Interim 52-Week Analysis of Immunogenicity to the Vector Capsid and Transgene-Expressed Human FVIII in GENEr8-1, a Phase 3 Clinical Study of Valoctocogene Roxaparvovec, an AAV5-Mediated Gene Therapy for Hemophilia

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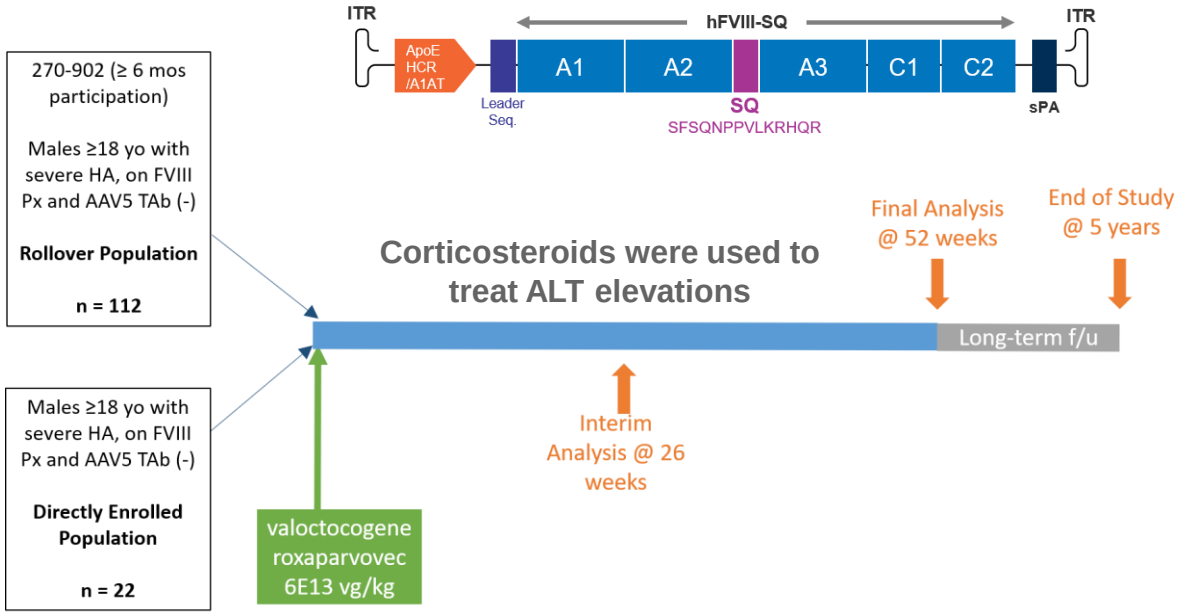
GENEr8-1: A Phase 3 Study of AAV5-Mediated Gene Therapy Encoding Human FVIII for the Treatment of Hemophilia A



Most common AE was an elevation in alanine aminotransferase (ALT) levels occurring in 115 of 134 participants (85.8%)

A total of 106 participants (79.1%) received glucocorticoids in accordance with the protocol

The median time to initiation of glucocorticoids was treatment was 8.1 weeks with a median treatment duration of 230 days (range, 22–551)

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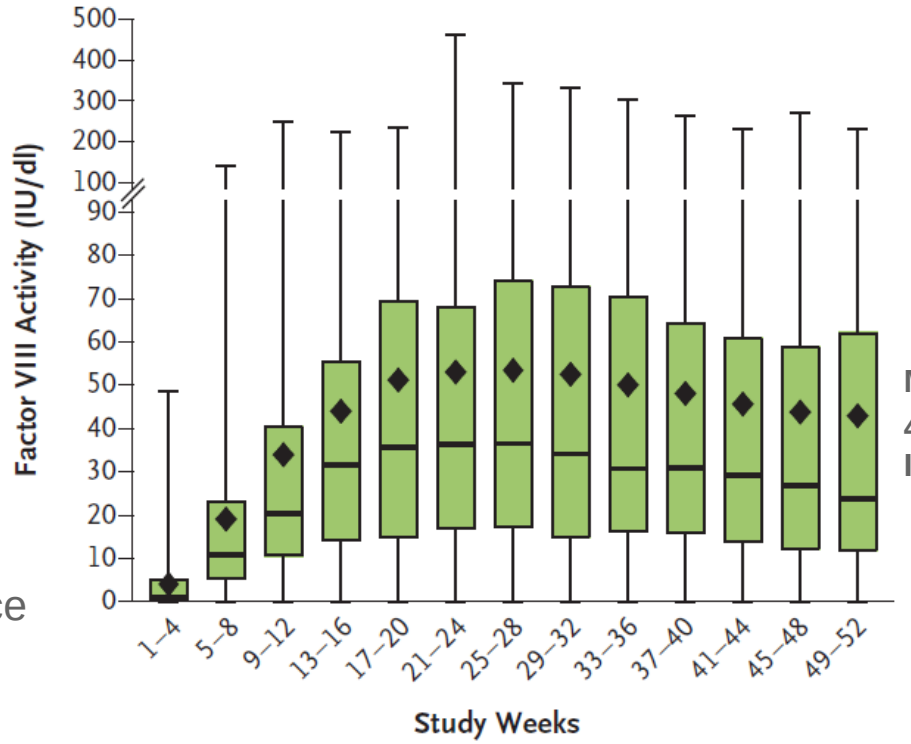
Valoctocogene Roxaparvovec Gene Therapy for Hemophilia A

M.C. Ozelo, J. Mahlangu, K.J. Pasi, A. Giermasz, A.D. Leavitt, M. Laffan, E. Symington, D.V. Quon, J.-D. Wang, K. Peerlinck, S.W. Pipe, B. Madan, N.S. Key, G.F. Pierce, B. O'Mahony, R. Kaczmarek, J. Henshaw, A. Lawal, K. Jayaram, M. Huang, X. Yang, W.Y. Wong, and B. Kim, for the GENEr8-1 Trial Group*

