European Association for Haemophilia and Allied Disorders (EAHAD) 2024

SLAM session 6

Safety and efficacy of valoctocogene roxaparvovec in participants with active and prior FVIII inhibitors: Preliminary results from GENEr8-INH, a phase 1/2 study

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Disclosures

I have the following potential conflicts of interest to report:

- **Research support**: Genentech/Roche and Takeda
- **Receipt of honoraria or consultation fees**: BioMarin Pharmaceutical Inc., Centessa, CSL Behring, Genentech/Roche, Hema Biologics, Novo Nordisk, Octapharma, Pfizer, Sanofi, Spark, and Takeda

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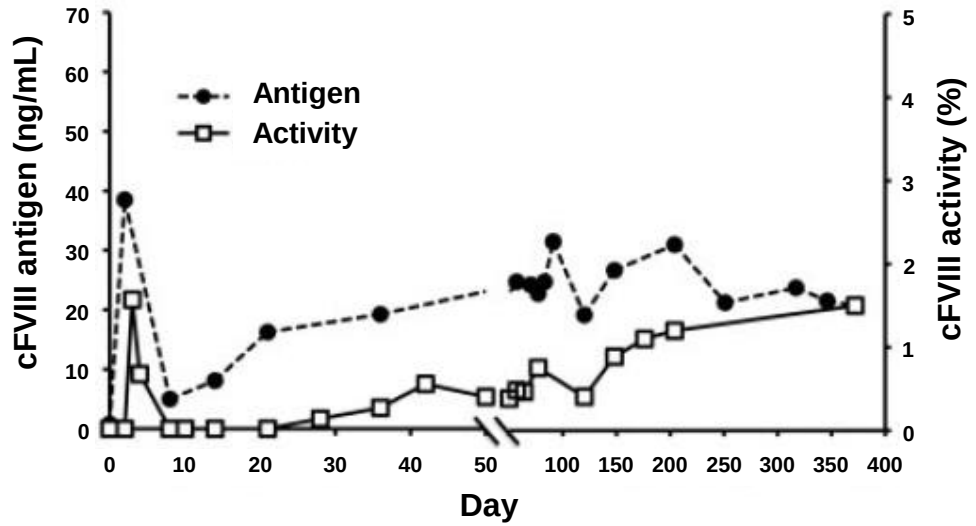
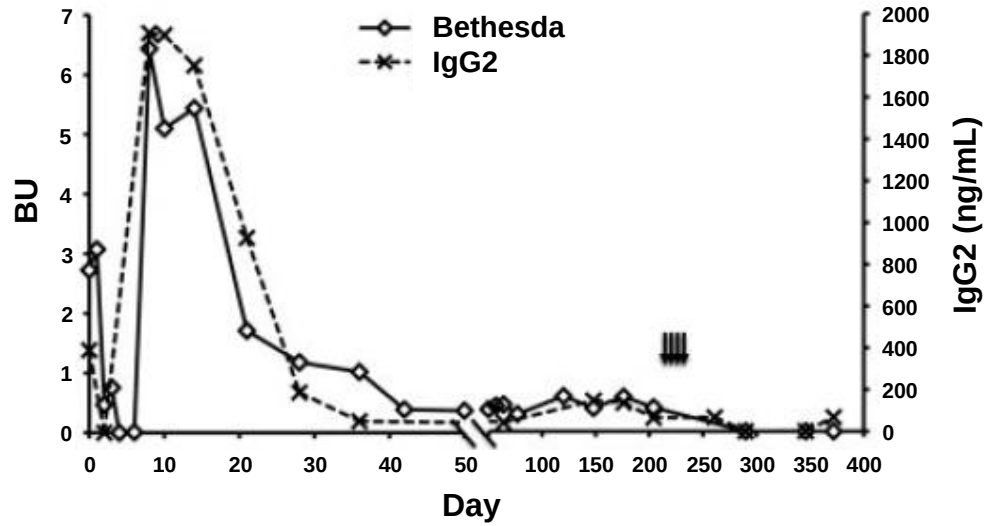
Rationale for the GENEr8-INH trial

