# Efficacy and safety of valoctocogene roxaparvovec gene transfer for severe hemophilia A: Results from the GENEr8-1 year two analysis.

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# DISCLOSURE FOR JOHNNY MAHLANGU

**In compliance with COI policy, EAHAD requires the following disclosures to the session audience:**

| | |
|---|---|
| Shareholder | No relevant conflicts of interest to declare |
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| Employee | No relevant conflicts of interest to declare |
| Paid Instructor | No relevant conflicts of interest to declare |
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| Other | No relevant conflicts of interest to declare |

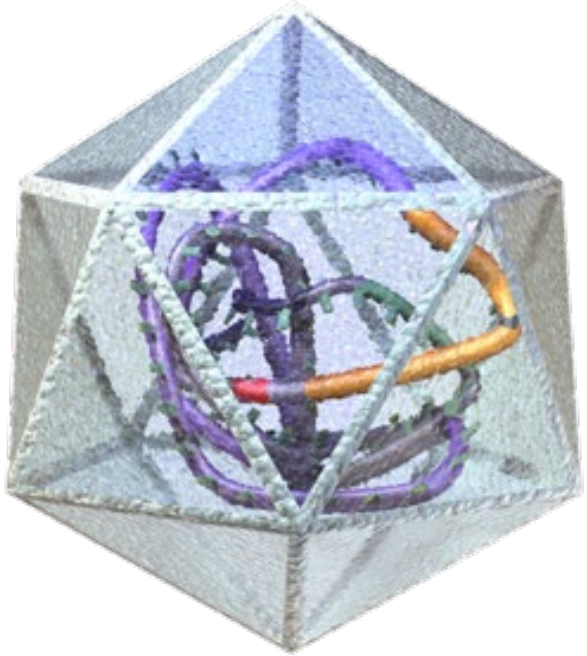
Presentation includes discussion of the following off-label use of a drug or medical device:
N/A

# VALOCTOCOGENE ROXAPARVOVEC GENER8-1 TRIAL

- Valoctocogene roxaparvovec (AAV5-hFVIII-SQ) transfers a B-domain deleted FVIII coding sequence to people with hemophilia A, enabling endogenous FVIII production from hepatocytes[1–3]

- GENEr8-1 study design
  - Open-label, single-arm, multicenter phase 3 trial (NCT03370913)
  - Single $6x10^{13}$ vg/kg infusion of valoctocogene roxaparvovec
  - Participants are adult men with severe hemophilia A (FVIII ≤1 IU/dL):
    - Previously receiving FVIII prophylaxis
    - No history of FVIII inhibitors or anti-AAV5 antibodies
    - No significant liver dysfunction, liver fibrosis, or cirrhosis

- Year two analysis:
  - ≥104 weeks post-gene transfer for all participants
  - Mean (median) follow-up of 122.3 (110.9) weeks



AAV5, adeno-associated virus serotype 5; FVIII, factor VIII; SD, standard deviation.

1. Rangarajan S, et al. *N Engl J Med*. 2017;377(26):2519–2530; 2. Pasi KJ, et al. *N Engl J Med.* 2020;382(1):29–40; 3. Pasi KJ, et al. *Haemophilia*. 2020;26(S4):151.

# BASELINE CHARACTERISTICS

| | | ITT n = 134 [a,b] | mITT n = 132 [a,b] | Rollover n = 112 [b,c] | mITT subset ≥156 weeks post-gene transfer, n = 17 [a] |
|---|---|---|---|---|---|
| **Age, years, mean ± SD** | | 31.7 ± 10.3 | 31.4 ± 10.1 | 31.8 ± 10.6 | 29.5 ± 6.0 |
| **Race, n (%)** | White | 96 (71.6) | 94 (71.2) | 78 (69.6) | 14 (82.4) |
| | Asian | 19 (14.2) | 19 (14.4) | 17 (15.2) | 1 (5.9) |
| | Black or African American | 15 (11.2) | 15 (11.4) | 14 (12.5) | 1 (5.9) |
| | Hawaiian or Pacific Islander | 1 (0.7) | 1 (0.8) | 1 (0.9) | 0 |
| | Not provided | 3 (2.2) | 3 (2.3) | 2 (1.8) | 1 (5.9) |
| **Hispanic or Latino ethnicity, n (%)** | | 7 (5.2) | 7 (5.3) | 5 (4.5) | 1 (5.9) |
| **BMI, kg/m$^2$, mean ± SD** | | 25.3 ± 4.6 | 25.3 ± 4.6 | 25.2 ± 4.7 | 26.4 ± 3.8 |
| **PMH of chronic infection, n (%)** | Hepatitis B | 20 (14.9) | 18 (13.6) | 17 (15.2) | 1 (5.9) |
| | Hepatitis C | 41 (30.6) | 39 (29.5) | 33 (29.5) | 6 (35.3) |
| | HIV | 2 (1.5) | 0 | 0 | 0 |
| **Number of problem joints,[d] n (%)** | 0 | 97 (72.4) | 95 (72.0) | 82 (73.2) | 10 (58.8) |
| | 1 | 17 (12.7) | 17 (12.9) | 13 (11.6) | 4 (23.5) |
| | 2 | 9 (6.7) | 9 (6.8) | 9 (8.0) | 0 |
| | 3 | 8 (6.0) | 8 (6.1) | 6 (5.4) | 2 (11.8) |
| | >3 | 3 (2.2) | 3 (2.3) | 2 (1.8) | 1 (5.9) |

BMI, body mass index; ITT, intent-to-treat; mITT, modified ITT; PMH, previous medical history; SD, standard deviation.

[a]Includes one participant lost to follow-up at week 66. [b]Includes one participant with an unrelated fatal SAE of suicide at week 95. [c]Rolled over from study 270-902, an observational, non-interventional study of men with severe hemophilia A receiving prophylaxis, after ≥6 months of prospectively collected data. [d]Problem joints were defined as those with chronic joint pain, chronic synovitis, hemophilic arthropathy, limited motion, or recurrent bleeding.

# Key Insights

- No new safety signals were detected
  - No delayed serious AEs attributed to valoctocogene roxaparvovec or immunosuppressants
  - The most common valoctocogene roxaparvovec-associated AEs occurred early and included transient infusion-associated reactions and asymptomatic, mild to moderate rise in liver enzymes
- A single infusion of valoctocogene roxaparvovec provided superior bleed control relative to FVIII prophylaxis for 2+ years
  - 84% of participants had zero treated bleeds during year 2
  - 95% of participants remain off prophylaxis through last follow-up
  - 98% reduction in mean exogenous FVIII use overall
- Endogenous, transgene-derived FVIII levels near and below the lower limit of quantitation by CSA can be associated with zero bleeding

AE, adverse event; FVIII, factor VIII; CSA, chromogenic substrate assay.