A Modified Intention-to-Treat Population (N=132)



Mean (SD)
49.52 (45.5) IU/dL

Immunogenicity Monitoring for GENEr8-1

Two measures of vector specific humoral immunity

- AAV5 Total Binding Antibody (TAb): ECLA
- AAV5 Transduction Inhibition (TI): Cell-Based

Immunogenicity Related Inclusion/Exclusion Criteria:

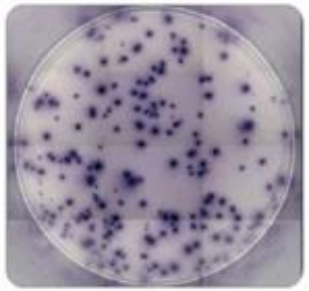
- Detection of AAV5 TAb
- Required to have ≥ 150 exposure days to FVIII replacement with no evidence of FVIII Inhibitors

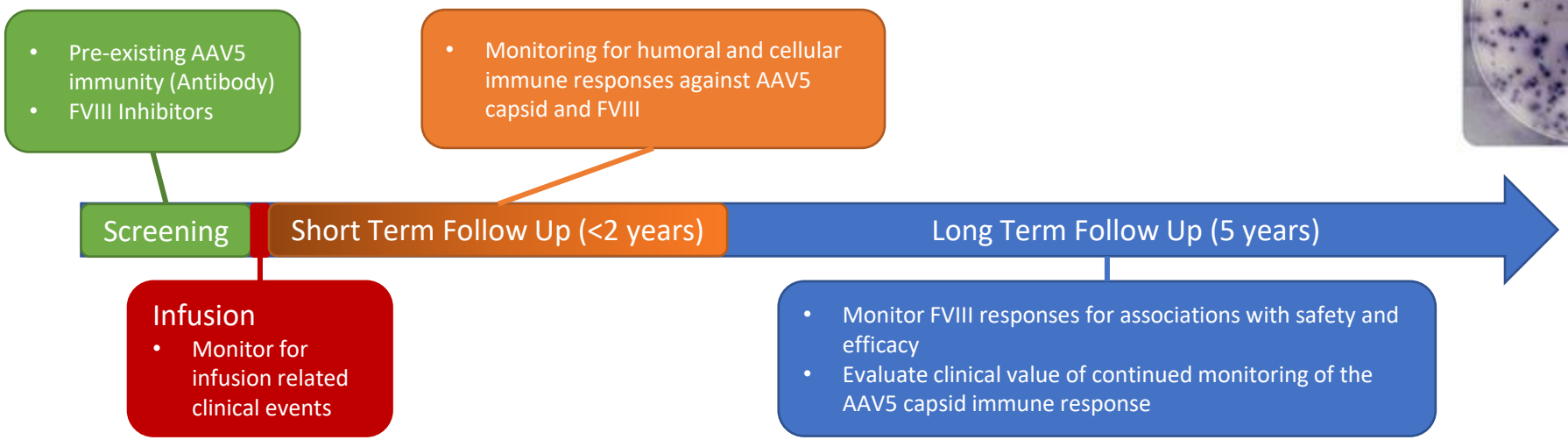
Two measures of FVIII specific humoral immunity

- FVIII TAb - ECLA
- FVIII Inhibitor (Neutralizing Antibody, NAb) – Nijmegen Bethesda Assay

