

Dossier zur Nutzenbewertung gemäß § 35a SGB V

Etranacogen dezaparvovec (Hemgenix[®])

CSL Behring GmbH

Modul 4 Anhang 4-G – Subgruppenanalysen (Morbidity und gesundheitsbezogene Lebensqualität)

*Hemgenix ist indiziert zur Behandlung von schwerer und mittelschwerer Hämophilie B
(angeborener Faktor-IX-Mangel) bei erwachsenen Patienten ohne Faktor-IX-Inhibitoren in
ihrer Vorgeschichte*

**Medizinischer Nutzen und
medizinischer Zusatznutzen,
Patientengruppen mit therapeutisch
bedeutsamem Zusatznutzen**

Stand: 28.04.2023

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1. Annualisierte Blutungsrate – Alle Ereignisse – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.

Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted. Pxx = xx-th percentile. N = number of subjects under observation in the time interval.

For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.

* For Comparison with Post-Treatment Month 7-24.

** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.

[a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).

[b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.

[c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.

[d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.

[e] Two-sided P-value.

Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	28 (70.0)	21 (52.5)	18 (45.0)
Number of Bleeds, n	89	72	50
Number of Bleeds Treated With Factor IX, n (% of bleeds)	74 (83.1)	32 (44.4)	22 (44.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	15 (16.9)	40 (55.6)	28 (56.0)
Bleeds Per Subject			
Mean	2.2	1.8	1.3
SD	2.5	3.2	2.5
SE	0.4	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	1.0	0.0
P75	4.0	2.0	1.0
P90	5.5	6.0	3.0
Minimum, Maximum	0, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	3.58	0.96	0.87

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	89	72	50
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	3.58	0.96	0.87
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.56* (2.48, 5.10)	1.00 (0.58, 1.75)	0.91 (0.49, 1.70)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.28	0.26
Two-Sided 95% Wald CI [c] P-value [d]		(0.18, 0.44) <0.0001	(0.15, 0.43) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2142 (0.7835, 1.8816)	1.1898 (0.7392, 1.9150)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.34 (0.42, 4.29) 0.6256	1.32 (0.40, 4.35) 0.6510

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	11 (91.7)	8 (66.7)	7 (58.3)
Number of Bleeds, n	40	25	18
Number of Bleeds Treated With Factor IX, n (% of bleeds)	37 (92.5)	20 (80.0)	15 (83.3)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (7.5)	5 (20.0)	3 (16.7)
Bleeds Per Subject			
Mean	3.3	2.1	1.5
SD	2.5	2.3	1.8
SE	0.7	0.7	0.5
P10	1.0	0.0	0.0
P25	1.5	0.0	0.0
Median	3.0	1.0	1.0
P75	4.0	4.0	3.0
P90	7.0	6.0	4.0
Minimum, Maximum	0, 9	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	5.57	1.11	1.04

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	40	25	18
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	5.57	1.11	1.04
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	5.48* (3.86, 7.78)	1.15 (0.62, 2.13)	1.06 (0.55, 2.07)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.21	0.19
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.36) <0.0001	(0.11, 0.35) <0.0001

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	26 (78.8)	15 (45.5)	12 (36.4)
Number of Bleeds, n	88	35	23
Number of Bleeds Treated With Factor IX, n (% of bleeds)	80 (90.9)	16 (45.7)	12 (52.2)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	8 (9.1)	19 (54.3)	11 (47.8)
Bleeds Per Subject			
Mean	2.7	1.1	0.7
SD	2.4	1.7	1.3
SE	0.4	0.3	0.2
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	2.0	0.0	0.0
P75	4.0	1.0	1.0
P90	6.0	4.0	2.0
Minimum, Maximum	0, 9	0, 7	0, 6
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	4.25	0.56	0.49

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	88	35	23
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	4.25	0.56	0.49
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	4.10* (2.99, 5.62)	0.58 (0.34, 0.99)	0.50 (0.26, 0.95)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.14	0.12
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.22) <0.0001	(0.07, 0.22) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.0376 (0.6523, 1.6503)	1.0144 (0.6148, 1.6738)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.28 (0.11, 0.76) 0.0121	0.27 (0.10, 0.74) 0.0111

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	13 (68.4)	14 (73.7)	13 (68.4)
Number of Bleeds, n	41	62	45
Number of Bleeds Treated With Factor IX, n (% of bleeds)	31 (75.6)	36 (58.1)	25 (55.6)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	10 (24.4)	26 (41.9)	20 (44.4)
Bleeds Per Subject			
Mean	2.2	3.3	2.4
SD	2.7	4.2	3.3
SE	0.6	1.0	0.8
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	2.0	1.0
P75	4.0	6.0	3.0
P90	7.0	10.0	8.0
Minimum, Maximum	0, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	3.61	1.75	1.64

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	41	62	45
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	3.61	1.75	1.64
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.72* (2.12, 6.53)	1.82 (1.03, 3.24)	1.70 (0.91, 3.18)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.49	0.46
Two-Sided 95% Wald CI [c] P-value [d]		(0.34, 0.72) 0.0001	(0.30, 0.69) 0.0001

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	39 (100)	22 (56.4)	18 (46.2)
Number of Bleeds, n	129	83	58
Number of Bleeds Treated With Factor IX, n (% of bleeds)	111 (86.0)	45 (54.2)	31 (53.4)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	18 (14.0)	38 (45.8)	27 (46.6)
Bleeds Per Subject			
Mean	3.3	2.1	1.5
SD	2.4	3.4	2.7
SE	0.4	0.5	0.4
P10	1.0	0.0	0.0
P25	1.0	0.0	0.0
Median	3.0	1.0	0.0
P75	4.0	2.0	2.0
P90	8.0	7.0	5.0
Minimum, Maximum	1, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	5.37	1.14	1.05

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	129	83	58
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	5.37	1.14	1.05

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	7 (53.8)	7 (53.8)
Number of Bleeds, n	0	14	10
Number of Bleeds Treated With Factor IX, n (% of bleeds)	0	7 (50.0)	6 (60.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	7 (50.0)	4 (40.0)
Bleeds Per Subject			
Mean	0.0	1.1	0.8
SD	0.0	1.2	0.9
SE	0.0	0.3	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	1.0	1.0
P75	0.0	2.0	1.0
P90	0.0	3.0	2.0
Minimum, Maximum	0, 0	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.56	0.52

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	14	10
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.56	0.52

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	30 (69.8)	22 (51.2)	21 (48.8)
Number of Bleeds, n	86	63	43
Number of Bleeds Treated With Factor IX, n (% of bleeds)	75 (87.2)	40 (63.5)	29 (67.4)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	11 (12.8)	23 (36.5)	14 (32.6)
Bleeds Per Subject			
Mean	2.0	1.5	1.0
SD	2.2	2.2	1.6
SE	0.3	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	1.0	0.0
P75	3.0	2.0	1.0
P90	4.0	4.0	3.0
Minimum, Maximum	0, 9	0, 10	0, 8
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	3.23	0.78	0.70

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	86	63	43
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	3.23	0.78	0.70
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.14* (2.33, 4.24)	0.82 (0.52, 1.32)	0.73 (0.45, 1.19)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.23
Two-Sided 95% Wald CI [c] P-value [d]		(0.16, 0.43) <0.0001	(0.14, 0.40) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.0156 (0.6320, 1.6320)	0.9609 (0.5689, 1.6231)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		1.06 (0.33, 3.40) 0.9237	0.98 (0.30, 3.16) 0.9697

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	9 (100)	7 (77.8)	4 (44.4)
Number of Bleeds, n	43	34	25
Number of Bleeds Treated With Factor IX, n (% of bleeds)	36 (83.7)	12 (35.3)	8 (32.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	7 (16.3)	22 (64.7)	17 (68.0)
Bleeds Per Subject			
Mean	4.8	3.8	2.8
SD	2.9	5.2	4.5
SE	1.0	1.7	1.5
P10	1.0	0.0	0.0
P25	3.0	1.0	0.0
Median	4.0	1.0	0.0
P75	7.0	6.0	5.0
P90	10.0	16.0	13.0
Minimum, Maximum	1, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	7.92	2.01	1.94

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	43	34	25
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	7.92	2.01	1.94
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	8.29* (5.49, 12.53)	2.04 (0.87, 4.79)	1.96 (0.73, 5.26)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.25	0.24
Two-Sided 95% Wald CI [c] P-value [d]		(0.15, 0.40) <0.0001	(0.13, 0.44) <0.0001

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	22 (66.7)	17 (51.5)	14 (42.4)
Number of Bleeds, n	76	52	38
Number of Bleeds Treated With Factor IX, n (% of bleeds)	62 (81.6)	18 (34.6)	12 (31.6)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	14 (18.4)	34 (65.4)	26 (68.4)
Bleeds Per Subject			
Mean	2.3	1.6	1.2
SD	2.7	3.1	2.5
SE	0.5	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	2.0	1.0	0.0
P75	4.0	2.0	1.0
P90	6.0	3.0	3.0
Minimum, Maximum	0, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	3.76	0.82	0.79

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	76	52	38
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	3.76	0.82	0.79
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.80* (2.56, 5.64)	0.84 (0.44, 1.63)	0.80 (0.38, 1.67)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.21
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.36) <0.0001	(0.12, 0.37) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1994 (0.7736, 1.8598)	1.1954 (0.7456, 1.9166)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.71 (0.25, 1.98) 0.5130	0.76 (0.26, 2.18) 0.6067

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 1.1.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	17 (89.5)	12 (63.2)	11 (57.9)
Number of Bleeds, n	53	45	30
Number of Bleeds Treated With Factor IX, n (% of bleeds)	49 (92.5)	34 (75.6)	25 (83.3)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (7.5)	11 (24.4)	5 (16.7)
Bleeds Per Subject			
Mean	2.8	2.4	1.6
SD	2.3	2.9	2.1
SE	0.5	0.7	0.5
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	3.0	1.0	1.0
P75	4.0	4.0	2.0
P90	7.0	7.0	5.0
Minimum, Maximum	0, 9	0, 10	0, 8
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	4.47	1.31	1.15

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	53	45	30
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	4.47	1.31	1.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	4.37* (3.09, 6.18)	1.39 (0.79, 2.45)	1.23 (0.66, 2.29)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.31	0.28
Two-Sided 95% Wald CI [c] P-value [d]		(0.18, 0.55) <0.0001	(0.15, 0.53) <0.0001

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	23 (74.2)	14 (45.2)	12 (38.7)
Number of Bleeds, n	67	41	25
Number of Bleeds Treated With Factor IX, n (% of bleeds)	65 (97.0)	21 (51.2)	14 (56.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (3.0)	20 (48.8)	11 (44.0)
Bleeds Per Subject			
Mean	2.2	1.3	0.8
SD	2.2	2.0	1.4
SE	0.4	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.0	2.0	1.0
P90	4.0	4.0	2.0
Minimum, Maximum	0, 9	0, 7	0, 6
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	3.45	0.71	0.57

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	67	41	25
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	3.45	0.71	0.57
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.38* (2.33, 4.90)	0.74 (0.43, 1.26)	0.59 (0.32, 1.08)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.21	0.17
Two-Sided 95% Wald CI [c] P-value [d]		(0.13, 0.34) <0.0001	(0.10, 0.30) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1429 (0.7304, 1.7885)	1.0774 (0.6587, 1.7623)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		0.71 (0.26, 1.91) 0.4965	0.58 (0.21, 1.60) 0.2902

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	16 (76.2)	15 (71.4)	13 (61.9)
Number of Bleeds, n	62	56	43
Number of Bleeds Treated With Factor IX, n (% of bleeds)	46 (74.2)	31 (55.4)	23 (53.5)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	16 (25.8)	25 (44.6)	20 (46.5)
Bleeds Per Subject			
Mean	3.0	2.7	2.0
SD	2.9	4.0	3.2
SE	0.6	0.9	0.7
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	2.0	1.0	1.0
P75	4.0	3.0	2.0
P90	7.0	6.0	5.0
Minimum, Maximum	0, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	4.90	1.41	1.41

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	62	56	43
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	4.90	1.41	1.41
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	4.89* (3.26, 7.33)	1.48 (0.78, 2.80)	1.47 (0.75, 2.86)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.30	0.30
Two-Sided 95% Wald CI [c] P-value [d]		(0.18, 0.50) <0.0001	(0.17, 0.52) <0.0001

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	20 (74.1)	16 (59.3)	13 (48.1)
Number of Bleeds, n	63	50	34
Number of Bleeds Treated With Factor IX, n (% of bleeds)	53 (84.1)	22 (44.0)	14 (41.2)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	10 (15.9)	28 (56.0)	20 (58.8)
Bleeds Per Subject			
Mean	2.3	1.9	1.3
SD	2.3	3.3	2.6
SE	0.4	0.6	0.5
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	2.0	1.0	0.0
P75	4.0	2.0	1.0
P90	4.0	5.0	4.0
Minimum, Maximum	0, 10	0, 16	0, 13
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	3.84	0.98	0.86

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	63	50	34
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	3.84	0.98	0.86
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.98* (2.72, 5.81)	0.99 (0.52, 1.92)	0.87 (0.40, 1.88)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.25	0.22
Two-Sided 95% Wald CI [c] P-value [d]		(0.16, 0.40) <0.0001	(0.12, 0.39) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2493 (0.7482, 2.0859)	1.2273 (0.7046, 2.1378)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.94 (0.25, 3.53) 0.9306	0.88 (0.23, 3.42) 0.8551

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Table 1.1.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	8 (72.7)	5 (45.5)	5 (45.5)
Number of Bleeds, n	25	18	13
Number of Bleeds Treated With Factor IX, n (% of bleeds)	24 (96.0)	13 (72.2)	10 (76.9)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	1 (4.0)	5 (27.8)	3 (23.1)
Bleeds Per Subject			
Mean	2.3	1.6	1.2
SD	2.6	3.0	2.4
SE	0.8	0.9	0.7
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	2.0	0.0	0.0
P75	3.0	2.0	1.0
P90	4.0	4.0	2.0
Minimum, Maximum	0, 9	0, 10	0, 8
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	3.86	0.87	0.83

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Table 1.1.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - All Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	25	18	13
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	3.86	0.87	0.83
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.57* (2.07, 6.15)	0.96 (0.32, 2.92)	0.91 (0.28, 2.94)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.27	0.25
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.81) 0.0098	(0.08, 0.83) 0.0118

Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

2. Annualisierte Blutungsrate – Blutungsschwere sehr mild – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
* For Comparison with Post-Treatment Month 7-24.
** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.

- [a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
- [b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
- [c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
- [d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
- [e] Two-sided P-value.

Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	12 (30.0)	15 (37.5)	9 (22.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	9 (75.0)	1 (6.7)	1 (11.1)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (33.3)	14 (93.3)	8 (88.9)
Bleeds Per Subject			
Mean	0.5	0.5	0.3
SD	1.0	0.7	0.6
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	1.0	1.5	1.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.80	0.25	0.21

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	20	19	12
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.80	0.25	0.21
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.82* (0.43, 1.58)	0.26 (0.16, 0.40)	0.22 (0.12, 0.40)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.31	0.26
Two-Sided 95% Wald CI [c] P-value [d]		(0.15, 0.67) 0.0015	(0.10, 0.70) 0.0039
Negative Binomial Dispersion Parameter (95% CI)		1.0285 (0.3336, 3.1711)	1.7630 (0.6389, 4.8652)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		4.78 (0.42, 53.93) 0.2057	3.02 (0.23, 39.45) 0.3998

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	3 (25.0)	1 (8.3)	1 (8.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	3 (100)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	1 (100)	1 (100)
Bleeds Per Subject			
Mean	0.4	0.1	0.1
SD	0.8	0.3	0.3
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.5	0.0	0.0
P90	2.0	0.0	0.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.70	0.04	0.06

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	5	1	1
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.70	0.04	0.06
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.66* (0.24, 1.77)	0.04 (0.01, 0.28)	0.06 (0.01, 0.38)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.07	0.09
Two-Sided 95% Wald CI [c] P-value [d]		(0.01, 0.41) 0.0017	(0.01, 0.55) 0.0049

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	11 (33.3)	8 (24.2)	5 (15.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	8 (72.7)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (27.3)	8 (100)	5 (100)
Bleeds Per Subject			
Mean	0.5	0.3	0.2
SD	0.8	0.6	0.5
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.72	0.16	0.15

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	15	10	7
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.72	0.16	0.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.71* (0.41, 1.22)	0.16 (0.08, 0.31)	0.15 (0.06, 0.36)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.23	0.22
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.56) 0.0006	(0.07, 0.64) 0.0029
Negative Binomial Dispersion Parameter (95% CI)		1.1072 (0.3685, 3.3268)	1.8133 (0.6602, 4.9806)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.75 (0.17, 3.20) 0.6928	0.91 (0.16, 5.17) 0.9198

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	4 (21.1)	8 (42.1)	5 (26.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	4 (100)	1 (12.5)	1 (20.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (25.0)	7 (87.5)	4 (80.0)
Bleeds Per Subject			
Mean	0.5	0.5	0.3
SD	1.3	0.7	0.6
SE	0.3	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.88	0.28	0.22

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	10	10	6
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.88	0.28	0.22
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.93* (0.31, 2.78)	0.28 (0.16, 0.50)	0.22 (0.10, 0.49)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.31	0.24
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.94) 0.0197	(0.06, 1.02) 0.0269

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	15 (38.5)	13 (33.3)	8 (20.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	12 (80.0)	1 (7.7)	1 (12.5)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (26.7)	12 (92.3)	7 (87.5)
Bleeds Per Subject			
Mean	0.6	0.4	0.3
SD	1.1	0.6	0.6
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.04	0.22	0.20

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	25	16	11
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.04	0.22	0.20

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	3 (23.1)	2 (15.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	0	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	3 (100)	2 (100)
Bleeds Per Subject			
Mean	0.0	0.3	0.2
SD	0.0	0.6	0.4
SE	0.0	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 0	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.16	0.10

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	4	2
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.16	0.10

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	12 (27.9)	13 (30.2)	9 (20.9)
Number of subjects with Bleeds Treated With Factor IX, n (%)	9 (75.0)	1 (7.7)	1 (11.1)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (25.0)	12 (92.3)	8 (88.9)
Bleeds Per Subject			
Mean	0.3	0.4	0.3
SD	0.7	0.6	0.5
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.56	0.20	0.18

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	15	16	11
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.56	0.20	0.18
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.56* (0.32, 0.95)	0.20 (0.12, 0.33)	0.18 (0.10, 0.34)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.36	0.33
Two-Sided 95% Wald CI [c] P-value [d]		(0.17, 0.77) 0.0045	(0.14, 0.78) 0.0060
Negative Binomial Dispersion Parameter (95% CI)		0.8873 (0.2614, 3.0111)	1.4163 (0.4589, 4.3712)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		2.94 (0.56, 15.49) 0.2040	4.10 (0.50, 33.25) 0.1868

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	3 (33.3)	3 (33.3)	1 (11.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	3 (100)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (33.3)	3 (100)	1 (100)
Bleeds Per Subject			
Mean	1.1	0.4	0.2
SD	1.8	0.7	0.7
SE	0.6	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	2.0	1.0	0.0
P90	5.0	2.0	2.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	1.84	0.24	0.15

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	10	4	2
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	1.84	0.24	0.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.94* (0.69, 5.51)	0.24 (0.09, 0.65)	0.16 (0.02, 1.00)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.12	0.08
Two-Sided 95% Wald CI [c] P-value [d]		(0.04, 0.39) 0.0002	(0.01, 0.81) 0.0162

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	11 (33.3)	11 (33.3)	7 (21.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	8 (72.7)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (36.4)	11 (100)	7 (100)
Bleeds Per Subject			
Mean	0.5	0.5	0.3
SD	1.1	0.7	0.6
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.89	0.24	0.21

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	18	15	10
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.89	0.24	0.21
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.90* (0.45, 1.78)	0.24 (0.14, 0.40)	0.21 (0.10, 0.42)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.23
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.59) 0.0007	(0.08, 0.67) 0.0036
Negative Binomial Dispersion Parameter (95% CI)		1.0968 (0.3620, 3.3232)	1.7400 (0.6217, 4.8699)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		1.02 (0.21, 4.95) 0.9812	1.09 (0.16, 7.19) 0.9309

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	4 (21.1)	5 (26.3)	3 (15.8)
Number of subjects with Bleeds Treated With Factor IX, n (%)	4 (100)	1 (20.0)	1 (33.3)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	4 (80.0)	2 (66.7)
Bleeds Per Subject			
Mean	0.4	0.3	0.2
SD	0.8	0.5	0.4
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 3	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.59	0.15	0.11

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	7	5	3
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.59	0.15	0.11
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.59* (0.23, 1.53)	0.15 (0.07, 0.33)	0.12 (0.04, 0.37)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.21
Two-Sided 95% Wald CI [c] P-value [d]		(0.07, 0.90) 0.0170	(0.05, 0.87) 0.0159

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	8 (25.8)	8 (25.8)	5 (16.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	7 (87.5)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (12.5)	8 (100)	5 (100)
Bleeds Per Subject			
Mean	0.4	0.4	0.2
SD	0.8	0.7	0.6
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.62	0.19	0.16

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	12	11	7
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.62	0.19	0.16
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.61* (0.31, 1.19)	0.19 (0.10, 0.37)	0.16 (0.07, 0.39)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.32	0.27
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.86) 0.0118	(0.08, 0.85) 0.0125
Negative Binomial Dispersion Parameter (95% CI)		1.1075 (0.3684, 3.3294)	1.7498 (0.6264, 4.8878)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		1.46 (0.35, 6.19) 0.6054	1.43 (0.26, 7.86) 0.6782

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	7 (33.3)	8 (38.1)	5 (23.8)
Number of subjects with Bleeds Treated With Factor IX, n (%)	5 (71.4)	1 (12.5)	1 (20.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (42.9)	7 (87.5)	4 (80.0)
Bleeds Per Subject			
Mean	0.6	0.4	0.3
SD	1.2	0.6	0.6
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.03	0.23	0.20

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	13	9	6
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.03	0.23	0.20
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.05* (0.44, 2.51)	0.23 (0.13, 0.41)	0.20 (0.09, 0.45)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.19
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.53) 0.0004	(0.05, 0.69) 0.0059

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	8 (29.6)	9 (33.3)	5 (18.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	8 (100)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (12.5)	9 (100)	5 (100)
Bleeds Per Subject			
Mean	0.6	0.4	0.3
SD	1.2	0.7	0.6
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 5	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.04	0.23	0.18

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	17	12	7
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.04	0.23	0.18
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.07* (0.51, 2.27)	0.23 (0.13, 0.42)	0.18 (0.08, 0.41)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.16
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.52) 0.0003	(0.05, 0.55) 0.0018
Negative Binomial Dispersion Parameter (95% CI)		1.7237 (0.5926, 5.0140)	2.6172 (0.9150, 7.4866)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		1.88 (0.12, 28.57) 0.6482	1.05 (0.06, 19.37) 0.9755

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	2 (18.2)	1 (9.1)	1 (9.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.3	0.1	0.1
SD	0.6	0.3	0.3
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	0.0	0.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.46	0.05	0.06

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Table 25.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	3	1	1
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.46	0.05	0.06
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.43* (0.13, 1.50)	0.05 (0.01, 0.34)	0.07 (0.01, 0.45)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.12	0.15
Two-Sided 95% Wald CI [c] P-value [d]		(0.01, 1.35) 0.0428	(0.01, 1.73) 0.0642

Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

3. Annualisierte Blutungsrate – Blutungsschwere mild – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
* For Comparison with Post-Treatment Month 7-24.
** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.

- [a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
- [b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
- [c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
- [d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
- [e] Two-sided P-value.

Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	15 (37.5)	6 (15.0)	4 (10.0)
Number of subjects with Bleeds Treated With Factor IX, n (%)	13 (86.7)	3 (50.0)	1 (25.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (26.7)	4 (66.7)	3 (75.0)
Bleeds Per Subject			
Mean	0.7	0.3	0.2
SD	1.1	1.0	0.6
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.0	0.5
Minimum, Maximum	0, 5	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	1.05	0.17	0.12

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	26	13	7
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	1.05	0.17	0.12
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.05* (0.62, 1.77)	0.18 (0.07, 0.44)	0.12 (0.04, 0.35)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.17	0.12
Two-Sided 95% Wald CI [c] P-value [d]		(0.08, 0.38) <0.0001	(0.05, 0.30) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		2.0211 (0.9430, 4.3318)	1.7046 (0.7103, 4.0907)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.12 (0.19, 6.42) 0.9006	0.72 (0.12, 4.28) 0.7184

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	5 (41.7)	5 (41.7)	4 (33.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	5 (100)	5 (100)	4 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (20.0)	0	0
Bleeds Per Subject			
Mean	1.2	0.5	0.4
SD	2.0	0.7	0.7
SE	0.6	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	2.0	1.0	1.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 7	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	1.95	0.27	0.29

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	14	6	5
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	1.95	0.27	0.29
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.80* (0.78, 4.16)	0.27 (0.13, 0.57)	0.29 (0.12, 0.71)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.15	0.16
Two-Sided 95% Wald CI [c] P-value [d]		(0.04, 0.56) 0.0023	(0.04, 0.69) 0.0067

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	15 (45.5)	6 (18.2)	4 (12.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	14 (93.3)	3 (50.0)	2 (50.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (20.0)	3 (50.0)	2 (50.0)
Bleeds Per Subject			
Mean	1.0	0.2	0.1
SD	1.6	0.5	0.3
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 7	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	1.55	0.11	0.08

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	32	7	4
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	1.55	0.11	0.08
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.51* (0.90, 2.52)	0.11 (0.05, 0.25)	0.09 (0.03, 0.21)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.08	0.06
Two-Sided 95% Wald CI [c] P-value [d]		(0.03, 0.18) <0.0001	(0.02, 0.16) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.7916 (0.8176, 3.9262)	1.5679 (0.6431, 3.8229)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.16 (0.03, 0.78) 0.0240	0.14 (0.02, 0.79) 0.0263

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	5 (26.3)	5 (26.3)	4 (21.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	4 (80.0)	5 (100)	3 (75.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (40.0)	1 (20.0)	1 (25.0)
Bleeds Per Subject			
Mean	0.4	0.6	0.4
SD	0.8	1.3	0.9
SE	0.2	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	2.0	3.0	2.0
Minimum, Maximum	0, 3	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.70	0.34	0.29

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	8	12	8
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.70	0.34	0.29
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.72* (0.30, 1.73)	0.35 (0.14, 0.89)	0.30 (0.12, 0.76)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.49	0.41
Two-Sided 95% Wald CI [c] P-value [d]		(0.26, 0.92) 0.0130	(0.19, 0.88) 0.0109

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	20 (51.3)	9 (23.1)	6 (15.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	18 (90.0)	7 (77.8)	4 (66.7)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	5 (25.0)	3 (33.3)	2 (33.3)
Bleeds Per Subject			
Mean	1.0	0.4	0.3
SD	1.5	1.0	0.7
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	0.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 7	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.66	0.23	0.18

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	40	17	10
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.66	0.23	0.18

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	2 (15.4)	2 (15.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	0	1 (50.0)	1 (50.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	1 (50.0)	1 (50.0)
Bleeds Per Subject			
Mean	0.0	0.2	0.2
SD	0.0	0.4	0.4
SE	0.0	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 0	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.08	0.10

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	2	2
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.08	0.10

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	15 (34.9)	7 (16.3)	5 (11.6)
Number of subjects with Bleeds Treated With Factor IX, n (%)	13 (86.7)	5 (71.4)	4 (80.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (26.7)	2 (28.6)	1 (20.0)
Bleeds Per Subject			
Mean	0.7	0.2	0.2
SD	1.4	0.6	0.5
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 7	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.16	0.12	0.11

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	31	10	7
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.16	0.12	0.11
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.12* (0.64, 1.95)	0.13 (0.06, 0.28)	0.11 (0.05, 0.28)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.11	0.10
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.28) <0.0001	(0.04, 0.28) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.7766 (0.8111, 3.8912)	1.7082 (0.7258, 4.0205)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		0.37 (0.06, 2.22) 0.2780	0.46 (0.07, 3.10) 0.4251

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	5 (55.6)	4 (44.4)	3 (33.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	5 (100)	3 (75.0)	1 (33.3)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (20.0)	2 (50.0)	2 (66.7)
Bleeds Per Subject			
Mean	1.0	1.0	0.6
SD	1.1	1.7	1.0
SE	0.4	0.6	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	5.0	3.0
Minimum, Maximum	0, 3	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	1.66	0.53	0.39

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	9	9	5
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	1.66	0.53	0.39
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.75* (0.86, 3.57)	0.54 (0.19, 1.49)	0.39 (0.13, 1.19)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.31	0.22
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.69) 0.0022	(0.08, 0.61) 0.0018

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	13 (39.4)	6 (18.2)	5 (15.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	12 (92.3)	4 (66.7)	2 (40.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (23.1)	3 (50.0)	3 (60.0)
Bleeds Per Subject			
Mean	0.7	0.4	0.2
SD	1.1	1.0	0.7
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 5	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.14	0.19	0.17

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	23	12	8
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.14	0.19	0.17
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.13* (0.65, 1.96)	0.19 (0.08, 0.49)	0.17 (0.07, 0.42)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.17	0.15
Two-Sided 95% Wald CI [c] P-value [d]		(0.07, 0.43) <0.0001	(0.06, 0.40) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		2.1278 (1.0124, 4.4719)	1.8747 (0.8082, 4.3487)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		1.14 (0.22, 5.75) 0.8772	1.35 (0.24, 7.71) 0.7375

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	7 (36.8)	5 (26.3)	3 (15.8)
Number of subjects with Bleeds Treated With Factor IX, n (%)	6 (85.7)	4 (80.0)	3 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (28.6)	1 (20.0)	0
Bleeds Per Subject			
Mean	0.9	0.4	0.2
SD	1.7	0.8	0.5
SE	0.4	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	3.0	1.0	1.0
Minimum, Maximum	0, 7	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.43	0.20	0.15

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	17	7	4
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.43	0.20	0.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.39* (0.65, 2.99)	0.21 (0.08, 0.53)	0.15 (0.05, 0.47)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.15	0.11
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.44) 0.0003	(0.03, 0.38) 0.0002

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	11 (35.5)	6 (19.4)	4 (12.9)
Number of subjects with Bleeds Treated With Factor IX, n (%)	11 (100)	3 (50.0)	2 (50.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (9.1)	3 (50.0)	2 (50.0)
Bleeds Per Subject			
Mean	0.8	0.3	0.2
SD	1.5	0.7	0.5
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 7	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.29	0.16	0.11

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	25	9	5
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.29	0.16	0.11
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.25* (0.68, 2.28)	0.16 (0.07, 0.37)	0.11 (0.04, 0.31)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.13	0.09
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.29) <0.0001	(0.03, 0.24) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		2.1025 (0.9996, 4.4222)	1.8385 (0.7925, 4.2652)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		0.58 (0.12, 2.83) 0.5005	0.47 (0.09, 2.55) 0.3805

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	9 (42.9)	5 (23.8)	4 (19.0)
Number of subjects with Bleeds Treated With Factor IX, n (%)	7 (77.8)	5 (100)	3 (75.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (44.4)	1 (20.0)	1 (25.0)
Bleeds Per Subject			
Mean	0.7	0.5	0.3
SD	1.2	1.2	0.8
SE	0.3	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 5	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.19	0.25	0.23

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	15	10	7
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.19	0.25	0.23
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.19* (0.60, 2.36)	0.26 (0.09, 0.72)	0.23 (0.09, 0.63)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.20
Two-Sided 95% Wald CI [c] P-value [d]		(0.07, 0.68) 0.0043	(0.06, 0.63) 0.0031

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	10 (37.0)	7 (25.9)	5 (18.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	9 (90.0)	5 (71.4)	3 (60.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	4 (40.0)	3 (42.9)	2 (40.0)
Bleeds Per Subject			
Mean	0.7	0.4	0.3
SD	1.1	1.1	0.7
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 5	0, 5	0, 3
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.10	0.23	0.20

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	18	12	8
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.10	0.23	0.20
Adjusted Annualized Bleeding Rate [b]		0.24	
Adjusted Rate (95% CI) [b]		(0.10, 0.57)	
Rate Ratio (Post-Treatment/Lead-In) [b]		0.21	
Two-Sided 95% Wald CI [c]		(0.08, 0.58)	
P-value [d]		0.0013	
Negative Binomial Dispersion Parameter (95% CI)		2.0633 (0.8595, 4.9531)	
Ratio (<S2 vs. >=S2) of rate ratio (95% CI)		6.29 (0.47, 84.98)	
P-value [e]		0.1661	

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Table 25.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	4 (36.4)	1 (9.1)	0
Number of subjects with Bleeds Treated With Factor IX, n (%)	4 (100)	1 (100)	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	1.0	0.1	0.0
SD	2.1	0.3	0.0
SE	0.6	0.1	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	0.0	0.0
Minimum, Maximum	0, 7	0, 1	0, 0
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	1.70	0.05	0.0

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Table 25.2.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Mild Bleeding by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	11	1	0
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	1.70	0.05	0.0
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]		0.05 (0.01, 0.34)	
Rate Ratio (Post-Treatment/Lead-In) [b]		0.03	
Two-Sided 95% Wald CI [c] P-value [d]		(0.00, 0.30) 0.0012	

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

4. Annualisierte Blutungsrate – Blutungsschwere moderat – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.

* For Comparison with Post-Treatment Month 7-24.

** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.

[a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).

[b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.

[c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.

[d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.

[e] Two-sided P-value.

Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	15 (37.5)	12 (30.0)	8 (20.0)
Number of subjects with Bleeds Treated With Factor IX, n (%)	14 (93.3)	8 (66.7)	6 (75.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (20.0)	6 (50.0)	4 (50.0)
Bleeds Per Subject			
Mean	0.9	0.7	0.5
SD	1.4	1.5	1.4
SE	0.2	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	3.0	2.0	1.5
Minimum, Maximum	0, 5	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	1.37	0.36	0.35

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	34	27	20
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	1.37	0.36	0.35
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.35* (0.81, 2.26)	0.38 (0.19, 0.77)	0.37 (0.16, 0.87)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.28	0.27
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.55) 0.0001	(0.13, 0.60) 0.0006
Negative Binomial Dispersion Parameter (95% CI)		2.0003 (1.0859, 3.6844)	2.3247 (1.2195, 4.4313)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.07 (0.21, 5.41) 0.9375	1.34 (0.22, 8.05) 0.7478

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	8 (66.7)	5 (41.7)	4 (33.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	8 (100)	4 (80.0)	3 (75.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	2 (40.0)	2 (50.0)
Bleeds Per Subject			
Mean	1.0	0.8	0.5
SD	1.0	1.2	0.8
SE	0.3	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	1.5	1.5	1.0
P90	2.0	3.0	2.0
Minimum, Maximum	0, 3	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	1.67	0.44	0.35

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	12	10	6
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	1.67	0.44	0.35
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.74* (1.02, 2.99)	0.45 (0.21, 0.98)	0.35 (0.15, 0.84)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.20
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.48) <0.0001	(0.12, 0.34) <0.0001

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	15 (45.5)	7 (21.2)	5 (15.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	15 (100)	5 (71.4)	4 (80.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (6.7)	3 (42.9)	2 (40.0)
Bleeds Per Subject			
Mean	1.0	0.3	0.2
SD	1.5	0.7	0.5
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	3.0	1.0	1.0
Minimum, Maximum	0, 5	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	1.59	0.18	0.15

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	33	11	7
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	1.59	0.18	0.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.53* (0.89, 2.63)	0.18 (0.09, 0.38)	0.15 (0.06, 0.35)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.11	0.10
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.21) <0.0001	(0.05, 0.20) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.5763 (0.8107, 3.0647)	1.8630 (0.9362, 3.7070)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.17 (0.04, 0.68) 0.0119	0.15 (0.03, 0.71) 0.0168

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	8 (42.1)	10 (52.6)	7 (36.8)
Number of subjects with Bleeds Treated With Factor IX, n (%)	7 (87.5)	7 (70.0)	5 (71.4)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (25.0)	5 (50.0)	4 (57.1)
Bleeds Per Subject			
Mean	0.7	1.4	1.0
SD	1.0	2.1	1.9
SE	0.2	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	1.0	0.0
P75	1.0	2.0	1.0
P90	3.0	6.0	5.0
Minimum, Maximum	0, 3	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	1.15	0.73	0.69

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	13	26	19
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	1.15	0.73	0.69
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.15* (0.61, 2.18)	0.77 (0.39, 1.52)	0.72 (0.31, 1.70)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.67	0.63
Two-Sided 95% Wald CI [c] P-value [d]		(0.43, 1.03) 0.0352	(0.39, 1.03) 0.0327

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	23 (59.0)	14 (35.9)	10 (25.6)
Number of subjects with Bleeds Treated With Factor IX, n (%)	22 (95.7)	11 (78.6)	8 (80.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (13.0)	6 (42.9)	5 (50.0)
Bleeds Per Subject			
Mean	1.2	0.8	0.6
SD	1.4	1.6	1.4
SE	0.2	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	3.0	2.0
Minimum, Maximum	0, 5	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.91	0.45	0.41

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	46	33	23
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.91	0.45	0.41

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	3 (23.1)	2 (15.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	0	1 (33.3)	1 (50.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	2 (66.7)	1 (50.0)
Bleeds Per Subject			
Mean	0.0	0.3	0.2
SD	0.0	0.6	0.6
SE	0.0	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 0	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.16	0.16

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	4	3
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.16	0.16

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	16 (37.2)	12 (27.9)	9 (20.9)
Number of subjects with Bleeds Treated With Factor IX, n (%)	15 (93.8)	9 (75.0)	7 (77.8)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (12.5)	4 (33.3)	3 (33.3)
Bleeds Per Subject			
Mean	0.7	0.5	0.3
SD	1.1	1.2	0.9
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	2.0	2.0	1.0
Minimum, Maximum	0, 5	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.05	0.29	0.24

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	28	23	15
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.05	0.29	0.24
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.03* (0.63, 1.68)	0.30 (0.15, 0.58)	0.26 (0.12, 0.56)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.29	0.25
Two-Sided 95% Wald CI [c] P-value [d]		(0.15, 0.56) 0.0001	(0.12, 0.53) 0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.5340 (0.7688, 3.0612)	1.7114 (0.8183, 3.5794)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		1.17 (0.25, 5.48) 0.8414	0.98 (0.19, 5.11) 0.9788

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	7 (77.8)	5 (55.6)	3 (33.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	7 (100)	3 (60.0)	2 (66.7)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (14.3)	4 (80.0)	3 (100)
Bleeds Per Subject			
Mean	2.0	1.6	1.2
SD	1.7	2.3	2.3
SE	0.6	0.8	0.8
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	2.0	1.0	0.0
P75	3.0	2.0	2.0
P90	5.0	7.0	7.0
Minimum, Maximum	0, 5	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	3.32	0.83	0.85

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	18	14	11
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	3.32	0.83	0.85
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.43* (1.98, 5.93)	0.84 (0.34, 2.08)	0.86 (0.27, 2.76)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.24	0.25
Two-Sided 95% Wald CI [c] P-value [d]		(0.11, 0.57) 0.0005	(0.09, 0.70) 0.0043

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	10 (30.3)	8 (24.2)	5 (15.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	10 (100)	5 (62.5)	3 (60.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (20.0)	4 (50.0)	3 (60.0)
Bleeds Per Subject			
Mean	0.7	0.5	0.4
SD	1.4	1.3	1.3
SE	0.2	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	3.0	1.0	1.0
Minimum, Maximum	0, 5	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.14	0.25	0.27

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	23	16	13
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.14	0.25	0.27
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.15* (0.59, 2.22)	0.26 (0.11, 0.63)	0.27 (0.09, 0.82)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.24
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.52) 0.0002	(0.09, 0.63) 0.0019
Negative Binomial Dispersion Parameter (95% CI)		1.7656 (0.9333, 3.3404)	2.1647 (1.1196, 4.1853)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.69 (0.17, 2.74) 0.5993	0.88 (0.19, 4.03) 0.8672

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	13 (68.4)	9 (47.4)	7 (36.8)
Number of subjects with Bleeds Treated With Factor IX, n (%)	12 (92.3)	7 (77.8)	6 (85.7)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (7.7)	4 (44.4)	3 (42.9)
Bleeds Per Subject			
Mean	1.2	1.1	0.7
SD	1.1	1.6	1.2
SE	0.3	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	2.0	1.0
P90	3.0	3.0	2.0
Minimum, Maximum	0, 3	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.94	0.61	0.50

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	23	21	13
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.94	0.61	0.50
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.96* (1.28, 3.00)	0.65 (0.33, 1.28)	0.54 (0.24, 1.24)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.33	0.28
Two-Sided 95% Wald CI [c] P-value [d]		(0.17, 0.62) 0.0003	(0.13, 0.59) 0.0004

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	13 (41.9)	8 (25.8)	6 (19.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	13 (100)	6 (75.0)	5 (83.3)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	3 (37.5)	2 (33.3)
Bleeds Per Subject			
Mean	0.8	0.5	0.3
SD	1.2	0.9	0.6
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 5	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.29	0.24	0.18

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	25	14	8
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.29	0.24	0.18
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.29* (0.71, 2.33)	0.25 (0.13, 0.49)	0.18 (0.08, 0.40)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.19	0.14
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.36) <0.0001	(0.08, 0.27) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.8358 (0.9769, 3.4497)	2.0463 (1.0463, 4.0020)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		0.49 (0.12, 1.97) 0.3175	0.37 (0.08, 1.68) 0.1984

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	10 (47.6)	9 (42.9)	6 (28.6)
Number of subjects with Bleeds Treated With Factor IX, n (%)	9 (90.0)	6 (66.7)	4 (66.7)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	3 (30.0)	5 (55.6)	4 (66.7)
Bleeds Per Subject			
Mean	1.0	1.1	0.9
SD	1.4	2.0	1.9
SE	0.3	0.4	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	1.0
P90	3.0	3.0	2.0
Minimum, Maximum	0, 5	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.66	0.58	0.59

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	21	23	18
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.66	0.58	0.59
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.61* (0.92, 2.80)	0.61 (0.28, 1.33)	0.62 (0.25, 1.54)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.38	0.39
Two-Sided 95% Wald CI [c] P-value [d]		(0.19, 0.76) 0.0029	(0.18, 0.85) 0.0088

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	9 (33.3)	6 (22.2)	2 (7.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	9 (100)	4 (66.7)	1 (50.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (11.1)	2 (33.3)	1 (50.0)
Bleeds Per Subject			
Mean	0.7	0.5	0.3
SD	1.1	1.4	1.4
SE	0.2	0.3	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	3.0	1.0	0.0
Minimum, Maximum	0, 3	0, 7	0, 7
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.10	0.25	0.23

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	18	13	9
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.10	0.25	0.23
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.14* (0.61, 2.13)	0.26 (0.09, 0.75)	0.23 (0.05, 1.07)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.23	0.20
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.51) 0.0002	(0.06, 0.73) 0.0075
Negative Binomial Dispersion Parameter (95% CI)		2.2793 (1.0861, 4.7831)	2.8971 (1.3398, 6.2645)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.50 (0.08, 3.28) 0.4738	0.46 (0.06, 3.68) 0.4623

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Table 25.2.3.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	6 (54.5)	5 (45.5)	5 (45.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	5 (83.3)	3 (60.0)	3 (60.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (16.7)	3 (60.0)	3 (60.0)
Bleeds Per Subject			
Mean	0.8	1.1	0.8
SD	1.0	1.9	1.5
SE	0.3	0.6	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	1.0	1.0	1.0
P90	2.0	3.0	1.0
Minimum, Maximum	0, 3	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	1.39	0.58	0.57

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Table 25.2.3.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Moderate Bleeding by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	9	12	9
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	1.39	0.58	0.57
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.41* (0.74, 2.68)	0.63 (0.22, 1.80)	0.63 (0.21, 1.88)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.45	0.45
Two-Sided 95% Wald CI [c] P-value [d]		(0.22, 0.94) 0.0166	(0.21, 0.94) 0.0175

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Table 25.2.4.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

5. Annualisierte Blutungsrate – Blutungsschwere schwer – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
* For Comparison with Post-Treatment Month 7-24.
** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.
[a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
[b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
[c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
[d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
[e] Two-sided P-value.

Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	7 (17.5)	7 (17.5)	7 (17.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	7 (100)	6 (85.7)	6 (85.7)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	1 (14.3)	1 (14.3)
Bleeds Per Subject			
Mean	0.2	0.3	0.2
SD	0.5	0.6	0.5
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	1.5	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.32	0.15	0.16

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	8	11	9
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.32	0.15	0.16
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.32* (0.16, 0.66)	0.15 (0.07, 0.31)	0.16 (0.08, 0.33)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.47	0.50
Two-Sided 95% Wald CI [c] P-value [d]		(0.17, 1.30) 0.0721	(0.17, 1.43) 0.0977
Negative Binomial Dispersion Parameter (95% CI)		1.6628 (0.4786, 5.7768)	1.3009 (0.2847, 5.9446)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.27 (0.20, 8.05) 0.8001	1.47 (0.23, 9.29) 0.6849

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	3 (25.0)	5 (41.7)	4 (33.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	3 (100)	5 (100)	4 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (66.7)	0	0
Bleeds Per Subject			
Mean	0.5	0.6	0.4
SD	1.0	0.8	0.7
SE	0.3	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.5	1.0	1.0
P90	2.0	2.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.84	0.31	0.29

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	6	7	5
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.84	0.31	0.29
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.86* (0.29, 2.55)	0.32 (0.15, 0.67)	0.29 (0.12, 0.70)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.37	0.34
Two-Sided 95% Wald CI [c] P-value [d]		(0.13, 0.99) 0.0242	(0.11, 1.03) 0.0287

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	6 (18.2)	6 (18.2)	5 (15.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	6 (100)	6 (100)	5 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.2	0.2	0.2
SD	0.5	0.6	0.5
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.34	0.13	0.13

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	7	8	6
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.34	0.13	0.13
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.34* (0.16, 0.74)	0.13 (0.06, 0.29)	0.13 (0.05, 0.30)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.38	0.37
Two-Sided 95% Wald CI [c] P-value [d]		(0.13, 1.10) 0.0374	(0.12, 1.21) 0.0500
Negative Binomial Dispersion Parameter (95% CI)		1.7499 (0.5190, 5.9005)	1.3399 (0.3005, 5.9744)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.82 (0.14, 4.75) 0.8243	0.79 (0.14, 4.55) 0.7878

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	4 (21.1)	6 (31.6)	6 (31.6)
Number of subjects with Bleeds Treated With Factor IX, n (%)	4 (100)	5 (83.3)	5 (83.3)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (50.0)	1 (16.7)	1 (16.7)
Bleeds Per Subject			
Mean	0.4	0.5	0.4
SD	0.8	0.8	0.7
SE	0.2	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	2.0	2.0	2.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.62	0.28	0.29

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	7	10	8
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.62	0.28	0.29
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.63* (0.23, 1.69)	0.29 (0.14, 0.60)	0.30 (0.14, 0.63)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.47	0.48
Two-Sided 95% Wald CI [c] P-value [d]		(0.16, 1.35) 0.0805	(0.16, 1.47) 0.0993

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	10 (25.6)	10 (25.6)	9 (23.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	10 (100)	9 (90.0)	8 (88.9)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (20.0)	1 (10.0)	1 (11.1)
Bleeds Per Subject			
Mean	0.4	0.4	0.3
SD	0.7	0.7	0.6
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	0.58	0.21	0.22

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	14	15	12
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	0.58	0.21	0.22

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	2 (15.4)	2 (15.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	0	2 (100)	2 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.2	0.2
SD	0.0	0.6	0.4
SE	0.0	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 0	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.12	0.10

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	3	2
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.12	0.10

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	8 (18.6)	8 (18.6)	7 (16.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	8 (100)	8 (100)	7 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (12.5)	0	0
Bleeds Per Subject			
Mean	0.2	0.3	0.2
SD	0.5	0.7	0.5
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.38	0.16	0.15

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	10	13	9
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.38	0.16	0.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.38* (0.19, 0.75)	0.16 (0.08, 0.32)	0.15 (0.07, 0.31)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.43	0.39
Two-Sided 95% Wald CI [c] P-value [d]		(0.19, 1.01) 0.0270	(0.15, 1.02) 0.0270
Negative Binomial Dispersion Parameter (95% CI)		1.8690 (0.5704, 6.1236)	1.2897 (0.2768, 6.0100)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		1.07 (0.13, 8.63) 0.9475	0.74 (0.10, 5.28) 0.7601

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	2 (22.2)	4 (44.4)	4 (44.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	3 (75.0)	3 (75.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (50.0)	1 (25.0)	1 (25.0)
Bleeds Per Subject			
Mean	0.4	0.6	0.6
SD	1.0	0.7	0.7
SE	0.3	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	3.0	2.0	2.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	0.74	0.30	0.39

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	4	5	5
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	0.74	0.30	0.39
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.75* (0.19, 3.01)	0.30 (0.13, 0.68)	0.39 (0.17, 0.89)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.40	0.53
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 1.82) 0.1190	(0.12, 2.41) 0.2046

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	8 (24.2)	5 (15.2)	4 (12.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	8 (100)	4 (80.0)	3 (75.0)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (12.5)	1 (20.0)	1 (25.0)
Bleeds Per Subject			
Mean	0.3	0.2	0.2
SD	0.6	0.5	0.4
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.50	0.11	0.10

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	10	7	5
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.50	0.11	0.10
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.50* (0.26, 0.97)	0.11 (0.05, 0.27)	0.10 (0.04, 0.28)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.21
Two-Sided 95% Wald CI [c] P-value [d]		(0.08, 0.59) 0.0012	(0.07, 0.64) 0.0033
Negative Binomial Dispersion Parameter (95% CI)		1.6248 (0.4580, 5.7640)	1.2155 (0.2541, 5.8141)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.23 (0.04, 1.43) 0.1154	0.20 (0.03, 1.25) 0.0847

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	2 (10.5)	7 (36.8)	7 (36.8)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	7 (100)	7 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (50.0)	0	0
Bleeds Per Subject			
Mean	0.2	0.6	0.5
SD	0.7	0.8	0.7
SE	0.2	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	1.0	2.0	2.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.34	0.32	0.34

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	4	11	9
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.34	0.32	0.34
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.34* (0.08, 1.50)	0.33 (0.17, 0.62)	0.35 (0.18, 0.68)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.96	1.03
Two-Sided 95% Wald CI [c] P-value [d]		(0.22, 4.21) 0.4789	(0.23, 4.57) 0.5141

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	3 (9.7)	6 (19.4)	5 (16.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	3 (100)	6 (100)	5 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.1	0.3	0.2
SD	0.4	0.6	0.5
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.21	0.14	0.14

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	4	8	6
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.21	0.14	0.14
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.21* (0.07, 0.65)	0.14 (0.06, 0.30)	0.14 (0.06, 0.32)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.67	0.66
Two-Sided 95% Wald CI [c] P-value [d]		(0.19, 2.40) 0.2690	(0.16, 2.67) 0.2795
Negative Binomial Dispersion Parameter (95% CI)		1.5266 (0.4242, 5.4942)	1.0872 (0.2088, 5.6621)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		2.08 (0.35, 12.29) 0.4188	1.98 (0.34, 11.66) 0.4493

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	7 (33.3)	6 (28.6)	6 (28.6)
Number of subjects with Bleeds Treated With Factor IX, n (%)	7 (100)	5 (83.3)	5 (83.3)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	2 (28.6)	1 (16.7)	1 (16.7)
Bleeds Per Subject			
Mean	0.5	0.5	0.4
SD	0.8	0.8	0.7
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	1.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 3	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	0.79	0.25	0.26

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	10	10	8
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	0.79	0.25	0.26
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.80* (0.39, 1.65)	0.26 (0.13, 0.54)	0.27 (0.13, 0.57)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.33	0.33
Two-Sided 95% Wald CI [c] P-value [d]		(0.13, 0.83) 0.0096	(0.12, 0.90) 0.0151

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	6 (22.2)	6 (22.2)	6 (22.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	6 (100)	5 (83.3)	5 (83.3)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	1 (16.7)	1 (16.7)	1 (16.7)
Bleeds Per Subject			
Mean	0.3	0.4	0.3
SD	0.6	0.8	0.6
SE	0.1	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	0.49	0.21	0.20

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	8	11	8
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	0.49	0.21	0.20
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.49* (0.23, 1.07)	0.22 (0.11, 0.46)	0.21 (0.10, 0.44)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.44	0.42
Two-Sided 95% Wald CI [c] P-value [d]		(0.18, 1.11) 0.0418	(0.15, 1.17) 0.0486
Negative Binomial Dispersion Parameter (95% CI)		1.8330 (0.4716, 7.1240)	1.2998 (0.2090, 8.0826)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.69 (0.07, 7.26) 0.7581	0.66 (0.06, 6.84) 0.7289

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Table 25.2.4.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	2 (18.2)	3 (27.3)	2 (18.2)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	3 (100)	2 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.2	0.4	0.3
SD	0.4	0.7	0.6
SE	0.1	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 1	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.31	0.19	0.19

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Table 25.2.4.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Severe Bleeding by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	2	4	3
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.31	0.19	0.19
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.32* (0.09, 1.15)	0.20 (0.07, 0.61)	0.20 (0.05, 0.79)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.64	0.63
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 4.37) 0.3259	(0.08, 4.97) 0.3294

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Table 25.2.5.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

6. Annualisierte Blutungsrate – Blutungsschwere sehr schwer – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
* For Comparison with Post-Treatment Month 7-24.
** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.
[a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
[b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
[c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
[d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
[e] Two-sided P-value.

Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	1 (2.5)	2 (5.0)	2 (5.0)
Number of subjects with Bleeds Treated With Factor IX, n (%)	1 (100)	2 (100)	2 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.1	0.1
SD	0.2	0.2	0.2
SE	0.0	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 1	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.04	0.03	0.03

Footnotes are on the first page.

Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	1	2	2
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.04	0.03	0.03

Footnotes are on the first page.

Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	2 (16.7)	0	0
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.3	0.0	0.0
SD	0.6	0.0	0.0
SE	0.2	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	0.0	0.0
Minimum, Maximum	0, 2	0, 0	0, 0
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.42	0.0	0.0

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	3	0	0
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.42	0.0	0.0

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	1 (3.0)	0	0
Number of subjects with Bleeds Treated With Factor IX, n (%)	1 (100)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.0	0.0
SD	0.2	0.0	0.0
SE	0.0	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 1	0, 0	0, 0
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.05	0.0	0.0

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	1	0	0
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.05	0.0	0.0

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	2 (10.5)	2 (10.5)	2 (10.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	2 (100)	2 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.2	0.1	0.1
SD	0.5	0.3	0.3
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	1.0	1.0	1.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.26	0.06	0.07

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	3	2	2
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.26	0.06	0.07

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	3 (7.7)	1 (2.6)	1 (2.6)
Number of subjects with Bleeds Treated With Factor IX, n (%)	3 (100)	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.1	0.0	0.0
SD	0.4	0.2	0.2
SE	0.1	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	0.17	0.01	0.02

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	4	1	1
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	0.17	0.01	0.02

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	1 (7.7)	1 (7.7)
Number of subjects with Bleeds Treated With Factor IX, n (%)	0	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.1	0.1
SD	0.0	0.3	0.3
SE	0.0	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 0	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.04	0.05

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	1	1
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.04	0.05

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	2 (4.7)	1 (2.3)	1 (2.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.0	0.0
SD	0.2	0.2	0.2
SE	0.0	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 1	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.08	0.01	0.02

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	2	1	1
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.08	0.01	0.02

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	1 (11.1)	1 (11.1)	1 (11.1)
Number of subjects with Bleeds Treated With Factor IX, n (%)	1 (100)	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.2	0.1	0.1
SD	0.7	0.3	0.3
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	0.37	0.06	0.08

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	2	1	1
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	0.37	0.06	0.08

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	2 (6.1)	1 (3.0)	1 (3.0)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.1	0.0	0.0
SD	0.2	0.2	0.2
SE	0.0	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 1	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.10	0.02	0.02

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	2	1	1
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.10	0.02	0.02

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	1 (5.3)	1 (5.3)	1 (5.3)
Number of subjects with Bleeds Treated With Factor IX, n (%)	1 (100)	1 (100)	1 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.1	0.1	0.1
SD	0.5	0.2	0.2
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.17	0.03	0.04

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	2	1	1
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.17	0.03	0.04

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	1 (3.2)	0	0
Number of subjects with Bleeds Treated With Factor IX, n (%)	1 (100)	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.0	0.0
SD	0.2	0.0	0.0
SE	0.0	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 1	0, 0	0, 0
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.05	0.0	0.0

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	1	0	0
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.05	0.0	0.0

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	2 (9.5)	2 (9.5)	2 (9.5)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	2 (100)	2 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.1	0.1	0.1
SD	0.5	0.3	0.3
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 2	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	0.24	0.05	0.07

Footnotes are on the first page.

Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	3	2	2
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	0.24	0.05	0.07

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	2 (7.4)	2 (7.4)	2 (7.4)
Number of subjects with Bleeds Treated With Factor IX, n (%)	2 (100)	2 (100)	2 (100)
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.1	0.1	0.1
SD	0.3	0.3	0.3
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 1	0, 1	0, 1
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	0.12	0.04	0.05

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	2	2	2
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	0.12	0.04	0.05

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Table 25.2.5.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	0	0	0
Number of subjects with Bleeds Treated With Factor IX, n (%)	0	0	0
Number of subjects with Bleeds Not Treated With Factor IX, n (%)	0	0	0
Bleeds Per Subject			
Mean	0.0	0.0	0.0
SD	0.0	0.0	0.0
SE	0.0	0.0	0.0
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	0.0	0.0
Minimum, Maximum	0, 0	0, 0	0, 0
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.0	0.0	0.0

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Table 25.2.5.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Very Severe Bleeding by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	0	0	0
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.0	0.0	0.0

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

7. Annualisierte Blutungsrate – Mit FIX-Präparaten behandelte Blutungen – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.

* For Comparison with Post-Treatment Month 7-24.

** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.

[a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).

[b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.

[c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.

[d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.

[e] Two-sided P-value.

Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	25 (62.5)	12 (30.0)	11 (27.5)
Number of Bleeds, n	74	32	22
Bleeds Per Subject			
Mean	1.9	0.8	0.6
SD	2.0	1.8	1.3
SE	0.3	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.5	1.0	1.0
P90	4.5	2.5	2.0
Minimum, Maximum	0, 8	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	2.98	0.43	0.38

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	74	32	22
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	2.98	0.43	0.38
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.97* (2.11, 4.19)	0.45 (0.22, 0.93)	0.40 (0.19, 0.84)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.15	0.14
Two-Sided 95% Wald CI [c] P-value [d]		(0.08, 0.31) <0.0001	(0.06, 0.28) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2957 (0.7564, 2.2193)	1.0336 (0.5550, 1.9247)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		0.83 (0.24, 2.87) 0.7643	0.76 (0.23, 2.55) 0.6604

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	11 (91.7)	7 (58.3)	6 (50.0)
Number of Bleeds, n	37	20	15
Bleeds Per Subject			
Mean	3.1	1.7	1.3
SD	2.4	2.1	1.7
SE	0.7	0.6	0.5
P10	1.0	0.0	0.0
P25	1.5	0.0	0.0
Median	3.0	1.0	0.5
P75	3.5	3.0	2.5
P90	6.0	5.0	4.0
Minimum, Maximum	0, 9	0, 6	0, 4
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	5.15	0.89	0.87

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	37	20	15
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	5.15	0.89	0.87
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	5.02* (3.53, 7.13)	0.92 (0.45, 1.88)	0.89 (0.42, 1.87)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.18	0.18
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.36) <0.0001	(0.09, 0.36) <0.0001

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	25 (75.8)	9 (27.3)	8 (24.2)
Number of Bleeds, n	80	16	12
Bleeds Per Subject			
Mean	2.4	0.5	0.4
SD	2.3	1.0	0.8
SE	0.4	0.2	0.1
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	2.0	0.0	0.0
P75	4.0	1.0	0.0
P90	5.0	2.0	1.0
Minimum, Maximum	0, 9	0, 4	0, 4
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	3.86	0.26	0.25

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	80	16	12
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	3.86	0.26	0.25
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.79* (2.77, 5.19)	0.26 (0.13, 0.52)	0.26 (0.12, 0.56)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.07	0.07
Two-Sided 95% Wald CI [c] P-value [d]		(0.04, 0.13) <0.0001	(0.03, 0.14) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1214 (0.6429, 1.9558)	0.9647 (0.5185, 1.7948)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.18 (0.06, 0.54) 0.0023	0.20 (0.06, 0.61) 0.0049

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	11 (57.9)	10 (52.6)	9 (47.4)
Number of Bleeds, n	31	36	25
Bleeds Per Subject			
Mean	1.6	1.9	1.3
SD	1.9	2.7	1.9
SE	0.4	0.6	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	1.0	0.0
P75	3.0	3.0	2.0
P90	4.0	6.0	4.0
Minimum, Maximum	0, 6	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	2.73	1.02	0.91

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	31	36	25
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	2.73	1.02	0.91
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.77* (1.66, 4.64)	1.09 (0.56, 2.10)	0.96 (0.48, 1.90)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.39	0.34
Two-Sided 95% Wald CI [c] P-value [d]		(0.22, 0.69) 0.0006	(0.18, 0.64) 0.0004

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	36 (92.3)	15 (38.5)	13 (33.3)
Number of Bleeds, n	111	45	31
Bleeds Per Subject			
Mean	2.8	1.2	0.8
SD	2.0	2.1	1.6
SE	0.3	0.3	0.2
P10	1.0	0.0	0.0
P25	1.0	0.0	0.0
Median	3.0	0.0	0.0
P75	4.0	1.0	1.0
P90	5.0	5.0	4.0
Minimum, Maximum	0, 9	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	4.62	0.62	0.56

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	111	45	31
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	4.62	0.62	0.56

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	4 (30.8)	4 (30.8)
Number of Bleeds, n	0	7	6
Bleeds Per Subject			
Mean	0.0	0.5	0.5
SD	0.0	1.0	0.8
SE	0.0	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	0.0	2.0	2.0
Minimum, Maximum	0, 0	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.28	0.31

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	7	6
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.28	0.31

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	27 (62.8)	13 (30.2)	13 (30.2)
Number of Bleeds, n	75	40	29
Bleeds Per Subject			
Mean	1.7	0.9	0.7
SD	2.0	2.0	1.4
SE	0.3	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.0	1.0	1.0
P90	4.0	3.0	2.0
Minimum, Maximum	0, 9	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	2.82	0.50	0.47

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	75	40	29
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	2.82	0.50	0.47
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.75* (2.01, 3.76)	0.53 (0.28, 1.01)	0.49 (0.26, 0.94)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.19	0.18
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.36) <0.0001	(0.09, 0.34) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2580 (0.7271, 2.1763)	0.9886 (0.5193, 1.8821)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		1.83 (0.47, 7.21) 0.3862	1.95 (0.51, 7.43) 0.3301

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	9 (100)	6 (66.7)	4 (44.4)
Number of Bleeds, n	36	12	8
Bleeds Per Subject			
Mean	4.0	1.3	0.9
SD	2.1	1.6	1.4
SE	0.7	0.5	0.5
P10	1.0	0.0	0.0
P25	3.0	0.0	0.0
Median	4.0	1.0	0.0
P75	4.0	2.0	1.0
P90	8.0	5.0	4.0
Minimum, Maximum	1, 8	0, 5	0, 4
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	6.63	0.71	0.62

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	36	12	8
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	6.63	0.71	0.62
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	6.90* (4.82, 9.86)	0.72 (0.34, 1.51)	0.63 (0.24, 1.63)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.10	0.09
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.19) <0.0001	(0.04, 0.20) <0.0001

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	21 (63.6)	9 (27.3)	7 (21.2)
Number of Bleeds, n	62	18	12
Bleeds Per Subject			
Mean	1.9	0.5	0.4
SD	2.0	1.2	0.9
SE	0.4	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.0	1.0	0.0
P90	5.0	2.0	1.0
Minimum, Maximum	0, 8	0, 6	0, 4
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	3.07	0.28	0.25

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	62	18	12
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	3.07	0.28	0.25
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.10* (2.14, 4.49)	0.29 (0.14, 0.62)	0.25 (0.11, 0.56)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.09	0.08
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.19) <0.0001	(0.04, 0.18) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1671 (0.6735, 2.0224)	0.9558 (0.5139, 1.7776)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.37 (0.12, 1.10) 0.0744	0.33 (0.11, 1.00) 0.0499

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	15 (78.9)	10 (52.6)	10 (52.6)
Number of Bleeds, n	49	34	25
Bleeds Per Subject			
Mean	2.6	1.8	1.3
SD	2.3	2.6	1.9
SE	0.5	0.6	0.4
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	3.0	1.0	1.0
P75	4.0	3.0	2.0
P90	6.0	6.0	4.0
Minimum, Maximum	0, 9	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	4.14	0.99	0.95

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	49	34	25
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	4.14	0.99	0.95
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	4.08* (2.83, 5.88)	1.05 (0.55, 2.03)	1.01 (0.52, 1.95)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.25
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.49) <0.0001	(0.13, 0.48) <0.0001

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	23 (74.2)	9 (29.0)	8 (25.8)
Number of Bleeds, n	65	21	14
Bleeds Per Subject			
Mean	2.1	0.7	0.5
SD	2.2	1.4	1.0
SE	0.4	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.0	1.0	1.0
P90	4.0	2.0	1.0
Minimum, Maximum	0, 9	0, 6	0, 4
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	3.35	0.36	0.32

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	65	21	14
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	3.35	0.36	0.32
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.31* (2.29, 4.79)	0.38 (0.18, 0.78)	0.33 (0.16, 0.68)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.11	0.10
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.22) <0.0001	(0.05, 0.19) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.3277 (0.7847, 2.2465)	1.0835 (0.5962, 1.9693)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		0.49 (0.16, 1.51) 0.2147	0.45 (0.15, 1.38) 0.1632

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	13 (61.9)	10 (47.6)	9 (42.9)
Number of Bleeds, n	46	31	23
Bleeds Per Subject			
Mean	2.2	1.5	1.1
SD	2.1	2.4	1.8
SE	0.5	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	2.0	0.0	0.0
P75	4.0	2.0	1.0
P90	5.0	5.0	4.0
Minimum, Maximum	0, 6	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	3.64	0.78	0.75

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	46	31	23
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	3.64	0.78	0.75
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.62* (2.45, 5.35)	0.84 (0.40, 1.74)	0.79 (0.38, 1.66)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.23	0.22
Two-Sided 95% Wald CI [c] P-value [d]		(0.11, 0.48) <0.0001	(0.10, 0.47) <0.0001

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	19 (70.4)	9 (33.3)	7 (25.9)
Number of Bleeds, n	53	22	14
Bleeds Per Subject			
Mean	2.0	0.8	0.5
SD	1.7	1.5	1.1
SE	0.3	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	2.0	0.0	0.0
P75	4.0	1.0	1.0
P90	4.0	3.0	2.0
Minimum, Maximum	0, 5	0, 6	0, 4
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	3.23	0.43	0.36

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	53	22	14
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	3.23	0.43	0.36
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.30* (2.39, 4.56)	0.44 (0.22, 0.89)	0.36 (0.16, 0.81)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.13	0.11
Two-Sided 95% Wald CI [c] P-value [d]		(0.07, 0.26) <0.0001	(0.05, 0.24) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.3617 (0.7231, 2.5642)	1.1287 (0.5473, 2.3279)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.65 (0.16, 2.74) 0.5606	0.54 (0.13, 2.25) 0.4008

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Table 26.2.1.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	7 (63.6)	4 (36.4)	4 (36.4)
Number of Bleeds, n	24	13	10
Bleeds Per Subject			
Mean	2.2	1.2	0.9
SD	2.7	2.7	2.1
SE	0.8	0.8	0.6
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	2.0	0.0	0.0
P75	3.0	1.0	1.0
P90	4.0	2.0	1.0
Minimum, Maximum	0, 9	0, 9	0, 7
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	3.70	0.63	0.64

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Table 26.2.1.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - FIX- Treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	24	13	10
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	3.70	0.63	0.64
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.44* (1.91, 6.19)	0.71 (0.19, 2.70)	0.70 (0.18, 2.66)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.21	0.20
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.77) 0.0091	(0.05, 0.76) 0.0087

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Table 26.2.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

8. Annualisierte Blutungsrate – Blutungen ohne Behandlung mit FIX Präparaten – Subgruppenanalysen – Studie HOPE-B – Monat 24

-
- Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
- * For Comparison with Post-Treatment Month 7-24.
 - ** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.
- [a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
 - [b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
 - [c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
 - [d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
 - [e] Two-sided P-value.

Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	7 (17.5)	18 (45.0)	12 (30.0)
Number of Bleeds, n	15	40	28
Bleeds Per Subject			
Mean	0.4	1.0	0.7
SD	1.1	2.3	2.0
SE	0.2	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	1.0	2.0	1.5
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.60	0.53	0.49

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	15	40	28
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.60	0.53	0.49
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.60* (0.23, 1.55)	0.55 (0.27, 1.10)	0.50 (0.22, 1.18)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.89	0.84
Two-Sided 95% Wald CI [c] P-value [d]		(0.49, 1.62) 0.3557	(0.45, 1.58) 0.2955
Negative Binomial Dispersion Parameter (95% CI)		2.6424 (1.3840, 5.0451)	3.7492 (1.8860, 7.4531)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.77 (0.21, 15.20) 0.6014	2.14 (0.18, 25.26) 0.5463

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	3 (25.0)	3 (25.0)	3 (25.0)
Number of Bleeds, n	3	5	3
Bleeds Per Subject			
Mean	0.3	0.4	0.3
SD	0.5	0.9	0.5
SE	0.1	0.3	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.5	0.5	0.5
P90	1.0	1.0	1.0
Minimum, Maximum	0, 1	0, 3	0, 1
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.42	0.22	0.17

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	3	5	3
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	0.42	0.22	0.17
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.44* (0.16, 1.17)	0.22 (0.07, 0.74)	0.17 (0.06, 0.47)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.50	0.39
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 2.04) 0.1677	(0.15, 1.02) 0.0279

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	5 (15.2)	10 (30.3)	7 (21.2)
Number of Bleeds, n	8	19	11
Bleeds Per Subject			
Mean	0.2	0.6	0.3
SD	0.7	1.1	0.8
SE	0.1	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	0.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 3	0, 5	0, 4
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.39	0.31	0.23

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	8	19	11
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	0.39	0.31	0.23
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.37* (0.15, 0.91)	0.32 (0.17, 0.61)	0.25 (0.11, 0.56)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.85	0.68
Two-Sided 95% Wald CI [c] P-value [d]		(0.29, 2.47) 0.3793	(0.20, 2.32) 0.2672
Negative Binomial Dispersion Parameter (95% CI)		2.4418 (1.2616, 4.7260)	3.3243 (1.6312, 6.7747)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		1.07 (0.20, 5.66) 0.9386	0.85 (0.13, 5.59) 0.8663

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	5 (26.3)	11 (57.9)	8 (42.1)
Number of Bleeds, n	10	26	20
Bleeds Per Subject			
Mean	0.5	1.4	1.1
SD	1.4	3.1	2.7
SE	0.3	0.7	0.6
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	1.0	0.0
P75	1.0	1.0	1.0
P90	1.0	2.0	2.0
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.88	0.73	0.73

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	10	26	20
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	0.88	0.73	0.73
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.93* (0.29, 2.98)	0.73 (0.27, 1.99)	0.73 (0.24, 2.26)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.79	0.78
Two-Sided 95% Wald CI [c] P-value [d]		(0.48, 1.28) 0.1692	(0.49, 1.25) 0.1547

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	10 (25.6)	16 (41.0)	11 (28.2)
Number of Bleeds, n	18	38	27
Bleeds Per Subject			
Mean	0.5	1.0	0.7
SD	1.1	2.4	2.0
SE	0.2	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	1.0
P90	1.0	2.0	2.0
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	0.75	0.52	0.49

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	18	38	27
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	0.75	0.52	0.49

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	5 (38.5)	4 (30.8)
Number of Bleeds, n	0	7	4
Bleeds Per Subject			
Mean	0.0	0.5	0.3
SD	0.0	0.8	0.5
SE	0.0	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	0.0	2.0	1.0
Minimum, Maximum	0, 0	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.28	0.21

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	7	4
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.28	0.21

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	8 (18.6)	16 (37.2)	12 (27.9)
Number of Bleeds, n	11	23	14
Bleeds Per Subject			
Mean	0.3	0.5	0.3
SD	0.6	0.8	0.6
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 3	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.41	0.29	0.23

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	11	23	14
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	0.41	0.29	0.23
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.40* (0.20, 0.81)	0.29 (0.19, 0.45)	0.23 (0.14, 0.39)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.71	0.58
Two-Sided 95% Wald CI [c] P-value [d]		(0.31, 1.65) 0.2156	(0.23, 1.45) 0.1228
Negative Binomial Dispersion Parameter (95% CI)		1.9711 (0.9597, 4.0485)	2.7008 (1.2505, 5.8328)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		0.74 (0.12, 4.50) 0.7400	0.59 (0.08, 4.61) 0.6176

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	2 (22.2)	5 (55.6)	3 (33.3)
Number of Bleeds, n	7	22	17
Bleeds Per Subject			
Mean	0.8	2.4	1.9
SD	2.0	4.6	4.0
SE	0.7	1.5	1.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	1.0	0.0
P75	0.0	1.0	1.0
P90	6.0	14.0	12.0
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	1.29	1.30	1.32

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	7	22	17
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	1.29	1.30	1.32
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.36* (0.28, 6.70)	1.31 (0.41, 4.19)	1.32 (0.36, 4.85)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.96	0.97
Two-Sided 95% Wald CI [c] P-value [d]		(0.50, 1.88) 0.4574	(0.54, 1.76) 0.4613

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	6 (18.2)	13 (39.4)	10 (30.3)
Number of Bleeds, n	14	34	26
Bleeds Per Subject			
Mean	0.4	1.0	0.8
SD	1.2	2.6	2.2
SE	0.2	0.4	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	1.0	2.0	2.0
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.69	0.54	0.54

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	14	34	26
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	0.69	0.54	0.54
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.70* (0.26, 1.85)	0.56 (0.24, 1.26)	0.55 (0.22, 1.39)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.79	0.79
Two-Sided 95% Wald CI [c] P-value [d]		(0.44, 1.42) 0.2159	(0.42, 1.48) 0.2320
Negative Binomial Dispersion Parameter (95% CI)		2.6582 (1.3937, 5.0699)	3.5881 (1.7804, 7.2315)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.84 (0.13, 5.33) 0.8549	1.34 (0.16, 11.15) 0.7871

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Table 26.2.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	4 (21.1)	8 (42.1)	5 (26.3)
Number of Bleeds, n	4	11	5
Bleeds Per Subject			
Mean	0.2	0.6	0.3
SD	0.4	0.8	0.5
SE	0.1	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	1.0	2.0	1.0
Minimum, Maximum	0, 1	0, 3	0, 1
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.34	0.32	0.19

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	4	11	5
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	0.34	0.32	0.19
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.29* (0.09, 0.90)	0.32 (0.16, 0.63)	0.18 (0.08, 0.41)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.94	0.61
Two-Sided 95% Wald CI [c] P-value [d]		(0.29, 3.12) 0.4628	(0.16, 2.39) 0.2389

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	2 (6.5)	10 (32.3)	7 (22.6)
Number of Bleeds, n	2	20	11
Bleeds Per Subject			
Mean	0.1	0.6	0.4
SD	0.2	1.2	0.8
SE	0.0	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	0.0
P90	0.0	2.0	1.0
Minimum, Maximum	0, 1	0, 5	0, 4
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.10	0.35	0.25

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	2	20	11
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	0.10	0.35	0.25
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.10* (0.03, 0.39)	0.36 (0.19, 0.67)	0.26 (0.12, 0.59)
Rate Ratio (Post-Treatment/Lead-In) [b]		3.37	2.59
Two-Sided 95% Wald CI [c] P-value [d]		(0.81, 14.10) 0.9520	(0.55, 12.09) 0.8863
Negative Binomial Dispersion Parameter (95% CI)		2.0927 (1.0778, 4.0632)	2.6894 (1.2972, 5.5758)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		6.94 (0.99, 48.77) 0.0516	4.92 (0.61, 39.89) 0.1352

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	8 (38.1)	11 (52.4)	8 (38.1)
Number of Bleeds, n	16	25	20
Bleeds Per Subject			
Mean	0.8	1.2	1.0
SD	1.4	3.0	2.6
SE	0.3	0.7	0.6
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	1.0	0.0
P75	1.0	1.0	1.0
P90	2.0	1.0	1.0
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.27	0.63	0.66

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	16	25	20
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.27	0.63	0.66
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.27* (0.56, 2.86)	0.64 (0.22, 1.82)	0.66 (0.21, 2.06)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.50	0.52
Two-Sided 95% Wald CI [c] P-value [d]		(0.28, 0.88) 0.0082	(0.27, 1.00) 0.0249

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	5 (18.5)	10 (37.0)	7 (25.9)
Number of Bleeds, n	10	28	20
Bleeds Per Subject			
Mean	0.4	1.0	0.7
SD	1.2	2.7	2.3
SE	0.2	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	1.0	2.0	2.0
Minimum, Maximum	0, 6	0, 14	0, 12
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	0.61	0.55	0.51

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	10	28	20
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	0.61	0.55	0.51
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.65* (0.20, 2.13)	0.55 (0.20, 1.45)	0.50 (0.16, 1.64)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.84	0.77
Two-Sided 95% Wald CI [c] P-value [d]		(0.51, 1.38) 0.2439	(0.50, 1.20) 0.1237
Negative Binomial Dispersion Parameter (95% CI)		3.8410 (1.8142, 8.1318)	4.7957 (2.1439, 10.7276)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.54 (0.03, 10.71) 0.6853	0.63 (0.02, 15.91) 0.7781

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Table 26.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	1 (9.1)	3 (27.3)	3 (27.3)
Number of Bleeds, n	1	5	3
Bleeds Per Subject			
Mean	0.1	0.5	0.3
SD	0.3	0.9	0.5
SE	0.1	0.3	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 1	0, 3	0, 1
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.15	0.24	0.19

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Table 26.2.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - non-treated Bleeding by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	1	5	3
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.15	0.24	0.19
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.13* (0.02, 1.09)	0.23 (0.07, 0.84)	0.17 (0.06, 0.53)
Rate Ratio (Post-Treatment/Lead-In) [b]		1.61	1.31
Two-Sided 95% Wald CI [c] P-value [d]		(0.13, 20.36) 0.6442	(0.08, 20.40) 0.5767

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

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Post-treatment period time is the number of days of observation within the time interval starting from Day 1. Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted. Pxx = xx-th percentile. N = number of subjects under observation in the time interval. For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.

* For Comparison with Post-Treatment Month 7-24.

** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.

- [a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
- [b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
- [c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
- [d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
- [e] Two-sided P-value.

Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	22 (55.0)	10 (25.0)	8 (20.0)
Number of Bleeds, n	48	18	10
Number of Bleeds Treated With Factor IX, n (% of bleeds)	44 (91.7)	13 (72.2)	7 (70.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (8.3)	5 (27.8)	3 (30.0)
Bleeds Per Subject			
Mean	1.2	0.5	0.3
SD	1.6	1.1	0.5
SE	0.3	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	0.5	0.0
P90	3.5	1.5	1.0
Minimum, Maximum	0, 7	0, 6	0, 2
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	1.93	0.24	0.17

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	48	18	10
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	1.93	0.24	0.17
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.90* (1.28, 2.80)	0.25 (0.12, 0.53)	0.18 (0.09, 0.35)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.13	0.09
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.28) <0.0001	(0.04, 0.20) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.0614 (0.5266, 2.1396)	0.8266 (0.3650, 1.8721)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		0.73 (0.20, 2.63) 0.6307	0.48 (0.13, 1.73) 0.2599

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	9 (75.0)	6 (50.0)	5 (41.7)
Number of Bleeds, n	24	13	11
Number of Bleeds Treated With Factor IX, n (% of bleeds)	21 (87.5)	11 (84.6)	10 (90.9)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (12.5)	2 (15.4)	1 (9.1)
Bleeds Per Subject			
Mean	2.0	1.1	0.9
SD	1.9	1.6	1.6
SE	0.6	0.5	0.5
P10	0.0	0.0	0.0
P25	0.5	0.0	0.0
Median	2.0	0.5	0.0
P75	2.5	1.5	1.0
P90	5.0	3.0	3.0
Minimum, Maximum	0, 6	0, 5	0, 5
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	3.34	0.58	0.64

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	24	13	11
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	3.34	0.58	0.64
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.27* (2.05, 5.22)	0.58 (0.26, 1.28)	0.64 (0.25, 1.62)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.18	0.20
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.37) <0.0001	(0.08, 0.46) <0.0001

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	19 (57.6)	8 (24.2)	6 (18.2)
Number of Bleeds, n	48	12	8
Number of Bleeds Treated With Factor IX, n (% of bleeds)	44 (91.7)	10 (83.3)	7 (87.5)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (8.3)	2 (16.7)	1 (12.5)
Bleeds Per Subject			
Mean	1.5	0.4	0.2
SD	1.8	0.7	0.6
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	0.0	0.0
P90	4.0	1.0	1.0
Minimum, Maximum	0, 7	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	2.32	0.19	0.17

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	48	12	8
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	2.32	0.19	0.17
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.24* (1.50, 3.35)	0.20 (0.10, 0.39)	0.17 (0.07, 0.41)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.09	0.08
Two-Sided 95% Wald CI [c] P-value [d]		(0.04, 0.19) <0.0001	(0.03, 0.20) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.0913 (0.5527, 2.1547)	0.9531 (0.4444, 2.0441)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.34 (0.10, 1.14) 0.0795	0.34 (0.10, 1.22) 0.0986

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	12 (63.2)	8 (42.1)	7 (36.8)
Number of Bleeds, n	24	19	13
Number of Bleeds Treated With Factor IX, n (% of bleeds)	21 (87.5)	14 (73.7)	10 (76.9)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (12.5)	5 (26.3)	3 (23.1)
Bleeds Per Subject			
Mean	1.3	1.0	0.7
SD	1.4	1.7	1.2
SE	0.3	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	5.0	2.0
Minimum, Maximum	0, 5	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	2.11	0.54	0.47

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	24	19	13
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	2.11	0.54	0.47
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.14* (1.32, 3.48)	0.55 (0.26, 1.20)	0.49 (0.22, 1.09)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.23
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.48) <0.0001	(0.12, 0.42) <0.0001

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	31 (79.5)	11 (28.2)	8 (20.5)
Number of Bleeds, n	72	25	16
Number of Bleeds Treated With Factor IX, n (% of bleeds)	65 (90.3)	21 (84.0)	14 (87.5)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	7 (9.7)	4 (16.0)	2 (12.5)
Bleeds Per Subject			
Mean	1.8	0.6	0.4
SD	1.7	1.4	1.0
SE	0.3	0.2	0.2
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.0	1.0	0.0
P90	4.0	2.0	2.0
Minimum, Maximum	0, 7	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	3.00	0.34	0.29

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	72	25	16
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	3.00	0.34	0.29

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	5 (38.5)	5 (38.5)
Number of Bleeds, n	0	6	5
Number of Bleeds Treated With Factor IX, n (% of bleeds)	0	3 (50.0)	3 (60.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	3 (50.0)	2 (40.0)
Bleeds Per Subject			
Mean	0.0	0.5	0.4
SD	0.0	0.7	0.5
SE	0.0	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	0.0	1.0	1.0
Minimum, Maximum	0, 0	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.24	0.26

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	6	5
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.24	0.26

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	22 (51.2)	12 (27.9)	11 (25.6)
Number of Bleeds, n	53	23	15
Number of Bleeds Treated With Factor IX, n (% of bleeds)	47 (88.7)	18 (78.3)	13 (86.7)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	6 (11.3)	5 (21.7)	2 (13.3)
Bleeds Per Subject			
Mean	1.2	0.5	0.3
SD	1.7	1.1	0.7
SE	0.3	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 7	0, 6	0, 3
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.99	0.29	0.24

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	53	23	15
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.99	0.29	0.24
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.94* (1.32, 2.85)	0.30 (0.16, 0.56)	0.25 (0.14, 0.45)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.15	0.13
Two-Sided 95% Wald CI [c] P-value [d]		(0.08, 0.30) <0.0001	(0.07, 0.25) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1311 (0.5720, 2.2367)	0.9363 (0.4278, 2.0496)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		1.13 (0.27, 4.81) 0.8680	0.98 (0.23, 4.22) 0.9739

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	9 (100)	4 (44.4)	2 (22.2)
Number of Bleeds, n	19	8	6
Number of Bleeds Treated With Factor IX, n (% of bleeds)	18 (94.7)	6 (75.0)	4 (66.7)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	1 (5.3)	2 (25.0)	2 (33.3)
Bleeds Per Subject			
Mean	2.1	0.9	0.7
SD	1.5	1.6	1.7
SE	0.5	0.5	0.6
P10	1.0	0.0	0.0
P25	1.0	0.0	0.0
Median	2.0	0.0	0.0
P75	2.0	1.0	0.0
P90	5.0	5.0	5.0
Minimum, Maximum	1, 5	0, 5	0, 5
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	3.50	0.47	0.46

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	19	8	6
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	3.50	0.47	0.46
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.56* (2.33, 5.43)	0.48 (0.15, 1.48)	0.47 (0.10, 2.17)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.13	0.13
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.33) <0.0001	(0.04, 0.48) 0.0010

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	17 (51.5)	8 (24.2)	6 (18.2)
Number of Bleeds, n	36	9	6
Number of Bleeds Treated With Factor IX, n (% of bleeds)	32 (88.9)	5 (55.6)	3 (50.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (11.1)	4 (44.4)	3 (50.0)
Bleeds Per Subject			
Mean	1.1	0.3	0.2
SD	1.6	0.5	0.4
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	0.0	0.0
P90	3.0	1.0	1.0
Minimum, Maximum	0, 7	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.78	0.14	0.12

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	36	9	6
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.78	0.14	0.12
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.74* (1.11, 2.74)	0.14 (0.08, 0.27)	0.12 (0.06, 0.26)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.08	0.07
Two-Sided 95% Wald CI [c] P-value [d]		(0.04, 0.19) <0.0001	(0.03, 0.19) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.8941 (0.4308, 1.8554)	0.7985 (0.3537, 1.8027)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.38 (0.12, 1.23) 0.1058	0.37 (0.10, 1.32) 0.1255

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	14 (73.7)	8 (42.1)	7 (36.8)
Number of Bleeds, n	36	22	15
Number of Bleeds Treated With Factor IX, n (% of bleeds)	33 (91.7)	19 (86.4)	14 (93.3)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (8.3)	3 (13.6)	1 (6.7)
Bleeds Per Subject			
Mean	1.9	1.2	0.8
SD	1.8	1.8	1.4
SE	0.4	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	3.0	2.0	1.0
P90	5.0	5.0	3.0
Minimum, Maximum	0, 6	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	3.04	0.64	0.57

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	36	22	15
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	3.04	0.64	0.57
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	3.07* (2.07, 4.55)	0.66 (0.34, 1.32)	0.59 (0.28, 1.25)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.19
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.40) <0.0001	(0.10, 0.38) <0.0001

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	17 (54.8)	8 (25.8)	6 (19.4)
Number of Bleeds, n	38	17	9
Number of Bleeds Treated With Factor IX, n (% of bleeds)	36 (94.7)	14 (82.4)	8 (88.9)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (5.3)	3 (17.6)	1 (11.1)
Bleeds Per Subject			
Mean	1.2	0.5	0.3
SD	1.5	1.3	0.7
SE	0.3	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 6	0, 6	0, 3
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.96	0.29	0.20

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	38	17	9
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.96	0.29	0.20
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.92* (1.26, 2.92)	0.30 (0.14, 0.68)	0.21 (0.09, 0.48)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.16	0.11
Two-Sided 95% Wald CI [c] P-value [d]		(0.07, 0.34) <0.0001	(0.05, 0.26) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1903 (0.6114, 2.3176)	0.9712 (0.4511, 2.0907)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		1.16 (0.35, 3.87) 0.8095	0.72 (0.21, 2.51) 0.6054

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	14 (66.7)	8 (38.1)	7 (33.3)
Number of Bleeds, n	34	14	12
Number of Bleeds Treated With Factor IX, n (% of bleeds)	29 (85.3)	10 (71.4)	9 (75.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	5 (14.7)	4 (28.6)	3 (25.0)
Bleeds Per Subject			
Mean	1.6	0.7	0.6
SD	1.9	1.2	1.2
SE	0.4	0.3	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	4.0	2.0	1.0
Minimum, Maximum	0, 7	0, 5	0, 5
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	2.69	0.35	0.39

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	34	14	12
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	2.69	0.35	0.39
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.64* (1.68, 4.15)	0.36 (0.17, 0.77)	0.40 (0.17, 0.95)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.14	0.15
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.29) <0.0001	(0.07, 0.35) <0.0001

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	15 (55.6)	8 (29.6)	5 (18.5)
Number of Bleeds, n	31	11	7
Number of Bleeds Treated With Factor IX, n (% of bleeds)	29 (93.5)	9 (81.8)	5 (71.4)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (6.5)	2 (18.2)	2 (28.6)
Bleeds Per Subject			
Mean	1.1	0.4	0.3
SD	1.3	0.7	0.7
SE	0.3	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	0.0
P90	3.0	1.0	1.0
Minimum, Maximum	0, 4	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.89	0.21	0.18

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	31	11	7
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.89	0.21	0.18
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.94* (1.26, 3.00)	0.22 (0.11, 0.43)	0.18 (0.07, 0.46)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.11	0.09
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.23) <0.0001	(0.03, 0.26) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.7811 (0.2768, 2.2046)	0.8328 (0.2902, 2.3894)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.76 (0.17, 3.29) 0.7092	0.57 (0.12, 2.81) 0.4884

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	6 (54.5)	4 (36.4)	4 (36.4)
Number of Bleeds, n	14	6	5
Number of Bleeds Treated With Factor IX, n (% of bleeds)	13 (92.9)	4 (66.7)	4 (80.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	1 (7.1)	2 (33.3)	1 (20.0)
Bleeds Per Subject			
Mean	1.3	0.5	0.5
SD	1.8	0.8	0.7
SE	0.6	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 6	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	2.16	0.29	0.32

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Table 1.3.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Joint Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	14	6	5
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	2.16	0.29	0.32
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.03* (0.99, 4.17)	0.30 (0.13, 0.72)	0.33 (0.13, 0.80)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.15	0.16
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.40) <0.0001	(0.06, 0.46) 0.0003

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

10. Annualisierte Blutungsrate – Spontane Blutungen – Subgruppenanalysen – Studie HOPE-B – Monat 24

-
- Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
- * For Comparison with Post-Treatment Month 7-24.
 - ** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.
- [a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
 - [b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
 - [c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
 - [d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
 - [e] Two-sided P-value.

Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	15 (37.5)	9 (22.5)	6 (15.0)
Number of Bleeds, n	24	15	7
Number of Bleeds Treated With Factor IX, n (% of bleeds)	21 (87.5)	9 (60.0)	5 (71.4)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (12.5)	6 (40.0)	2 (28.6)
Bleeds Per Subject			
Mean	0.6	0.4	0.2
SD	0.9	0.8	0.4
SE	0.1	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	1.5	1.0
Minimum, Maximum	0, 3	0, 4	0, 2
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.96	0.20	0.12

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	24	15	7
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	0.96	0.20	0.12
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.95* (0.60, 1.50)	0.20 (0.10, 0.41)	0.12 (0.06, 0.27)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.13
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.46) <0.0001	(0.05, 0.31) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2156 (0.5124, 2.8837)	0.9103 (0.3175, 2.6104)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.56 (0.37, 6.50) 0.5437	1.09 (0.24, 4.98) 0.9070

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	8 (66.7)	4 (33.3)	3 (25.0)
Number of Bleeds, n	21	9	6
Number of Bleeds Treated With Factor IX, n (% of bleeds)	18 (85.7)	7 (77.8)	5 (83.3)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (14.3)	2 (22.2)	1 (16.7)
Bleeds Per Subject			
Mean	1.8	0.8	0.5
SD	2.1	1.1	1.0
SE	0.6	0.3	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.5	2.0	0.5
P90	4.0	2.0	2.0
Minimum, Maximum	0, 7	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	2.93	0.40	0.35

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	21	9	6
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	2.93	0.40	0.35
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.94* (1.56, 5.54)	0.41 (0.18, 0.94)	0.35 (0.12, 1.04)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.14	0.12
Two-Sided 95% Wald CI [c] P-value [d]		(0.07, 0.29) <0.0001	(0.05, 0.27) <0.0001

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	15 (45.5)	5 (15.2)	4 (12.1)
Number of Bleeds, n	29	10	5
Number of Bleeds Treated With Factor IX, n (% of bleeds)	26 (89.7)	5 (50.0)	3 (60.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (10.3)	5 (50.0)	2 (40.0)
Bleeds Per Subject			
Mean	0.9	0.3	0.2
SD	1.2	0.8	0.4
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	2.0	0.0	0.0
P90	3.0	1.0	1.0
Minimum, Maximum	0, 4	0, 4	0, 2
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	1.40	0.16	0.11

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	29	10	5
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	1.40	0.16	0.11
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.39* (0.90, 2.14)	0.16 (0.06, 0.42)	0.11 (0.04, 0.28)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.12	0.08
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.31) <0.0001	(0.03, 0.21) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.5191 (0.7086, 3.2567)	1.3371 (0.5620, 3.1813)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.41 (0.10, 1.71) 0.2229	0.37 (0.08, 1.78) 0.2145

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	8 (42.1)	8 (42.1)	5 (26.3)
Number of Bleeds, n	16	14	8
Number of Bleeds Treated With Factor IX, n (% of bleeds)	13 (81.3)	11 (78.6)	7 (87.5)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (18.8)	3 (21.4)	1 (12.5)
Bleeds Per Subject			
Mean	0.8	0.7	0.4
SD	1.7	1.0	0.8
SE	0.4	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	2.0	1.0
P90	3.0	2.0	2.0
Minimum, Maximum	0, 7	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	1.41	0.40	0.29

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	16	14	8
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	1.41	0.40	0.29
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.41* (0.60, 3.35)	0.41 (0.22, 0.75)	0.30 (0.12, 0.73)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.29	0.21
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.59) 0.0004	(0.10, 0.42) <0.0001

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	23 (59.0)	10 (25.6)	8 (20.5)
Number of Bleeds, n	45	20	12
Number of Bleeds Treated With Factor IX, n (% of bleeds)	39 (86.7)	14 (70.0)	9 (75.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	6 (13.3)	6 (30.0)	3 (25.0)
Bleeds Per Subject			
Mean	1.2	0.5	0.3
SD	1.5	1.0	0.7
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 7	0, 4	0, 3
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.87	0.28	0.22

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	45	20	12
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	1.87	0.28	0.22

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	3 (23.1)	1 (7.7)
Number of Bleeds, n	0	4	1
Number of Bleeds Treated With Factor IX, n (% of bleeds)	0	2 (50.0)	1 (100)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	2 (50.0)	0
Bleeds Per Subject			
Mean	0.0	0.3	0.1
SD	0.0	0.6	0.3
SE	0.0	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	0.0	0.0
P90	0.0	1.0	0.0
Minimum, Maximum	0, 0	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.16	0.05

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	4	1
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.16	0.05

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	16 (37.2)	10 (23.3)	7 (16.3)
Number of Bleeds, n	29	19	9
Number of Bleeds Treated With Factor IX, n (% of bleeds)	25 (86.2)	13 (68.4)	7 (77.8)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (13.8)	6 (31.6)	2 (22.2)
Bleeds Per Subject			
Mean	0.7	0.4	0.2
SD	1.0	0.9	0.5
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	2.0	1.0
Minimum, Maximum	0, 3	0, 4	0, 2
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.09	0.24	0.15

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	29	19	9
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.09	0.24	0.15
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.07* (0.69, 1.67)	0.24 (0.13, 0.45)	0.15 (0.07, 0.31)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.23	0.14
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.44) <0.0001	(0.06, 0.30) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.3928 (0.6170, 3.1440)	1.0754 (0.4020, 2.8762)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		2.22 (0.42, 11.79) 0.3487	1.30 (0.24, 7.07) 0.7633

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	7 (77.8)	3 (33.3)	2 (22.2)
Number of Bleeds, n	16	5	4
Number of Bleeds Treated With Factor IX, n (% of bleeds)	14 (87.5)	3 (60.0)	3 (75.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (12.5)	2 (40.0)	1 (25.0)
Bleeds Per Subject			
Mean	1.8	0.6	0.4
SD	2.3	1.0	1.0
SE	0.8	0.3	0.3
P10	0.0	0.0	0.0
P25	1.0	0.0	0.0
Median	1.0	0.0	0.0
P75	1.0	1.0	0.0
P90	7.0	3.0	3.0
Minimum, Maximum	0, 7	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	2.95	0.30	0.31

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	16	5	4
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	2.95	0.30	0.31
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.94* (1.37, 6.35)	0.30 (0.10, 0.93)	0.31 (0.08, 1.27)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.10	0.11
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.21) <0.0001	(0.04, 0.26) <0.0001

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	11 (33.3)	6 (18.2)	3 (9.1)
Number of Bleeds, n	22	8	3
Number of Bleeds Treated With Factor IX, n (% of bleeds)	18 (81.8)	3 (37.5)	1 (33.3)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (18.2)	5 (62.5)	2 (66.7)
Bleeds Per Subject			
Mean	0.7	0.2	0.1
SD	1.1	0.6	0.3
SE	0.2	0.1	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	3.0	1.0	0.0
Minimum, Maximum	0, 4	0, 2	0, 1
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.09	0.13	0.06

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	22	8	3
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	1.09	0.13	0.06
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.06* (0.61, 1.85)	0.13 (0.06, 0.28)	0.06 (0.02, 0.18)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.12	0.06
Two-Sided 95% Wald CI [c] P-value [d]		(0.05, 0.32) <0.0001	(0.02, 0.20) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2749 (0.5657, 2.8733)	1.0832 (0.4308, 2.7234)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.51 (0.13, 2.00) 0.3340	0.30 (0.06, 1.57) 0.1539

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	12 (63.2)	7 (36.8)	6 (31.6)
Number of Bleeds, n	23	16	10
Number of Bleeds Treated With Factor IX, n (% of bleeds)	21 (91.3)	13 (81.3)	9 (90.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (8.7)	3 (18.8)	1 (10.0)
Bleeds Per Subject			
Mean	1.2	0.8	0.5
SD	1.7	1.3	0.9
SE	0.4	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	2.0	1.0
P90	3.0	3.0	2.0
Minimum, Maximum	0, 7	0, 4	0, 3
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.94	0.47	0.38

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	23	16	10
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.94	0.47	0.38
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.00* (1.09, 3.64)	0.48 (0.25, 0.92)	0.39 (0.18, 0.82)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.24	0.19
Two-Sided 95% Wald CI [c] P-value [d]		(0.13, 0.44) <0.0001	(0.11, 0.35) <0.0001

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	14 (45.2)	5 (16.1)	4 (12.9)
Number of Bleeds, n	24	11	5
Number of Bleeds Treated With Factor IX, n (% of bleeds)	22 (91.7)	7 (63.6)	4 (80.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (8.3)	4 (36.4)	1 (20.0)
Bleeds Per Subject			
Mean	0.8	0.4	0.2
SD	1.1	0.9	0.5
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	2.0	1.0
Minimum, Maximum	0, 4	0, 4	0, 2
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.24	0.19	0.11

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	24	11	5
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.24	0.19	0.11
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.24* (0.78, 1.99)	0.19 (0.08, 0.48)	0.11 (0.04, 0.30)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.16	0.09
Two-Sided 95% Wald CI [c] P-value [d]		(0.06, 0.38) <0.0001	(0.03, 0.24) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.5778 (0.7400, 3.3642)	1.3296 (0.5539, 3.1917)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		0.75 (0.19, 3.05) 0.6899	0.56 (0.12, 2.64) 0.4629

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	9 (42.9)	8 (38.1)	5 (23.8)
Number of Bleeds, n	21	13	8
Number of Bleeds Treated With Factor IX, n (% of bleeds)	17 (81.0)	9 (69.2)	6 (75.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	4 (19.0)	4 (30.8)	2 (25.0)
Bleeds Per Subject			
Mean	1.0	0.6	0.4
SD	1.7	0.9	0.8
SE	0.4	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 7	0, 3	0, 3
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.66	0.33	0.26

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	21	13	8
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	1.66	0.33	0.26
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.61* (0.79, 3.32)	0.34 (0.18, 0.64)	0.27 (0.11, 0.66)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.21	0.17
Two-Sided 95% Wald CI [c] P-value [d]		(0.10, 0.42) <0.0001	(0.08, 0.36) <0.0001

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	12 (44.4)	8 (29.6)	4 (14.8)
Number of Bleeds, n	21	13	5
Number of Bleeds Treated With Factor IX, n (% of bleeds)	18 (85.7)	8 (61.5)	3 (60.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	3 (14.3)	5 (38.5)	2 (40.0)
Bleeds Per Subject			
Mean	0.8	0.5	0.2
SD	1.1	0.9	0.5
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	1.0	0.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 4	0, 4	0, 2
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.28	0.25	0.13

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	21	13	5
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	1.28	0.25	0.13
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.30* (0.76, 2.22)	0.26 (0.12, 0.54)	0.13 (0.05, 0.33)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.20	0.10
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.45) <0.0001	(0.03, 0.28) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.2750 (0.4496, 3.6159)	0.9527 (0.2398, 3.7859)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		0.88 (0.14, 5.50) 0.8931	0.45 (0.06, 3.16) 0.4205

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Table 1.2.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	4 (36.4)	2 (18.2)	2 (18.2)
Number of Bleeds, n	6	4	3
Number of Bleeds Treated With Factor IX, n (% of bleeds)	6 (100)	2 (50.0)	2 (66.7)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	2 (50.0)	1 (33.3)
Bleeds Per Subject			
Mean	0.5	0.4	0.3
SD	0.8	0.8	0.6
SE	0.2	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	1.0	0.0	0.0
P90	2.0	2.0	1.0
Minimum, Maximum	0, 2	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.93	0.19	0.19

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Table 1.2.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Spontaneous Bleeding by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	6	4	3
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	0.93	0.19	0.19
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	0.89* (0.39, 2.05)	0.20 (0.06, 0.72)	0.20 (0.05, 0.78)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.23	0.22
Two-Sided 95% Wald CI [c] P-value [d]		(0.08, 0.63) 0.0023	(0.06, 0.78) 0.0091

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Table 1.4.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

11. Annualisierte Blutungsrate – Traumatische Blutungen – Subgruppenanalysen – Studie HOPE-B – Monat 24

-
- Post-treatment period time is the number of days of observation within the time interval starting from Day 1.
Person-time during the post-treatment period (on any day that began) within 5 half-lives subsequent to exogenous factor IX use is not considered to be time at risk of (having) a bleeding event. Nevertheless, bleeds during such person-time are still counted.
Pxx = xx-th percentile. N = number of subjects under observation in the time interval.
For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.
* For Comparison with Post-Treatment Month 7-24.
** If a subject has zero person-time in Month 7-24 because of "contamination" from exogenous factor IX, to avoid exclusion of the subject from the regression analysis, the bleeding event counts and uncontaminated person-time from the adjacent 6-month time intervals (After Day 21 through Month 6 and Month 25-30) are added, respectively, to those of the Month 7-24 time interval for that subject; however, the descriptive statistics are not affected.
- [a] Unadjusted ABR is calculated as the ratio of the number of bleeds to the time of observation (in years).
 - [b] Adjusted ABR and comparison of ABR between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
 - [c] The upper limit of the confidence interval of the rate ratio is compared to the non-inferiority margin of 1.8. If the upper limit is less than 1.8, then non-inferiority will be declared.
 - [d] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
 - [e] Two-sided P-value.

Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Number of Subjects With a Bleed, n (%)	24 (60.0)	17 (42.5)	14 (35.0)
Number of Bleeds, n	56	47	37
Number of Bleeds Treated With Factor IX, n (% of bleeds)	44 (78.6)	16 (34.0)	12 (32.4)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	12 (21.4)	31 (66.0)	25 (67.6)
Bleeds Per Subject			
Mean	1.4	1.2	0.9
SD	1.9	2.6	2.1
SE	0.3	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.5	2.5	2.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	2.25	0.63	0.65

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 ** (N = 40)
Cumulative Number of Bleeds	56	47	37
Cumulative Number of Person-years Observed for Bleeding Events	24.87	74.99	57.26
Unadjusted Annualized Bleeding Rate [a]	2.25	0.63	0.65
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.26* (1.44, 3.52)	0.65 (0.33, 1.28)	0.68 (0.34, 1.35)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.28	0.30
Two-Sided 95% Wald CI [c] P-value [d]		(0.18, 0.46) <0.0001	(0.18, 0.50) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.6542 (0.9975, 2.7434)	1.8064 (1.0549, 3.0933)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI) P-value [e]		1.21 (0.28, 5.34) 0.7976	1.62 (0.32, 8.15) 0.5560

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Number of Subjects With a Bleed, n (%)	5 (41.7)	6 (50.0)	4 (33.3)
Number of Bleeds, n	14	10	6
Number of Bleeds Treated With Factor IX, n (% of bleeds)	14 (100)	8 (80.0)	5 (83.3)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	2 (20.0)	1 (16.7)
Bleeds Per Subject			
Mean	1.2	0.8	0.5
SD	1.7	1.0	0.8
SE	0.5	0.3	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.5	0.0
P75	2.5	1.5	1.0
P90	3.0	2.0	2.0
Minimum, Maximum	0, 5	0, 3	0, 2
Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	1.95	0.44	0.35

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 ** (N = 12)
Cumulative Number of Bleeds	14	10	6
Cumulative Number of Person-years Observed for Bleeding Events	7.18	22.59	17.30
Unadjusted Annualized Bleeding Rate [a]	1.95	0.44	0.35
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.92* (0.92, 4.03)	0.45 (0.23, 0.88)	0.35 (0.15, 0.83)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.24	0.18
Two-Sided 95% Wald CI [c] P-value [d]		(0.09, 0.64) 0.0024	(0.06, 0.55) 0.0012

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	21 (63.6)	12 (36.4)	8 (24.2)
Number of Bleeds, n	48	20	14
Number of Bleeds Treated With Factor IX, n (% of bleeds)	43 (89.6)	9 (45.0)	7 (50.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	5 (10.4)	11 (55.0)	7 (50.0)
Bleeds Per Subject			
Mean	1.5	0.6	0.4
SD	1.6	1.2	1.0
SE	0.3	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	0.0
P90	4.0	2.0	1.0
Minimum, Maximum	0, 6	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	2.32	0.32	0.30

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	48	20	14
Cumulative Number of Person-years Observed for Bleeding Events	20.70	62.14	47.17
Unadjusted Annualized Bleeding Rate [a]	2.32	0.32	0.30
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.19* (1.44, 3.33)	0.33 (0.17, 0.64)	0.31 (0.14, 0.68)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.15	0.14
Two-Sided 95% Wald CI [c] P-value [d]		(0.08, 0.26) <0.0001	(0.07, 0.29) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.4255 (0.8346, 2.4348)	1.5672 (0.8889, 2.7630)
Ratio (Europe vs. USA) of rate ratio (95% CI) P-value [e]		0.28 (0.08, 0.93) 0.0380	0.26 (0.07, 0.95) 0.0419

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	8 (42.1)	11 (57.9)	10 (52.6)
Number of Bleeds, n	22	37	29
Number of Bleeds Treated With Factor IX, n (% of bleeds)	15 (68.2)	15 (40.5)	10 (34.5)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	7 (31.8)	22 (59.5)	19 (65.5)
Bleeds Per Subject			
Mean	1.2	1.9	1.5
SD	2.2	3.5	2.8
SE	0.5	0.8	0.6
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	1.0	1.0
P75	2.0	2.0	2.0
P90	3.0	5.0	4.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	1.94	1.04	1.06

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	22	37	29
Cumulative Number of Person-years Observed for Bleeding Events	11.35	35.43	27.39
Unadjusted Annualized Bleeding Rate [a]	1.94	1.04	1.06
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.03* (0.88, 4.69)	1.06 (0.48, 2.31)	1.07 (0.48, 2.39)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.52	0.53
Two-Sided 95% Wald CI [c] P-value [d]		(0.31, 0.87) 0.0065	(0.31, 0.91) 0.0110

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Number of Subjects With a Bleed, n (%)	29 (74.4)	17 (43.6)	12 (30.8)
Number of Bleeds, n	70	48	35
Number of Bleeds Treated With Factor IX, n (% of bleeds)	58 (82.9)	20 (41.7)	13 (37.1)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	12 (17.1)	28 (58.3)	22 (62.9)
Bleeds Per Subject			
Mean	1.8	1.2	0.9
SD	1.9	2.7	2.2
SE	0.3	0.4	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	5.0	3.0	2.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	2.91	0.66	0.63

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 ** (N = 39)
Cumulative Number of Bleeds	70	48	35
Cumulative Number of Person-years Observed for Bleeding Events	24.02	72.62	55.45
Unadjusted Annualized Bleeding Rate [a]	2.91	0.66	0.63

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Number of Subjects With a Bleed, n (%)	0	6 (46.2)	6 (46.2)
Number of Bleeds, n	0	9	8
Number of Bleeds Treated With Factor IX, n (% of bleeds)	0	4 (44.4)	4 (50.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	5 (55.6)	4 (50.0)
Bleeds Per Subject			
Mean	0.0	0.7	0.6
SD	0.0	0.9	0.8
SE	0.0	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	0.0	1.0	1.0
P90	0.0	2.0	2.0
Minimum, Maximum	0, 0	0, 2	0, 2
Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.36	0.42

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 ** (N = 13)
Cumulative Number of Bleeds	0	9	8
Cumulative Number of Person-years Observed for Bleeding Events	8.02	24.96	19.11
Unadjusted Annualized Bleeding Rate [a]	0.0	0.36	0.42

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Number of Subjects With a Bleed, n (%)	23 (53.5)	16 (37.2)	14 (32.6)
Number of Bleeds, n	47	29	23
Number of Bleeds Treated With Factor IX, n (% of bleeds)	40 (85.1)	16 (55.2)	13 (56.5)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	7 (14.9)	13 (44.8)	10 (43.5)
Bleeds Per Subject			
Mean	1.1	0.7	0.5
SD	1.4	1.1	0.9
SE	0.2	0.2	0.1
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	2.0	2.0
Minimum, Maximum	0, 6	0, 5	0, 4
Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.77	0.36	0.37

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 ** (N = 43)
Cumulative Number of Bleeds	47	29	23
Cumulative Number of Person-years Observed for Bleeding Events	26.62	80.64	61.66
Unadjusted Annualized Bleeding Rate [a]	1.77	0.36	0.37
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.72* (1.18, 2.51)	0.37 (0.23, 0.62)	0.39 (0.23, 0.67)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.22	0.23
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.39) <0.0001	(0.12, 0.43) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.1787 (0.6580, 2.1115)	1.3795 (0.7556, 2.5185)
Ratio (Absence vs. Presence) of rate ratio (95% CI) P-value [e]		0.58 (0.16, 2.18) 0.4240	0.66 (0.16, 2.74) 0.5656

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Number of Subjects With a Bleed, n (%)	6 (66.7)	7 (77.8)	4 (44.4)
Number of Bleeds, n	23	28	20
Number of Bleeds Treated With Factor IX, n (% of bleeds)	18 (78.3)	8 (28.6)	4 (20.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	5 (21.7)	20 (71.4)	16 (80.0)
Bleeds Per Subject			
Mean	2.6	3.1	2.2
SD	3.0	4.8	4.0
SE	1.0	1.6	1.3
P10	0.0	0.0	0.0
P25	0.0	1.0	0.0
Median	2.0	1.0	0.0
P75	3.0	3.0	2.0
P90	9.0	15.0	12.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	4.24	1.65	1.55

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 ** (N = 9)
Cumulative Number of Bleeds	23	28	20
Cumulative Number of Person-years Observed for Bleeding Events	5.43	16.93	12.91
Unadjusted Annualized Bleeding Rate [a]	4.24	1.65	1.55
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	4.57* (2.20, 9.48)	1.67 (0.64, 4.36)	1.57 (0.52, 4.72)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.37	0.34
Two-Sided 95% Wald CI [c] P-value [d]		(0.23, 0.58) <0.0001	(0.20, 0.60) <0.0001

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Number of Subjects With a Bleed, n (%)	18 (54.5)	14 (42.4)	11 (33.3)
Number of Bleeds, n	48	37	28
Number of Bleeds Treated With Factor IX, n (% of bleeds)	38 (79.2)	9 (24.3)	5 (17.9)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	10 (20.8)	28 (75.7)	23 (82.1)
Bleeds Per Subject			
Mean	1.5	1.1	0.8
SD	2.1	2.8	2.2
SE	0.4	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	4.0	2.0	2.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	2.38	0.59	0.58

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 ** (N = 33)
Cumulative Number of Bleeds	48	37	28
Cumulative Number of Person-years Observed for Bleeding Events	20.20	63.23	48.37
Unadjusted Annualized Bleeding Rate [a]	2.38	0.59	0.58
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.45* (1.49, 4.02)	0.59 (0.26, 1.37)	0.59 (0.24, 1.43)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.24	0.24
Two-Sided 95% Wald CI [c] P-value [d]		(0.14, 0.43) <0.0001	(0.13, 0.45) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.6602 (1.0016, 2.7522)	1.8367 (1.0745, 3.1395)
Ratio (Negative vs. Positive) of rate ratio (95% CI) P-value [e]		0.70 (0.20, 2.51) 0.5882	0.68 (0.17, 2.64) 0.5759

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Number of Subjects With a Bleed, n (%)	11 (57.9)	9 (47.4)	7 (36.8)
Number of Bleeds, n	22	20	15
Number of Bleeds Treated With Factor IX, n (% of bleeds)	20 (90.9)	15 (75.0)	12 (80.0)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	2 (9.1)	5 (25.0)	3 (20.0)
Bleeds Per Subject			
Mean	1.2	1.1	0.8
SD	1.3	1.4	1.2
SE	0.3	0.3	0.3
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	2.0	2.0
P90	3.0	3.0	2.0
Minimum, Maximum	0, 5	0, 5	0, 4
Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.86	0.58	0.57

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 ** (N = 19)
Cumulative Number of Bleeds	22	20	15
Cumulative Number of Person-years Observed for Bleeding Events	11.85	34.34	26.19
Unadjusted Annualized Bleeding Rate [a]	1.86	0.58	0.57
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.73* (1.04, 2.88)	0.63 (0.34, 1.17)	0.63 (0.32, 1.26)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.35	0.36
Two-Sided 95% Wald CI [c] P-value [d]		(0.17, 0.74) 0.0028	(0.16, 0.83) 0.0080

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Number of Subjects With a Bleed, n (%)	15 (48.4)	12 (38.7)	9 (29.0)
Number of Bleeds, n	33	24	17
Number of Bleeds Treated With Factor IX, n (% of bleeds)	33 (100)	11 (45.8)	8 (47.1)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	0	13 (54.2)	9 (52.9)
Bleeds Per Subject			
Mean	1.1	0.8	0.5
SD	1.4	1.3	1.1
SE	0.3	0.2	0.2
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	0.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	2.0	2.0
Minimum, Maximum	0, 5	0, 6	0, 5
Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.70	0.41	0.39

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 ** (N = 31)
Cumulative Number of Bleeds	33	24	17
Cumulative Number of Person-years Observed for Bleeding Events	19.40	57.84	44.07
Unadjusted Annualized Bleeding Rate [a]	1.70	0.41	0.39
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	1.64* (0.99, 2.70)	0.43 (0.24, 0.78)	0.41 (0.20, 0.81)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.26	0.25
Two-Sided 95% Wald CI [c] P-value [d]		(0.15, 0.42) <0.0001	(0.13, 0.46) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.5213 (0.9020, 2.5658)	1.6600 (0.9503, 2.8997)
Ratio (Yes vs. No) of rate ratio (95% CI) P-value [e]		0.89 (0.27, 2.95) 0.8470	0.83 (0.23, 2.98) 0.7782

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Number of Subjects With a Bleed, n (%)	14 (66.7)	11 (52.4)	9 (42.9)
Number of Bleeds, n	37	33	26
Number of Bleeds Treated With Factor IX, n (% of bleeds)	25 (67.6)	13 (39.4)	9 (34.6)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	12 (32.4)	20 (60.6)	17 (65.4)
Bleeds Per Subject			
Mean	1.8	1.6	1.2
SD	2.3	3.3	2.7
SE	0.5	0.7	0.6
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	1.0	0.0
P75	2.0	1.0	1.0
P90	4.0	3.0	2.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	2.93	0.83	0.85

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 ** (N = 21)
Cumulative Number of Bleeds	37	33	26
Cumulative Number of Person-years Observed for Bleeding Events	12.65	39.74	30.49
Unadjusted Annualized Bleeding Rate [a]	2.93	0.83	0.85
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.97* (1.71, 5.17)	0.85 (0.35, 2.07)	0.87 (0.35, 2.15)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.29	0.29
Two-Sided 95% Wald CI [c] P-value [d]		(0.15, 0.55) <0.0001	(0.15, 0.59) 0.0003

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Number of Subjects With a Bleed, n (%)	14 (51.9)	12 (44.4)	9 (33.3)
Number of Bleeds, n	38	30	23
Number of Bleeds Treated With Factor IX, n (% of bleeds)	31 (81.6)	10 (33.3)	7 (30.4)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	7 (18.4)	20 (66.7)	16 (69.6)
Bleeds Per Subject			
Mean	1.4	1.1	0.9
SD	2.1	2.9	2.3
SE	0.4	0.6	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	2.0	2.0
Minimum, Maximum	0, 9	0, 15	0, 12
Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	2.32	0.59	0.58

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 ** (N = 27)
Cumulative Number of Bleeds	38	30	23
Cumulative Number of Person-years Observed for Bleeding Events	16.40	51.24	39.41
Unadjusted Annualized Bleeding Rate [a]	2.32	0.59	0.58
Adjusted Annualized Bleeding Rate [b] Adjusted Rate (95% CI) [b]	2.41* (1.37, 4.25)	0.59 (0.22, 1.55)	0.59 (0.21, 1.62)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.24	0.24
Two-Sided 95% Wald CI [c] P-value [d]		(0.12, 0.48) <0.0001	(0.12, 0.50) <0.0001
Negative Binomial Dispersion Parameter (95% CI)		1.8298 (1.0267, 3.2613)	2.0341 (1.1001, 3.7611)
Ratio (<S2 vs. >=S2) of rate ratio (95% CI) P-value [e]		1.04 (0.20, 5.45) 0.9630	1.19 (0.20, 7.12) 0.8484

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Table 1.4.2.2
Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Number of Subjects With a Bleed, n (%)	7 (63.6)	4 (36.4)	3 (27.3)
Number of Bleeds, n	14	9	6
Number of Bleeds Treated With Factor IX, n (% of bleeds)	13 (92.9)	6 (66.7)	4 (66.7)
Number of Bleeds Not Treated With Factor IX, n (% of bleeds)	1 (7.1)	3 (33.3)	2 (33.3)
Bleeds Per Subject			
Mean	1.3	0.8	0.5
SD	1.6	1.5	1.2
SE	0.5	0.5	0.4
P10	0.0	0.0	0.0
P25	0.0	0.0	0.0
Median	1.0	0.0	0.0
P75	2.0	1.0	1.0
P90	3.0	2.0	1.0
Minimum, Maximum	0, 5	0, 5	0, 4
Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	2.16	0.44	0.38

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Table 1.4.2.2

Annualized Bleeding Rates During Lead-In and Post-Treatment Period - Traumatic Bleeding by Subgroup
Baseline Steatosis Grade Category: $\geq$ S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 ** (N = 11)
Cumulative Number of Bleeds	14	9	6
Cumulative Number of Person-years Observed for Bleeding Events	6.48	20.59	15.68
Unadjusted Annualized Bleeding Rate [a]	2.16	0.44	0.38
Adjusted Annualized Bleeding Rate [b]	1.97*	0.47	0.41
Adjusted Rate (95% CI) [b]	(1.07, 3.66)	(0.16, 1.44)	(0.11, 1.50)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.24	0.21
Two-Sided 95% Wald CI [c]		(0.07, 0.77)	(0.05, 0.81)
P-value [d]		0.0083	0.0115

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Table 1.4.2.2

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

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SD: Standard deviation. SE: Standard error. LS: Least squares. CI: Confidence interval.

"Uncontaminated" means that the blood sampling did not occur within 5 half-lives of exogenous factor IX use. Both the date and time exogenous factor IX use and the blood sampling are considered in determining contamination. Factor IX levels beginning with the Week 1 assessment are used in the analysis. Subjects with zero uncontaminated central-laboratory post-AMT-061 values have their change from baseline assigned to zero for this analysis, and have their post-baseline values set equal to their baseline value. Any remaining missing data were imputed using the most recent previous uncontaminated post-treatment value that was observed for the subject (LOCF). LOCF denotes last (uncontaminated) post-treatment observation carried forward.

- [a] Baseline factor IX is imputed based on subject's historical hemophilia B severity documented on the CRF. If the patient has documented severe factor IX deficiency (factor IX plasma level < 1%) their baseline factor IX activity level is imputed as 1%. If the subject has documented moderately severe factor IX deficiency (factor IX plasma level $\geq 1\%$ and $\leq 2\%$) their baseline factor IX activity level is imputed as 2%.
- [b] LS Mean = least squares mean from repeated measures linear mixed model with visit as a categorical covariate, subgroup and its interaction with visit.
- [c] One-sided P-value ≤ 0.025 for Post-treatment > baseline is regarded as statistically significant.
- [d] Hedges' g was calculated as in the case of studies that used matched groups following the formula in Chapter 4 of Borenstein, Michael, et al. Introduction to meta-analysis. John Wiley & Sons, 2021.
- [e] Difference between subgroups in change from baseline. This p-value is two-sided.

CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	40	NA	
Mean (SD)	1.20 (0.41)		
SE	0.06		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	40	40	
Mean (SD)	40.20 (20.31)	39.00 (20.40)	
SE	3.21	3.23	
Q1	28.85	27.65	
Median	37.30	36.30	
Q3	50.90	49.90	
Minimum, Maximum	7.7, 97.1	5.7, 96.1	
LS Mean [b] (SE)	40.20 (2.668)	39.00 (2.682)	7.99 (5.582)
95% CI		(33.64, 44.36)	(-3.16, 19.15)
One-sided P-Value [c] [e]		<0.0001	0.1571
Hedges' g (95% CI) [d]		2.91(1.82, 4.01)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	40	40	
Mean (SD)	43.01 (22.89)	41.81 (22.98)	
SE	3.62	3.63	
Q1	29.65	28.60	
Median	38.65	37.65	
Q3	55.65	54.15	
Minimum, Maximum	8.5, 113.0	6.5, 112.0	
LS Mean [b] (SE)	43.01 (2.668)	41.81 (2.682)	9.27 (5.582)
95% CI		(36.45, 47.17)	(-1.88, 20.43)
One-sided P-Value [c] [e]		<0.0001	0.1017
Hedges' g (95% CI) [d]		2.78(1.72, 3.84)	
Post-Treatment Month 18			
n	40	40	
Mean (SD)	38.43 (22.92)	37.23 (23.01)	
SE	3.62	3.64	
Q1	25.80	24.30	
Median	35.05	34.05	
Q3	47.95	46.45	
Minimum, Maximum	8.5, 122.9	6.5, 121.9	
LS Mean [b] (SE)	38.43 (2.668)	37.22 (2.682)	8.37 (5.582)
95% CI		(31.86, 42.59)	(-2.79, 19.52)
One-sided P-Value [c] [e]		<0.0001	0.1390

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.47(1.50, 3.44)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	40	40	
Mean (SD)	38.28 (20.09)	37.08 (20.17)	
SE	3.18	3.19	
Q1	26.50	25.50	
Median	35.60	34.55	
Q3	47.30	46.30	
Minimum, Maximum	8.5, 99.2	6.5, 98.2	
LS Mean [b] (SE)	38.28 (2.668)	37.08 (2.682)	8.77 (5.582)
95% CI		(31.72, 42.44)	(-2.38, 19.93)
One-sided P-Value [c] [e]		<0.0001	0.1211
Hedges' g (95% CI) [d]		2.80(1.74, 3.86)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	12	NA	
Mean (SD)	1.17 (0.39)		
SE	0.11		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	12	12	
Mean (SD)	32.18 (12.78)	31.01 (12.86)	
SE	3.69	3.71	
Q1	24.95	23.45	
Median	31.50	30.10	
Q3	43.05	42.05	
Minimum, Maximum	10.0, 52.7	9.0, 51.7	
LS Mean [b] (SE)	32.18 (4.872)	31.01 (4.896)	
95% CI		(21.22, 40.79)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		3.45(1.18, 5.72)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	12	12	
Mean (SD)	33.70 (14.73)	32.53 (14.83)	
SE	4.25	4.28	
Q1	25.35	23.35	
Median	34.50	33.50	
Q3	48.05	47.05	
Minimum, Maximum	5.9, 50.1	4.9, 49.1	
LS Mean [b] (SE)	33.70 (4.872)	32.53 (4.896)	
95% CI		(22.75, 42.32)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		3.25(1.02, 5.47)	
Post-Treatment Month 18			
n	12	12	
Mean (SD)	30.03 (13.96)	28.86 (14.08)	
SE	4.03	4.06	
Q1	21.10	19.10	
Median	31.70	30.70	
Q3	41.15	40.15	
Minimum, Maximum	4.5, 51.8	3.5, 50.8	
LS Mean [b] (SE)	30.02 (4.872)	28.86 (4.896)	
95% CI		(19.07, 38.64)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		3.07(0.92, 5.23)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	12	12	
Mean (SD)	29.48 (13.44)	28.31 (13.52)	
SE	3.88	3.90	
Q1	23.70	22.20	
Median	31.40	30.40	
Q3	36.85	35.85	
Minimum, Maximum	4.7, 51.7	3.7, 50.7	
LS Mean [b] (SE)	29.47 (4.872)	28.31 (4.896)	
95% CI		(18.52, 38.09)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.98 (0.99, 4.98)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Baseline [a]			
n	33	NA	
Mean (SD)	1.12 (0.33)		
SE	0.06		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	33	33	
Mean (SD)	42.14 (17.14)	41.02 (17.18)	
SE	2.98	2.99	
Q1	33.00	32.00	
Median	38.90	37.90	
Q3	50.40	49.40	
Minimum, Maximum	8.2, 90.4	7.2, 89.4	
LS Mean [b] (SE)	42.14 (3.121)	41.02 (3.132)	10.57 (5.181)
95% CI		(34.76, 47.28)	(0.22, 20.93)
One-sided P-Value [c] [e]		<0.0001	0.0455
Hedges' g (95% CI) [d]		3.48 (2.13, 4.84)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	33	33	
Mean (SD)	43.97 (18.18)	42.85 (18.22)	
SE	3.16	3.17	
Q1	30.70	29.70	
Median	42.40	41.40	
Q3	50.10	49.10	
Minimum, Maximum	5.9, 83.8	4.9, 82.8	
LS Mean [b] (SE)	43.97 (3.121)	42.85 (3.132)	8.71 (5.181)
95% CI		(36.59, 49.11)	(-1.64, 19.07)
One-sided P-Value [c] [e]		<0.0001	0.0975
Hedges' g (95% CI) [d]		3.43(2.10, 4.76)	
Post-Treatment Month 18			
n	33	33	
Mean (SD)	40.39 (20.76)	39.27 (20.81)	
SE	3.61	3.62	
Q1	26.40	25.40	
Median	39.80	37.80	
Q3	48.40	47.40	
Minimum, Maximum	4.5, 122.9	3.5, 121.9	
LS Mean [b] (SE)	40.39 (3.121)	39.27 (3.132)	10.88 (5.181)
95% CI		(33.01, 45.53)	(0.53, 21.23)
One-sided P-Value [c] [e]		<0.0001	0.0398

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.76(1.64, 3.87)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	33	33	
Mean (SD)	39.89 (17.07)	38.77 (17.11)	
SE	2.97	2.98	
Q1	27.30	26.30	
Median	36.70	34.80	
Q3	48.20	47.20	
Minimum, Maximum	4.7, 88.3	3.7, 87.3	
LS Mean [b] (SE)	39.89 (3.121)	38.77 (3.132)	10.15 (5.181)
95% CI		(32.51, 45.03)	(-0.20, 20.51)
One-sided P-Value [c] [e]		<0.0001	0.0545
Hedges' g (95% CI) [d]		3.27(2.00, 4.54)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	19	NA	
Mean (SD)	1.32 (0.48)		
SE	0.11		
Q1	1.00		
Median	1.00		
Q3	2.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	19	19	
Mean (SD)	31.76 (20.80)	30.45 (20.88)	
SE	4.77	4.79	
Q1	15.90	13.90	
Median	30.60	29.60	
Q3	37.30	36.30	
Minimum, Maximum	7.7, 97.1	5.7, 96.1	
LS Mean [b] (SE)	31.76 (4.113)	30.45 (4.127)	
95% CI		(22.20, 38.70)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.13(0.91, 3.35)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	19	19	
Mean (SD)	35.45 (26.00)	34.14 (26.11)	
SE	5.97	5.99	
Q1	13.20	12.20	
Median	31.70	29.70	
Q3	41.10	40.10	
Minimum, Maximum	8.5, 113.0	6.5, 112.0	
LS Mean [b] (SE)	35.45 (4.113)	34.14 (4.127)	
95% CI		(25.89, 42.39)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		1.96(0.77, 3.14)	
Post-Treatment Month 18			
n	19	19	
Mean (SD)	29.71 (21.22)	28.39 (21.33)	
SE	4.87	4.89	
Q1	13.10	11.10	
Median	28.60	27.60	
Q3	35.60	34.60	
Minimum, Maximum	8.5, 102.7	6.5, 101.7	
LS Mean [b] (SE)	29.71 (4.113)	28.39 (4.127)	
95% CI		(20.14, 36.64)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		1.99(0.80, 3.19)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	19	19	
Mean (SD)	29.93 (20.98)	28.62 (21.07)	
SE	4.81	4.83	
Q1	11.90	9.90	
Median	27.30	26.30	
Q3	35.80	34.80	
Minimum, Maximum	8.5, 99.2	6.5, 98.2	
LS Mean [b] (SE)	29.93 (4.113)	28.62 (4.127)	
95% CI		(20.37, 36.86)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.00 (0.82, 3.18)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Baseline [a]			
n	39	NA	
Mean (SD)	1.18 (0.39)		
SE	0.06		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	39	39	
Mean (SD)	35.40 (14.70)	34.22 (14.73)	
SE	2.35	2.36	
Q1	26.70	25.10	
Median	37.30	36.30	
Q3	48.60	47.60	
Minimum, Maximum	7.7, 62.4	5.7, 61.4	
LS Mean [b] (SE)	35.40 (2.704)	34.22 (2.719)	-11.75 (5.437)
95% CI		(28.79, 39.66)	(-22.62, -0.88)
One-sided P-Value [c] [e]		<0.0001	0.0346
Hedges' g (95% CI) [d]		3.33(2.16, 4.50)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	39	39	
Mean (SD)	38.41 (18.22)	37.23 (18.26)	
SE	2.92	2.92	
Q1	28.30	26.30	
Median	38.80	37.80	
Q3	49.00	48.00	
Minimum, Maximum	5.9, 80.5	4.9, 79.5	
LS Mean [b] (SE)	38.41 (2.704)	37.23 (2.719)	-9.76 (5.437)
95% CI		(31.79, 42.66)	(-20.63, 1.11)
One-sided P-Value [c] [e]		<0.0001	0.0776
Hedges' g (95% CI) [d]		2.97(1.89, 4.04)	
Post-Treatment Month 18			
n	39	39	
Mean (SD)	34.59 (19.88)	33.42 (19.94)	
SE	3.18	3.19	
Q1	23.30	22.30	
Median	35.00	34.00	
Q3	43.10	42.10	
Minimum, Maximum	4.5, 122.9	3.5, 121.9	
LS Mean [b] (SE)	34.59 (2.704)	33.42 (2.719)	-7.52 (5.437)
95% CI		(27.98, 38.85)	(-18.38, 3.35)
One-sided P-Value [c] [e]		<0.0001	0.1719

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.47(1.53, 3.42)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	39	39	
Mean (SD)	33.13 (14.14)	31.95 (14.16)	
SE	2.26	2.27	
Q1	25.60	23.60	
Median	34.20	33.20	
Q3	44.20	43.20	
Minimum, Maximum	4.7, 64.6	3.7, 63.6	
LS Mean [b] (SE)	33.13 (2.704)	31.95 (2.719)	-12.42 (5.437)
95% CI		(26.52, 37.39)	(-23.28, -1.55)
One-sided P-Value [c] [e]		<0.0001	0.0258
Hedges' g (95% CI) [d]		3.21(2.09, 4.34)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Baseline [a]			
n	13	NA	
Mean (SD)	1.23 (0.44)		
SE	0.12		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	13	13	
Mean (SD)	47.20 (27.25)	45.97 (27.46)	
SE	7.56	7.62	
Q1	31.30	30.30	
Median	35.30	34.30	
Q3	68.60	67.60	
Minimum, Maximum	15.9, 97.1	13.9, 96.1	
LS Mean [b] (SE)	47.20 (4.684)	45.97 (4.709)	
95% CI		(36.56, 55.38)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.67 (0.72, 4.63)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	13	13	
Mean (SD)	48.22 (28.96)	46.98 (29.16)	
SE	8.03	8.09	
Q1	31.60	29.70	
Median	34.30	33.30	
Q3	68.10	67.10	
Minimum, Maximum	12.7, 113.0	10.7, 112.0	
LS Mean [b] (SE)	48.22 (4.684)	46.98 (4.709)	
95% CI		(37.57, 56.40)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.57 (0.68, 4.46)	
Post-Treatment Month 18			
n	13	13	
Mean (SD)	42.16 (25.33)	40.93 (25.52)	
SE	7.02	7.08	
Q1	25.60	24.60	
Median	32.10	30.10	
Q3	57.90	56.90	
Minimum, Maximum	13.1, 102.7	11.1, 101.7	
LS Mean [b] (SE)	42.16 (4.684)	40.93 (4.709)	
95% CI		(31.52, 50.34)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.54(0.68, 4.40)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	13	13	
Mean (SD)	45.60 (27.89)	44.37 (28.09)	
SE	7.73	7.79	
Q1	27.30	26.30	
Median	32.60	30.60	
Q3	60.40	59.40	
Minimum, Maximum	11.9, 99.2	9.9, 98.2	
LS Mean [b] (SE)	45.60 (4.684)	44.37 (4.709)	
95% CI		(34.96, 53.78)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.52(0.65, 4.39)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Baseline [a]			
n	43	NA	
Mean (SD)	1.19 (0.39)		
SE	0.06		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	43	43	
Mean (SD)	38.80 (20.18)	37.62 (20.29)	
SE	3.08	3.09	
Q1	26.70	25.10	
Median	37.30	36.30	
Q3	50.40	49.40	
Minimum, Maximum	7.7, 97.1	5.7, 96.1	
LS Mean [b] (SE)	38.80 (2.623)	37.62 (2.635)	2.65 (6.333)
95% CI		(32.35, 42.88)	(-10.01, 15.31)
One-sided P-Value [c] [e]		<0.0001	0.6771
Hedges' g (95% CI) [d]		2.91(1.82, 4.00)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	43	43	
Mean (SD)	41.26 (22.85)	40.07 (22.97)	
SE	3.48	3.50	
Q1	28.30	26.30	
Median	38.80	37.80	
Q3	50.10	49.10	
Minimum, Maximum	5.9, 113.0	4.9, 112.0	
LS Mean [b] (SE)	41.26 (2.623)	40.07 (2.635)	2.34 (6.333)
95% CI		(34.81, 45.34)	(-10.32, 15.00)
One-sided P-Value [c] [e]		<0.0001	0.7132
Hedges' g (95% CI) [d]		2.75 (1.71, 3.80)	
Post-Treatment Month 18			
n	43	43	
Mean (SD)	36.93 (22.83)	35.75 (22.95)	
SE	3.48	3.50	
Q1	24.10	22.10	
Median	35.00	34.00	
Q3	44.00	43.00	
Minimum, Maximum	4.5, 122.9	3.5, 121.9	
LS Mean [b] (SE)	36.93 (2.623)	35.75 (2.635)	2.61 (6.333)
95% CI		(30.48, 41.01)	(-10.05, 15.27)
One-sided P-Value [c] [e]		<0.0001	0.6813