# Safety Summary

- Most common AE remains ALT elevation (89%)
  - Others include headache (41%), arthralgia (40%), nausea (38%), aspartate aminotransferase elevation (35%), and fatigue (30%)
- One new treatment-related grade 3 AE:
  - Week 70 grade 3 ALT elevation
- No thromboembolic events, FVIII inhibitors, or non-cutaneous cancers

| Number of Participants (%) | | ITT (N=134) |
|---|---|---|
| AEs | | 134 (100%) |
| SAEs | | 24 (17.9%) |
| Treatment-related AEs | | 123 (91.8%) |
| AEs ≥ Grade 3 | | 42 (31.3%) |
| Corticosteroid-related AEs | | 81 (60.4%) |
| Alternative immunosuppressant-related AEs | | 15 (11.2%) |
| AEs of special interest | ALT elevation | 119 (88.8%) |
| | ALT elevation ≥ Grade 3 | 11 (8.2%) |
| | Potential Hy's law case | 0 |
| | Infusion-associated reactions[a] | 50 (37.3%) |
| | Systemic hypersensitivity[a] | 7 (5.2%) |
| | Anaphylactic or anaphylactoid reactions[a,b] | 3 (2.2%) |
| | Thromboembolic events | 0 |
| | Anti-FVIII neutralizing antibodies | 0 |
| | Malignancy (except non-melanoma skin cancer) | 0 |

ITT, intent to treat; SAE, serious adverse event; AE, adverse event; ALT, alanine aminotransferase.
[a]Limited to events that occurred within 48 hours of infusion. [b]All anaphylactic or anaphylatoid reactions were also counted as hypersensitivity reactions.

# Safety Summary

- Four new SAEs in GENEr8-1
  - None attributed to valoctocogene roxaparvovec or immunosuppression
  - Apnoea, anaphylactic reaction, suicide, and coronary artery disease
- SAE from Phase 1/2 Study
  - An SAE of a salivary gland carcinoma not attributed to treatment was reported in a participant from the phase 1/2 study

| Number of Participants (%) | ITT (N=134) |
|---|---|
| All SAEs | 24 (17.9%) |
| Treatment-related SAEs | 5 (3.7%) |
| Corticosteroid-related SAEs | 3 (2.2%) |
| Alternative immunosuppressant-related SAEs | 1 (0.7%) |

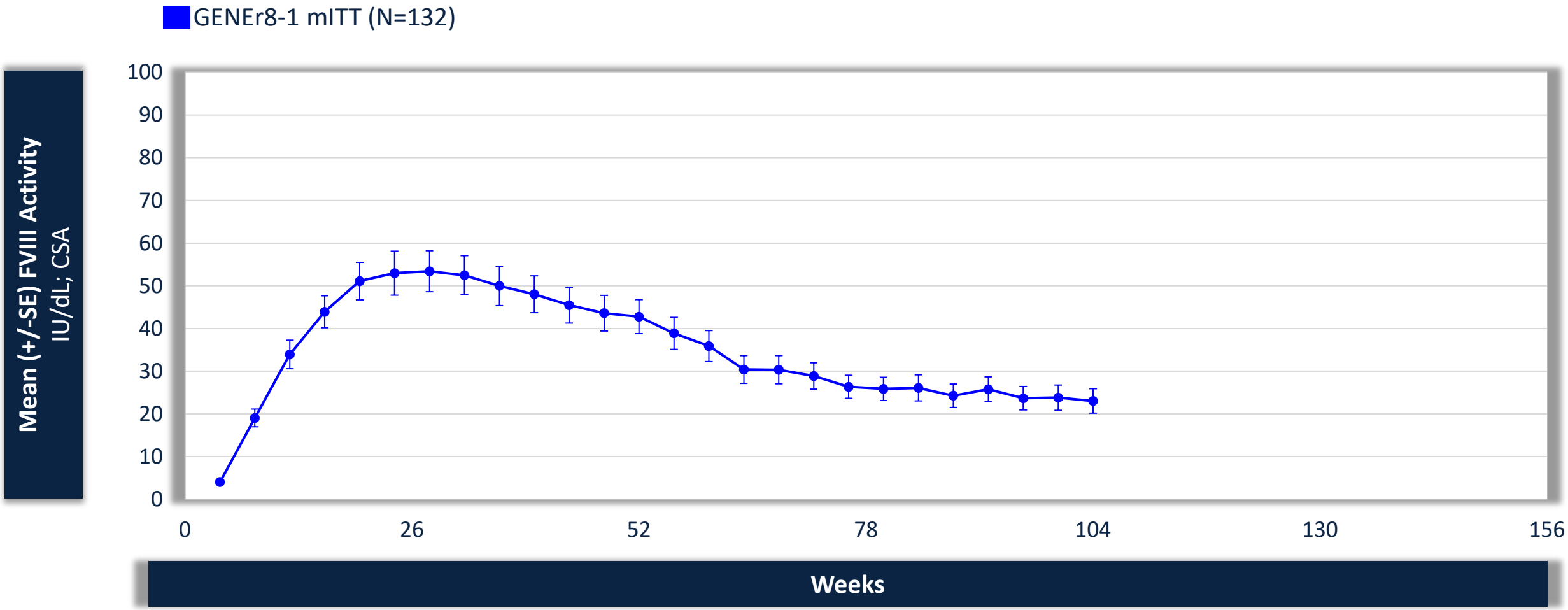
ITT, intent to treat; SAE, serious adverse event.