AAV5 Capsid and FVIII specific cellular immunity

- IFN-γ ELISpot Assay in PBMCs



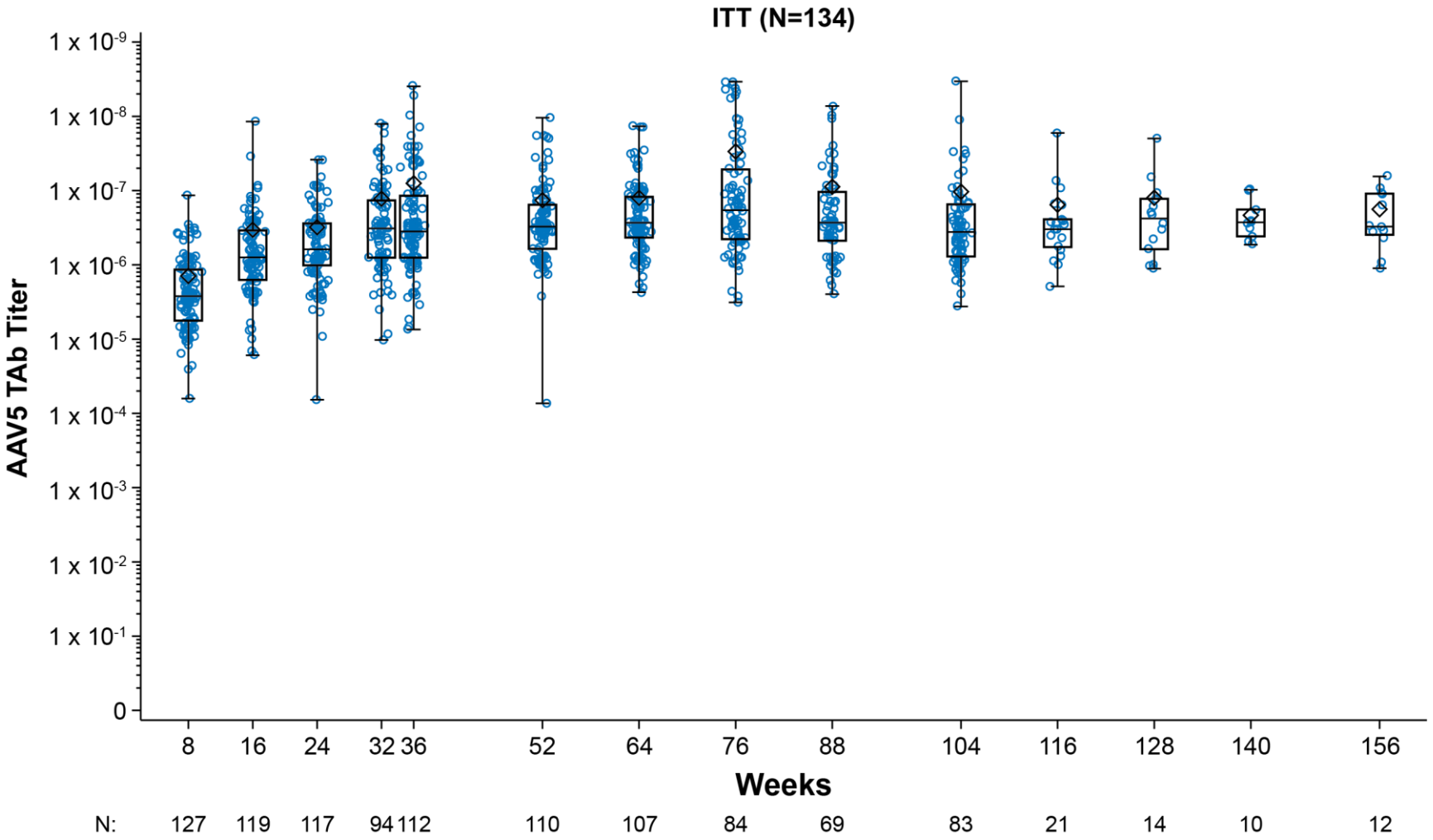


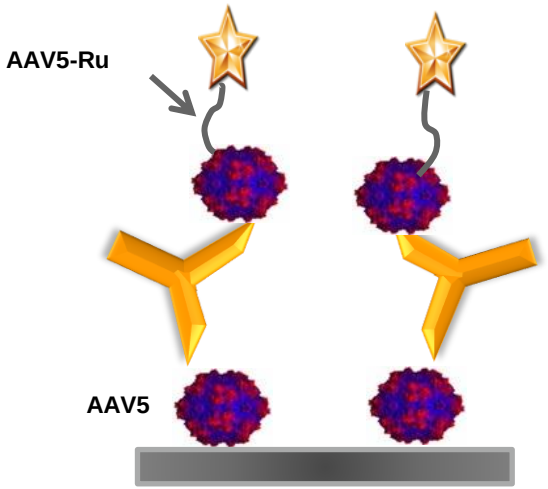
No FVIII Inhibitors, Sporadic FVIII Total Binding Antibody (FVIII TAb)

- No patients have developed a FVIII Inhibitor response (Nijmegen modified Bethesda assay)
- 12 of 134 (9%) GENEr8-1 participants tested positive at one or more time points for FVIII TAb; no association with ALT elevations or FVIII activity measures
- Majority are low titer, single positive results that revert to negative at the next time point
- No cellular immune response to FVIII (INF-γ ELISpot) was detected at those time points
- These results are consistent with low titer, transient antibody responses described in the literature* for both healthy donors and HA patients that do not progress to inhibitors

*Reipert BM, et al. Blood Adv. 2020 Nov 24;4(22):5785-5796.
Whelan SF, et al. Blood. 2013 Feb 7;121(6):1039-48.