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.46(1.50, 3.42)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	43	43	
Mean (SD)	36.63 (20.06)	35.45 (20.17)	
SE	3.06	3.08	
Q1	25.60	23.60	
Median	33.50	32.50	
Q3	45.00	43.50	
Minimum, Maximum	4.7, 99.2	3.7, 98.2	
LS Mean [b] (SE)	36.63 (2.623)	35.45 (2.635)	2.25 (6.333)
95% CI		(30.18, 40.71)	(-10.41, 14.91)
One-sided P-Value [c] [e]		<0.0001	0.7240
Hedges' g (95% CI) [d]		2.75 (1.71, 3.79)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	9	NA	
Mean (SD)	1.22 (0.44)		
SE	0.15		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	9	9	
Mean (SD)	36.19 (12.90)	34.97 (12.73)	
SE	4.30	4.24	
Q1	28.40	27.40	
Median	37.30	35.40	
Q3	48.60	47.60	
Minimum, Maximum	13.8, 53.7	12.8, 51.7	
LS Mean [b] (SE)	36.19 (5.733)	34.97 (5.759)	
95% CI		(23.46, 46.48)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.69(1.20, 4.19)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	9	9	
Mean (SD)	38.96 (14.36)	37.73 (14.20)	
SE	4.79	4.73	
Q1	30.20	29.20	
Median	36.30	35.30	
Q3	49.00	48.00	
Minimum, Maximum	13.2, 60.5	12.2, 59.5	
LS Mean [b] (SE)	38.96 (5.733)	37.73 (5.759)	
95% CI		(26.22, 49.24)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.66(1.15, 4.18)	
Post-Treatment Month 18			
n	9	9	
Mean (SD)	34.36 (12.90)	33.13 (12.72)	
SE	4.30	4.24	
Q1	26.20	25.20	
Median	32.00	31.00	
Q3	47.50	45.50	
Minimum, Maximum	12.0, 49.3	11.0, 48.3	
LS Mean [b] (SE)	34.36 (5.733)	33.13 (5.759)	
95% CI		(21.62, 44.64)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.56(1.12, 3.99)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	9	9	
Mean (SD)	34.42 (13.74)	33.20 (13.58)	
SE	4.58	4.53	
Q1	27.20	26.20	
Median	35.40	34.40	
Q3	47.40	46.40	
Minimum, Maximum	9.1, 50.7	8.1, 49.0	
LS Mean [b] (SE)	34.42 (5.733)	33.20 (5.759)	
95% CI		(21.69, 44.71)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.45(1.03, 3.87)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	33	NA	
Mean (SD)	1.15 (0.36)		
SE	0.06		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	33	33	
Mean (SD)	40.61 (18.64)	39.46 (18.72)	
SE	3.24	3.26	
Q1	31.30	30.30	
Median	37.30	36.30	
Q3	51.40	50.40	
Minimum, Maximum	8.4, 97.1	7.4, 96.1	
LS Mean [b] (SE)	40.61 (2.929)	39.46 (2.941)	6.29 (4.865)
95% CI		(33.58, 45.34)	(-3.43, 16.02)
One-sided P-Value [c] [e]		<0.0001	0.2006
Hedges' g (95% CI) [d]		3.22(1.90, 4.53)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	33	33	
Mean (SD)	44.14 (23.18)	42.99 (23.27)	
SE	4.03	4.05	
Q1	30.70	29.60	
Median	36.30	35.30	
Q3	54.80	53.80	
Minimum, Maximum	5.9, 113.0	4.9, 112.0	
LS Mean [b] (SE)	44.14 (2.929)	42.99 (2.941)	9.09 (4.865)
95% CI		(37.11, 48.87)	(-0.64, 18.81)
One-sided P-Value [c] [e]		<0.0001	0.0665
Hedges' g (95% CI) [d]		2.86(1.65, 4.08)	
Post-Treatment Month 18			
n	33	33	
Mean (SD)	39.87 (24.08)	38.72 (24.16)	
SE	4.19	4.21	
Q1	25.60	24.60	
Median	35.00	34.00	
Q3	48.50	47.50	
Minimum, Maximum	4.5, 122.9	3.5, 121.9	
LS Mean [b] (SE)	39.87 (2.929)	38.72 (2.941)	9.38 (4.865)
95% CI		(32.84, 44.60)	(-0.35, 19.10)
One-sided P-Value [c] [e]		<0.0001	0.0585

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.45(1.39, 3.50)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	33	33	
Mean (SD)	38.55 (19.19)	37.40 (19.27)	
SE	3.34	3.35	
Q1	26.10	25.10	
Median	35.40	34.40	
Q3	47.40	46.40	
Minimum, Maximum	4.7, 99.2	3.7, 98.2	
LS Mean [b] (SE)	38.55 (2.929)	37.40 (2.941)	6.40 (4.865)
95% CI		(31.52, 43.28)	(-3.32, 16.13)
One-sided P-Value [c] [e]		<0.0001	0.1930
Hedges' g (95% CI) [d]		2.96(1.73, 4.19)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	19	NA	
Mean (SD)	1.26 (0.45)		
SE	0.10		
Q1	1.00		
Median	1.00		
Q3	2.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	19	19	
Mean (SD)	34.43 (19.58)	33.16 (19.64)	
SE	4.49	4.51	
Q1	16.30	15.30	
Median	33.80	32.80	
Q3	43.50	42.50	
Minimum, Maximum	7.7, 90.4	5.7, 89.4	
LS Mean [b] (SE)	34.43 (3.860)	33.16 (3.876)	
95% CI		(25.42, 40.91)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.41(1.10, 3.73)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Post-Treatment Month 12			
n	19	19	
Mean (SD)	35.16 (17.42)	33.90 (17.45)	
SE	4.00	4.00	
Q1	16.30	15.30	
Median	38.80	37.80	
Q3	47.90	46.90	
Minimum, Maximum	8.5, 73.6	6.5, 72.6	
LS Mean [b] (SE)	35.16 (3.860)	33.90 (3.876)	
95% CI		(26.15, 41.65)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.72 (1.31, 4.12)	
Post-Treatment Month 18			
n	19	19	
Mean (SD)	30.61 (14.31)	29.34 (14.39)	
SE	3.28	3.30	
Q1	13.80	12.80	
Median	32.00	31.00	
Q3	39.80	38.80	
Minimum, Maximum	8.5, 57.9	6.5, 56.9	
LS Mean [b] (SE)	30.61 (3.860)	29.34 (3.876)	
95% CI		(21.59, 37.09)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.96(1.39, 4.53)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Post-Treatment Month 24			
n	19	19	
Mean (SD)	32.26 (18.54)	30.99 (18.59)	
SE	4.25	4.26	
Q1	14.80	13.80	
Median	33.50	32.50	
Q3	39.10	38.10	
Minimum, Maximum	8.5, 88.3	6.5, 87.3	
LS Mean [b] (SE)	32.26 (3.860)	30.99 (3.876)	
95% CI		(23.25, 38.74)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.37 (1.08, 3.66)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Baseline [a]			
n	31	NA	
Mean (SD)	1.16 (0.37)		
SE	0.07		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	31	31	
Mean (SD)	43.00 (20.42)	41.84 (20.45)	
SE	3.67	3.67	
Q1	31.30	30.30	
Median	37.90	36.90	
Q3	52.60	50.60	
Minimum, Maximum	8.2, 97.1	7.2, 96.1	
LS Mean [b] (SE)	43.00 (2.972)	41.84 (2.985)	11.59 (4.697)
95% CI		(35.87, 47.80)	(2.21, 20.98)
One-sided P-Value [c] [e]		<0.0001	0.0163
Hedges' g (95% CI) [d]		2.91(1.74, 4.08)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	31	31	
Mean (SD)	45.87 (22.78)	44.71 (22.81)	
SE	4.09	4.10	
Q1	30.70	29.70	
Median	42.30	41.30	
Q3	54.80	53.80	
Minimum, Maximum	5.9, 113.0	4.9, 112.0	
LS Mean [b] (SE)	45.87 (2.972)	44.71 (2.985)	12.49 (4.697)
95% CI		(38.75, 50.67)	(3.10, 21.87)
One-sided P-Value [c] [e]		<0.0001	0.0099
Hedges' g (95% CI) [d]		2.80 (1.66, 3.94)	
Post-Treatment Month 18			
n	31	31	
Mean (SD)	41.49 (24.04)	40.33 (24.09)	
SE	4.32	4.33	
Q1	26.40	25.40	
Median	39.80	37.80	
Q3	48.40	47.40	
Minimum, Maximum	4.5, 122.9	3.5, 121.9	
LS Mean [b] (SE)	41.49 (2.972)	40.33 (2.985)	12.46 (4.697)
95% CI		(34.36, 46.29)	(3.07, 21.84)
One-sided P-Value [c] [e]		<0.0001	0.0101

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.44(1.40, 3.49)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	31	31	
Mean (SD)	40.33 (20.49)	39.17 (20.52)	
SE	3.68	3.69	
Q1	27.30	26.30	
Median	35.80	34.70	
Q3	48.20	47.20	
Minimum, Maximum	4.7, 99.2	3.7, 98.2	
LS Mean [b] (SE)	40.33 (2.972)	39.17 (2.985)	10.18 (4.697)
95% CI		(33.20, 45.13)	(0.79, 19.56)
One-sided P-Value [c] [e]		<0.0001	0.0340
Hedges' g (95% CI) [d]		2.71(1.61, 3.81)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Baseline [a]			
n	21	NA	
Mean (SD)	1.24 (0.44)		
SE	0.10		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	21	21	
Mean (SD)	31.49 (14.68)	30.25 (14.85)	
SE	3.20	3.24	
Q1	22.10	21.10	
Median	32.70	31.70	
Q3	42.60	41.60	
Minimum, Maximum	7.7, 62.4	5.7, 61.4	
LS Mean [b] (SE)	31.49 (3.611)	30.25 (3.627)	
95% CI		(23.00, 37.49)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		3.25 (1.48, 5.02)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Post-Treatment Month 12			
n	21	21	
Mean (SD)	33.46 (17.50)	32.22 (17.68)	
SE	3.82	3.86	
Q1	22.30	20.30	
Median	31.70	29.70	
Q3	42.40	41.40	
Minimum, Maximum	8.5, 73.4	6.5, 72.4	
LS Mean [b] (SE)	33.46 (3.611)	32.22 (3.627)	
95% CI		(24.98, 39.47)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.93 (1.30, 4.56)	
Post-Treatment Month 18			
n	21	21	
Mean (SD)	29.10 (14.18)	27.87 (14.35)	
SE	3.09	3.13	
Q1	20.40	18.60	
Median	26.60	25.60	
Q3	37.30	36.30	
Minimum, Maximum	8.5, 57.8	6.5, 56.8	
LS Mean [b] (SE)	29.10 (3.611)	27.87 (3.627)	
95% CI		(20.62, 35.11)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		3.11(1.40, 4.81)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	21	21	
Mean (SD)	30.23 (15.11)	28.99 (15.28)	
SE	3.30	3.33	
Q1	23.10	21.40	
Median	27.20	26.20	
Q3	40.60	39.60	
Minimum, Maximum	8.5, 64.6	6.5, 63.6	
LS Mean [b] (SE)	30.23 (3.611)	28.99 (3.627)	
95% CI		(21.74, 36.24)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		3.03(1.36, 4.69)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	27	NA	
Mean (SD)	1.11 (0.32)		
SE	0.06		
Q1	1.00		
Median	1.00		
Q3	1.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	27	27	
Mean (SD)	40.79 (20.12)	39.68 (20.19)	
SE	3.87	3.89	
Q1	27.10	25.10	
Median	37.30	36.30	
Q3	51.40	50.40	
Minimum, Maximum	8.2, 97.1	7.2, 96.1	
LS Mean [b] (SE)	40.79 (3.323)	39.68 (3.345)	8.87 (6.218)
95% CI		(32.95, 46.41)	(-3.64, 21.38)
One-sided P-Value [c] [e]		<0.0001	0.1605
Hedges' g (95% CI) [d]		2.95(1.61, 4.29)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups (i.e. interaction) [e]
Post-Treatment Month 12			
n	27	27	
Mean (SD)	45.49 (24.12)	44.37 (24.19)	
SE	4.64	4.66	
Q1	28.80	27.80	
Median	41.00	40.00	
Q3	54.80	53.80	
Minimum, Maximum	11.4, 113.0	10.4, 112.0	
LS Mean [b] (SE)	45.49 (3.323)	44.37 (3.345)	13.47 (6.218)
95% CI		(37.64, 51.11)	(0.96, 25.99)
One-sided P-Value [c] [e]		<0.0001	0.0354
Hedges' g (95% CI) [d]		2.76 (1.49, 4.04)	
Post-Treatment Month 18			
n	27	27	
Mean (SD)	41.57 (25.73)	40.46 (25.79)	
SE	4.95	4.96	
Q1	25.60	24.00	
Median	35.10	34.10	
Q3	51.80	50.80	
Minimum, Maximum	10.3, 122.9	9.3, 121.9	
LS Mean [b] (SE)	41.57 (3.323)	40.46 (3.345)	14.40 (6.218)
95% CI		(33.73, 47.19)	(1.88, 26.91)
One-sided P-Value [c] [e]		<0.0001	0.0251

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.34(1.23, 3.45)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	27	27	
Mean (SD)	40.16 (19.77)	39.04 (19.84)	
SE	3.81	3.82	
Q1	27.20	26.20	
Median	35.40	34.40	
Q3	50.00	49.00	
Minimum, Maximum	10.1, 99.2	9.1, 98.2	
LS Mean [b] (SE)	40.16 (3.323)	39.04 (3.345)	13.74 (6.218)
95% CI		(32.31, 45.78)	(1.23, 26.26)
One-sided P-Value [c] [e]		<0.0001	0.0320
Hedges' g (95% CI) [d]		2.94(1.61, 4.28)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Baseline [a]			
n	11	NA	
Mean (SD)	1.27 (0.47)		
SE	0.14		
Q1	1.00		
Median	1.00		
Q3	2.00		
Minimum, Maximum	1.0, 2.0		
Post-Treatment Month 6			
n	11	11	
Mean (SD)	32.08 (15.27)	30.81 (15.56)	
SE	4.61	4.69	
Q1	15.90	13.90	
Median	33.00	32.00	
Q3	42.60	41.60	
Minimum, Maximum	7.7, 52.7	5.7, 51.7	
LS Mean [b] (SE)	32.08 (5.206)	30.81 (5.241)	
95% CI		(20.26, 41.36)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		3.28(0.63, 5.92)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 12			
n	11	11	
Mean (SD)	32.17 (17.68)	30.90 (17.95)	
SE	5.33	5.41	
Q1	12.70	10.70	
Median	33.00	32.00	
Q3	48.60	47.60	
Minimum, Maximum	5.9, 60.5	4.9, 59.5	
LS Mean [b] (SE)	32.17 (5.206)	30.90 (5.241)	
95% CI		(20.35, 41.45)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.81(0.52, 5.11)	
Post-Treatment Month 18			
n	11	11	
Mean (SD)	27.34 (14.41)	26.06 (14.69)	
SE	4.35	4.43	
Q1	13.10	11.10	
Median	28.60	27.60	
Q3	39.80	38.80	
Minimum, Maximum	4.5, 49.3	3.5, 48.3	
LS Mean [b] (SE)	27.34 (5.206)	26.06 (5.241)	
95% CI		(15.52, 36.61)	
One-sided P-Value [c]		<0.0001	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Hedges' g (95% CI) [d]		2.91(0.54, 5.27)	

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 3.2a Imputed (by LOCF) Missing Uncontaminated Central Laboratory Data for Factor IX Activity (%) by Visit in the Post-Treatment Period - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

One-Stage aPTT Assay			
	Value	Change From Baseline	Difference between Subgroups(i.e. interaction) [e]
Post-Treatment Month 24			
n	11	11	
Mean (SD)	26.57 (13.82)	25.30 (14.07)	
SE	4.17	4.24	
Q1	11.90	9.90	
Median	27.30	26.30	
Q3	35.80	34.80	
Minimum, Maximum	4.7, 47.4	3.7, 46.4	
LS Mean [b] (SE)	26.57 (5.206)	25.30 (5.241)	
95% CI		(14.75, 35.85)	
One-sided P-Value [c]		<0.0001	
Hedges' g (95% CI) [d]		2.90 (0.58, 5.21)	

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Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
Analysis Set: Modified Intent to Treat Population

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Factor IX replacement therapy use for invasive procedures is not included in analysis.

N = number of subjects under observation in the time interval.

Lead-In period time is the total number of days during which the subject is in the lead-in period divided by 365.25.

Post-treatment period time is the number of days of observation within the time interval.

Annualized consumption was calculated as the normalized amount of therapy administered, extrapolated where necessary from any time period less or greater than one year. Therapy administered includes the total dosage of factor IX given as replacement therapy excluding use for invasive procedures. Having no records of exogenous factor IX use means zero consumption.

[a] Adjusted mean from repeated measures linear mixed model with phase as a categorical covariate, subgroup and its interaction with phase. One-sided P-value ≤ 0.025 for Post-treatment - Lead-In < 0 is regarded as statistically significant.

[b] Hedges' g was calculated as in the case of studies that used matched groups following the formula in Chapter 4 of Borenstein, Michael, et al. Introduction to meta-analysis. John Wiley & Sons, 2021.

[c] This p-value is two-sided.

CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Post-Treatment Period	
		Month 0-24 (N = 40)	Month 7-24 (N = 40)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	40	40	40
n (%)	40 (100.0)	40 (100.0)	40 (100.0)
Mean	255796.1	4561.5	2711.7
SD	148562.0	6540.8	6144.8
SE	23489.72	1034.19	971.58
Median	204764.5	2001.4	0.0
Minimum, Maximum	88545, 755892	0, 24517	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

		Post-Treatment Period	
	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 (N = 40)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-251234.6 (146281.9)	-253084.4 (148348.3)
Adjusted Mean (SE) [a]		-251234.6 (23104.27)	-253084.4 (23694.02)
95% CI		(-297640.9, -204828.3)	(-300675.2, -205493.6)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.89(-2.47, -1.32)	-2.30(-3.11, -1.49)
Difference (White vs. Non-White or Not Specified) of			
change from Lead-In [a]		18987.9	23012.0
95% CI		(-77614.5, 115590.3)	(-76056.2, 122080.2)
P-value [c]		0.6947	0.6428

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup

Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Post-Treatment Period	
		Month 0-24 (N = 12)	Month 7-24 (N = 12)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	12	12	12
n (%)	12 (100.0)	12 (100.0)	12 (100.0)
Mean	283014.4	12791.9	6918.1
SD	158722.9	20267.5	9307.0
SE	45819.34	5850.72	2686.71
Median	251990.8	4036.0	670.2
Minimum, Maximum	83541, 682839	0, 70116	0, 24252

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

		Post-Treatment Period	
	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 (N = 12)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-270222.5 (145563.8)	-276096.4 (155075.1)
Adjusted Mean (SE) [a]		-270222.5 (42182.44)	-276096.4 (43259.16)
95% CI		(-354948.5, -185496.6)	(-362984.9, -189207.8)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.37(-1.97, -0.77)	-1.79(-2.75, -0.83)

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Post-Treatment Period	
		Month 0-24 (N = 33)	Month 7-24 (N = 33)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	33	33	33
n (%)	33 (100.0)	33 (100.0)	33 (100.0)
Mean	229159.4	3407.1	1897.8
SD	94014.8	4910.9	4562.6
SE	16365.87	854.89	794.25
Median	204388.6	1503.1	0.0
Minimum, Maximum	83541, 435845	0, 19513	0, 20700

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

		Post-Treatment Period	
	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 (N = 33)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-225752.2 (92415.2)	-227261.5 (93437.5)
Adjusted Mean (SE) [a]		-225752.2 (24499.76)	-227261.5 (25107.76)
95% CI		(-274961.5, -176543.0)	(-277692.0, -176831.1)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-2.72(-3.56, -1.88)	-3.10(-4.16, -2.03)
Difference (Europe vs. USA) of change from Lead-In			
[a]		81733.6	85207.0
95% CI		(324.8, 163142.4)	(1777.9, 168636.0)
P-value [c]		0.0491	0.0455

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup

Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Post-Treatment Period	
		Month 0-24 (N = 19)	Month 7-24 (N = 19)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	19	19	19
n (%)	19 (100.0)	19 (100.0)	19 (100.0)
Mean	319250.5	11764.7	6782.0
SD	206022.0	16993.9	9530.4
SE	47264.68	3898.67	2186.43
Median	241367.4	6079.1	0.0
Minimum, Maximum	88545, 755892	0, 70116	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

		Post-Treatment Period	
	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 (N = 19)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-307485.8 (199596.1)	-312468.5 (205586.0)
Adjusted Mean (SE) [a]		-307485.8 (32288.06)	-312468.5 (33089.34)
95% CI		(-372338.3, -242633.4)	(-378930.4, -246006.6)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.60 (-2.32, -0.88)	-1.99 (-3.03, -0.94)

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup

Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

	Lead-In Period (N = 39)	Post-Treatment Period	
		Month 0-24 (N = 39)	Month 7-24 (N = 39)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	39	39	39
n (%)	39 (100.0)	39 (100.0)	39 (100.0)
Mean	274984.8	7327.3	3854.6
SD	156142.7	12815.7	7034.6
SE	25002.85	2052.16	1126.45
Median	225432.3	3006.2	0.0
Minimum, Maximum	83541, 755892	0, 70116	0, 24252

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

		Post-Treatment Period	
	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 (N = 39)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-267657.5 (150576.9)	-271130.2 (155341.4)
Adjusted Mean (SE) [a]		-267657.5 (23186.26)	-271130.2 (23776.73)
95% CI		(-314228.5, -221086.6)	(-318887.2, -223373.2)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.80(-2.32, -1.28)	-2.25(-3.02, -1.48)
Difference (>=1 vs. 0) of change from Lead-In [a]			
95% CI		-48164.3 (-141306.2, 44977.6)	-50941.3 (-146455.3, 44572.6)
P-value [c]		0.3040	0.2892

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Post-Treatment Period	
		Month 0-24 (N = 13)	Month 7-24 (N = 13)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	13	13	13
n (%)	13 (100.0)	13 (100.0)	13 (100.0)
Mean	223354.8	3861.6	3166.0
SD	126578.7	6150.2	7657.4
SE	35106.60	1705.75	2123.79
Median	187014.3	1503.1	0.0
Minimum, Maximum	100068, 588053	0, 22530	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

		Post-Treatment Period	
	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 (N = 13)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-219493.2 (124745.0)	-220188.9 (124306.0)
Adjusted Mean (SE) [a]		-219493.2 (40159.77)	-220188.9 (41182.51)
95% CI		(-300156.5, -138829.9)	(-302906.4, -137471.3)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.92(-2.97, -0.88)	-1.93(-2.97, -0.88)

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Post-Treatment Period	
		Month 0-24 (N = 43)	Month 7-24 (N = 43)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	43	43	43
n (%)	43 (100.0)	43 (100.0)	43 (100.0)
Mean	242080.1	5298.1	3577.8
SD	129529.2	7814.0	7061.5
SE	19753.02	1191.62	1076.87
Median	205140.4	2001.4	0.0
Minimum, Maximum	83541, 755892	0, 30021	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Post-Treatment Period	
		Month 0-24 (N = 43)	Month 7-24 (N = 43)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-236782.0 (127996.4)	-238502.2 (129214.4)
Adjusted Mean (SE) [a]		-236782.0 (21380.39)	-238502.2 (21881.15)
95% CI		(-279725.8, -193838.2)	(-282451.8, -194552.6)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-2.26(-2.96, -1.56)	-2.47(-3.29, -1.65)
Difference (Absence vs. Presence) of change from		108821.1	114935.0
Lead-In [a]			
95% CI		(5597.1, 212045.2)	(9293.4, 220576.7)
P-value [c]		0.0392	0.0336

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Post-Treatment Period	
		Month 0-24 (N = 9)	Month 7-24 (N = 9)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	9	9	9
n (%)	9 (100.0)	9 (100.0)	9 (100.0)
Mean	357619.6	12016.4	4182.3
SD	206367.0	22113.1	7839.6
SE	68788.98	7371.02	2613.21
Median	320538.4	4515.5	0.0
Minimum, Maximum	157384, 682839	0, 70116	0, 24252

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Post-Treatment Period	
		Month 0-24 (N = 9)	Month 7-24 (N = 9)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-345603.2 (191937.8)	-353437.3 (202528.0)
Adjusted Mean (SE) [a]		-345603.2 (46733.54)	-353437.3 (47828.11)
95% CI		(-439470.2, -251736.1)	(-449502.9, -257371.7)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.29(-1.96, -0.63)	-1.57(-2.50, -0.64)

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Post-Treatment Period	
		Month 0-24 (N = 33)	Month 7-24 (N = 33)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	33	33	33
n (%)	33 (100.0)	33 (100.0)	33 (100.0)
Mean	264888.0	4213.7	1864.4
SD	153545.0	6226.3	4739.5
SE	26728.76	1083.86	825.03
Median	222111.5	2001.4	0.0
Minimum, Maximum	93922, 755892	0, 30021	0, 20700

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

		Post-Treatment Period	
	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 (N = 33)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-260674.3 (152043.8)	-263023.6 (153609.8)
Adjusted Mean (SE) [a]		-260674.3 (25449.09)	-263023.6 (26120.54)
95% CI		(-311790.3, -209558.3)	(-315488.3, -210559.0)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-2.04(-2.76, -1.31)	-2.36(-3.29, -1.43)
Difference (Negative vs. Positive) of change from			
Lead-In [a]		-13842.6	-12668.3
95% CI		(-98405.9, 70720.6)	(-99462.6, 74126.1)
P-value [c]		0.7437	0.7706

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Post-Treatment Period	
		Month 0-24 (N = 19)	Month 7-24 (N = 19)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	19	19	19
n (%)	19 (100.0)	19 (100.0)	19 (100.0)
Mean	257195.5	10363.8	6840.1
SD	147114.7	16858.3	9343.5
SE	33750.42	3867.56	2143.54
Median	241367.4	3959.3	2670.9
Minimum, Maximum	83541, 682839	0, 70116	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Post-Treatment Period	
		Month 0-24 (N = 19)	Month 7-24 (N = 19)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-246831.7 (135170.4)	-250355.4 (143506.6)
Adjusted Mean (SE) [a]		-246831.7 (33539.17)	-250355.4 (34424.07)
95% CI		(-314197.1, -179466.3)	(-319498.2, -181212.6)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.27(-1.70, -0.84)	-1.81(-2.59, -1.03)

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Post-Treatment Period	
		Month 0-24 (N = 31)	Month 7-24 (N = 31)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	31	31	31
n (%)	31 (100.0)	31 (100.0)	31 (100.0)
Mean	251508.3	4222.5	2386.3
SD	136722.3	6443.1	5169.0
SE	24556.05	1157.22	928.37
Median	204388.6	1010.4	0.0
Minimum, Maximum	83541, 755892	0, 24517	0, 20700

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Post-Treatment Period	
		Month 0-24 (N = 31)	Month 7-24 (N = 31)
		Post-Treatment Period - Lead-In Period Differences	
Unadjusted Mean (SD)		-247285.8 (134144.6)	-249122.0 (136115.7)
Adjusted Mean (SE) [a]		-247285.8 (26220.11)	-249122.0 (26894.06)
95% CI		(-299950.5, -194621.2)	(-303140.3, -195103.7)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.94(-2.57, -1.30)	-2.35(-3.24, -1.46)
Difference (Yes vs. No) of change from Lead-In [a]			
95% CI		(-62244.5, 103500.8)	(-62041.5, 107964.1)
P-value [c]		0.6193	0.5898

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Post-Treatment Period	
		Month 0-24 (N = 21)	Month 7-24 (N = 21)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	21	21	21
n (%)	21 (100.0)	21 (100.0)	21 (100.0)
Mean	277679.1	9765.1	5595.8
SD	169610.2	16096.9	9105.6
SE	37011.99	3512.64	1987.00
Median	225117.0	4002.7	0.0
Minimum, Maximum	88545, 682839	0, 70116	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup

Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

		Post-Treatment Period	
	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 (N = 21)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-267914.0 (162137.6)	-272083.3 (168118.5)
Adjusted Mean (SE) [a]		-267914.0 (31857.06)	-272083.3 (32675.91)
95% CI		(-331900.8, -203927.2)	(-337714.8, -206451.8)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.59(-2.22, -0.96)	-1.98(-2.91, -1.06)

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Post-Treatment Period	
		Month 0-24 (N = 27)	Month 7-24 (N = 27)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	27	27	27
n (%)	27 (100.0)	27 (100.0)	27 (100.0)
Mean	246943.4	5135.5	2636.0
SD	163395.3	7813.8	6418.6
SE	31445.45	1503.77	1235.27
Median	202704.2	1017.2	0.0
Minimum, Maximum	83541, 755892	0, 30021	0, 27061

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

		Post-Treatment Period	
	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 (N = 27)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-241807.9 (160628.8)	-244307.5 (163349.4)
Adjusted Mean (SE) [a]		-241807.9 (27496.53)	-244307.5 (27947.34)
95% CI		(-297573.5, -186042.4)	(-300987.3, -187627.6)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-1.63(-2.27, -1.00)	-2.03(-2.94, -1.12)
Difference (<S2 vs. >=S2) of change from Lead-In [a]			
95% CI		-24693.3 (-128341.4, 78954.8)	-25980.4 (-131327.8, 79367.1)
P-value [c]		0.6319	0.6200

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup
 Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Post-Treatment Period	
		Month 0-24 (N = 11)	Month 7-24 (N = 11)
Annualized Exogenous Factor IX Consumption (IU/yr.)			
N	11	11	11
n (%)	11 (100.0)	11 (100.0)	11 (100.0)
Mean	223426.1	6311.6	5099.1
SD	75600.1	7453.0	8859.9
SE	22794.29	2247.16	2671.35
Median	205140.4	3265.6	0.0
Minimum, Maximum	88545, 322958	0, 22015	0, 24038

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Table 5.2a Annualized consumption of FIX replacement therapy (IU/year; Excluding invasive procedure) - by Subgroup

Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

		Post-Treatment Period	
	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 (N = 11)
Post-Treatment Period - Lead-In Period Differences			
Unadjusted Mean (SD)		-217114.6 (80029.6)	-218327.1 (80886.2)
Adjusted Mean (SE) [a]		-217114.6 (43078.78)	-218327.1 (43785.07)
95% CI		(-304482.4, -129746.8)	(-307127.3, -129526.9)
P-value [a]		<0.0001	<0.0001
Hedges' g (95% CI) [b]		-4.43(-7.84, -1.02)	-4.40(-7.79, -1.01)

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

14. FIX-Ersatztherapie – Annualisierte Infusionsrate der FIX-Ersatztherapie – Subgruppenanalysen – Studie HOPE-B – Monat 24

Post-treatment period time is the number of days of observation within the time interval starting from Day 1.

Pxx = xx-th percentile. N = number of subjects under observation in the time interval.

For subgroups based on "Lead-In Bleed Count Category", model-based statistics are not calculated.

* For Comparison with Post-Treatment Month 7-24.

- [a] Unadjusted infusion rate is calculated as the ratio of the number of infusions of factor IX to the time of observation (in years). Usage related to invasive procedures is not included.
- [b] Adjusted infusion rate and comparison of infusion rate between lead-in and post-treatment period is estimated from a repeated measures generalized estimating equations negative binomial regression model accounting for the paired design of the trial with an offset parameter to account for the differential collection periods. The model includes Treatment period and subgroup as categorical variables and an interaction term between treatment period and the subgroup. Dispersion parameter and the associated confidence interval are presented to more fully characterize the distribution of the endpoint.
- [c] One-sided P-value ≤ 0.025 for Post-treatment/Lead-In < 1 is regarded as statistically significant.
- [d] Two-sided P-value.

Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 (N = 40)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	40 (100)	29 (72.5)	12 (30.0)
Number of Infusions of Factor IX Replacement Therapy, n	1655	81	32
Infusions Per Subject			
Mean	41.4	2.0	0.8
SD	21.6	2.4	1.9
SE	3.4	0.4	0.3
P10	18.5	0.0	0.0
P25	29.0	0.0	0.0
Median	35.5	1.0	0.0
P75	54.0	2.5	1.0
P90	66.5	5.5	2.0
Minimum, Maximum	12, 107	0, 11	0, 9
Number of Person-years Observed for Factor IX Usage	24.87	78.78	58.74
Unadjusted Annualized Infusion Rate [a]	66.54	1.03	0.54

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Race group: White (N=40)

	Lead-In Period (N = 40)	Month 0-24 (N = 40)	Month 7-24 (N = 40)
Cumulative Number of Infusions of Factor IX Therapy	1655	81	32
Cumulative Number of Person-years Observed for Factor IX Usage	24.87	78.78	58.74
Unadjusted Annualized Infusion Rate [a]	66.54	1.03	0.54
Adjusted Annualized Infusion Rate [b]	66.76*	1.03	0.55
Adjusted Rate (95% CI) [b]	(57.25, 77.85)	(0.72, 1.48)	(0.27, 1.12)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.02	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.02)	(0.00, 0.02)
P-value [c]		<0.0001	<0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.3326 (0.2196, 0.5037)	0.3542 (0.2142, 0.5858)
Ratio (White vs. Non-White or Not Specified) of rate ratio (95% CI)		0.44 (0.24, 0.81)	0.37 (0.18, 0.77)
P-value [d]		0.0085	0.0077

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 (N = 12)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	12 (100)	10 (83.3)	6 (50.0)
Number of Infusions of Factor IX Replacement Therapy, n	659	79	37
Infusions Per Subject			
Mean	54.9	6.6	3.1
SD	23.6	7.8	4.5
SE	6.8	2.3	1.3
P10	31.0	0.0	0.0
P25	37.5	1.0	0.0
Median	55.5	4.0	0.5
P75	68.5	10.5	5.0
P90	75.0	17.0	9.0
Minimum, Maximum	19, 105	0, 25	0, 14
Number of Person-years Observed for Factor IX Usage	7.18	23.93	17.92
Unadjusted Annualized Infusion Rate [a]	91.80	3.30	2.06

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Race group: Non-White or Not Specified (N=12)

	Lead-In Period (N = 12)	Month 0-24 (N = 12)	Month 7-24 (N = 12)
Cumulative Number of Infusions of Factor IX Therapy	659	79	37
Cumulative Number of Person-years Observed for Factor IX Usage	7.18	23.93	17.92
Unadjusted Annualized Infusion Rate [a]	91.80	3.30	2.06
Adjusted Annualized Infusion Rate [b]	93.26*	3.30	2.06
Adjusted Rate (95% CI) [b]	(73.86, 117.75)	(1.74, 6.27)	(0.93, 4.56)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.04	0.02
Two-Sided 95% Wald CI [c]		(0.02, 0.06)	(0.01, 0.05)
P-value [c]		<0.0001	<0.0001

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 (N = 33)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	33 (100)	25 (75.8)	9 (27.3)
Number of Infusions of Factor IX Replacement Therapy, n	1631	81	35
Infusions Per Subject			
Mean	49.4	2.5	1.1
SD	19.3	3.4	2.9
SE	3.4	0.6	0.5
P10	29.0	0.0	0.0
P25	36.0	1.0	0.0
Median	43.0	1.0	0.0
P75	65.0	3.0	1.0
P90	70.0	5.0	2.0
Minimum, Maximum	21, 107	0, 17	0, 14
Number of Person-years Observed for Factor IX Usage	20.70	64.79	48.26
Unadjusted Annualized Infusion Rate [a]	78.79	1.25	0.73

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Geographic region: Europe (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 (N = 33)
Cumulative Number of Infusions of Factor IX Therapy	1631	81	35
Cumulative Number of Person-years Observed for Factor IX Usage	20.70	64.79	48.26
Unadjusted Annualized Infusion Rate [a]	78.79	1.25	0.73
Adjusted Annualized Infusion Rate [b]	79.81*	1.25	0.73
Adjusted Rate (95% CI) [b]	(70.10, 90.87)	(0.78, 2.00)	(0.30, 1.81)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.02	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.02)	(0.00, 0.02)
P-value [c]		<0.0001	<0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.4176 (0.2777, 0.6278)	0.4401 (0.2610, 0.7422)
Ratio (Europe vs. USA) of rate ratio (95% CI)		0.45 (0.25, 0.83)	0.46 (0.23, 0.95)
P-value [d]		0.0110	0.0348

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 (N = 19)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	19 (100)	14 (73.7)	9 (47.4)
Number of Infusions of Factor IX Replacement Therapy, n	683	79	34
Infusions Per Subject			
Mean	35.9	4.2	1.8
SD	25.7	6.1	2.8
SE	5.9	1.4	0.6
P10	14.0	0.0	0.0
P25	19.0	0.0	0.0
Median	30.0	2.0	0.0
P75	46.0	7.0	3.0
P90	96.0	11.0	7.0
Minimum, Maximum	12, 105	0, 25	0, 9
Number of Person-years Observed for Factor IX Usage	11.35	37.92	28.41
Unadjusted Annualized Infusion Rate [a]	60.18	2.08	1.20

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Geographic region: USA (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 (N = 19)
Cumulative Number of Infusions of Factor IX Therapy	683	79	34
Cumulative Number of Person-years Observed for Factor IX Usage	11.35	37.92	28.41
Unadjusted Annualized Infusion Rate [a]	60.18	2.08	1.20
Adjusted Annualized Infusion Rate [b]	60.37*	2.08	1.20
Adjusted Rate (95% CI) [b]	(44.24, 82.39)	(1.09, 3.97)	(0.61, 2.35)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.03	0.02
Two-Sided 95% Wald CI [c]		(0.02, 0.06)	(0.01, 0.04)
P-value [c]		<0.0001	<0.0001

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: >=1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 (N = 39)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	39 (100)	31 (79.5)	14 (35.9)
Number of Infusions of Factor IX Replacement Therapy, n	1871	139	58
Infusions Per Subject			
Mean	48.0	3.6	1.5
SD	24.7	5.1	3.1
SE	3.9	0.8	0.5
P10	16.0	0.0	0.0
P25	31.0	1.0	0.0
Median	42.0	2.0	0.0
P75	66.0	4.0	2.0
P90	81.0	11.0	6.0
Minimum, Maximum	12, 107	0, 25	0, 14
Number of Person-years Observed for Factor IX Usage	24.02	76.81	57.27
Unadjusted Annualized Infusion Rate [a]	77.88	1.81	1.01

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: ≥ 1 (N=39)

	Lead-In Period (N = 39)	Month 0-24 (N = 39)	Month 7-24 (N = 39)
Cumulative Number of Infusions of Factor IX Therapy	1871	139	58
Cumulative Number of Person-years Observed for Factor IX Usage	24.02	76.81	57.27
Unadjusted Annualized Infusion Rate [a]	77.88	1.81	1.01

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 (N = 13)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	13 (100)	8 (61.5)	4 (30.8)
Number of Infusions of Factor IX Replacement Therapy, n	443	21	11
Infusions Per Subject			
Mean	34.1	1.6	0.8
SD	9.2	2.3	2.0
SE	2.5	0.6	0.5
P10	24.0	0.0	0.0
P25	30.0	0.0	0.0
Median	31.0	1.0	0.0
P75	36.0	2.0	1.0
P90	46.0	4.0	2.0
Minimum, Maximum	21, 53	0, 8	0, 7
Number of Person-years Observed for Factor IX Usage	8.02	25.91	19.39
Unadjusted Annualized Infusion Rate [a]	55.20	0.81	0.57

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Lead-in Bleeding Episode Count Category: 0 (N=13)

	Lead-In Period (N = 13)	Month 0-24 (N = 13)	Month 7-24 (N = 13)
Cumulative Number of Infusions of Factor IX Therapy	443	21	11
Cumulative Number of Person-years Observed for Factor IX Usage	8.02	25.91	19.39
Unadjusted Annualized Infusion Rate [a]	55.20	0.81	0.57

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 (N = 43)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	43 (100)	31 (72.1)	14 (32.6)
Number of Infusions of Factor IX Replacement Therapy, n	1841	116	58
Infusions Per Subject			
Mean	42.8	2.7	1.3
SD	21.9	3.7	3.0
SE	3.3	0.6	0.5
P10	19.0	0.0	0.0
P25	29.0	0.0	0.0
Median	36.0	1.0	0.0
P75	57.0	3.0	1.0
P90	70.0	8.0	4.0
Minimum, Maximum	12, 107	0, 17	0, 14
Number of Person-years Observed for Factor IX Usage	26.62	84.78	63.23
Unadjusted Annualized Infusion Rate [a]	69.15	1.37	0.92

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In Period (N = 43)	Month 0-24 (N = 43)	Month 7-24 (N = 43)
Cumulative Number of Infusions of Factor IX Therapy	1841	116	58
Cumulative Number of Person-years Observed for Factor IX Usage	26.62	84.78	63.23
Unadjusted Annualized Infusion Rate [a]	69.15	1.37	0.92
Adjusted Annualized Infusion Rate [b]	69.39*	1.37	0.92
Adjusted Rate (95% CI) [b]	(59.91, 80.38)	(0.91, 2.05)	(0.48, 1.77)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.02	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.03)	(0.01, 0.03)
P-value [c]		<0.0001	<0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.4274 (0.2852, 0.6404)	0.4711 (0.2803, 0.7918)
Ratio (Absence vs. Presence) of rate ratio (95% CI)		0.71 (0.34, 1.52)	1.44 (0.56, 3.76)
P-value [d]		0.3838	0.4502

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 (N = 9)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	9 (100)	8 (88.9)	4 (44.4)
Number of Infusions of Factor IX Replacement Therapy, n	473	44	11
Infusions Per Subject			
Mean	52.6	4.9	1.2
SD	25.2	7.7	2.0
SE	8.4	2.6	0.7
P10	21.0	0.0	0.0
P25	36.0	2.0	0.0
Median	53.0	2.0	0.0
P75	66.0	4.0	2.0
P90	105.0	25.0	6.0
Minimum, Maximum	21, 105	0, 25	0, 6
Number of Person-years Observed for Factor IX Usage	5.43	17.94	13.43
Unadjusted Annualized Infusion Rate [a]	87.17	2.45	0.82

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In Period (N = 9)	Month 0-24 (N = 9)	Month 7-24 (N = 9)
Cumulative Number of Infusions of Factor IX Therapy	473	44	11
Cumulative Number of Person-years Observed for Factor IX Usage	5.43	17.94	13.43
Unadjusted Annualized Infusion Rate [a]	87.17	2.45	0.82
Adjusted Annualized Infusion Rate [b]	88.92*	2.45	0.82
Adjusted Rate (95% CI) [b]	(65.84, 120.08)	(0.93, 6.47)	(0.30, 2.23)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.03	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.06)	(0.00, 0.02)
P-value [c]		<0.0001	<0.0001

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 (N = 33)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	33 (100)	25 (75.8)	8 (24.2)
Number of Infusions of Factor IX Replacement Therapy, n	1537	78	26
Infusions Per Subject			
Mean	46.6	2.4	0.8
SD	22.9	3.3	2.5
SE	4.0	0.6	0.4
P10	21.0	0.0	0.0
P25	30.0	1.0	0.0
Median	38.0	2.0	0.0
P75	65.0	3.0	0.0
P90	75.0	4.0	2.0
Minimum, Maximum	16, 107	0, 17	0, 14
Number of Person-years Observed for Factor IX Usage	20.20	65.78	49.24
Unadjusted Annualized Infusion Rate [a]	76.09	1.19	0.53

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

	Lead-In Period (N = 33)	Month 0-24 (N = 33)	Month 7-24 (N = 33)
Cumulative Number of Infusions of Factor IX Therapy	1537	78	26
Cumulative Number of Person-years Observed for Factor IX Usage	20.20	65.78	49.24
Unadjusted Annualized Infusion Rate [a]	76.09	1.19	0.53
Adjusted Annualized Infusion Rate [b]	77.08*	1.19	0.53
Adjusted Rate (95% CI) [b]	(65.49, 90.72)	(0.74, 1.89)	(0.18, 1.55)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.02	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.02)	(0.00, 0.02)
P-value [c]		<0.0001	<0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.4179 (0.2792, 0.6257)	0.4091 (0.2479, 0.6749)
Ratio (Negative vs. Positive) of rate ratio (95% CI)		0.45 (0.25, 0.84)	0.28 (0.14, 0.58)
P-value [d]		0.0111	0.0005

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 (N = 19)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	19 (100)	14 (73.7)	10 (52.6)
Number of Infusions of Factor IX Replacement Therapy, n	777	82	43
Infusions Per Subject			
Mean	40.9	4.3	2.3
SD	22.1	6.2	3.1
SE	5.1	1.4	0.7
P10	14.0	0.0	0.0
P25	29.0	0.0	0.0
Median	36.0	1.0	1.0
P75	55.0	7.0	3.0
P90	66.0	11.0	9.0
Minimum, Maximum	12, 105	0, 25	0, 9
Number of Person-years Observed for Factor IX Usage	11.85	36.94	27.42
Unadjusted Annualized Infusion Rate [a]	65.57	2.22	1.57

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

	Lead-In Period (N = 19)	Month 0-24 (N = 19)	Month 7-24 (N = 19)
Cumulative Number of Infusions of Factor IX Therapy	777	82	43
Cumulative Number of Person-years Observed for Factor IX Usage	11.85	36.94	27.42
Unadjusted Annualized Infusion Rate [a]	65.57	2.22	1.57
Adjusted Annualized Infusion Rate [b]	65.39*	2.22	1.59
Adjusted Rate (95% CI) [b]	(51.85, 82.48)	(1.19, 4.13)	(0.87, 2.89)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.03	0.02
Two-Sided 95% Wald CI [c]		(0.02, 0.06)	(0.01, 0.04)
P-value [c]		<0.0001	<0.0001

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 (N = 31)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	31 (100)	20 (64.5)	8 (25.8)
Number of Infusions of Factor IX Replacement Therapy, n	1349	73	36
Infusions Per Subject			
Mean	43.5	2.4	1.2
SD	18.2	3.7	3.0
SE	3.3	0.7	0.5
P10	29.0	0.0	0.0
P25	30.0	0.0	0.0
Median	36.0	1.0	0.0
P75	57.0	3.0	1.0
P90	66.0	6.0	3.0
Minimum, Maximum	14, 96	0, 17	0, 14
Number of Person-years Observed for Factor IX Usage	19.40	60.81	45.28
Unadjusted Annualized Infusion Rate [a]	69.52	1.20	0.80

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: Yes (N=31)

	Lead-In Period (N = 31)	Month 0-24 (N = 31)	Month 7-24 (N = 31)
Cumulative Number of Infusions of Factor IX Therapy	1349	73	36
Cumulative Number of Person-years Observed for Factor IX Usage	19.40	60.81	45.28
Unadjusted Annualized Infusion Rate [a]	69.52	1.20	0.80
Adjusted Annualized Infusion Rate [b]	70.65*	1.20	0.81
Adjusted Rate (95% CI) [b]	(60.53, 82.46)	(0.70, 2.07)	(0.33, 1.94)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.02	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.03)	(0.01, 0.03)
P-value [c]		<0.0001	<0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.4303 (0.2881, 0.6426)	0.4789 (0.2868, 0.7996)
Ratio (Yes vs. No) of rate ratio (95% CI)		0.62 (0.34, 1.14)	0.82 (0.40, 1.69)
P-value [d]		0.1237	0.5924

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 (N = 21)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	21 (100)	19 (90.5)	10 (47.6)
Number of Infusions of Factor IX Replacement Therapy, n	965	87	33
Infusions Per Subject			
Mean	46.0	4.1	1.6
SD	28.2	5.7	2.6
SE	6.2	1.2	0.6
P10	16.0	1.0	0.0
P25	21.0	1.0	0.0
Median	38.0	2.0	0.0
P75	65.0	4.0	1.0
P90	81.0	10.0	6.0
Minimum, Maximum	12, 107	0, 25	0, 9
Number of Person-years Observed for Factor IX Usage	12.65	41.91	31.38
Unadjusted Annualized Infusion Rate [a]	76.31	2.08	1.05

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Hepatitis B or C Category: No (N=21)

	Lead-In Period (N = 21)	Month 0-24 (N = 21)	Month 7-24 (N = 21)
Cumulative Number of Infusions of Factor IX Therapy	965	87	33
Cumulative Number of Person-years Observed for Factor IX Usage	12.65	41.91	31.38
Unadjusted Annualized Infusion Rate [a]	76.31	2.08	1.05
Adjusted Annualized Infusion Rate [b]	75.84*	2.08	1.05
Adjusted Rate (95% CI) [b]	(59.68, 96.36)	(1.17, 3.67)	(0.52, 2.12)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.03	0.01
Two-Sided 95% Wald CI [c]		(0.02, 0.05)	(0.01, 0.03)
P-value [c]		<0.0001	<0.0001

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 (N = 27)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	27 (100)	20 (74.1)	7 (25.9)
Number of Infusions of Factor IX Replacement Therapy, n	1137	65	25
Infusions Per Subject			
Mean	42.1	2.4	0.9
SD	18.4	3.0	2.2
SE	3.5	0.6	0.4
P10	19.0	0.0	0.0
P25	30.0	0.0	0.0
Median	39.0	1.0	0.0
P75	55.0	3.0	1.0
P90	65.0	8.0	4.0
Minimum, Maximum	12, 96	0, 11	0, 9
Number of Person-years Observed for Factor IX Usage	16.40	53.83	40.30
Unadjusted Annualized Infusion Rate [a]	69.33	1.21	0.62

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In Period (N = 27)	Month 0-24 (N = 27)	Month 7-24 (N = 27)
Cumulative Number of Infusions of Factor IX Therapy	1137	65	25
Cumulative Number of Person-years Observed for Factor IX Usage	16.40	53.83	40.30
Unadjusted Annualized Infusion Rate [a]	69.33	1.21	0.62
Adjusted Annualized Infusion Rate [b]	70.09*	1.21	0.62
Adjusted Rate (95% CI) [b]	(59.15, 83.06)	(0.76, 1.92)	(0.25, 1.51)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.02	0.01
Two-Sided 95% Wald CI [c]		(0.01, 0.03)	(0.00, 0.02)
P-value [c]		<0.0001	<0.0001
Negative Binomial Dispersion Parameter (95% CI)		0.3403 (0.2061, 0.5620)	0.4972 (0.2655, 0.9311)
Ratio (<S2 vs. ≥S2) of rate ratio (95% CI)		0.60 (0.30, 1.21)	0.39 (0.16, 0.94)
P-value [d]		0.1542	0.0364

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 (N = 11)
Number of Subjects Using Factor IX Replacement Therapy, n (%)	11 (100)	9 (81.8)	4 (36.4)
Number of Infusions of Factor IX Replacement Therapy, n	457	45	27
Infusions Per Subject			
Mean	41.5	4.1	2.5
SD	21.2	5.3	4.7
SE	6.4	1.6	1.4
P10	21.0	0.0	0.0
P25	21.0	1.0	0.0
Median	36.0	2.0	0.0
P75	66.0	4.0	3.0
P90	70.0	11.0	9.0
Minimum, Maximum	14, 75	0, 17	0, 14
Number of Person-years Observed for Factor IX Usage	6.48	21.92	16.41
Unadjusted Annualized Infusion Rate [a]	70.55	2.05	1.64

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Table 24.2.2

Annualized Infusion Rate of Factor IX Replacement Therapy (infusions/yr.) Excluding Invasive Procedures by Period by Subgroups
Analysis Set: Modified Intent to Treat Population

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In Period (N = 11)	Month 0-24 (N = 11)	Month 7-24 (N = 11)
Cumulative Number of Infusions of Factor IX Therapy	457	45	27
Cumulative Number of Person-years Observed for Factor IX Usage	6.48	21.92	16.41
Unadjusted Annualized Infusion Rate [a]	70.55	2.05	1.64
Adjusted Annualized Infusion Rate [b]	71.59*	2.05	1.64
Adjusted Rate (95% CI) [b]	(53.21, 96.31)	(0.99, 4.23)	(0.56, 4.82)
Rate Ratio (Post-Treatment/Lead-In) [b]		0.03	0.02
Two-Sided 95% Wald CI [c]		(0.01, 0.06)	(0.01, 0.07)
P-value [c]		<0.0001	<0.0001

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15. Hem-A-QoL-Score (15 % MCID) – Hem-A-QoL (körperliche Gesundheit) – Subgruppenanalysen – Studie HOPE-B – Monat 24

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Race Group: White (N=40)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 40/35/34/40/39/35)	[d]				
(nb: 40/40/40/40/40/37)	[e]				
Improvement	10/40/25.00	15/39/38.461.83 (23.36, 55.38) 0.2253	(0.68, 4.96)	1.50 (0.78, 2.90) 0.2253	0.13 (-0.08, 0.33) 0.2253
Deterioration	3/40/7.50	5/39/12.821.67 (4.30, 27.43) 0.4795	(0.40, 6.97)	1.67 (0.40, 6.97) 0.4795	0.05 (-0.09, 0.19) 0.4795
Post-Treatment Month 24					
Improvement	10/40/25.00	11/35/31.431.13 (16.85, 49.29) 0.8084	(0.43, 2.92)	1.10 (0.51, 2.38) 0.8084	0.03 (-0.20, 0.26) 0.8084
Deterioration	3/40/7.50	6/35/17.142.00 (6.56, 33.65) 0.3173	(0.50, 8.00)	2.00 (0.50, 8.00) 0.3173	0.09 (-0.08, 0.25) 0.3173

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of

Life Index (Hem-A-QoL) by Subgroups

Analysis

Set: Modified Intent to Treat Population [N=52]

Race Group: Non-White or Not Specified (N=12)

Domain: Physical Health Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Difference, 95% CI, and p-value
(n: 12/8/8/12/9/12) [d]					
[e]					
(nb:12/12/12/12/11/12)					
Improvement	4/12/33.33	3/9/33.33 (7.49, 70.07)	1.50 (0.25, 8.98) 0.6547	1.50 (0.25, 8.98) 0.6547	0.11 (-0.37, 0.59) 0.6547
Deterioration	0/12/0.00	0/9/0.00	1.32 (0.02, 72.54) 0.8953 @	1.30 (0.03, 60.02) 0.8953 @	0.01 (-0.16, 0.18) 0.8953 @
Post-Treatment Month 24					
Improvement	4/12/33.33	2/12/16.67 (2.09, 48.41)	0.50 (0.09, 2.73) 0.4142	0.50 (0.09, 2.73) 0.4142	-0.17 (-0.56, 0.22) 0.4142
Deterioration	0/12/0.00	3/12/25.00 (5.49, 57.19)	9.21 (0.42, 200.59) 0.1098 @	7.00 (0.40, 122.44) 0.1098 @	0.23 (-0.03, 0.49) 0.1098 @

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Race Group Interactions									
		Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference	
		Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]	P value [h]
Post-Treatment Month Improvement	12	1.22			1.00			0.02	0.5509
		1.27	@		1.28	@		0.04 @	NA @
Post-Treatment Month Improvement	24	2.26			2.20			0.20	0.2610
		0.22	@		0.29	@		-0.14 @	NA @

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Geographic Region: Europe (N=33)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 33/27/26/33/30/31)	[d]				
(nb: 33/33/33/33/32/32)	[e]				
Improvement	9/33/27.27	11/30/36.67 (19.93, 56.14)	1.60 (0.52, 4.89) 0.4054	1.38 (0.65, 2.92) 0.4054	0.10 (-0.13, 0.33) 0.4054
Deterioration	1/33/3.03	3/30/10.00 (2.11, 26.53)	3.00 (0.31, 28.84) 0.3173	3.00 (0.31, 28.84) 0.3173	0.07 (-0.06, 0.20) 0.3173
Post-Treatment Month 24					
Improvement	9/33/27.27	9/31/29.03 (14.22, 48.04)	1.00 (0.38, 2.66) 1.0000	1.00 (0.42, 2.39) 1.0000	0.00 (-0.25, 0.25) 1.0000
Deterioration	1/33/3.03	5/31/16.13 (5.45, 33.73)	5.00 (0.58, 42.80) 0.1025	5.00 (0.58, 42.80) 0.1025	0.13 (-0.02, 0.28) 0.1025

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Geographic Region: USA (N=19)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 19/16/16/19/18/16)	[d]				
(nb: 19/19/19/19/19/17)	[e]				
Improvement	5/19/26.32	7/18/38.892.00 (17.30, 64.25) 0.3173	(0.50, 8.00)	1.75 (0.58, 5.32) 0.3173	0.17 (-0.15, 0.48) 0.3173
Deterioration	2/19/10.53	2/18/11.111.00 (1.38, 34.71) 1.0000	(0.14, 7.10)	1.00 (0.14, 7.10) 1.0000	0.00 (-0.22, 0.22) 1.0000
Post-Treatment Month 24					
Improvement	5/19/26.32	4/16/25.000.75 (7.27, 52.38) 0.7055	(0.17, 3.35)	0.80 (0.25, 2.55) 0.7055	-0.06 (-0.39, 0.26) 0.7055
Deterioration	2/19/10.53	4/16/25.002.00 (7.27, 52.38) 0.4142	(0.37, 10.92)	2.00 (0.37, 10.92) 0.4142	0.13 (-0.17, 0.42) 0.4142

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Geographic Region Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	0.80	0.79	-0.07	0.8728
Deterioration	3.00	3.00	0.07	0.4405
Post-Treatment Month 24				
Improvement	1.33	1.25	0.06	0.8704
Deterioration	2.50	2.50	0.00	0.5939

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Physical Health Domain Score

		Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 39/30/29/39/35/35)		[d]				
(nb: 39/39/39/39/38/37)		[e]				
Improvement		9/39/23.08	17/35/48.57 (31.38, 66.01)	4.33 (1.23, 15.21) 0.0124	2.43 (1.18, 4.98) 0.0124	0.29 (0.08, 0.49) 0.0124
Deterioration		3/39/7.69	3/35/8.57 (1.80, 23.06)	1.00 (0.20, 4.95) 1.0000	1.00 (0.20, 4.95) 1.0000	0.00 (-0.14, 0.14) 1.0000
Post-Treatment	Month 24					
Improvement		9/39/23.08	10/35/28.57 (14.64, 46.30)	1.13 (0.43, 2.92) 0.8084	1.11 (0.47, 2.60) 0.8084	0.03 (-0.20, 0.26) 0.8084
Deterioration		3/39/7.69	7/35/20.00 (8.44, 36.94)	2.33 (0.60, 9.02) 0.2059	2.33 (0.60, 9.02) 0.2059	0.11 (-0.06, 0.29) 0.2059

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Physical Health Domain Score

		Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Difference, 95% CI, and p-value
(n: 13/13/13/13/13/12)		[d]				
(nb: 13/13/13/13/13/12)		[e]				
Improvement	5/13/38.46	1/13/7.69 (0.19, 36.03)	0.20 (0.02, 1.71) 0.1025	0.20 (0.02, 1.71) 0.1025	-0.31 (-0.64, 0.02) 0.1025	
Deterioration	0/13/0.00	2/13/15.38 (1.92, 45.45)	5.87 (0.25, 135.15) 0.2301 @	5.00 (0.26, 95.02) 0.2301 @	0.14 (-0.08, 0.37) 0.2301 @	
Post-Treatment Month 24						
Improvement	5/13/38.46	3/12/25.00 (5.49, 57.19)	0.50 (0.09, 2.73) 0.4142	0.60 (0.17, 2.07) 0.4142	-0.17 (-0.56, 0.22) 0.4142	
Deterioration	0/13/0.00	2/12/16.67 (2.09, 48.41)	6.43 (0.28, 148.77) 0.2043 @	5.38 (0.28, 101.96) 0.2043 @	0.16 (-0.08, 0.39) 0.2043 @	

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Lead-in Bleeding Episode Count Category Interactions											
			Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference		
			Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction		
			Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]		P value [h]
Post-Treatment Improvement Deterioration	Month 12		21.65			12.15			0.60		0.0061
			0.17	@		0.20	@		-0.14	@	NA @
Post-Treatment Improvement Deterioration	Month 24		2.26			1.85			0.20		0.3696
			0.36	@		0.43	@		-0.05	@	NA @

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
 Analysis Set: Modified Intent to Treat Population [N=52]
 Domain: Physical Health Domain Score

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 9/7/6/9/9/8) [d]					
(nb: 9/9/9/9/9/9) [e]					
Improvement	1/9/11.11	7/9/77.78NC (39.99, 97.19) 0.0143	(NC, NC)	7.00 (1.14, 42.97) 0.0143	0.67 (0.36, 0.97) 0.0143
Deterioration	0/9/0.00	1/9/11.113.35 (0.28, 48.25) 0.4675 @	(0.12, 93.83)	3.00 (0.14, 65.16) 0.4675 @	0.10 (-0.16, 0.36) 0.4675 @
Post-Treatment Month 24					
Improvement	1/9/11.11	3/8/37.503.00 (8.52, 75.51) 0.3173	(0.31, 28.84)	3.00 (0.31, 28.84) 0.3173	0.25 (-0.21, 0.71) 0.3173
Deterioration	0/9/0.00	2/8/25.007.31 (3.19, 65.09) 0.1857 @	(0.30, 178.57)	5.56 (0.31, 100.94) 0.1857 @	0.23 (-0.09, 0.55) 0.1857 @

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
 Analysis Set: Modified Intent to Treat Population [N=52]
 Domain: Physical Health Domain Score

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 43/36/36/43/39/39)	[d]				
(nb: 43/43/43/43/42/40)	[e]				
Improvement	13/43/30.23	11/39/28.211.00 (15.00, 44.87)	1.00 (0.38, 2.66) 1.0000	1.00 (0.49, 2.04) 1.0000	0.00 (-0.20, 0.20) 1.0000
Deterioration	3/43/6.98	4/39/10.261.33 (2.87, 24.22)	1.33 (0.30, 5.96) 0.7055	1.33 (0.30, 5.96) 0.7055	0.03 (-0.11, 0.16) 0.7055
Post-Treatment Month 24					
Improvement	13/43/30.23	10/39/25.640.73 (13.04, 42.13)	0.77 (0.29, 1.81) 0.4913	0.77 (0.36, 1.63) 0.4913	-0.08 (-0.29, 0.14) 0.4913
Deterioration	3/43/6.98	7/39/17.952.33 (7.54, 33.53)	2.33 (0.60, 9.02) 0.2059	2.33 (0.60, 9.02) 0.2059	0.10 (-0.05, 0.26) 0.2059

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Status of Target Joint at Screening Category Interactions											
			Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference		
			Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction		
			Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g] P value [h]		
Post-Treatment Improvement Deterioration	Month	12	NC			7.00			0.67		0.0082
			2.52	@		2.26	@		0.07	@	
Post-Treatment Improvement Deterioration	Month	24	4.11			3.90			0.33		0.1744
			3.14	@		2.39	@		0.13	@	

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 19/16/16/19/18/17)	[d]				
(nb: 19/19/19/19/18/17)	[e]				
Improvement	2/19/10.53	5/18/27.782.50 (0.49, 12.89)	2.50 (0.49, 12.89)	0.17 (-0.11, 0.44)	
Deterioration	1/19/5.26	2/18/11.112.00 (0.18, 22.06)	2.00 (0.18, 22.06)	0.06 (-0.13, 0.24)	
		(9.69, 53.48) 0.2568	0.2568	0.2568	
		(1.38, 34.71) 0.5637	0.5637	0.5637	
Post-Treatment Month 24					
Improvement	2/19/10.53	4/17/23.532.00 (0.37, 10.92)	2.00 (0.37, 10.92)	0.12 (-0.16, 0.39)	
Deterioration	1/19/5.26	4/17/23.534.00 (0.45, 35.79)	4.00 (0.45, 35.79)	0.18 (-0.07, 0.42)	
		(6.81, 49.90) 0.4142	0.4142	0.4142	
		(6.81, 49.90) 0.1797	0.1797	0.1797	

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 33/27/26/33/30/30)		[d]			
(nb: 33/33/33/33/33/32)		[e]			
Improvement	12/33/36.36	13/30/43.331.50 (0.53, 4.21)	1.30 (0.67, 2.53)	0.10 (-0.15, 0.35)	
		(25.46, 62.57) 0.4386	0.4386	0.4386	
Deterioration	2/33/6.06	3/30/10.001.50 (0.25, 8.98)	1.50 (0.25, 8.98)	0.03 (-0.11, 0.18)	
		(2.11, 26.53) 0.6547	0.6547	0.6547	
Post-Treatment Month 24					
Improvement	12/33/36.36	9/30/30.000.70 (0.27, 1.84)	0.75 (0.34, 1.63)	-0.10 (-0.37, 0.17)	
		(14.73, 49.40) 0.4669	0.4669	0.4669	
Deterioration	2/33/6.06	5/30/16.672.50 (0.49, 12.89)	2.50 (0.49, 12.89)	0.10 (-0.07, 0.27)	
		(5.64, 34.72) 0.2568	0.2568	0.2568	

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Baseline anti-AAV5 NAb Titer Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	1.67	1.92	0.07	0.3908
Deterioration	1.33	1.33	0.03	0.8662
Post-Treatment Month 24				
Improvement	2.86	2.67	0.22	0.2416
Deterioration	1.60	1.60	0.08	0.6914

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
 Analysis Set: Modified Intent to Treat Population [N=52]
 Domain: Physical Health Domain Score

Hepatitis B or C Category: Yes
 (N=31)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 31/25/27/31/29/29)	[d]				
(nb: 31/31/31/31/30/29)	[e]				
Improvement	7/31/22.58	10/29/34.482.00 (17.94, 54.33) 0.2482	(0.60, 6.64)	1.67 (0.69, 4.00) 0.2482	0.14 (-0.09, 0.37) 0.2482
Deterioration	1/31/3.23	4/29/13.794.00 (3.89, 31.66) 0.1797	(0.45, 35.79)	4.00 (0.45, 35.79) 0.1797	0.10 (-0.04, 0.25) 0.1797
Post-Treatment Month 24					
Improvement	7/31/22.58	8/29/27.591.20 (12.73, 47.24) 0.7630	(0.37, 3.93)	1.14 (0.48, 2.72) 0.7630	0.03 (-0.19, 0.26) 0.7630
Deterioration	1/31/3.23	6/29/20.696.00 (7.99, 39.72) 0.0588	(0.72, 49.84)	6.00 (0.72, 49.84) 0.0588	0.17 (0.00, 0.34) 0.0588

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
 Analysis Set: Modified Intent to Treat Population [N=52]
 Domain: Physical Health Domain Score

Hepatitis B or C Category: No
 (N=21)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 21/18/15/21/19/18)	[d]				
(nb: 21/21/21/21/21/20)	[e]				
Improvement	7/21/33.33	8/19/42.11 (20.25, 66.50)	1.50 (0.42, 5.32) 0.5271	1.33 (0.55, 3.26) 0.5271	0.11 (-0.22, 0.43) 0.5271
Deterioration	2/21/9.52	1/19/5.26 (0.13, 26.03)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.05 (-0.23, 0.12) 0.5637
Post-Treatment Month 24					
Improvement	7/21/33.33	5/18/27.78 (9.69, 53.48)	0.71 (0.23, 2.25) 0.5637	0.71 (0.23, 2.25) 0.5637	-0.11 (-0.48, 0.26) 0.5637
Deterioration	2/21/9.52	3/18/16.67 (3.58, 41.42)	1.50 (0.25, 8.98) 0.6547	1.50 (0.25, 8.98) 0.6547	0.06 (-0.19, 0.30) 0.6547

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Hepatitis B or C Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	1.33	1.26	0.03	0.8056
Deterioration	8.00	8.00	0.15	0.1771
Post-Treatment Month 24				
Improvement	1.69	1.61	0.14	0.5650
Deterioration	4.00	4.00	0.11	0.3270

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
 Analysis Set: Modified Intent to Treat Population [N=52]
 Domain: Physical Health Domain Score

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 27/23/22/27/25/25)	[d]				
(nb: 27/27/27/27/27/27)	[e]				
Improvement	9/27/33.33	11/25/44.00 (24.40, 65.07)	1.60 (0.52, 4.89) 0.4054	1.38 (0.65, 2.92) 0.4054	0.12 (-0.16, 0.40) 0.4054
Deterioration	2/27/7.41	3/25/12.00 (2.55, 31.22)	1.50 (0.25, 8.98) 0.6547	1.50 (0.25, 8.98) 0.6547	0.04 (-0.13, 0.21) 0.6547
Post-Treatment Month 24					
Improvement	9/27/33.33	8/25/32.00 (14.95, 53.50)	0.86 (0.29, 2.55) 0.7815	0.89 (0.39, 2.04) 0.7815	-0.04 (-0.32, 0.24) 0.7815
Deterioration	2/27/7.41	6/25/24.00 (9.36, 45.13)	3.00 (0.61, 14.86) 0.1573	3.00 (0.61, 14.86) 0.1573	0.16 (-0.05, 0.37) 0.1573

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Physical Health Domain Score

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 11/9/9/11/9/11) [d]					
[e]					
(nb:11/11/11/11/10/11)					
Improvement	3/11/27.27	1/9/11.11 (0.28, 48.25)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.11 (-0.48, 0.26) 0.5637
Deterioration	0/11/0.00	0/9/0.00	1.21 (0.02, 66.96) 0.9273 @	1.20 (0.03, 55.22) 0.9273 @	0.01 (-0.17, 0.18) 0.9273 @
Post-Treatment Month 24					
Improvement	3/11/27.27	1/11/9.09 (0.23, 41.28)	0.33 (0.03, 3.20) 0.3173	0.33 (0.03, 3.20) 0.3173	-0.18 (-0.52, 0.16) 0.3173
Deterioration	0/11/0.00	2/11/18.18 (2.28, 51.78)	6.05 (0.26, 142.04) 0.2269 @	5.00 (0.27, 93.55) 0.2269 @	0.17 (-0.09, 0.42) 0.2269 @

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Baseline Steatosis Grade Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference		
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction		
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]		P value [h]
Post-Treatment Month Improvement	12	3.20		2.76		0.23		0.2473
		1.24	@	1.25	@	0.03	@	NA @
Post-Treatment Month Improvement	24	2.61		2.70		0.14		0.3510
		0.50	@	0.60	@	-0.01	@	NA @

16. Hem-A-QoL-Score (15 % MCID) – Hem-A-QoL (Gefühle) – Subgruppenanalysen – Studie HOPE-B – Monat 24

Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
 Analysis Set: Modified Intent to Treat Population [N=52]
 Domain: Feelings Domain Score

Race Group: White (N=40)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 40/35/34/40/39/35)	[d]				
(nb: 40/40/40/40/40/37)	[e]				
Improvement	7/40/17.50	13/39/33.33 (19.09, 50.22)	3.00 (0.81, 11.08) 0.0833	1.86 (0.91, 3.78) 0.0833	0.15 (-0.01, 0.32) 0.0833
Deterioration	5/40/12.50	1/39/2.56 (0.06, 13.48)	0.20 (0.02, 1.71) 0.1025	0.20 (0.02, 1.71) 0.1025	-0.10 (-0.22, 0.02) 0.1025
Post-Treatment Month 24					
Improvement	7/40/17.50	11/35/31.43 (16.85, 49.29)	2.00 (0.60, 6.64) 0.2482	1.57 (0.72, 3.41) 0.2482	0.11 (-0.08, 0.30) 0.2482
Deterioration	5/40/12.50	1/35/2.86 (0.07, 14.92)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.09 (-0.21, 0.04) 0.1797