# IMMUNOSUPPRESSANT USE

| | Corticosteroids | Budesonide | Tacrolimus | Mycophenolate |
|---|---|---|---|---|
| **Participants with any use**, n (%) | 106 (79.1%) | 6 (4.5%) | 24 (17.9%) | 13 (9.7%) |
| **Participants with use at week 104**, n (%) | 1 (0.7%) | 0 | 0 | 1 (0.7%) |
| **Time from gene transfer to first use** (mean/median), weeks | 10.9 / 8.1 | 15.4 / 16.9 | 30.9 / 31.6 | 21.8 / 21.3 |
| **Total duration per participant** (mean/median), weeks | 34.7 / 32.9 | 20.9 / 18.2 | 18.5 / 18.3 | 36.4 / 34.6 |
| **Total dose per participant** (mean/median), mg | 8738.6 / 6420.0 | 1382.5 / 805.5 | 643.3 / 507.0 | 421,423.1 / 458,500.0 |

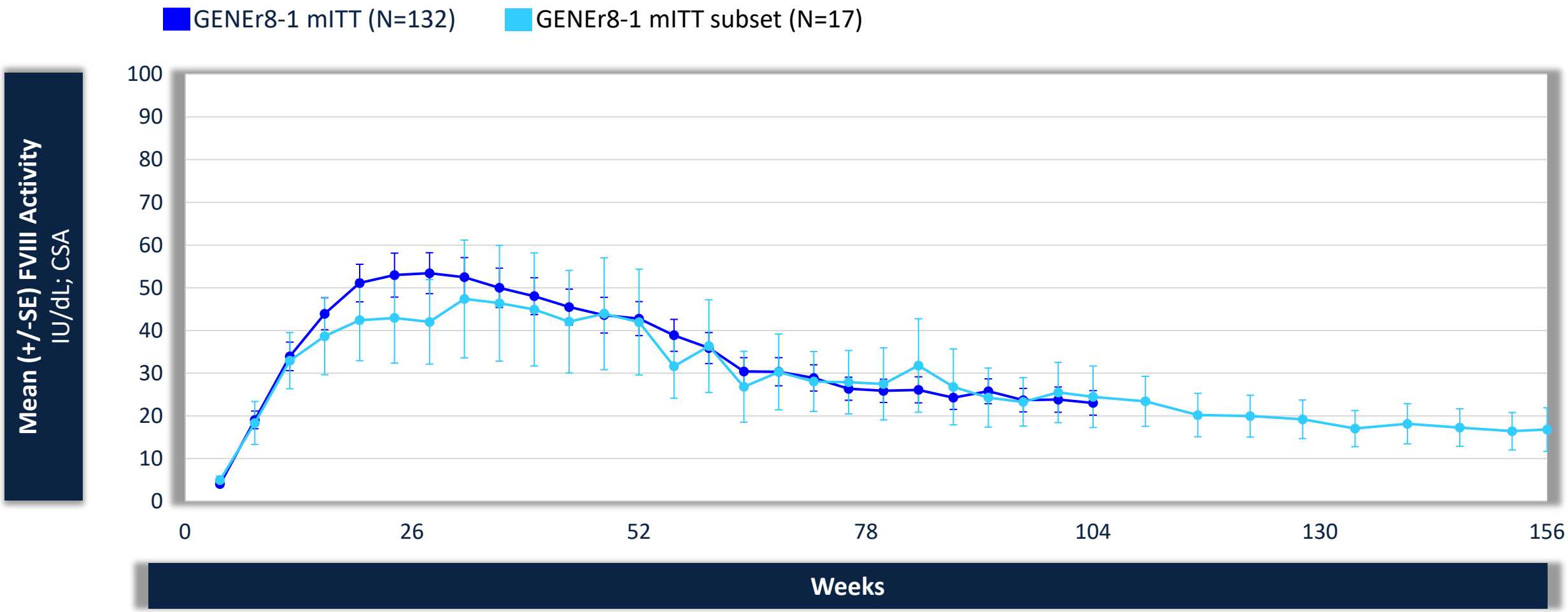
- 83% received immunosuppressive treatment in response to liver enzyme elevations
  - 53% of those participants were off immunosuppression at week 52; 99% were off at week 104

# FVIII Activity by Chromogenic Substrate Assay




FVIII, factor VIII; mITT, modified intent-to-treat population; SE, standard error; CSA, chromogenic substrate assay.
Missing FVIII values are imputed as follows: smaller of adjacent non-missing values; 0 if participant has discontinued study; linear extrapolation if there are no subsequent valid values.

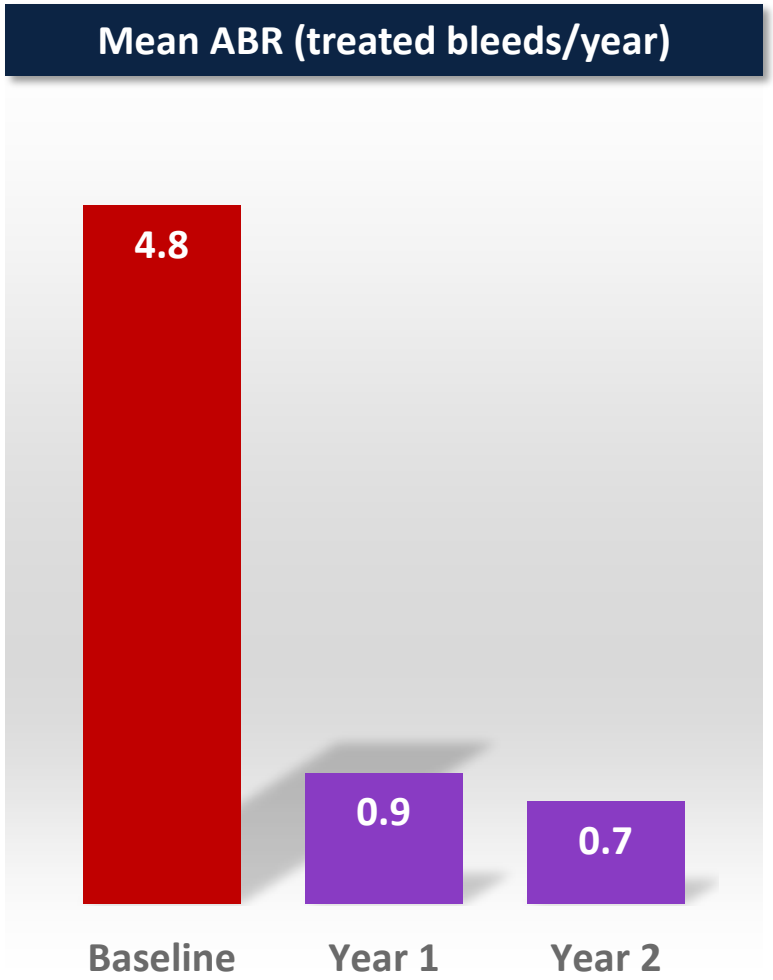
# FVIII Activity by Chromogenic Substrate Assay