All Subjects Develop a Sustained anti-AAV5 Antibody Response

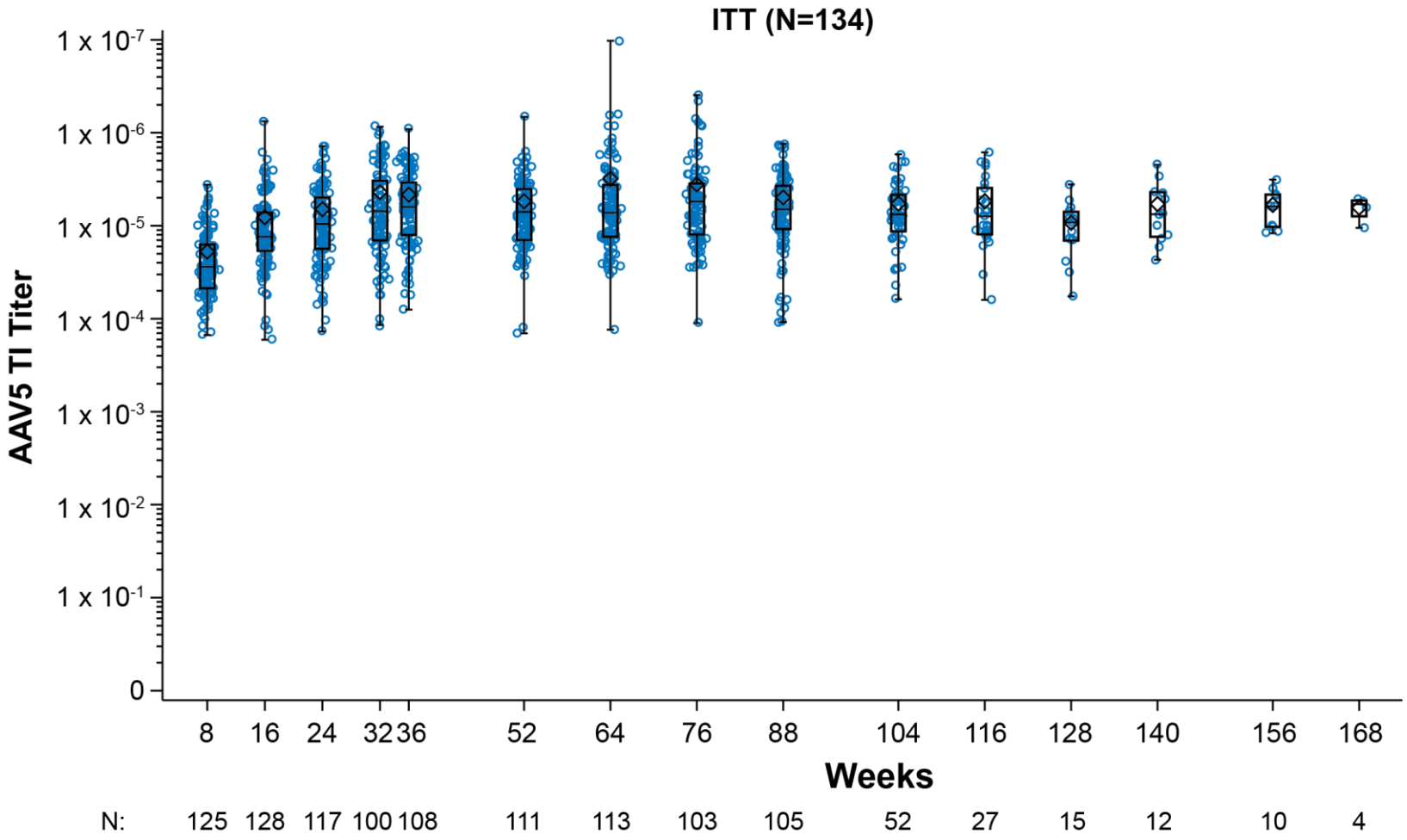


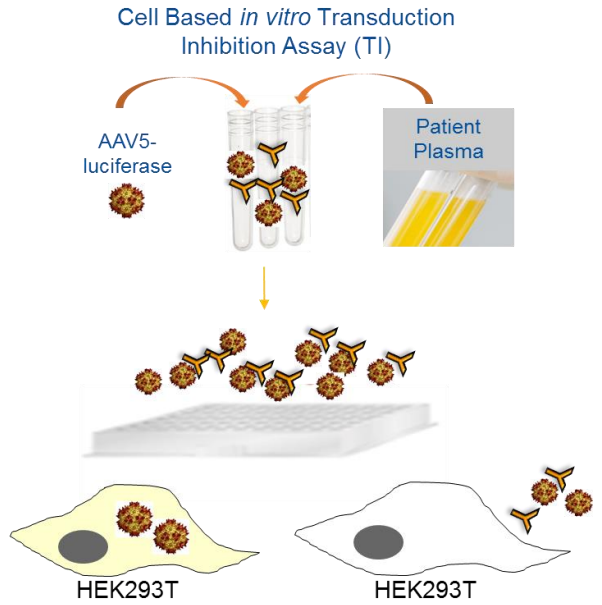


Bridging ECL Format
Detects all Isotypes.

Boxplots showing mean (diamond), median and IQR, whiskers showing min/max AAV5 TAb titer.

The AAV5 Antibody Response has Neutralizing Capacity In Vitro



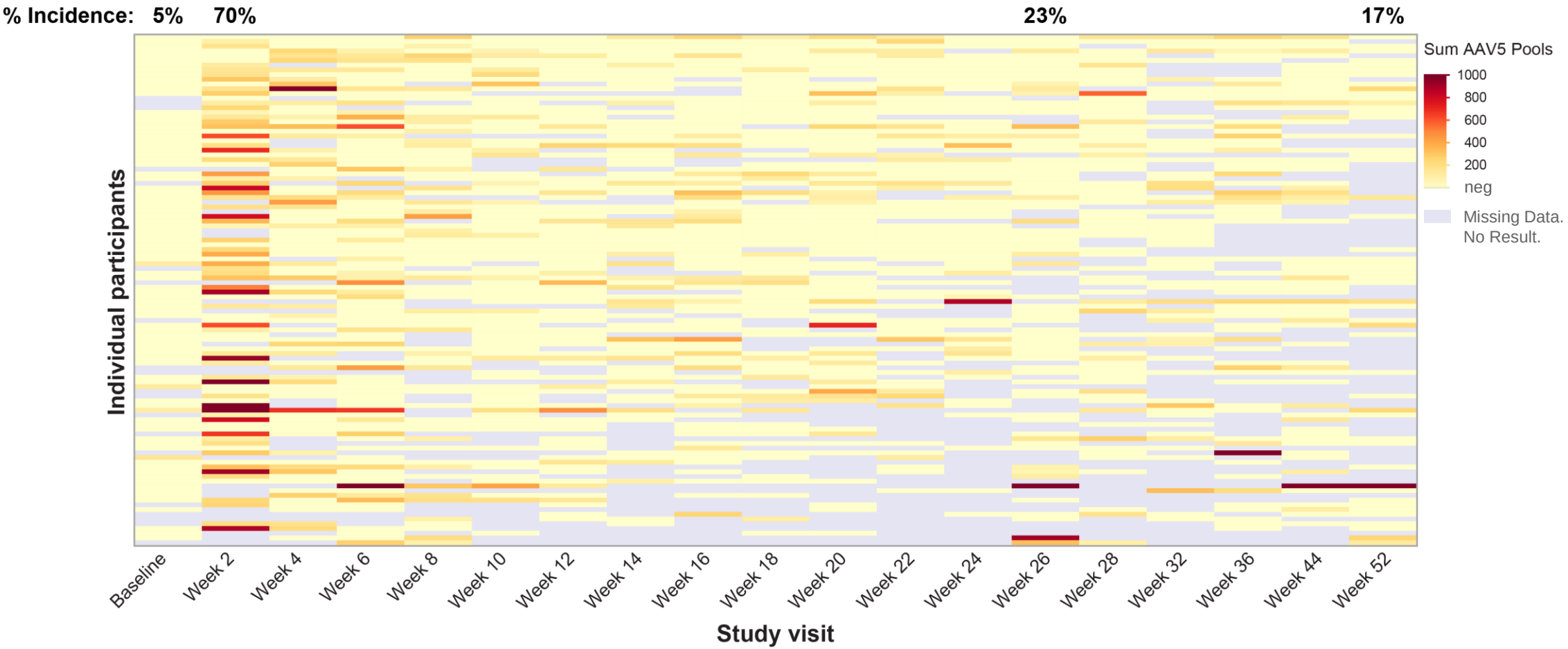


- Tests ability of plasma to block the *in vitro* transduction of HEK293T/17 cells by a AAV5-Luciferase vector
- Sensitivity (LOD) = 65.9 ng/mL