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of

Life Index (Hem-A-QoL) by Subgroups
Analysis
Set: Modified Intent to Treat Population [N=52]

Race Group: Non-White or Not Specified (N=12)

Domain: Feelings Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and @	Post Treatment vs Lead-In Risk Ratio, 95% CI, and @	Post Treatment vs Lead-In Risk Difference, 95% CI, @
(n: 12/8/8/12/9/12) [d]					
[e]					
(nb:12/12/12/12/11/12)					
Improvement	2/12/16.67	4/9/44.44 (13.70, 78.80)	4.00 (0.45, 35.79) 0.1797	4.00 (0.45, 35.79) 0.1797	0.33 (-0.10, 0.77) 0.1797
Deterioration	1/12/8.33	0/9/0.00	0.40 (0.01, 11.09) 0.5895 @	0.43 (0.02, 9.55) 0.5895 @	-0.07 (-0.29, 0.15) 0.5895 @
Post-Treatment Month 24					
Improvement	2/12/16.67	2/12/16.67 (2.09, 48.41)	1.00 (0.14, 7.10) 1.0000	1.00 (0.14, 7.10) 1.0000	0.00 (-0.33, 0.33) 1.0000
Deterioration	1/12/8.33	0/12/0.00	0.31 (0.01, 8.31) 0.4705 @	0.33 (0.01, 7.45) 0.4705 @	-0.08 (-0.28, 0.13) 0.4705 @

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Race Group Interactions		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference	
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]	
						P value [h]	
Post-Treatment Month 12	Improvement	0.75		0.47		-0.18	0.6469
	Deterioration	0.50	@	0.47	@	-0.03 @	NA @
Post-Treatment Month 24	Improvement	2.00		1.57		0.11	0.5270
	Deterioration	0.81	@	0.76	@	-0.01 @	NA @

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Geographic Region: Europe (N=33)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 33/27/26/33/30/31)	[d]				
(nb: 33/33/33/33/32/32)	[e]				
Improvement	4/33/12.12	9/30/30.00 (14.73, 49.40)	3.50 (0.73, 16.85) 0.0956	2.25 (0.84, 5.99) 0.0956	0.17 (-0.02, 0.35) 0.0956
Deterioration	2/33/6.06	0/30/0.00	0.21 (0.01, 4.48) 0.2743 @	0.22 (0.01, 4.39) 0.2743 @	-0.06 (-0.16, 0.04) 0.2743 @
Post-Treatment Month 24					
Improvement	4/33/12.12	6/31/19.35 (7.45, 37.47)	1.67 (0.40, 6.97) 0.4795	1.50 (0.48, 4.65) 0.4795	0.06 (-0.11, 0.24) 0.4795
Deterioration	2/33/6.06	0/31/0.00	0.20 (0.01, 4.34) 0.2627 @	0.21 (0.01, 4.26) 0.2627 @	-0.06 (-0.16, 0.04) 0.2627 @

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Feelings Domain Score

Geographic Region: USA (N=19)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 19/16/16/19/18/16)	[d]				
(nb: 19/19/19/19/19/17)	[e]				
Improvement	5/19/26.32	8/18/44.44 (21.53, 69.24)	3.00 (0.61, 14.86) 0.1573	2.00 (0.75, 5.33) 0.1573	0.22 (-0.07, 0.51) 0.1573
Deterioration	4/19/21.05	1/18/5.56 (0.14, 27.29)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.17 (-0.40, 0.06) 0.1797
Post-Treatment Month 24					
Improvement	5/19/26.32	7/16/43.75 (19.75, 70.12)	1.67 (0.40, 6.97) 0.4795	1.40 (0.55, 3.57) 0.4795	0.13 (-0.22, 0.47) 0.4795
Deterioration	4/19/21.05	1/16/6.25 (0.16, 30.23)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.19 (-0.45, 0.07) 0.1797

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AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Geographic Region Interactions									
		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference			
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction			
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]		P value [h]	
Post-Treatment Month 12	Improvement	1.17		1.13		-0.05		0.7355	
	Deterioration	0.84	@	0.88	@	0.11	@	NA	@
Post-Treatment Month 24	Improvement	1.00		1.07		-0.07		0.8238	
	Deterioration	0.80	@	0.84	@	0.13	@	NA	@

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Feelings Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 39/30/29/39/35/35)	[d]				
(nb: 39/39/39/39/38/37)	[e]				
Improvement	5/39/12.82	13/35/37.14 (21.47, 55.08)	5.50 (1.22, 24.81) 0.0126	3.25 (1.22, 8.66) 0.0126	0.26 (0.07, 0.44) 0.0126
Deterioration	5/39/12.82	1/35/2.86 (0.07, 14.92)	0.20 (0.02, 1.71) 0.1025	0.20 (0.02, 1.71) 0.1025	-0.11 (-0.25, 0.02) 0.1025
Post-Treatment Month 24					
Improvement	5/39/12.82	8/35/22.86 (10.42, 40.14)	1.75 (0.51, 5.98) 0.3657	1.60 (0.57, 4.47) 0.3657	0.09 (-0.10, 0.27) 0.3657
Deterioration	5/39/12.82	1/35/2.86 (0.07, 14.92)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.09 (-0.21, 0.04) 0.1797

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Feelings Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Difference, 95% CI, and p-value
(n: 13/13/13/13/13/12)	[d]				
(nb: 13/13/13/13/13/12)	[e]				
Improvement	4/13/30.77	4/13/30.77 (9.09, 61.43)	1.00 (0.14, 7.10) 1.0000	1.00 (0.38, 2.66) 1.0000	0.00 (-0.30, 0.30) 1.0000
Deterioration	1/13/7.69	0/13/0.00	0.31 (0.01, 8.30) 0.4712 @	0.33 (0.01, 7.50) 0.4712 @	-0.07 (-0.26, 0.12) 0.4712 @
Post-Treatment Month 24					
Improvement	4/13/30.77	5/12/41.67 (15.17, 72.33)	1.50 (0.25, 8.98) 0.6547	1.25 (0.47, 3.33) 0.6547	0.08 (-0.28, 0.45) 0.6547
Deterioration	1/13/7.69	0/12/0.00	0.33 (0.01, 8.99) 0.5040 @	0.36 (0.02, 8.05) 0.5040 @	-0.07 (-0.26, 0.12) 0.5040 @

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Lead-in Bleeding Episode Count Category Interactions									
		Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference	
		Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]	
								P value [h]	
Post-Treatment Month 12	Improvement	5.50			3.25			0.26	0.1749
	Deterioration	0.65	@		0.61	@		-0.04 @	NA @
Post-Treatment Month 24	Improvement	1.17			1.28			0.01	0.8289
	Deterioration	0.76	@		0.69	@		-0.02 @	NA @

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 9/7/6/9/9/8) [d]					
(nb: 9/9/9/9/9/9) [e]					
Improvement	2/9/22.22	7/9/77.78 (39.99, 97.19)	NC (NC, NC) 0.0253	3.50 (1.08, 11.29) 0.0253	0.56 (0.23, 0.88) 0.0253
Deterioration	1/9/11.11	0/9/0.00	0.30 (0.01, 8.35) 0.4675 @	0.33 (0.02, 7.24) 0.4675 @	-0.10 (-0.36, 0.16) 0.4675 @
Post-Treatment Month 24					
Improvement	2/9/22.22	3/8/37.50 (8.52, 75.51)	2.00 (0.18, 22.06) 0.5637	1.50 (0.38, 6.00) 0.5637	0.13 (-0.29, 0.54) 0.5637
Deterioration	1/9/11.11	0/8/0.00	0.33 (0.01, 9.40) 0.5145 @	0.37 (0.02, 7.99) 0.5145 @	-0.09 (-0.36, 0.17) 0.5145 @

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Feelings Domain Score

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 43/36/36/43/39/39)	[d]				
(nb: 43/43/43/43/42/40)	[e]				
Improvement	7/43/16.28	10/39/25.64 (13.04, 42.13)	2.00 (0.60, 6.64) 0.2482	1.67 (0.69, 4.00) 0.2482	0.10 (-0.07, 0.27) 0.2482
Deterioration	5/43/11.63	1/39/2.56 (0.06, 13.48)	0.20 (0.02, 1.71) 0.1025	0.20 (0.02, 1.71) 0.1025	-0.10 (-0.22, 0.02) 0.1025
Post-Treatment Month 24					
Improvement	7/43/16.28	10/39/25.64 (13.04, 42.13)	1.60 (0.52, 4.89) 0.4054	1.43 (0.61, 3.32) 0.4054	0.08 (-0.10, 0.26) 0.4054
Deterioration	5/43/11.63	1/39/2.56 (0.06, 13.48)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.08 (-0.19, 0.03) 0.1797

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AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Status of Target Joint at Screening Category Interactions									
		Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference	
		Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]	P value [h]
Post-Treatment Month Improvement	12	NC			2.10			0.46	0.1178
		1.50	@		1.65	@		0.00 @	NA @
Post-Treatment Month Improvement	24	1.25			1.05			0.05	0.8895
		1.32	@		1.48	@		-0.01 @	NA @

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 19/16/16/19/18/17)		[d]			
(nb: 19/19/19/19/18/17)		[e]			
Improvement	1/19/5.26	5/18/27.78 (9.69, 53.48)	5.00 (0.58, 42.80) 0.1025	5.00 (0.58, 42.80) 0.1025	0.22 (-0.02, 0.47) 0.1025
Deterioration	2/19/10.53	1/18/5.56 (0.14, 27.29)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.06 (-0.24, 0.13) 0.5637
Post-Treatment Month 24					
Improvement	1/19/5.26	3/17/17.65 (3.80, 43.43)	3.00 (0.31, 28.84) 0.3173	3.00 (0.31, 28.84) 0.3173	0.12 (-0.11, 0.34) 0.3173
Deterioration	2/19/10.53	1/17/5.88 (0.15, 28.69)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.06 (-0.26, 0.14) 0.5637

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 33/27/26/33/30/30)		[d]			
(nb: 33/33/33/33/33/32)		[e]			
Improvement	8/33/24.24	12/30/40.00 (22.66, 59.40)	2.67 (0.71, 10.05) 0.1317	1.71 (0.84, 3.48) 0.1317	0.17 (-0.04, 0.37) 0.1317
Deterioration	4/33/12.12	0/30/0.00	0.11 (0.01, 2.08) 0.0814 @	0.12 (0.01, 2.17) 0.0814 @	-0.12 (-0.24, 0.01) 0.0814 @
Post-Treatment Month 24					
Improvement	8/33/24.24	10/30/33.33 (17.29, 52.81)	1.40 (0.44, 4.41) 0.5637	1.25 (0.59, 2.67) 0.5637	0.07 (-0.16, 0.29) 0.5637
Deterioration	4/33/12.12	0/30/0.00	0.11 (0.01, 2.08) 0.0814 @	0.12 (0.01, 2.17) 0.0814 @	-0.12 (-0.24, 0.01) 0.0814 @

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Baseline anti-AAV5 NAb Titer Category Interactions									
		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference			
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction			
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]		P value [h]	
Post-Treatment Month 12	Improvement	1.87		2.92		0.05		0.3358	
	Deterioration	4.55	@	4.17	@	0.06	@	NA	@
Post-Treatment Month 24	Improvement	2.14		2.40		0.05		0.4914	
	Deterioration	4.55	@	4.17	@	0.06	@	NA	@

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Hepatitis B or C Category: Yes
(N=31)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 31/25/27/31/29/29)	[d]				
(nb: 31/31/31/31/30/29)	[e]				
Improvement	1/31/3.23	10/29/34.48 (17.94, 54.33)	NC (NC, NC) 0.0027	10.00 (1.56, 64.20) 0.0027	0.31 (0.14, 0.48) 0.0027
Deterioration	4/31/12.90	0/29/0.00	0.10 (0.01, 2.01) 0.0756 @	0.12 (0.01, 2.11) 0.0756 @	-0.12 (-0.25, 0.00) 0.0756 @
Post-Treatment Month 24					
Improvement	1/31/3.23	8/29/27.59 (12.73, 47.24)	NC (NC, NC) 0.0082	8.00 (1.28, 50.04) 0.0082	0.24 (0.09, 0.40) 0.0082
Deterioration	4/31/12.90	1/29/3.45 (0.09, 17.76)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.10 (-0.25, 0.04) 0.1797

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Hepatitis B or C Category: No
(N=21)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 21/18/15/21/19/18)	[d]				
(nb: 21/21/21/21/21/20)	[e]				
Improvement	8/21/38.10	7/19/36.84 (16.29, 61.64)	1.00 (0.25, 4.00) 1.0000	1.00 (0.45, 2.21) 1.0000	0.00 (-0.29, 0.29) 1.0000
Deterioration	2/21/9.52	1/19/5.26 (0.13, 26.03)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.05 (-0.23, 0.12) 0.5637
Post-Treatment Month 24					
Improvement	8/21/38.10	5/18/27.78 (9.69, 53.48)	0.50 (0.13, 2.00) 0.3173	0.63 (0.25, 1.58) 0.3173	-0.17 (-0.48, 0.15) 0.3173
Deterioration	2/21/9.52	0/18/0.00	0.21 (0.01, 4.69) 0.2903 @	0.23 (0.01, 4.53) 0.2903 @	-0.09 (-0.24, 0.06) 0.2903 @

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Hepatitis B or C Category Interactions									
		Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference	
		Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]	
								P value [h]	
Post-Treatment Improvement Deterioration	Month 12	NC			10.00			0.31	0.0158
		0.20	@		0.24	@		-0.07 @	NA @
Post-Treatment Improvement Deterioration	Month 24	NC			12.70			0.41	0.0148
		1.19	@		1.09	@		-0.01 @	NA @

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Feelings Domain Score

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 27/23/22/27/25/25)	[d]				
(nb: 27/27/27/27/27/27)	[e]				
Improvement	3/27/11.11	8/25/32.00 (14.95, 53.50)	7.00 (0.86, 56.89) 0.0339	4.00 (1.00, 15.99) 0.0339	0.24 (0.04, 0.44) 0.0339
Deterioration	5/27/18.52	0/25/0.00	0.08 (0.00, 1.53) 0.0403 @	0.10 (0.01, 1.68) 0.0403 @	-0.18 (-0.33, -0.02) 0.0403 @
Post-Treatment Month 24					
Improvement	3/27/11.11	7/25/28.00 (12.07, 49.39)	3.00 (0.61, 14.86) 0.1573	2.33 (0.70, 7.82) 0.1573	0.16 (-0.05, 0.37) 0.1573
Deterioration	5/27/18.52	0/25/0.00	0.08 (0.00, 1.53) 0.0403 @	0.10 (0.01, 1.68) 0.0403 @	-0.18 (-0.33, -0.02) 0.0403 @

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Feelings Domain Score

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 11/9/9/11/9/11) [d]					
[e]					
(nb:11/11/11/11/10/11)					
Improvement	4/11/36.36	3/9/33.33 (7.49, 70.07)	0.50 (0.05, 5.51) 0.5637	0.75 (0.28, 2.00) 0.5637	-0.11 (-0.48, 0.26) 0.5637
Deterioration	0/11/0.00	1/9/11.11 (0.28, 48.25)	4.06 (0.15, 112.39) 0.3899 @	3.60 (0.16, 79.01) 0.3899 @	0.11 (-0.14, 0.36) 0.3899 @
Post-Treatment Month 24					
Improvement	4/11/36.36	2/11/18.18 (2.28, 51.78)	0.33 (0.03, 3.20) 0.3173	0.50 (0.13, 2.00) 0.3173	-0.18 (-0.52, 0.16) 0.3173
Deterioration	0/11/0.00	0/11/0.00	1.00 (0.02, 54.83) 1.0000 @	1.00 (0.02, 46.40) 1.0000 @	0.00 (-0.16, 0.16) 1.0000 @

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Baseline Steatosis Grade Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference		
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In		Interaction
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]		P value [h]
Post-Treatment Improvement Deterioration	Month 12	14.00		5.33		0.35		0.2214
		0.02	@	0.03	@	-0.29	@	NA @
Post-Treatment Improvement Deterioration	Month 24	9.09		4.66		0.34		0.0899
		0.08	@	0.10	@	-0.18	@	NA @

17. Hem-A-QoL-Score (15 % MCID) – Hem-A-QoL (Einstellung) – Subgruppenanalysen – Studie HOPE-B – Monat 24

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Race Group: White (N=40)

		Post-Treatment			
	Lead-In [a]	Improvement or Post Treatment vs		Post Treatment vs	Post Treatment vs
	Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk			
	Deterioration	n/N1/Proportion	95% CI, and	95% CI, and	Difference, 95% CI,
	n/N1/Proportion	(95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 40/35/34/40/39/35)	[d]				
(nb: 40/40/40/40/40/37)	[e]				
Improvement	11/40/27.50	9/39/23.08	0.75 (0.26, 2.16)	0.82 (0.39, 1.71)	-0.05 (-0.24, 0.14)
		(11.13, 39.33)	0.5930	0.5930	0.5930
Deterioration	5/40/12.50	7/39/17.95	1.40 (0.44, 4.41)	1.40 (0.44, 4.41)	0.05 (-0.12, 0.22)
		(7.54, 33.53)	0.5637	0.5637	0.5637
Post-Treatment Month 24					
Improvement	11/40/27.50	8/35/22.86	0.75 (0.26, 2.16)	0.80 (0.35, 1.82)	-0.06 (-0.27, 0.15)
		(10.42, 40.14)	0.5930	0.5930	0.5930
Deterioration	5/40/12.50	7/35/20.00	1.40 (0.44, 4.41)	1.40 (0.44, 4.41)	0.06 (-0.14, 0.25)
		(8.44, 36.94)	0.5637	0.5637	0.5637

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Race Group: Non-White or Not Specified (N=12)

	Post-Treatment				
	Lead-In [a]	Improvement or Post Treatment vs		Post Treatment vs	Post Treatment vs
	Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk			
	Deterioration	n/N1/Proportion 95% CI, and		95% CI, and	Difference, 95% CI,
	n/N1/Proportion (95% CI*)	P-value [b]		P-value [b]	and P-value [b]
(n: 12/8/8/12/9/12) [d]					
[e]					
(nb:12/12/12/12/11/12)					
Improvement	2/12/16.67	5/9/55.56 (21.20, 86.30)	4.00 (0.45, 35.79) 0.1797	2.50 (0.63, 10.00) 0.1797	0.33 (-0.10, 0.77) 0.1797
Deterioration	3/12/25.00	0/9/0.00	0.14 (0.01, 3.16) 0.1787 @	0.19 (0.01, 3.20) 0.1787 @	-0.22 (-0.50, 0.06) 0.1787 @
Post-Treatment Month 24					
Improvement	2/12/16.67	6/12/50.00 (21.09, 78.91)	3.00 (0.61, 14.86) 0.1573	3.00 (0.61, 14.86) 0.1573	0.33 (-0.09, 0.76) 0.1573
Deterioration	3/12/25.00	3/12/25.00 (5.49, 57.19)	1.00 (0.20, 4.95) 1.0000	1.00 (0.20, 4.95) 1.0000	0.00 (-0.40, 0.40) 1.0000

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Race Group Interactions									
		Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference	
		Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]	P value [h]
Post-Treatment Improvement	Month 12	0.19	@		0.33	@		-0.38	0.0641
		10.00			7.37			0.27	NA @
Post-Treatment Deterioration	Month 24	0.25			0.27			-0.39	0.0854
		1.40			1.40			0.06	0.6223

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Geographic Region: Europe (N=33)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 33/27/26/33/30/31)		[d]			
(nb: 33/33/33/33/32/32)		[e]			
Improvement	7/33/21.21	9/30/30.001.50 (0.42, 5.32)	1.29 (0.59, 2.81)	0.07 (-0.14, 0.27)	
		(14.73, 49.40) 0.5271	0.5271	0.5271	
Deterioration	6/33/18.18	3/30/10.000.60 (0.14, 2.51)	0.60 (0.14, 2.51)	-0.07 (-0.25, 0.12)	
		(2.11, 26.53) 0.4795	0.4795	0.4795	
Post-Treatment Month 24					
Improvement	7/33/21.21	10/31/32.261.60 (0.52, 4.89)	1.43 (0.61, 3.32)	0.10 (-0.13, 0.32)	
		(16.68, 51.37) 0.4054	0.4054	0.4054	
Deterioration	6/33/18.18	7/31/22.581.17 (0.39, 3.47)	1.17 (0.39, 3.47)	0.03 (-0.20, 0.26)	
		(9.59, 41.10) 0.7815	0.7815	0.7815	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Geographic Region: USA (N=19)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 19/16/16/19/18/16)		[d]			
(nb: 19/19/19/19/19/17)		[e]			
Improvement		6/19/31.58	5/18/27.780.80 (0.21, 2.98) 0.7389	0.83 (0.28, 2.44) 0.7389	-0.06 (-0.38, 0.27) 0.7389
Deterioration		2/19/10.53	4/18/22.222.00 (0.37, 10.92) 0.4142	2.00 (0.37, 10.92) 0.4142	0.11 (-0.15, 0.37) 0.4142
Post-Treatment Month 24					
Improvement		6/19/31.58	4/16/25.000.80 (0.21, 2.98) 0.7389	0.80 (0.21, 2.98) 0.7389	-0.06 (-0.43, 0.30) 0.7389
Deterioration		2/19/10.53	3/16/18.751.50 (0.25, 8.98) 0.6547	1.50 (0.25, 8.98) 0.6547	0.06 (-0.21, 0.33) 0.6547

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Geographic Region Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
	Improvement	1.88	1.55	0.13
Deterioration		0.30	0.30	-0.18
				0.4845
Post-Treatment Month 24				
	Improvement	2.00	1.79	0.16
Deterioration		0.78	0.78	-0.03
				0.3447
				0.7298

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: View of Yourself Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 39/30/29/39/35/35)	[d]				
(nb: 39/39/39/39/38/37)	[e]				
Improvement	6/39/15.38	10/35/28.571.80 (14.64, 46.30) 0.2850	(0.60, 5.37)	1.67 (0.65, 4.30) 0.2850	0.11 (-0.09, 0.32) 0.2850
Deterioration	6/39/15.38	5/35/14.291.00 (4.81, 30.26) 1.0000	(0.29, 3.45)	1.00 (0.29, 3.45) 1.0000	0.00 (-0.18, 0.18) 1.0000
Post-Treatment Month 24					
Improvement	6/39/15.38	11/35/31.432.25 (16.85, 49.29) 0.1655	(0.69, 7.31)	1.83 (0.77, 4.38) 0.1655	0.14 (-0.05, 0.34) 0.1655
Deterioration	6/39/15.38	8/35/22.861.33 (10.42, 40.14) 0.5930	(0.46, 3.84)	1.33 (0.46, 3.84) 0.5930	0.06 (-0.15, 0.27) 0.5930

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: View of Yourself Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 13/13/13/13/13/12)	[d]				
(nb: 13/13/13/13/13/12)	[e]				
Improvement	7/13/53.85	4/13/30.77 (9.09, 61.43) 0.1797	0.25 (0.03, 2.24)	0.57 (0.25, 1.31) 0.1797	-0.23 (-0.54, 0.08) 0.1797
Deterioration	2/13/15.38	2/13/15.38 (1.92, 45.45) 1.0000	1.00 (0.14, 7.10)	1.00 (0.14, 7.10) 1.0000	0.00 (-0.30, 0.30) 1.0000
Post-Treatment Month 24					
Improvement	7/13/53.85	3/12/25.00 (5.49, 57.19) 0.3173	0.50 (0.13, 2.00)	0.50 (0.13, 2.00) 0.3173	-0.25 (-0.72, 0.22) 0.3173
Deterioration	2/13/15.38	2/12/16.67 (2.09, 48.41) 1.0000	1.00 (0.14, 7.10)	1.00 (0.14, 7.10) 1.0000	0.00 (-0.33, 0.33) 1.0000

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Lead-in Bleeding Episode Count Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	7.20	2.93	0.34	0.0769
Deterioration	1.00	1.00	0.00	0.9454
Post-Treatment Month 24				
Improvement	4.50	3.66	0.39	0.0326
Deterioration	1.33	1.33	0.06	0.7518

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 9/7/6/9/9/8) [d]					
(nb: 9/9/9/9/9/9) [e]					
Improvement	3/9/33.33	4/9/44.44 (13.70, 78.80)	1.33 (0.30, 5.96) 0.7055	1.33 (0.30, 5.96) 0.7055	0.11 (-0.46, 0.68) 0.7055
Deterioration	2/9/22.22	0/9/0.00	0.16 (0.01, 3.81) 0.2222 @	0.20 (0.01, 3.66) 0.2222 @	-0.20 (-0.50, 0.10) 0.2222 @
Post-Treatment Month 24					
Improvement	3/9/33.33	2/8/25.00 (3.19, 65.09)	0.50 (0.05, 5.51) 0.5637	0.67 (0.17, 2.67) 0.5637	-0.13 (-0.54, 0.29) 0.5637
Deterioration	2/9/22.22	1/8/12.50 (0.32, 52.65)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.13 (-0.54, 0.29) 0.5637

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 43/36/36/43/39/39)	[d]				
(nb: 43/43/43/43/42/40)	[e]				
Improvement	10/43/23.26	10/39/25.64 (13.04, 42.13)	1.00 (0.32, 3.10) 1.0000	1.00 (0.51, 1.97) 1.0000	0.00 (-0.17, 0.17) 1.0000
Deterioration	6/43/13.95	7/39/17.95 (7.54, 33.53)	1.40 (0.44, 4.41) 0.5637	1.40 (0.44, 4.41) 0.5637	0.05 (-0.12, 0.22) 0.5637
Post-Treatment Month 24					
Improvement	10/43/23.26	12/39/30.77 (17.02, 47.57)	1.38 (0.55, 3.42) 0.4913	1.33 (0.59, 3.03) 0.4913	0.08 (-0.14, 0.29) 0.4913
Deterioration	6/43/13.95	9/39/23.08 (11.13, 39.33)	1.50 (0.53, 4.21) 0.4386	1.50 (0.53, 4.21) 0.4386	0.08 (-0.12, 0.27) 0.4386

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Status of Target Joint at Screening Category Interactions									
		Between-subgroup ratio of			Between-subgroup ratio of			Between-subgroup difference	
		Post Treatment vs Lead-In			Post Treatment vs Lead-In			of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]			Risk Ratio [f]			Risk Difference [g]	P value [h]
Post-Treatment Month Improvement	12	1.33	@		1.33	@		0.11	0.7570
		0.11			0.14			-0.25 @	NA @
Post-Treatment Month Improvement	24	0.36			0.50			-0.21	0.5054
		0.33			0.33			-0.21	0.3579

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 19/16/16/19/18/17)		[d]			
(nb: 19/19/19/19/18/17)		[e]			
Improvement	1/19/5.26	4/18/22.22 (6.41, 47.64)	4.00 (0.45, 35.79) 0.1797	4.00 (0.45, 35.79) 0.1797	0.17 (-0.06, 0.40) 0.1797
Deterioration	5/19/26.32	1/18/5.56 (0.14, 27.29)	0.20 (0.02, 1.71) 0.1025	0.20 (0.02, 1.71) 0.1025	-0.22 (-0.47, 0.02) 0.1025
Post-Treatment Month 24					
Improvement	1/19/5.26	8/17/47.06 (22.98, 72.19)	8.00 (1.00, 63.96) 0.0196	8.00 (1.00, 63.96) 0.0196	0.41 (0.13, 0.70) 0.0196
Deterioration	5/19/26.32	2/17/11.76 (1.46, 36.44)	0.40 (0.08, 2.06) 0.2568	0.40 (0.08, 2.06) 0.2568	-0.18 (-0.47, 0.12) 0.2568

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 33/27/26/33/30/30)		[d]			
(nb: 33/33/33/33/33/32)		[e]			
Improvement	12/33/36.36	10/30/33.330.75 (17.29, 52.81) 0.5930	(0.26, 2.16)	0.83 (0.43, 1.63) 0.5930	-0.07 (-0.31, 0.18) 0.5930
Deterioration	3/33/9.09	6/30/20.003.00 (7.71, 38.57) 0.1573	(0.61, 14.86)	3.00 (0.61, 14.86) 0.1573	0.13 (-0.05, 0.31) 0.1573
Post-Treatment Month 24					
Improvement	12/33/36.36	6/30/20.000.44 (7.71, 38.57) 0.1655	(0.14, 1.44)	0.55 (0.23, 1.30) 0.1655	-0.17 (-0.39, 0.06) 0.1655
Deterioration	3/33/9.09	8/30/26.672.67 (12.28, 45.89) 0.1317	(0.71, 10.05)	2.67 (0.71, 10.05) 0.1317	0.17 (-0.04, 0.37) 0.1317

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Baseline anti-AAV5 NAb Titer Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	5.33	4.82	0.24	0.1483
Deterioration	0.07	0.07	-0.35	0.0348
Post-Treatment Month 24				
Improvement	18.18	14.55	0.58	0.0015
Deterioration	0.15	0.15	-0.35	0.0446

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Hepatitis B or C Category: Yes (N=31)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 31/25/27/31/29/29)	[d]				
(nb: 31/31/31/31/30/29)	[e]				
Improvement	5/31/16.13	7/29/24.141.67 (0.40, 6.97)	1.40 (0.55, 3.57)	0.07 (-0.12, 0.26)	
		(10.30, 43.54) 0.4795	0.4795	0.4795	
Deterioration	6/31/19.35	3/29/10.340.60 (0.14, 2.51)	0.60 (0.14, 2.51)	-0.07 (-0.26, 0.12)	
		(2.19, 27.35) 0.4795	0.4795	0.4795	
Post-Treatment Month 24					
Improvement	5/31/16.13	8/29/27.591.60 (0.52, 4.89)	1.60 (0.52, 4.89)	0.10 (-0.14, 0.34)	
		(12.73, 47.24) 0.4054	0.4054	0.4054	
Deterioration	6/31/19.35	5/29/17.240.83 (0.25, 2.73)	0.83 (0.25, 2.73)	-0.03 (-0.26, 0.19)	
		(5.85, 35.77) 0.7630	0.7630	0.7630	

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Hepatitis B or C Category: No (N=21)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 21/18/15/21/19/18)		[d]			
(nb: 21/21/21/21/21/20)		[e]			
Improvement	8/21/38.10	7/19/36.840.83 (16.29, 61.64) 0.7630	(0.25, 2.73)	0.88 (0.37, 2.09) 0.7630	-0.05 (-0.39, 0.29) 0.7630
Deterioration	2/21/9.52	4/19/21.052.00 (6.05, 45.57) 0.4142	(0.37, 10.92)	2.00 (0.37, 10.92) 0.4142	0.11 (-0.14, 0.35) 0.4142
Post-Treatment Month 24					
Improvement	8/21/38.10	6/18/33.330.80 (13.34, 59.01) 0.7389	(0.21, 2.98)	0.86 (0.35, 2.12) 0.7389	-0.06 (-0.38, 0.27) 0.7389
Deterioration	2/21/9.52	5/18/27.782.50 (9.69, 53.48) 0.2568	(0.49, 12.89)	2.50 (0.49, 12.89) 0.2568	0.17 (-0.11, 0.44) 0.2568

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Hepatitis B or C Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	2.01	1.59	0.12	0.5464
Deterioration	0.30	0.30	-0.18	0.1587
Post-Treatment Month 24				
Improvement	2.00	1.86	0.16	0.3358
Deterioration	0.33	0.33	-0.20	0.1966

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Baseline Steatosis Grade Category: <S2 (N=27)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 27/23/22/27/25/25)	[d]				
(nb: 27/27/27/27/27/27)	[e]				
Improvement	2/27/7.41	9/25/36.008.00 (1.00, 63.96)	4.50 (1.13, 17.99)	0.28(0.07, 0.49)	
		(17.97, 57.48) 0.0196	0.0196	0.0196	
Deterioration	6/27/22.22	3/25/12.000.50 (0.13, 2.00)	0.50 (0.13, 2.00)	-0.12 (-0.35, 0.11)	
		(2.55, 31.22) 0.3173	0.3173	0.3173	
Post-Treatment Month 24					
Improvement	2/27/7.41	8/25/32.004.00 (0.85, 18.84)	4.00 (0.85, 18.84)	0.24(0.01, 0.47)	
		(14.95, 53.50) 0.0578	0.0578	0.0578	
Deterioration	6/27/22.22	6/25/24.001.00 (0.32, 3.10)	1.00 (0.32, 3.10)	0.00 (-0.27, 0.27)	
		(9.36, 45.13) 1.0000	1.0000	1.0000	

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: View of Yourself Domain Score

Baseline Steatosis Grade Category: >=S2 (N=11)

	Post-Treatment			
	Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
	Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
	Deterioration	n/N1/Proportion 95% CI, and n/N1/Proportion (95% CI*)	95% CI, and P-value [b]	Difference, 95% CI, and P-value [b]
(n: 11/9/9/11/9/11) [d]				
[e]				
(nb:11/11/11/11/10/11)				
Improvement	4/11/36.36	2/9/22.22 (2.81, 60.01)	0.00 (NC, NC) 0.1573	0.50 (0.19, 1.33) 0.1573
Deterioration	2/11/18.18	2/9/22.22 (2.81, 60.01)	2.00 (0.18, 22.06) 0.5637	0.11 (-0.26, 0.48) 0.5637
Post-Treatment Month 24				
Improvement	4/11/36.36	5/11/45.45 (16.75, 76.62)	1.33 (0.30, 5.96) 0.7055	1.25 (0.39, 3.99) 0.7055
Deterioration	2/11/18.18	1/11/9.09 (0.23, 41.28)	0.50 (0.05, 5.51) 0.5637	-0.09 (-0.39, 0.21) 0.5637

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Baseline Steatosis Grade Category Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	NC	9.00	0.50	0.0382
Deterioration	0.25	0.25	-0.23	0.4624
Post-Treatment Month 24				
Improvement	3.01	3.20	0.15	0.2471
Deterioration	2.00	2.00	0.09	0.5349

18. Hem-A-QoL-Score (15 % MCID) – Hem-A-QoL (Sport und Freizeit) – Subgruppenanalysen – Studie HOPE-B – Monat 24

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Race Group: White (N=40)