- Inhibitors develop in up to 25–40% of individuals with severe HA[1,2]
- Preclinical studies provide strong evidence of gene therapy-mediated ITI[2-4]
  - Gene therapy in a canine model of HA with pre-existing inhibitors was able to establish ITI[4]
  - Inhibitors remained suppressed even after cFVIII challenge[4]



Finn JD, et al. *Blood*. 2010;116(26):5842-8.



Finn JD, et al. *Blood*. 2010;116(26):5842-8.

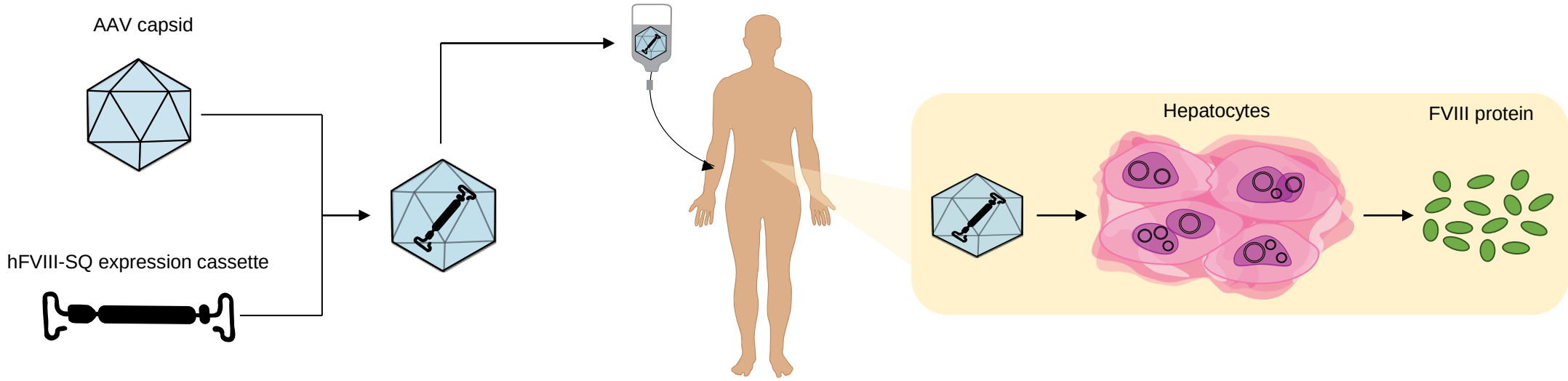
Black arrows denote 4 weekly challenges with 500 units of rBDD-cFVIII.

BU, Bethesda units; cFVIII, canine factor VIII; HA, hemophilia A; IgG2, immunoglobulin G2; ITI, immune tolerance induction; rBDD-cFVIII, recombinant, B-domain-deleted cFVIII.

1. Carcao M, et al. *Haemophilia*. 2019;25(4):676-684. 2. Merlin S, et al. *Front Immunol*. 2020;11:476. 3. Arruda VR, et al. *J Thromb Haemost.* 2016;14(6):1121-34.
4. Finn JD, et al. *Blood*. 2010;116(26):5842-8.

Valoctocogene roxaparvovec for severe hemophilia A

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a FVIII coding sequence that enables endogenous FVIII production in people with severe HA (FVIII ≤1 IU/dL)[1,2]
- Individuals with active or prior FVIII inhibitors were excluded from prior gene therapy trials
- Here, we present interim results from the GENEr8-INH trial (NCT04684940) for individuals treated with active or prior FVIII inhibitors



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; HA, hemophilia A; hFVIII-SQ, human FVIII, SQ variant.