Boxplots showing mean (diamond), median and IQR, whiskers showing min/max AAV5 TAb titer.

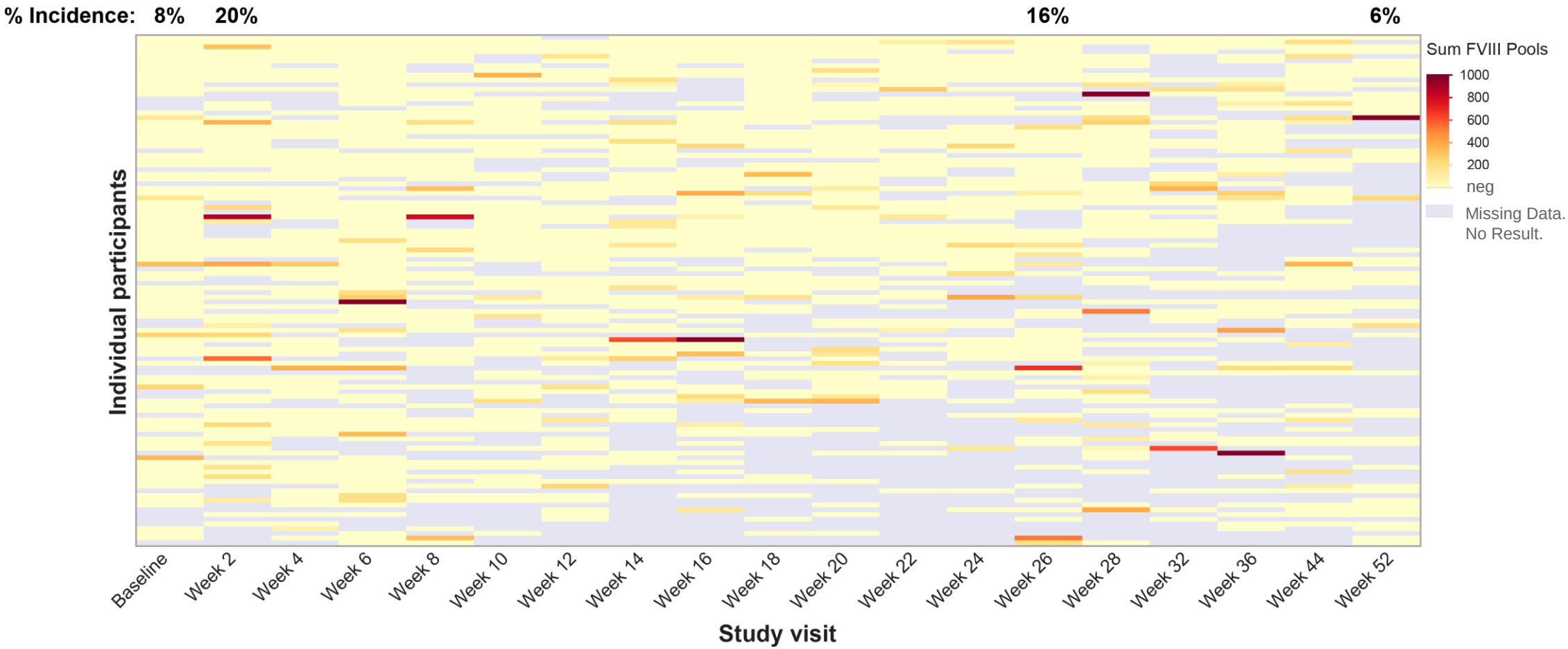
AAV5 Cellular Immune Response Detected in the Majority of Participants

- Peak incidence occurring 2 weeks post-dose, transient response with incidence declining over time.