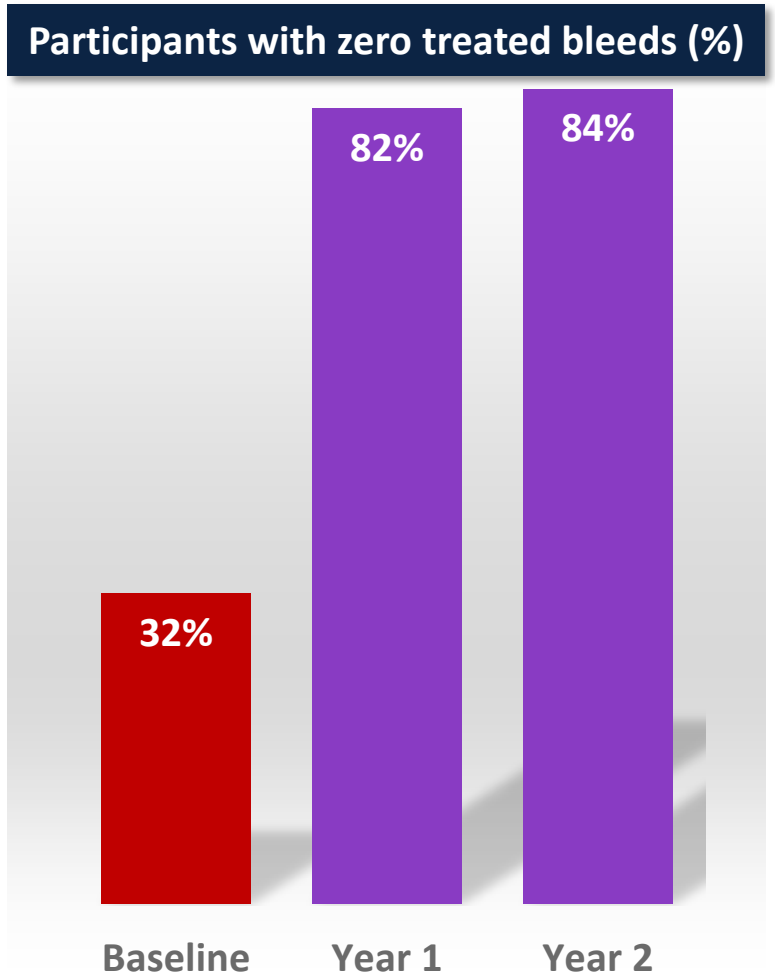



FVIII, factor VIII; mITT, modified intent-to-treat population; SE, standard error; CSA, chromogenic substrate assay.
Missing FVIII values are imputed as follows: smaller of adjacent non-missing values; 0 if participant has discontinued study; linear extrapolation if there are no subsequent valid values.

# ANNUALIZED TREATED BLEEDING RATE: SUPERIOR TO FVIII PROPHYLAXIS

- Rollover population, n=112
- Mean change from baseline 4.1 treated bleeds/year over the entire follow-up period
  - Cumulative mean ABR: 0.8 bleeds/year
  - *P*<0.0001
  - 85% reduction
  - 95% CI: – 5.3 to – 2.9 bleeds/year
- Median (IQR) ABR
  - Baseline: 2.8 (0.0, 7.6)
  - Year 1: 0.0 (0.0, 0.0)
  - Year 2: 0.0 (0.0, 0.0)
  - Cumulative: 0.0 (0.0, 0.4)