1. Ozelo M, et al. *N Engl J Med*. 2022;386(11):1013-25. 2. Mahlangu J, et al. *N Engl J Med*. 2023;388(8):694-705.

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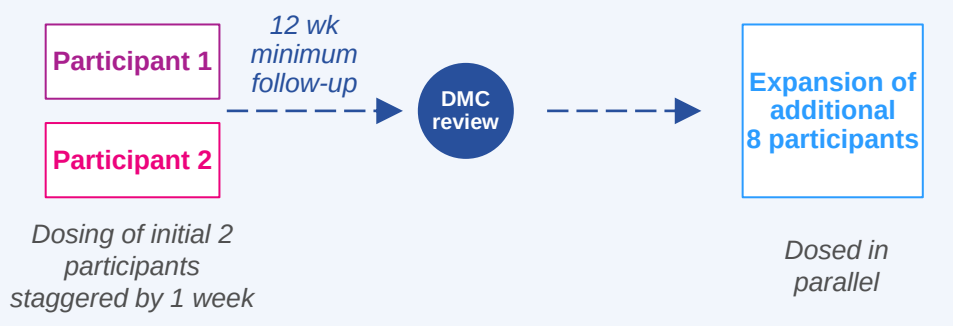
GENEr8-INH study design

Primary objective: To assess the safety of a single IV administration of valoctocogene roxaparvovec for individuals with severe HA and active (part A) or prior (part B) FVIII inhibitors

Part A – Active inhibitor population (N = 10)

Part B – Prior inhibitor population (N = 10)



- **Primary outcome: Safety**
- **Secondary outcomes: Efficacy**