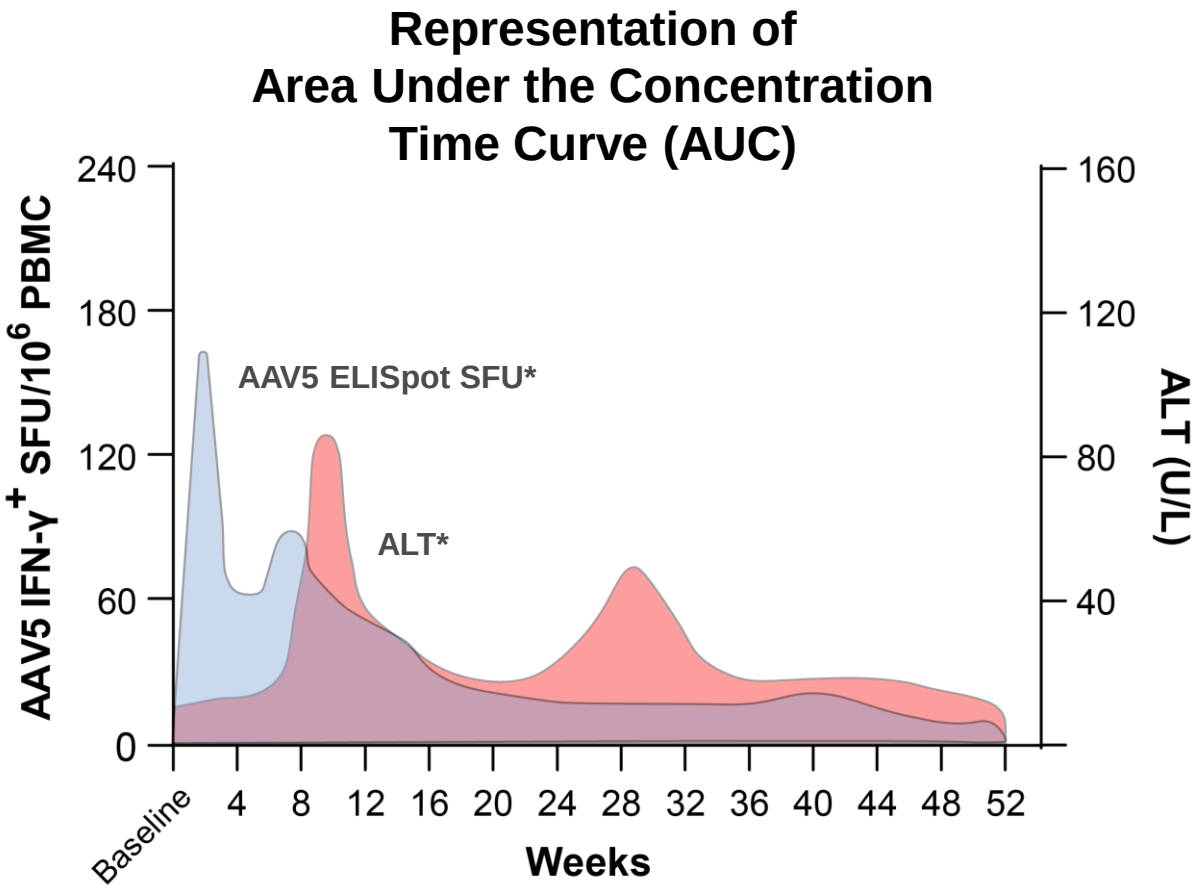


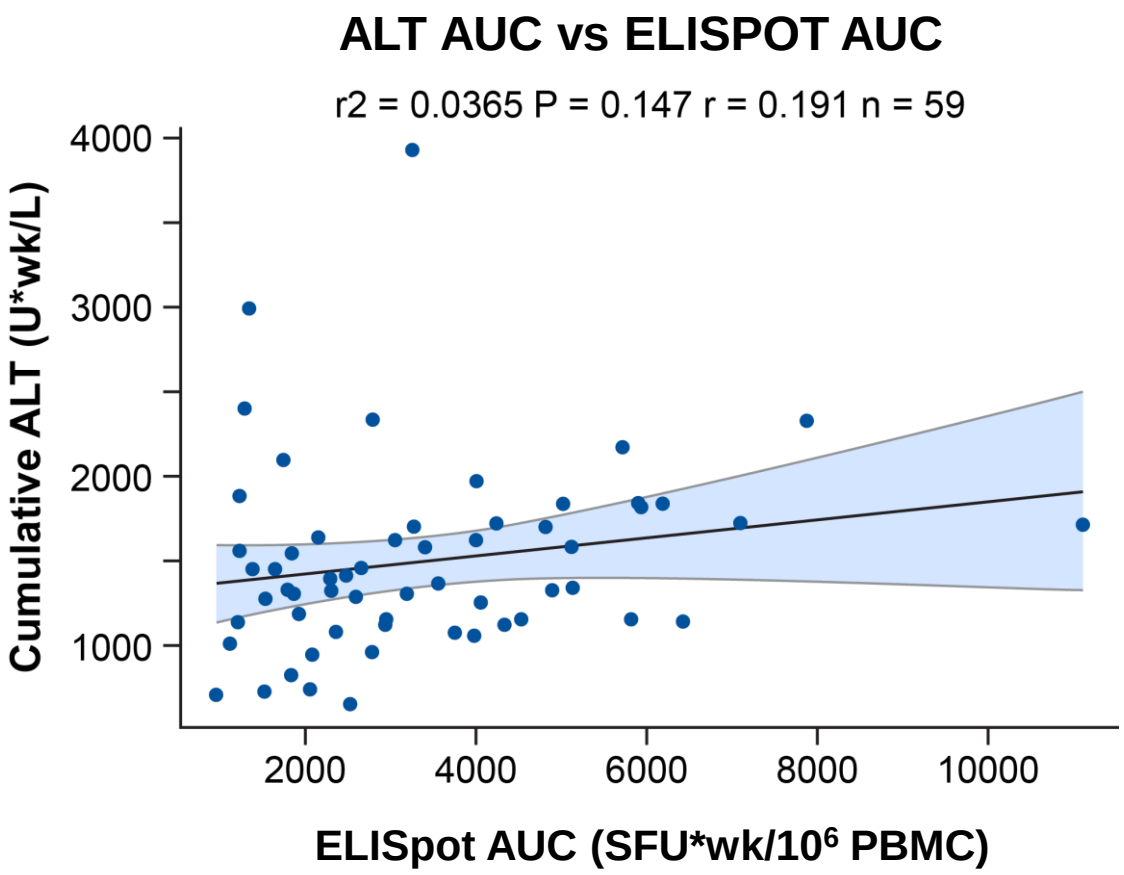
Fewer, More Sporadic FVIII Specific Cellular Immune Responses

- FVIII specific cellular immune response have been detected in fewer participants with a broader incidence distribution over time than for AAV5.