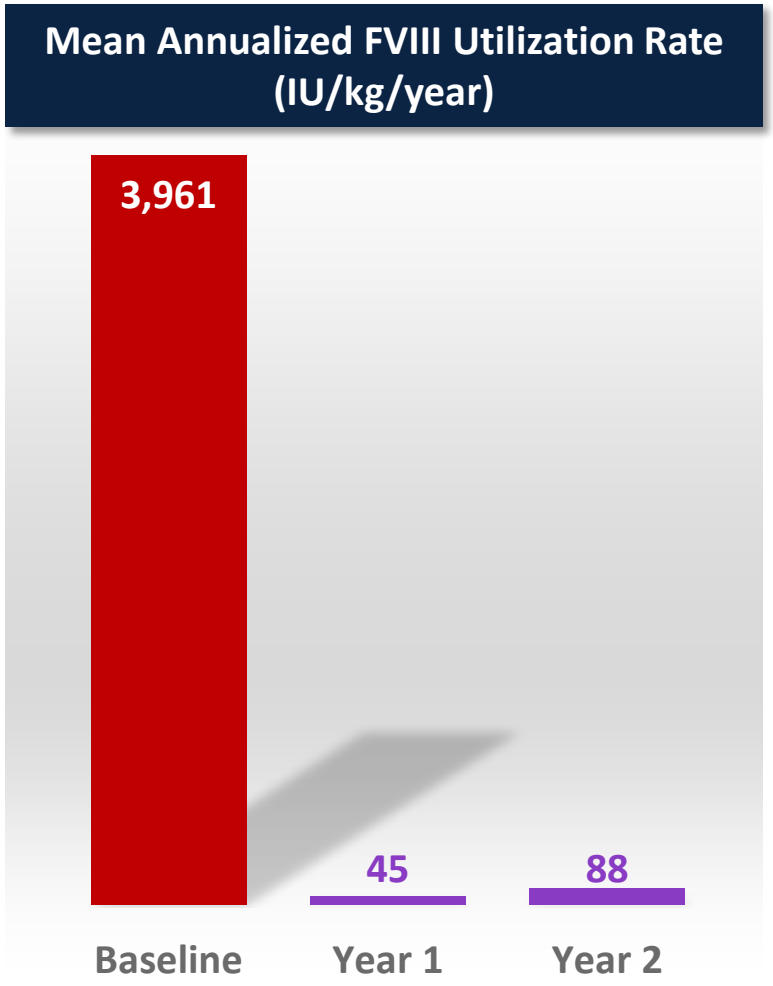


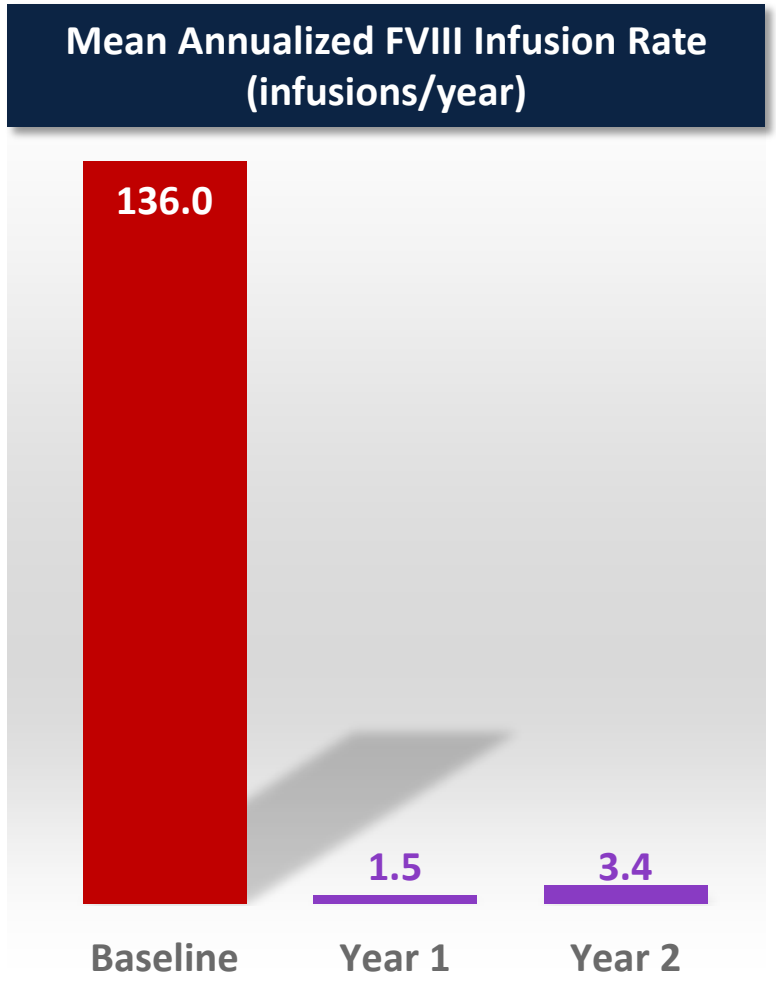




ABR, annualized bleeding rate; CI, confidence interval; IQR, interquartile range.
*P*-value is from a 2-sided, 1-sample t-test against the null hypothesis that the change from baseline is 0. Efficacy evaluation starts at later of week 5 or prophylaxis discontinuation (mean [SD] time to prophylaxis discontinuation 28.3 [10.9] days). Year 1, week 5/end of prophylaxis to week 52; Year 2, week 53 to week 104; Cumulative, week 5/end of prophylaxis through last follow-up at time of data cut.

# ANNUALIZED FVIII UTILIZATION & INFUSION RATES: 98% REDUCTION

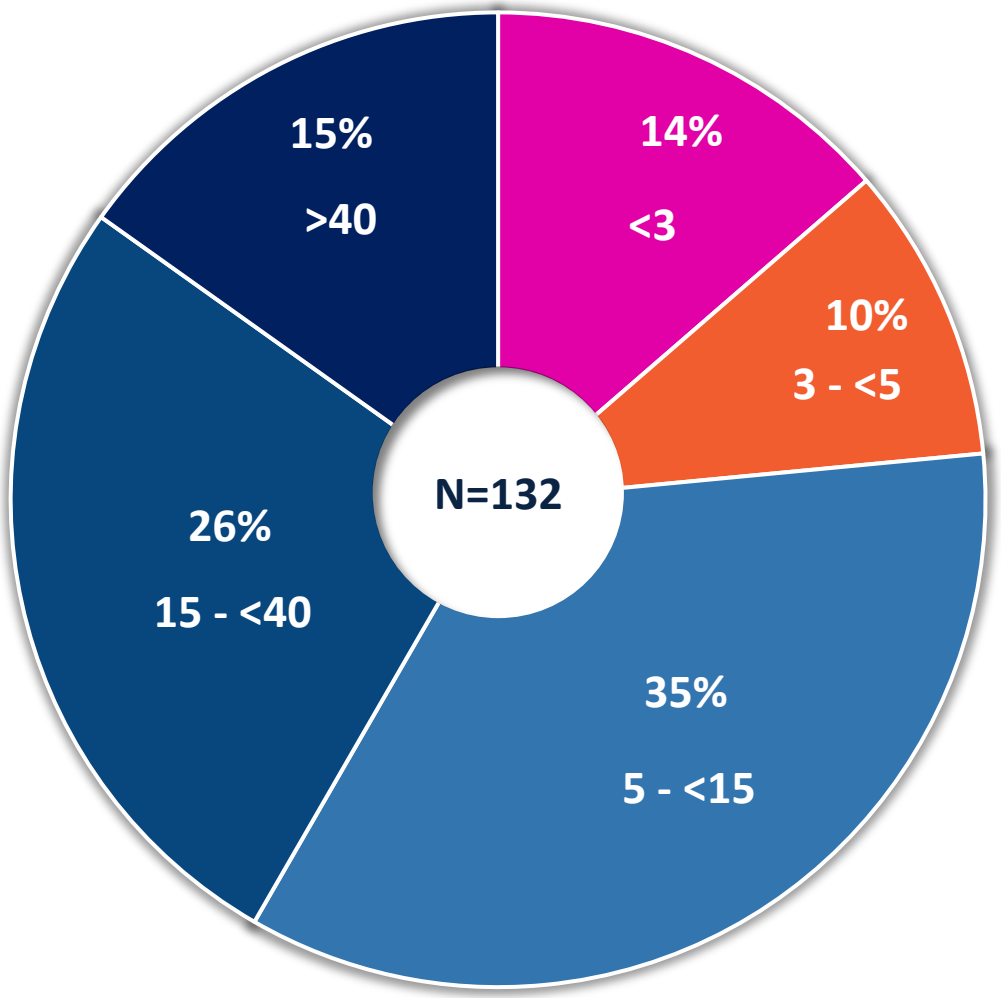
- Rollover population, n=112
- Utilization rate mean change from baseline –3,891 IU/kg/year over the entire follow-up period
  - Cumulative mean utilization: 70 IU/kg/year
  - *P*<0.0001
  - 98% reduction
  - 95% CI: –4,221 to –3,562 IU/kg/year
- Infusion rate mean change from baseline –133 infusions/year over the entire follow-up period
  - Cumulative mean infusion rate: 2.6 infusions/year
  - *P*<0.0001
  - 98% reduction
  - 95% CI: –143 to –124 infusions/year