  - Change from baseline:
    - FVIII activity and inhibitor titer
    - Annualized bleeding rate
    - Annualized utilization of hemophilia therapy
    - Haemo-QoL-A

5 DMC, data monitoring committee; FVIII, factor VIII; HA, hemophilia A; Haemo-QoL-A, hemophilia-specific quality of life questionnaire for adults; wk, week.

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Active inhibitors

Part A

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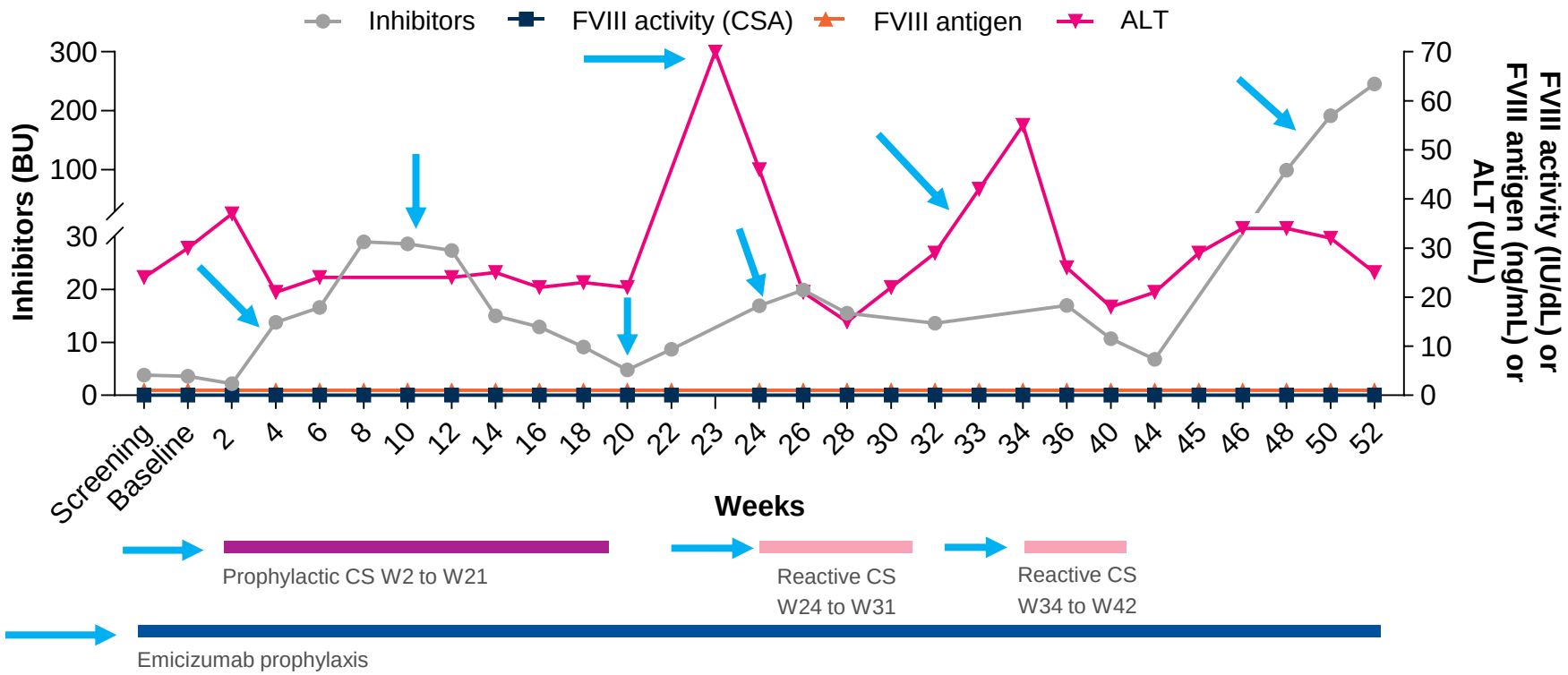
Participant 1 (active inhibitors): Early efficacy and safety results