Peak AAV5 ELISpot Precedes Peak ALT Showing a Weak Association

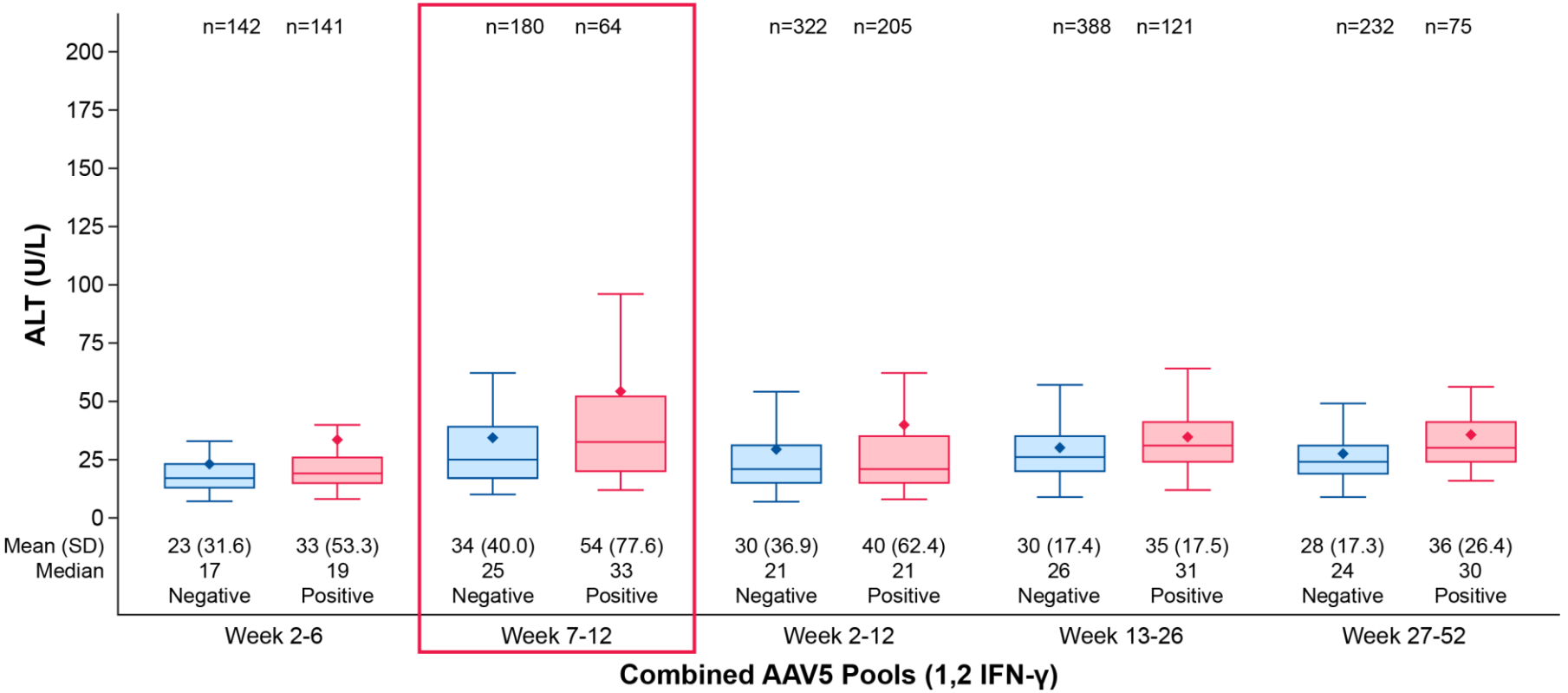




*Representative of typical clinical trial participant and not actual data

AAV5 Specific ELISpot associated with higher ALT values at Weeks 7–12

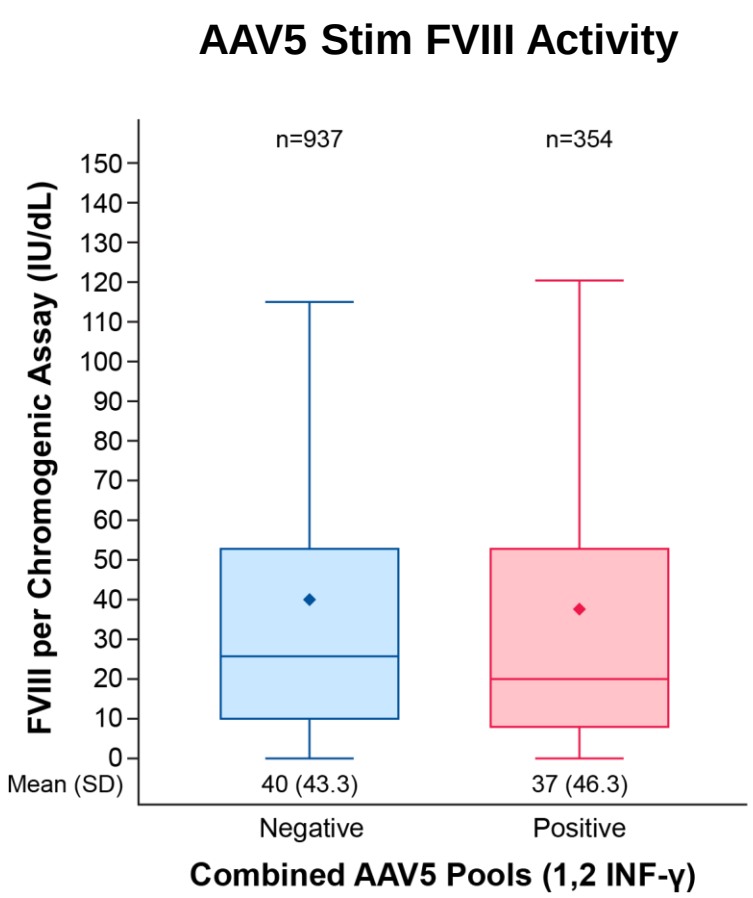
Mean ALT (U/L) at matched ELISpot negative and positive time points.