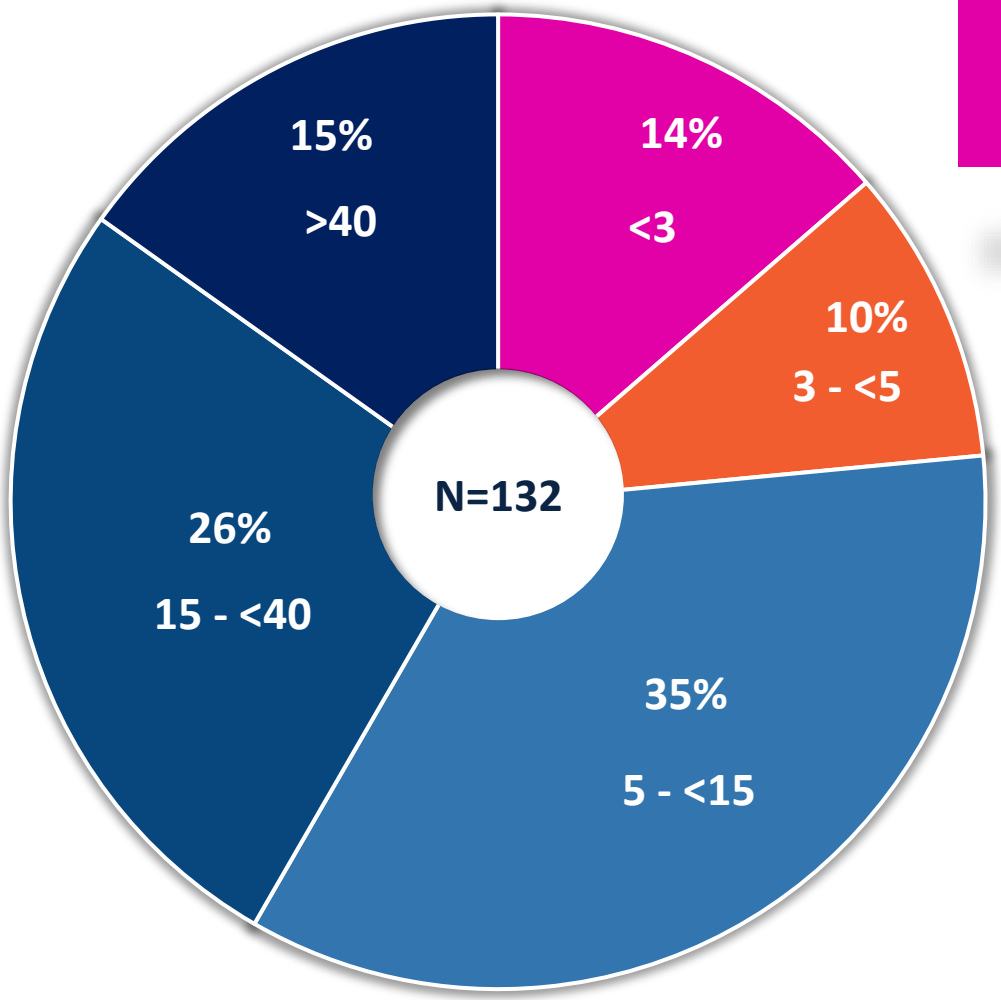

Efficacy evaluation starts at later of week 5 or prophylaxis discontinuation (mean [SD] time to prophylaxis discontinuation 28.3 [10.9] days). Year 1, week 5/end of prophylaxis to week 52; Year 2, week 52 to week 104; Cumulative, week 5/end of prophylaxis through last follow-up at time of data cut.

# Participant Distribution by Week 104 CSA FVIII Level




FVIII, factor VIII; CSA, chromogenic substrate assay.
*No treated bleeds within the past year of follow-up and not on prophylaxis.

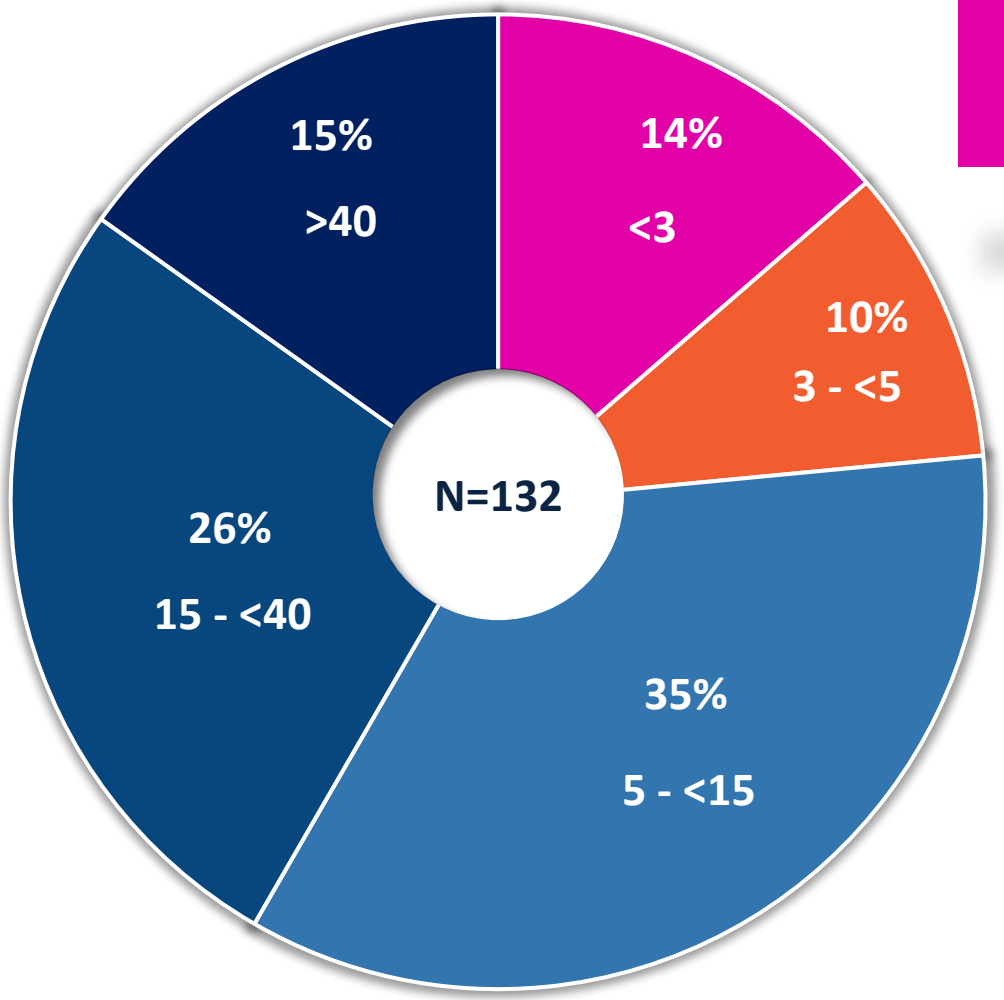
# Participant Distribution by Week 104 CSA FVIII Level




**FVIII <3**
N=18
28% bleed-free*
4 reinitiated prophylaxis

FVIII, factor VIII; CSA, chromogenic substrate assay.
*No treated bleeds within the past year of follow-up and not on prophylaxis.

