all 6 domains; i.e. Consequences of Bleeding, Emotional Impact, Physical Functioning, Role Functioning, Treatment Concern, Worry

*Std. Dev take from high, low and medium dose patients at baseline (n=9)

**Distribution based MCID

------ MCID upper & lower thresholds

Pocoski J et al., 2014 Spinart trial 3-year results: improved quality of life in adults using prophylaxis with Bayer's sucrose-formulated recombinant factor VIII. International Society on Thrombosis and Haemostasis 12 (Suppl. 1) (2014) 1–10620 ABSTRACTS

Summary & Next Steps

- At 6E13/kg, AAV5-FVIII produced sustained mean and median FVIII levels of 104% and 89% respectively over 1 year of observation
  - This dose eliminates occurrence of spontaneous bleeds
  - Provides FVIII coverage, eliminating the need for FVIII even in cases of major trauma or surgery except for 1 patient who required peri-operative FVIII infusions at endogenous FVIII level of ≈20 IU/dL

- AAV5-FVIII gene therapy was well-tolerated
  - Mild elevations in liver enzymes were transient
  - No sequelae related to transient steroid use
  - No inhibitors detected

- Dose response established
  - 4E13 dose level resulted in lower FVIII expression levels than 6E13 dose level with lower correction of FVIII activity

- NEXT STEPS – Initiate Phase 3 studies utilizing 6E13 dose to achieve normal levels of FVIII in subjects with hemophilia A

THANK YOU

All patients, teams and PIs

Hampshire Hospitals NHS Foundation Trust
Basingstoke, United Kingdom

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London, United Kingdom

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Cambridge, United Kingdom

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Queen Elizabeth Hospital Birmingham
Birmingham, United Kingdom

Imperial College Healthcare NHS Trust
London, United Kingdom