- 30-year-old male on emicizumab

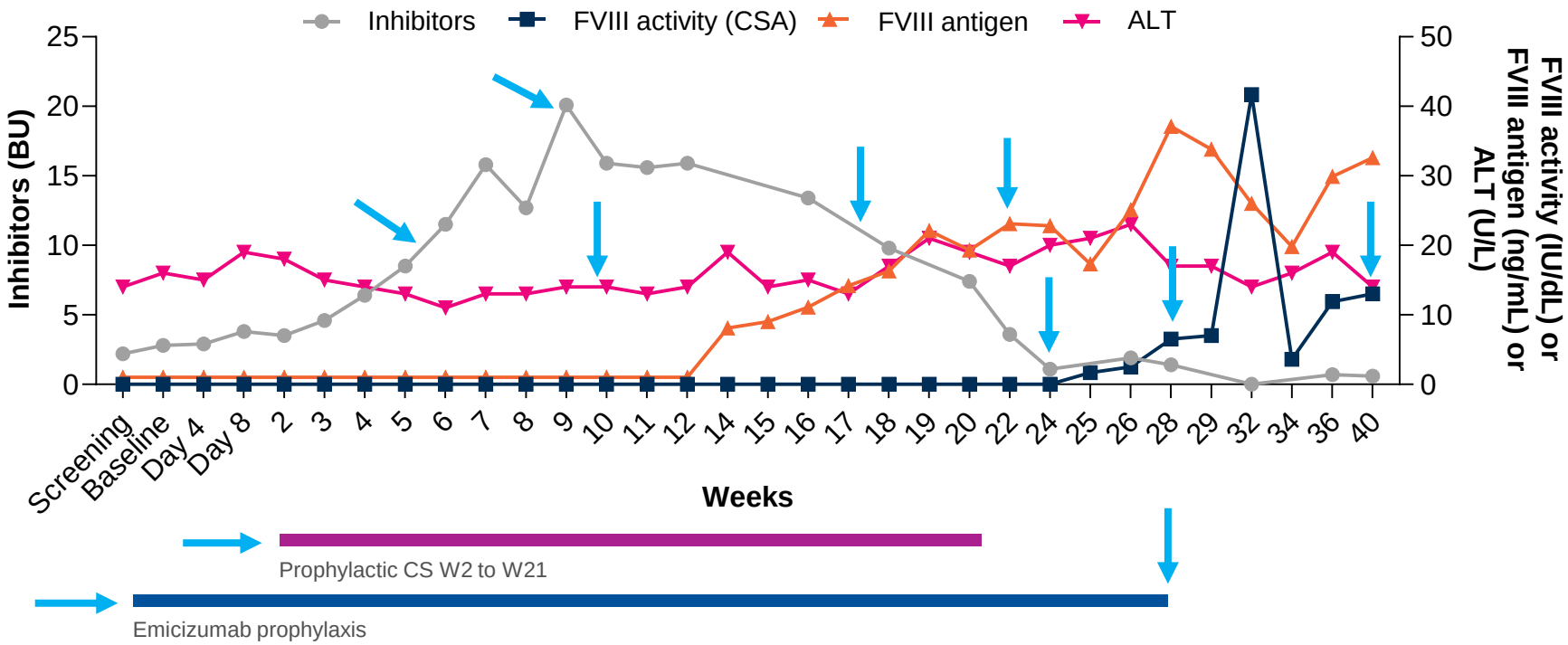


ALT normal range, 5–48 U/L; ALT 1.5x baseline, 45 U/L. FVIII activity values <1.5 IU/dL were imputed as 0 and FVIII antigen values <4.7 ng/mL were imputed as 1.

ALT, alanine aminotransferase; BU, Bethesda units; CS, corticosteroid; CSA, chromogenic substrate assay; FVIII, factor VIII; W, week.

Participant 2 (active inhibitors): Early efficacy and safety results

- 27-year-old male on emicizumab



ALT normal range, 5–48 U/L; ALT 1.5x baseline, 24 U/L. FVIII activity values <1.5 IU/dL were imputed as 0 and FVIII antigen values <4.7 ng/mL were imputed as 1.
ALT, alanine aminotransferase; BU, Bethesda units; CS, corticosteroid; CSA, chromogenic substrate assay; FVIII, factor VIII; W, week.