# Participant Distribution by Week 104 CSA FVIII Level

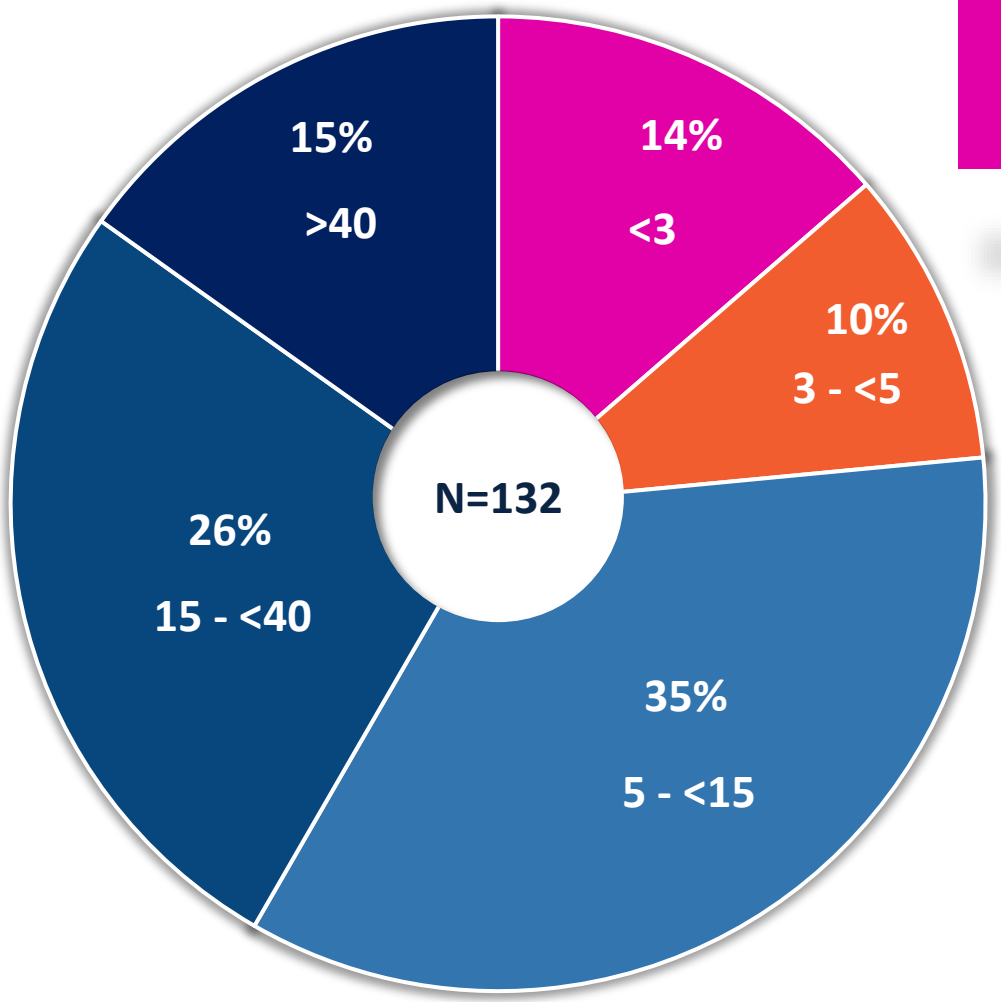



**FVIII <3**
N=18
28% bleed-free*
4 reinitiated prophylaxis

**FVIII 3 - <5**
N=13
77% bleed-free*
1 reinitiated prophylaxis

FVIII, factor VIII; CSA, chromogenic substrate assay.
*No treated bleeds within the past year of follow-up and not on prophylaxis.