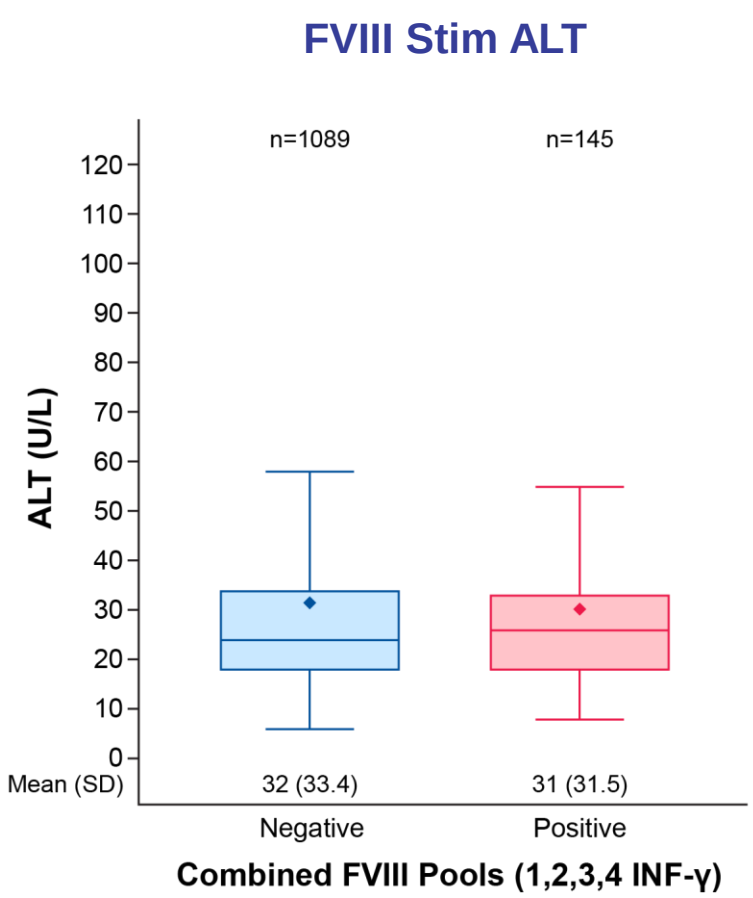


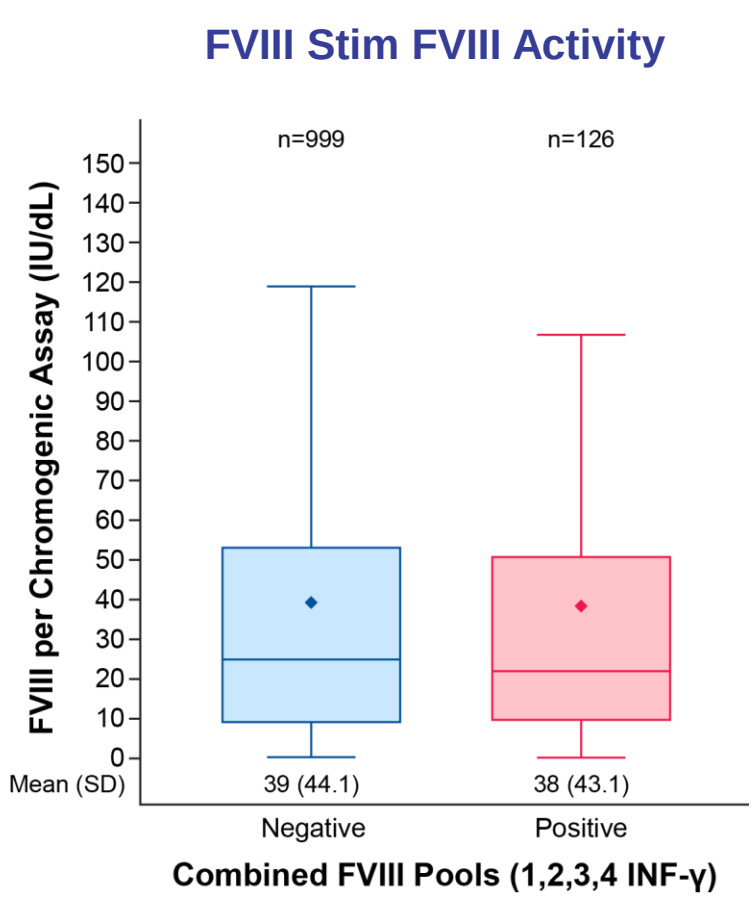
- Approximately half of the participants have ALT > ULN in the first 13 weeks, median time to onset is ~8.3 weeks

Cellular Immune Responses are not Associated with FVIII Activity

- No temporal association of AAV5 ELISpot positivity with FVIII activity
- FVIII-specific ELISpot is not associated with either ALT or FVIII activity







Immunogenicity Summary

- No patients developed a FVIII inhibitor response during the first 52 weeks following valoctocogene roxaparvovec administration
- Immune responses were primarily directed toward the AAV5 capsid, and all subjects seroconverted to a persistent high-titer AAV5-specific antibody response
- AAV5 capsid-specific cellular immune responses were detected beginning at Week 2 following dose administration and often declined or reverted to negative over the first 52 weeks
- Though there was no clear correlation, AAV5 ELISpot responses showed a weak trend with increased ALT at a population level over the first year (in the context of on-demand corticosteroid use).
- Closer temporal associations between AAV5 ELISpot responses and ALT were identified in a subset of patients over the first 3 months following dose administration
- AAV5 capsid-specific cellular immune responses may be a contributing factor leading to transient increases in ALT in some patients

Thank You!

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