Prior inhibitors

Part B

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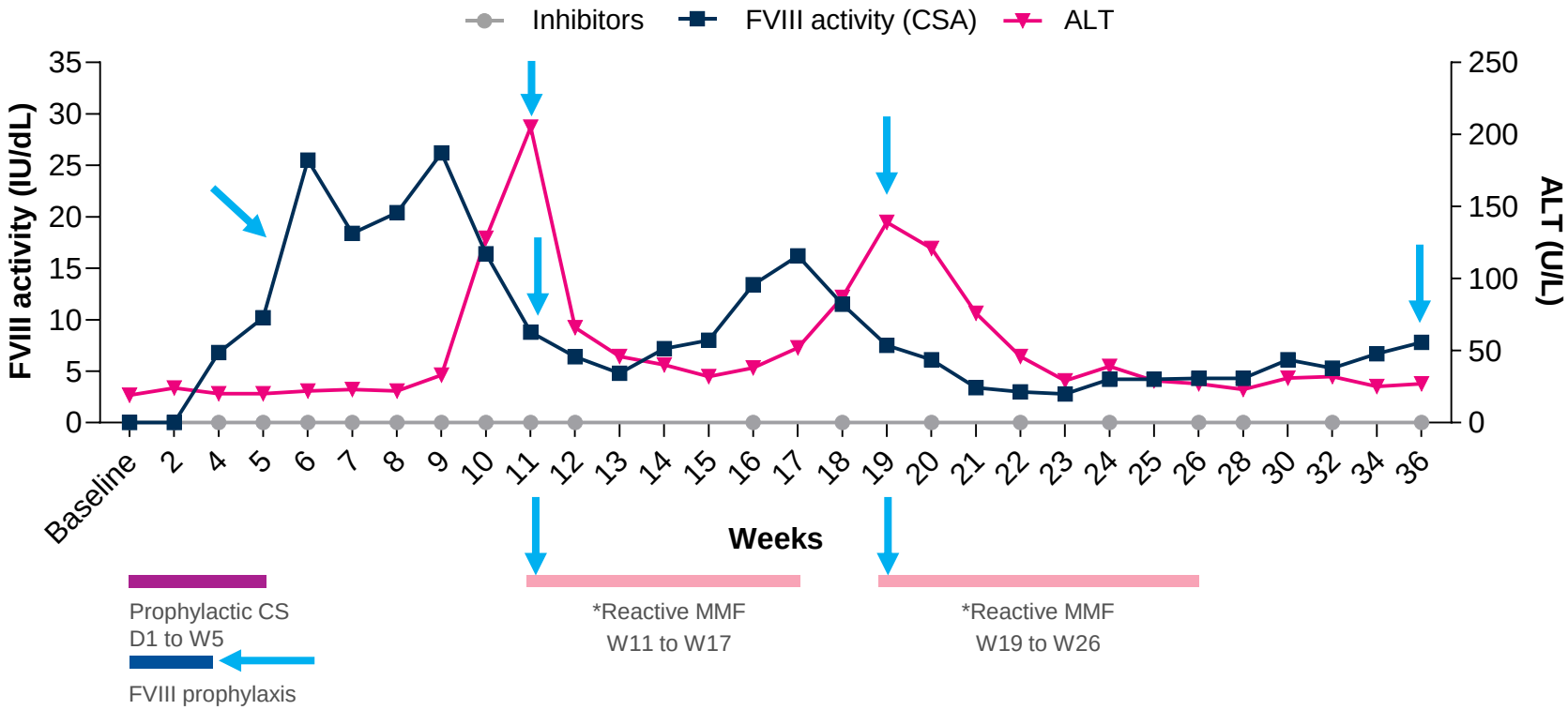
Participant 1 (prior inhibitors): Early efficacy and safety results

- 33-year-old male on FVIII prophylaxis



*MMF 1000 mg twice a day. ALT normal range, 5–48 U/L; ALT 1.5x baseline, 28.5 U/L.

ALT, alanine aminotransferase; CS, corticosteroid; CSA, chromogenic substrate assay; D, day; FVIII, factor VIII; MMF, mycophenolate mofetil; W, week.