# Participant Distribution by Week 104 CSA FVIII Level



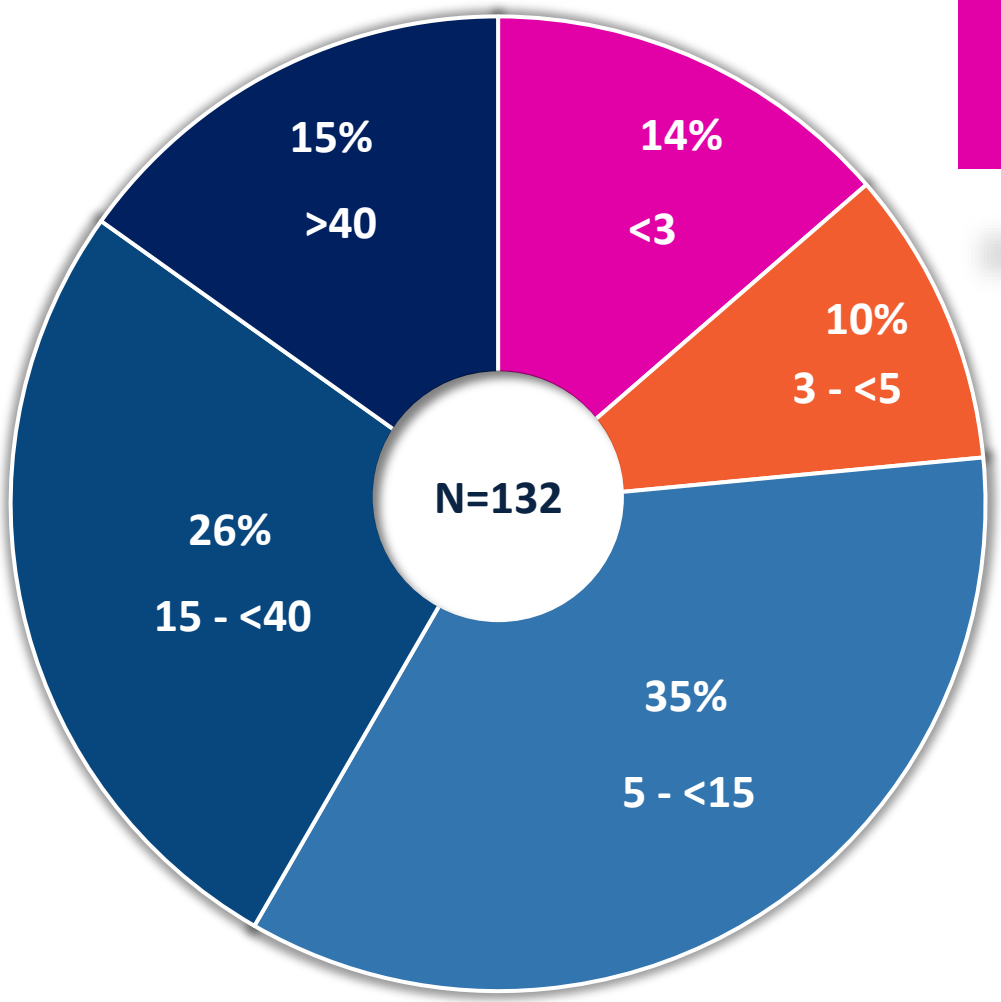

**FVIII <3**
N=18
28% bleed-free*
4 reinitiated prophylaxis

**FVIII 3 - <5**
N=13
77% bleed-free*
1 reinitiated prophylaxis

**FVIII 5 - <15**
N=46
85% bleed-free*
1 reinitiated prophylaxis

FVIII, factor VIII; CSA, chromogenic substrate assay.
*No treated bleeds within the past year of follow-up and not on prophylaxis.

# Participant Distribution by Week 104 CSA FVIII Level




**FVIII <3**
N=18
28% bleed-free*
4 reinitiated prophylaxis

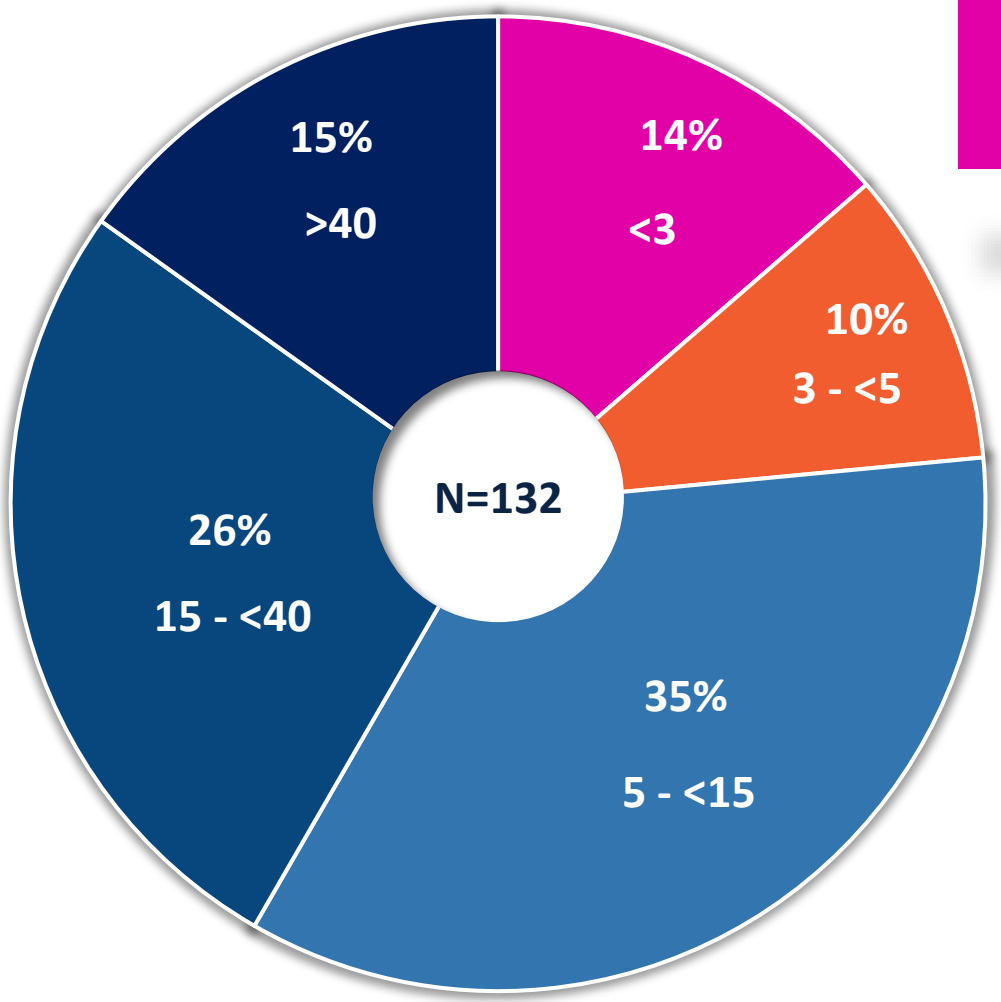
**FVIII 3 - <5**
N=13
77% bleed-free*
1 reinitiated prophylaxis

**FVIII 15 - <40**
N=35
97% bleed-free*

**FVIII 5 - <15**
N=46
85% bleed-free*
1 reinitiated prophylaxis

FVIII, factor VIII; CSA, chromogenic substrate assay.
*No treated bleeds within the past year of follow-up and not on prophylaxis.

# Participant Distribution by Week 104 CSA FVIII Level




**FVIII >40**
N=20
100% bleed-free*

**FVIII <3**
N=18
28% bleed-free*
4 reinitiated prophylaxis

**FVIII 3 - <5**
N=13
77% bleed-free*
1 reinitiated prophylaxis

**FVIII 15 - <40**
N=35
97% bleed-free*

**FVIII 5 - <15**
N=46
85% bleed-free*
1 reinitiated prophylaxis

FVIII, factor VIII; CSA, chromogenic substrate assay.
*No treated bleeds within the past year of follow-up and not on prophylaxis.

# CONCLUSIONS

- No new safety signals were detected
  - No delayed serious AEs attributed to valoctocogene roxaparvovec or immunosuppressants
  - The most common valoctocogene roxaparvovec-associated AEs occurred early and included transient infusion-associated reactions and asymptomatic, mild to moderate rise in liver enzymes
- A single infusion of valoctocogene roxaparvovec provided superior bleed control relative to FVIII prophylaxis for 2+ years
  - 84% of participants had zero treated bleeds during year 2
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# ACKNOWLEDGEMENTS

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