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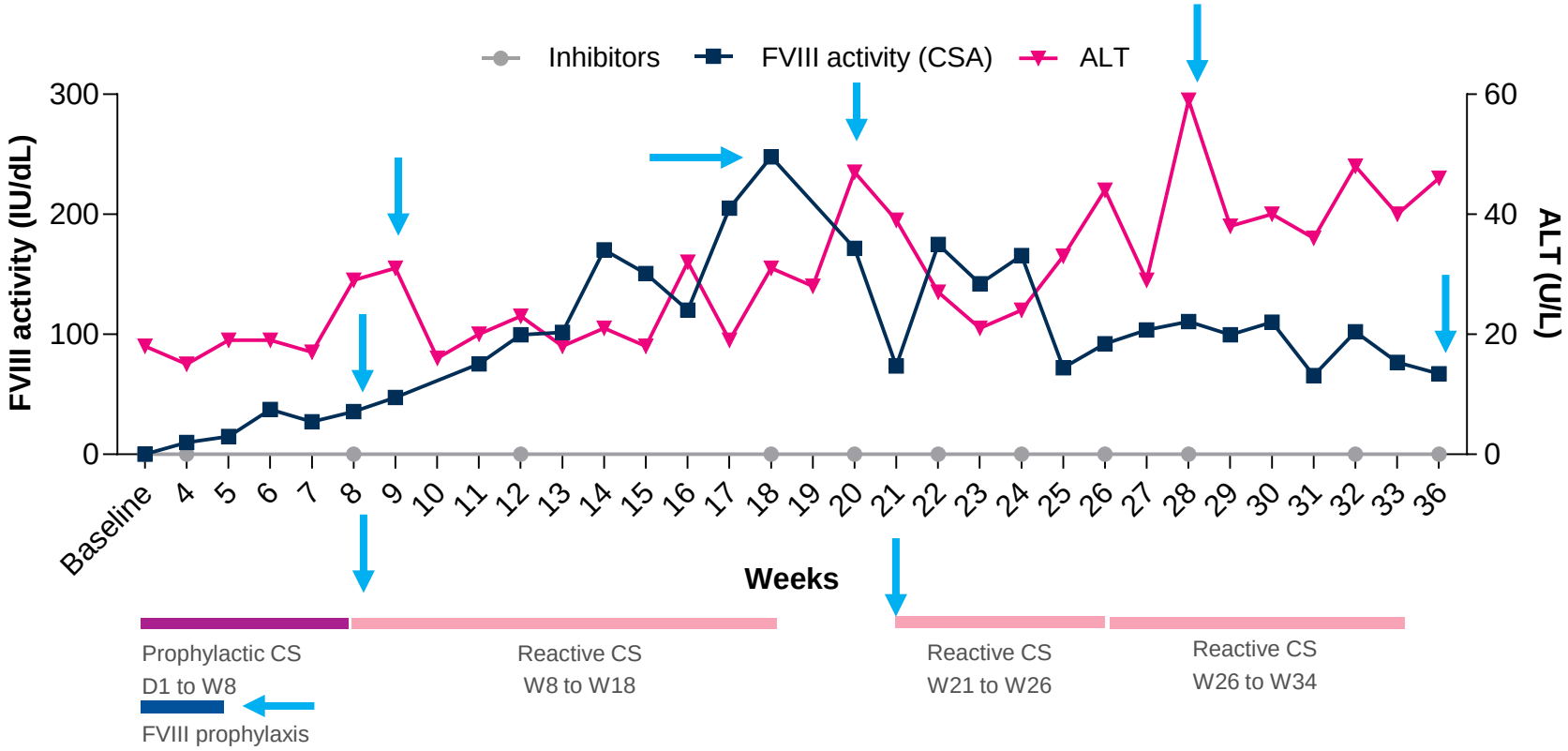
Participant 2 (prior inhibitors): Early efficacy and safety results

- 26-year-old male on FVIII prophylaxis



ALT normal range, 5–48 U/L; ALT 1.5x baseline, 27 U/L.

ALT, alanine aminotransferase; CS, corticosteroid; CSA, chromogenic substrate assay; D, day; FVIII, factor VIII; W, week.

GENEr8-INH summary: Early safety experience

- Participants showed a similar safety profile to the GENEr8-1 trial
  - The most common AE so far was ALT elevation (3/4 participants)
  - No serious or severe AEs have been reported related to valoctocogene roxaparvovec or IS therapy
  - No thromboembolic events or malignancy
  - No FVIII inhibitor recurrence in the prior inhibitor population (part B)

AE, adverse event; ALT, alanine aminotransferase; CSA, chromogenic substrate assay; FVIII, factor VIII; IS, immune suppression.

GENEr8-INH summary: Early efficacy experience

- Early, interim efficacy results are consistent with expectations and encouraging
  - Active inhibitors (2 participants):
    - FVIII Inhibitor titers increased as expected
    - Rise in FVIII inhibitor levels suggest FVIII is being produced in the liver although it is undetected by the CSA
    - Participant 1 exhibited fluctuations in FVIII inhibitor titers
    - Participant 2 exhibited a decrease in FVIII inhibitor titers and detectable FVIII activity by week 28
  - Prior inhibitors (2 participants):
    - FVIII activity levels increased by week 4 similar to the GENEr8-1 trial

CSA, chromogenic substrate assay; FVIII, factor VIII.

Acknowledgements

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