		Post-Treatment				
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Difference, 95% CI, and p-value	
(n: 40/34/33/40/37/35)	[d]					
(nb: 40/39/39/40/38/37)	[e]					
Improvement	15/40/37.50	11/37/29.73 (15.87, 46.98)	0.85 (0.38, 1.89) 0.6831	0.85 (0.38, 1.89) 0.6831	-0.05 (-0.31, 0.20) 0.6831	
Deterioration	10/40/25.00	9/37/24.32 (11.77, 41.20)	0.88 (0.32, 2.41) 0.7963	0.90 (0.40, 2.00) 0.7963	-0.03 (-0.23, 0.18) 0.7963	
Post-Treatment Month 24						
Improvement	15/40/37.50	11/35/31.43 (16.85, 49.29)	0.83 (0.36, 1.93) 0.6698	0.85 (0.39, 1.83) 0.6698	-0.06 (-0.32, 0.20) 0.6698	
Deterioration	10/40/25.00	8/35/22.86 (10.42, 40.14)	1.00 (0.38, 2.66) 1.0000	1.00 (0.38, 2.66) 1.0000	0.00 (-0.22, 0.22) 1.0000	

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AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of

		Life Index (Hem-A-QoL) by Subgroups			
		Analysis			
		Set: Modified Intent to Treat Population [N=52]			
Race Group: Non-White or Not Specified (N=12)		Domain: Sports and Leisure Domain Score			
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 12/7/8/12/8/12) [d]					
[e]					
(nb:12/11/12/12/10/12)					
Improvement	1/12/8.33	3/8/37.50 (8.52, 75.51)	3.00 (0.31,28.84) 0.3173	3.00 (0.31, 28.84) 0.3173	0.25 (-0.21, 0.71) 0.3173
Deterioration	4/12/33.33	1/8/12.50 (0.32, 52.65)	0.00 (NC, NC) 0.3173	0.50 (0.13, 2.00) 0.3173	-0.13 (-0.35, 0.10) 0.3173
Post-Treatment Month 24					
Improvement	1/12/8.33	5/12/41.67 (15.17, 72.33)	5.00 (0.58,42.80) 0.1025	5.00 (0.58, 42.80) 0.1025	0.33 (-0.02, 0.69) 0.1025
Deterioration	4/12/33.33	1/12/8.33 (0.21, 38.48)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.25 (-0.59, 0.09) 0.1797

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AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Race Group Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value
Post-Treatment Month 12				
Improvement	0.28	0.28	-0.30	0.0795
Deterioration	NC	1.80	0.10	0.3541
Post-Treatment Month 24				
Improvement	0.17	0.17	-0.39	0.0535
Deterioration	4.00	4.00	0.25	0.2157

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Geographic Region: Europe (N=33)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 33/25/25/33/27/31)	[d]				
(nb: 33/31/32/33/29/32)	[e]				
Improvement	11/33/33.33	7/27/25.930.78 (11.11, 46.28) 0.6171	(0.29, 2.09)	0.78 (0.29, 2.09) 0.6171	-0.07 (-0.36, 0.21) 0.6171
Deterioration	8/33/24.24	6/27/22.220.80 (8.62, 42.26) 0.7389	(0.21, 2.98)	0.86 (0.35, 2.12) 0.7389	-0.04 (-0.25, 0.18) 0.7389
Post-Treatment Month 24					
Improvement	11/33/33.33	10/31/32.261.00 (16.68, 51.37) 1.0000	(0.40, 2.52)	1.00 (0.44, 2.30) 1.0000	0.00 (-0.27, 0.27) 1.0000
Deterioration	8/33/24.24	8/31/25.811.14 (11.86, 44.61) 0.7963	(0.41, 3.15)	1.14 (0.41, 3.15) 0.7963	0.03 (-0.21, 0.28) 0.7963

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

Geographic Region: USA (N=19)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 19/16/16/19/18/16)	[d]				
(nb: 19/19/19/19/19/17)	[e]				
Improvement	5/19/26.32	7/18/38.89 (17.30, 64.25)	1.40 (0.44, 4.41) 0.5637	1.40 (0.44, 4.41) 0.5637	0.11 (-0.26, 0.48) 0.5637
Deterioration	6/19/31.58	4/18/22.22 (6.41, 47.64)	0.75 (0.17, 3.35) 0.7055	0.80 (0.25, 2.55) 0.7055	-0.06 (-0.34, 0.23) 0.7055
Post-Treatment Month 24					
Improvement	5/19/26.32	6/16/37.50 (15.20, 64.57)	1.50 (0.42, 5.32) 0.5271	1.50 (0.42, 5.32) 0.5271	0.13 (-0.26, 0.51) 0.5271
Deterioration	6/19/31.58	1/16/6.25 (0.16, 30.23)	0.20 (0.02, 1.71) 0.1025	0.20 (0.02, 1.71) 0.1025	-0.25 (-0.52, 0.02) 0.1025

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Geographic Region Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value
Post-Treatment Month 12				
Improvement	0.56	0.56	-0.18	0.3046
Deterioration	1.07	1.08	0.02	0.7061
Post-Treatment Month 24				
Improvement	0.67	0.67	-0.13	0.5307
Deterioration	5.70	5.70	0.28	0.0964

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 39/28/29/39/32/35)	[d]				
(nb: 39/37/39/39/35/37)	[e]				
Improvement	11/39/28.21	12/32/37.501.33 (21.10, 56.31) 0.5127	(0.56, 3.16)	1.33 (0.56, 3.16) 0.5127	0.09 (-0.19, 0.37) 0.5127
Deterioration	11/39/28.21	5/32/15.630.50 (5.28, 32.79) 0.2482	(0.15, 1.66)	0.56 (0.20, 1.53) 0.2482	-0.13 (-0.33, 0.08) 0.2482
Post-Treatment Month 24					
Improvement	11/39/28.21	10/35/28.571.11 (14.64, 46.30) 0.8185	(0.45, 2.73)	1.11 (0.45, 2.73) 0.8185	0.03 (-0.22, 0.27) 0.8185
Deterioration	11/39/28.21	7/35/20.000.70 (8.44, 36.94) 0.4669	(0.27, 1.84)	0.70 (0.27, 1.84) 0.4669	-0.09 (-0.31, 0.14) 0.4669

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Protocol: CT-AMT-061-02

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 13/13/12/13/13/12)	[d]				
(nb: 13/13/12/13/13/12)	[e]				
Improvement	5/13/38.46	2/13/15.38 (1.92, 45.45)	0.40 (0.08, 2.06) 0.2568	0.40 (0.08, 2.06) 0.2568	-0.23 (-0.61, 0.15) 0.2568
Deterioration	3/13/23.08	5/13/38.46 (13.86, 68.42)	1.67 (0.31, 28.84) 0.3173	1.67 (0.61, 4.59) 0.3173	0.15 (-0.14, 0.44) 0.3173
Post-Treatment Month 24					
Improvement	5/13/38.46	6/12/50.00 (21.09, 78.91)	1.25 (0.34, 4.65) 0.7389	1.20 (0.41, 3.51) 0.7389	0.08 (-0.40, 0.57) 0.7389
Deterioration	3/13/23.08	2/12/16.67 (2.09, 48.41)	1.00 (0.14, 7.10) 1.0000	1.00 (0.14, 7.10) 1.0000	0.00 (-0.33, 0.33) 1.0000

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Lead-in Bleeding Episode Count Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value
Post-Treatment Month 12				
Improvement	3.33	3.33	0.32	0.1176
Deterioration	0.17	0.34	-0.28	0.1556
Post-Treatment Month 24				
Improvement	0.89	0.93	-0.05	0.6381
Deterioration	0.70	0.70	-0.09	0.9679

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead In Odds Ratio, 95% CI, and	Post Treatment vs Lead In Risk Ratio, 95% CI, and	Post Treatment vs Lead In Risk Difference, 95% CI,
(n: 9/7/6/9/9/8) [d]					
(nb: 9/9/9/9/9/9) [e]					
Improvement	2/9/22.22	4/9/44.442.00 (13.70, 78.80) 0.4142	(0.37, 10.92)	2.00 (0.37, 10.92) 0.4142	0.22 (-0.29, 0.74) 0.4142
Deterioration	2/9/22.22	1/9/11.110.50 (0.28, 48.25) 0.5637	(0.05, 5.51)	0.50 (0.05, 5.51) 0.5637	-0.11 (-0.48, 0.26) 0.5637
Post-Treatment Month 24					
Improvement	2/9/22.22	3/8/37.501.50 (8.52, 75.51) 0.6547	(0.25, 8.98)	1.50 (0.25, 8.98) 0.6547	0.13 (-0.42, 0.67) 0.6547
Deterioration	2/9/22.22	2/8/25.001.00 (3.19, 65.09) 1.0000	(0.14, 7.10)	1.00 (0.14, 7.10) 1.0000	0.00 (-0.49, 0.49) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 43/34/35/43/36/39)	[d]				
(nb: 43/41/42/43/39/40)	[e]				
Improvement	14/43/32.56	10/36/27.78 (14.20, 45.19) 0.6698	0.83 (0.36, 1.93) 0.6698	0.83 (0.36, 1.93) 0.6698	-0.06 (-0.31, 0.20) 0.6698
Deterioration	12/43/27.91	9/36/25.00 (12.12, 42.20) 0.7815	0.86 (0.29, 2.55) 0.7815	0.90 (0.43, 1.90) 0.7815	-0.03 (-0.22, 0.17) 0.7815
Post-Treatment Month 24					
Improvement	14/43/32.56	13/39/33.33 (19.09, 50.22) 0.8348	1.09 (0.48, 2.47) 0.8348	1.08 (0.51, 2.30) 0.8348	0.03 (-0.22, 0.27) 0.8348
Deterioration	12/43/27.91	7/39/17.95 (7.54, 33.53) 0.4669	0.70 (0.27, 1.84) 0.4669	0.70 (0.27, 1.84) 0.4669	-0.08 (-0.28, 0.13) 0.4669

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Status of Target Joint at Screening Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	2.41	2.41	0.28	0.2712
Deterioration	0.58	0.56	-0.08	0.6321
Post-Treatment Month 24				
Improvement	1.38	1.39	0.10	0.5480
Deterioration	1.43	1.43	0.08	0.5643

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Baseline anti-AAV5 NAb Titer Category: Positive (N=19)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 19/15/16/19/16/17)		[d]			
(nb: 19/18/19/19/16/17)		[e]			
Improvement	4/19/21.05	7/16/43.752.33 (0.60, 9.02)	2.33 (0.60, 9.02)	0.25 (-0.12, 0.62)	
Deterioration	5/19/26.32	2/16/12.500.33 (1.55, 38.35) 0.3173	0.50 (0.13, 2.00) 0.3173	-0.13 (-0.36, 0.11)	
Post-Treatment Month 24					
Improvement	4/19/21.05	5/17/29.412.50 (10.31, 55.96) 0.2568	2.50 (0.49, 12.89) 0.2568	0.18 (-0.12, 0.47)	
Deterioration	5/19/26.32	2/17/11.760.40 (1.46, 36.44) 0.2568	0.40 (0.08, 2.06) 0.2568	-0.18 (-0.47, 0.12)	

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AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Baseline anti-AAV5 NAb Titer Category: Negative (N=33)

		Post-Treatment			
		Lead-In [a]	Improvement or Post Treatment vs	Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk		
		Deterioration	n/N1/Proportion 95% CI, and	95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]	P-value [b]	and P-value [b]
(n: 33/26/25/33/29/30)		[d]			
(nb: 33/32/32/33/32/32)		[e]			
Improvement	12/33/36.36	7/29/24.140.64 (0.25, 1.64)	0.64 (0.25, 1.64)	0.3458	-0.14 (-0.42, 0.14)
Deterioration	9/33/27.27	8/29/27.591.00 (0.32, 3.10)	1.00 (0.43, 2.34)	1.0000	0.3458
		(12.73, 47.24) 1.0000			0.00 (-0.23, 0.23)
					1.0000
Post-Treatment Month 24					
Improvement	12/33/36.36	11/30/36.670.91 (0.39, 2.14)	0.92 (0.42, 2.00)	0.8273	-0.03 (-0.33, 0.27)
Deterioration	9/33/27.27	7/30/23.331.00 (0.35, 2.85)	1.00 (0.35, 2.85)	1.0000	0.8273
		(9.93, 42.28) 1.0000			0.00 (-0.24, 0.24)
					1.0000

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Baseline anti-AAV5 NAb Titer Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In	Interaction
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value
Post-Treatment Month 12				
Improvement	3.64	3.64	0.39	0.0755
Deterioration	0.33	0.50	-0.13	0.3846
Post-Treatment Month 24				
Improvement	2.75	2.72	0.21	0.6428
Deterioration	0.40	0.40	-0.18	0.4716

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Hepatitis B or C Category: Yes
(N=31)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 31/24/26/31/26/29)	[d]				
(nb: 31/30/30/31/27/29)	[e]				
Improvement	12/31/38.71	7/26/26.920.64 (11.57, 47.79) 0.3458	(0.25, 1.64)	0.64 (0.25, 1.64) 0.3458	-0.15 (-0.47, 0.16) 0.3458
Deterioration	8/31/25.81	6/26/23.080.80 (8.97, 43.65) 0.7389	(0.21, 2.98)	0.86 (0.35, 2.12) 0.7389	-0.04 (-0.26, 0.19) 0.7389
Post-Treatment Month 24					
Improvement	12/31/38.71	9/29/31.030.89 (15.28, 50.83) 0.8084	(0.34, 2.30)	0.90 (0.38, 2.11) 0.8084	-0.03 (-0.31, 0.24) 0.8084
Deterioration	8/31/25.81	8/29/27.591.00 (12.73, 47.24) 1.0000	(0.38, 2.66)	1.00 (0.38, 2.66) 1.0000	0.00 (-0.27, 0.27) 1.0000

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Protocol: CT-AMT-061-02

AAV5-hFIXco-Padua

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

Hepatitis B or C Category: No
(N=21)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 21/17/15/21/19/18)	[d]				
(nb: 21/20/21/21/21/20)	[e]				
Improvement	4/21/19.05	7/19/36.84 (16.29, 61.64)	2.33 (0.60, 9.02) 0.2059	2.33 (0.60, 9.02) 0.2059	0.21 (-0.10, 0.52) 0.2059
Deterioration	6/21/28.57	4/19/21.05 (6.05, 45.57)	0.75 (0.17, 3.35) 0.7055	0.80 (0.25, 2.55) 0.7055	-0.05 (-0.32, 0.22) 0.7055
Post-Treatment Month 24					
Improvement	4/21/19.05	7/18/38.89 (17.30, 64.25)	1.75 (0.51, 5.98) 0.3657	1.75 (0.51, 5.98) 0.3657	0.17 (-0.19, 0.52) 0.3657
Deterioration	6/21/28.57	1/18/5.56 (0.14, 27.29)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.17 (-0.40, 0.06) 0.1797

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AAV5-hFIXco-Padua

Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Hepatitis B or C Category Interactions				
	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value
Post-Treatment Month 12				
Improvement	0.27	0.27	-0.36	0.1164
Deterioration	1.07	1.08	0.01	0.7899
Post-Treatment Month 24				
Improvement	0.51	0.51	-0.20	0.1420
Deterioration	4.00	4.00	0.17	0.0968

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CT-AMT-061-02/adhoc (Data Cutoff: 24 month post-lock)

Protocol: CT-AMT-061-02

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Sports and Leisure Domain Score

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 27/23/21/27/23/25)	[d]				
(nb: 27/27/26/27/25/27)	[e]				
Improvement	7/27/25.93	9/23/39.131.50 (19.71, 61.46) 0.4386	(0.53, 4.21)	1.50 (0.53, 4.21) 0.4386	0.13 (-0.20, 0.46) 0.4386
Deterioration	7/27/25.93	5/23/21.740.80 (7.46, 43.70) 0.7389	(0.21, 2.98)	0.83 (0.28, 2.44) 0.7389	-0.04 (-0.30, 0.21) 0.7389
Post-Treatment Month 24					
Improvement	7/27/25.93	8/25/32.001.14 (14.95, 53.50) 0.7963	(0.41, 3.15)	1.14 (0.41, 3.15) 0.7963	0.04 (-0.26, 0.34) 0.7963
Deterioration	7/27/25.93	7/25/28.001.17 (12.07, 49.39) 0.7815	(0.39, 3.47)	1.17 (0.39, 3.47) 0.7815	0.04 (-0.24, 0.32) 0.7815

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 11/8/9/11/9/11) [d]					
[e]					
(nb:11/10/11/11/10/11)					
Improvement	4/11/36.36	1/9/11.11 (0.28, 48.25)	0.25 (0.03, 2.24) 0.1797	0.25 (0.03, 2.24) 0.1797	-0.33 (-0.77, 0.10) 0.1797
Deterioration	3/11/27.27	3/9/33.33 (7.49, 70.07)	2.00 (0.18, 22.06) 0.5637	1.50 (0.38, 6.00) 0.5637	0.11 (-0.26, 0.48) 0.5637
Post-Treatment Month 24					
Improvement	4/11/36.36	5/11/45.45 (16.75, 76.62)	1.33 (0.30, 5.96) 0.7055	1.25 (0.39, 3.99) 0.7055	0.09 (-0.38, 0.56) 0.7055
Deterioration	3/11/27.27	1/11/9.09 (0.23, 41.28)	0.33 (0.03, 3.20) 0.3173	0.33 (0.03, 3.20) 0.3173	-0.18 (-0.52, 0.16) 0.3173

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Sports and Leisure Domain Score

Baseline Steatosis Grade Category Interactions

	Between-subgroup ratio of Post Treatment vs Lead-In Odds Ratio [f]	Between-subgroup ratio of Post Treatment vs Lead-In Risk Ratio [f]	Between-subgroup difference of Post Treatment vs Lead-In Interaction Risk Difference [g]	P value
Post-Treatment Month 12				
Improvement	6.00	6.00	0.46	0.1050
Deterioration	0.40	0.55	-0.15	0.6613
Post-Treatment Month 24				
Improvement	0.86	0.91	-0.05	0.9392
Deterioration	3.55	3.55	0.22	0.2944

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19. Hem-A-QoL-Score (15 % MCID) – Hem-A-QoL (Zurechtkommen mit Hämophilie) – Subgruppenanalysen – Studie HOPE-B – Monat 24

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Race Group: White (N=40)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Ratio, 95% CI, and p-value	Post Treatment vs Lead-In Risk Difference, 95% CI, and p-value
(n: 40/35/34/40/38/35)	[d]				
(nb: 40/40/40/40/39/37)	[e]				
Improvement	8/40/20.00	7/38/18.421.00 (7.74, 34.33)	1.00 (0.35, 2.85) 1.0000	1.00 (0.35, 2.85) 1.0000	0.00 (-0.19, 0.19) 1.0000
Deterioration	6/40/15.00	11/38/28.951.83 (15.42, 45.90)	0.2253 (0.68, 4.96) 0.2253	1.83 (0.68, 4.96) 0.2253	0.13 (-0.08, 0.34) 0.2253
Post-Treatment Month 24					
Improvement	8/40/20.00	5/35/14.290.83 (4.81, 30.26)	0.7630 (0.25, 2.73) 0.7630	0.83 (0.25, 2.73) 0.7630	-0.03 (-0.21, 0.16) 0.7630
Deterioration	6/40/15.00	11/35/31.432.00 (16.85, 49.29)	0.1967 (0.68, 5.85) 0.1967	1.83 (0.72, 4.67) 0.1967	0.14 (-0.07, 0.35) 0.1967

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Dealing with Hemophilia Domain Score						
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 12/8/8/12/9/12) [d]						
(nb:12/12/12/12/11/12)						
Improvement	2/12/16.67	3/9/33.33 (7.49, 70.07)	1.50 (0.25, 8.98) 0.6547	1.50 (0.25, 8.98) 0.6547	0.11 (-0.37, 0.59) 0.6547	
Deterioration	2/12/16.67	3/9/33.33 (7.49, 70.07)	3.00 (0.31, 28.84) 0.3173	3.00 (0.31, 28.84) 0.3173	0.22 (-0.19, 0.63) 0.3173	
Post-Treatment Month 24						
Improvement	2/12/16.67	5/12/41.67 (15.17, 72.33)	2.50 (0.49, 12.89) 0.2568	2.50 (0.49, 12.89) 0.2568	0.25 (-0.16, 0.66) 0.2568	
Deterioration	2/12/16.67	6/12/50.00 (21.09, 78.91)	3.00 (0.61, 14.86) 0.1573	3.00 (0.61, 14.86) 0.1573	0.33 (-0.09, 0.76) 0.1573	

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Race Group Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	0.67	0.67	-0.11	0.3906
Deterioration	0.61	0.61	-0.09	0.9468
Post-Treatment Month 24				
Improvement	0.33	0.33	-0.28	0.1387
Deterioration	0.67	0.61	-0.19	0.5586

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Geographic Region: Europe (N=33)						
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 33/27/26/33/29/31)	[d]					
(nb: 33/33/33/33/31/32)	[e]					
Improvement	6/33/18.18	6/29/20.691.20 (7.99, 39.72) 0.7630	(0.37, 3.93)	1.20 (0.37, 3.93) 0.7630	0.03 (-0.19, 0.26) 0.7630	
Deterioration	6/33/18.18	9/29/31.031.50 (15.28, 50.83) 0.4386	(0.53, 4.21)	1.50 (0.53, 4.21) 0.4386	0.10 (-0.16, 0.36) 0.4386	
Post-Treatment Month 24						
Improvement	6/33/18.18	5/31/16.131.00 (5.45, 33.73) 1.0000	(0.29, 3.45)	1.00 (0.29, 3.45) 1.0000	0.00 (-0.20, 0.20) 1.0000	
Deterioration	6/33/18.18	15/31/48.392.80 (30.15, 66.94) 0.0389	(1.01, 7.77)	2.50 (1.02, 6.15) 0.0389	0.29 (0.03, 0.55) 0.0389	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Geographic Region: USA (N=19)							
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,		
(n: 19/16/16/19/18/16)	[d]						
(nb: 19/19/19/19/19/17)	[e]						
Improvement	4/19/21.05	4/18/22.221.00 (0.25, 4.00) (6.41, 47.64) 1.0000	1.00 (0.25, 4.00) 1.0000	0.00 (-0.31, 0.31) 1.0000			
Deterioration	2/19/10.53	5/18/27.785.00 (0.58, 42.80) (9.69, 53.48) 0.1025	5.00 (0.58, 42.80) 0.1025	0.22 (-0.02, 0.47) 0.1025			
Post-Treatment Month 24							
Improvement	4/19/21.05	5/16/31.251.67 (0.40, 6.97) (11.02, 58.66) 0.4795	1.67 (0.40, 6.97) 0.4795	0.13 (-0.22, 0.47) 0.4795			
Deterioration	2/19/10.53	2/16/12.501.00 (0.14, 7.10) (1.55, 38.35) 1.0000	1.00 (0.14, 7.10) 1.0000	0.00 (-0.24, 0.24) 1.0000			

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Geographic Region Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	1.20	1.20	0.03	0.9290
Deterioration	0.30	0.30	-0.12	0.6613
Post-Treatment Month 24				
Improvement	0.60	0.60	-0.13	0.5072
Deterioration	2.80	2.50	0.29	0.2928

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Dealing with Hemophilia Domain Score						
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 39/30/29/39/35/35)	[d]					
(nb: 39/39/39/39/38/37)	[e]					
Improvement	9/39/23.08	7/35/20.000.88 (8.44, 36.94) 0.7963	(0.32, 2.41)	0.88 (0.32, 2.41) 0.7963	-0.03 (-0.25, 0.19) 0.7963	
Deterioration	6/39/15.38	9/35/25.711.80 (12.49, 43.26) 0.2850	(0.60, 5.37)	1.80 (0.60, 5.37) 0.2850	0.11 (-0.09, 0.32) 0.2850	
Post-Treatment Month 24						
Improvement	9/39/23.08	9/35/25.711.29 (12.49, 43.26) 0.6171	(0.48, 3.45)	1.29 (0.48, 3.45) 0.6171	0.06 (-0.17, 0.28) 0.6171	
Deterioration	6/39/15.38	12/35/34.292.00 (19.13, 52.21) 0.1573	(0.75, 5.33)	2.00 (0.75, 5.33) 0.1573	0.17 (-0.06, 0.40) 0.1573	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

		Domain: Dealing with Hemophilia Domain Score					
		Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 13/13/13/13/12/12)		[d]					
(nb: 13/13/13/13/12/12)		[e]					
Improvement	1/13/7.69	3/12/25.00 (5.49, 57.19)	3.00 (0.31, 28.84) 0.3173	3.00 (0.31, 28.84) 0.3173	0.17 (-0.15, 0.48) 0.3173		
Deterioration	2/13/15.38	5/12/41.67 (15.17, 72.33)	2.50 (0.49, 12.89) 0.2568	2.50 (0.49, 12.89) 0.2568	0.25 (-0.16, 0.66) 0.2568		
Post-Treatment Month 24							
Improvement	1/13/7.69	1/12/8.33 (0.21, 38.48)	1.00 (0.06, 15.99) 1.0000	1.00 (0.06, 15.99) 1.0000	0.00 (-0.23, 0.23) 1.0000		
Deterioration	2/13/15.38	5/12/41.67 (15.17, 72.33)	4.00 (0.45, 35.79) 0.1797	2.50 (0.63, 10.00) 0.1797	0.25 (-0.09, 0.59) 0.1797		

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Lead-in Bleeding Episode Count Category Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	0.29	0.29	-0.20	0.2324
Deterioration	0.72	0.72	-0.14	0.5204
Post-Treatment Month 24				
Improvement	1.29	1.29	0.06	0.9715
Deterioration	0.50	0.80	-0.08	0.7792

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 9/7/6/9/9/8) [d]					
(nb: 9/9/9/9/9/9) [e]					
Improvement	2/9/22.22	1/9/11.110.50 (0.28, 48.25) 0.5637	(0.05, 5.51)	0.50 (0.05, 5.51) 0.5637	-0.11 (-0.48, 0.26) 0.5637
Deterioration	0/9/0.00	3/9/33.3310.23 (7.49, 70.07) 0.1021 @	(0.45, 233.23)	7.00 (0.41, 118.69) 0.1021 @	0.30 (-0.03, 0.63) 0.1021 @
Post-Treatment Month 24					
Improvement	2/9/22.22	1/8/12.500.50 (0.32, 52.65) 0.5637	(0.05, 5.51)	0.50 (0.05, 5.51) 0.5637	-0.13 (-0.54, 0.29) 0.5637
Deterioration	0/9/0.00	4/8/50.0019.00 (15.70, 84.30) 0.0304 @	(0.83, 434.45)	10.00 (0.62, 161.11) 0.0304 @	0.45 (0.10, 0.80) 0.0304 @

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 43/36/36/43/38/39)	[d]				
(nb: 43/43/43/43/41/40)	[e]				
Improvement	8/43/18.60	9/38/23.68 (11.44, 40.24)	1.29 (0.48, 3.45) 0.6171	1.29 (0.48, 3.45) 0.6171	0.05 (-0.15, 0.26) 0.6171
Deterioration	8/43/18.60	11/38/28.95 (15.42, 45.90)	1.57 (0.61, 4.05) 0.3458	1.57 (0.61, 4.05) 0.3458	0.11 (-0.11, 0.32) 0.3458
Post-Treatment Month 24					
Improvement	8/43/18.60	9/39/23.08 (11.13, 39.33)	1.50 (0.53, 4.21) 0.4386	1.50 (0.53, 4.21) 0.4386	0.08 (-0.12, 0.27) 0.4386
Deterioration	8/43/18.60	13/39/33.33 (19.09, 50.22)	1.63 (0.67, 4.35) 0.2513	1.63 (0.70, 3.76) 0.2513	0.13 (-0.09, 0.34) 0.2513

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Status of Target Joint at Screening Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference		
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction		
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]		P value [h]
Post-Treatment Month Improvement	12	0.39		0.39		-0.16		0.4218
		6.52 @		4.46 @		0.19 @		NA @
Post-Treatment Month Improvement	24	0.33		0.33		-0.21		0.4977
		11.11 @		6.13 @		0.32 @		NA @

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

		Domain: Dealing with Hemophilia Domain Score			
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 19/16/16/19/18/17)	[d]				
(nb: 19/19/19/19/18/17)	[e]				
Improvement	4/19/21.05	4/18/22.221.00 (6.41, 47.64)	1.00 (0.25, 4.00) 1.0000	1.00 (0.25, 4.00) 1.0000	0.00 (-0.31, 0.31) 1.0000
Deterioration	2/19/10.53	6/18/33.333.00 (13.34, 59.01)	0.61, 14.86) 0.1573	3.00 (0.61, 14.86) 0.1573	0.22 (-0.07, 0.51) 0.1573
Post-Treatment Month 24					
Improvement	4/19/21.05	4/17/23.531.33 (6.81, 49.90)	0.30, 5.96) 0.7055	1.33 (0.30, 5.96) 0.7055	0.06 (-0.24, 0.36) 0.7055
Deterioration	2/19/10.53	7/17/41.183.50 (18.44, 67.08)	0.73, 16.85) 0.0956	3.50 (0.73, 16.85) 0.0956	0.29 (-0.02, 0.61) 0.0956

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

Domain: Dealing with Hemophilia Domain Score						
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 33/27/26/33/29/30)	[d]					
(nb: 33/33/33/33/32/32)	[e]					
Improvement	6/33/18.18	6/29/20.69 (7.99, 39.72) 0.7630	1.20 (0.37, 3.93) 0.7630	1.20 (0.37, 3.93) 0.7630	0.03 (-0.19, 0.26) 0.7630	
Deterioration	6/33/18.18	8/29/27.59 (12.73, 47.24) 0.4054	1.60 (0.52, 4.89) 0.4054	1.60 (0.52, 4.89) 0.4054	0.10 (-0.14, 0.34) 0.4054	
Post-Treatment Month 24						
Improvement	6/33/18.18	6/30/20.00 (7.71, 38.57) 0.7630	1.20 (0.37, 3.93) 0.7630	1.20 (0.37, 3.93) 0.7630	0.03 (-0.18, 0.25) 0.7630	
Deterioration	6/33/18.18	10/30/33.33 (17.29, 52.81) 0.2850	1.67 (0.60, 5.37) 0.2850	1.67 (0.65, 4.30) 0.2850	0.13 (-0.11, 0.37) 0.2850	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Baseline anti-AAV5 NAb Titer Category Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	0.83	0.83	-0.03	0.9290
Deterioration	1.88	1.88	0.12	0.4009
Post-Treatment Month 24				
Improvement	1.11	1.11	0.03	0.9803
Deterioration	1.94	2.10	0.16	0.3619

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Hepatitis B or C Category: Yes (N=31)						
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 31/25/27/31/28/29)	[d]					
(nb: 31/31/31/31/29/29)	[e]					
Improvement	5/31/16.13	6/28/21.431.20 (8.30, 40.95) 0.7630	(0.37, 3.93)	1.20 (0.37, 3.93) 0.7630	0.04 (-0.20, 0.27) 0.7630	
Deterioration	4/31/12.90	8/28/28.572.00 (13.22, 48.67) 0.2482	(0.60, 6.64)	2.00 (0.60, 6.64) 0.2482	0.14 (-0.09, 0.38) 0.2482	
Post-Treatment Month 24						
Improvement	5/31/16.13	5/29/17.241.25 (5.85, 35.77) 0.7389	(0.34, 4.65)	1.25 (0.34, 4.65) 0.7389	0.03 (-0.17, 0.24) 0.7389	
Deterioration	4/31/12.90	12/29/41.383.67 (23.52, 61.06) 0.0325	(1.02, 13.14)	3.00 (1.04, 8.65) 0.0325	0.28 (0.04, 0.51) 0.0325	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Hepatitis B or C Category: No (N=21)							
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,		
(n: 21/18/15/21/19/18)	[d]						
(nb: 21/21/21/21/21/20)	[e]						
Improvement	5/21/23.81	4/19/21.051.00 (6.05, 45.57)	1.00 (0.25, 4.00) 1.0000	1.00 (0.25, 4.00) 1.0000	0.00 (-0.29, 0.29) 1.0000		
Deterioration	4/21/19.05	6/19/31.582.00 (12.58, 56.55)	0.3173 (0.50, 8.00) 0.3173	2.00 (0.50, 8.00) 0.3173	0.16 (-0.14, 0.46) 0.3173		
Post-Treatment Month 24							
Improvement	5/21/23.81	5/18/27.781.25 (9.69, 53.48)	0.7389 (0.34, 4.65) 0.7389	1.25 (0.34, 4.65) 0.7389	0.06 (-0.27, 0.38) 0.7389		
Deterioration	4/21/19.05	5/18/27.781.25 (9.69, 53.48)	0.7389 (0.34, 4.65) 0.7389	1.25 (0.34, 4.65) 0.7389	0.06 (-0.27, 0.38) 0.7389		

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Hepatitis B or C Category Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	1.20	1.20	0.04	0.6162
Deterioration	1.00	1.00	-0.02	0.7509
Post-Treatment Month 24				
Improvement	1.00	1.00	-0.03	0.8994
Deterioration	2.94	2.40	0.22	0.2850

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 27/23/22/27/25/25)	[d]				
(nb: 27/27/27/27/27/27)	[e]				
Improvement	6/27/22.22	7/25/28.001.40 (12.07, 49.39) 0.5637	(0.44, 4.41)	1.40 (0.44, 4.41) 0.5637	0.08 (-0.19, 0.35) 0.5637
Deterioration	4/27/14.81	10/25/40.003.33 (21.13, 61.33) 0.0522	(0.92, 12.11)	3.33 (0.92, 12.11) 0.0522	0.28 (0.02, 0.54) 0.0522
Post-Treatment Month 24					
Improvement	6/27/22.22	5/25/20.001.00 (6.83, 40.70) 1.0000	(0.29, 3.45)	1.00 (0.29, 3.45) 1.0000	0.00 (-0.25, 0.25) 1.0000
Deterioration	4/27/14.81	9/25/36.002.67 (17.97, 57.48) 0.1317	(0.71, 10.05)	2.25 (0.76, 6.65) 0.1317	0.20 (-0.05, 0.45) 0.1317

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Baseline Steatosis Grade Category: >=S2 (N=11)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 11/9/9/11/8/11) [d]					
(nb: 11/11/11/11/9/11)					
Improvement	1/11/9.09	1/8/12.50 (0.32, 52.65)	1.00 (0.06, 15.99) 1.0000	1.00 (0.06, 15.99) 1.0000	0.00 (-0.35, 0.35) 1.0000
Deterioration	3/11/27.27	0/8/0.00	0.14 (0.01, 3.21) 0.1833 @	0.19 (0.01, 3.24) 0.1833 @	-0.24 (-0.53, 0.06) 0.1833 @
Post-Treatment Month 24					
Improvement	1/11/9.09	3/11/27.27 (6.02, 60.97)	3.00 (0.31, 28.84) 0.3173	3.00 (0.31, 28.84) 0.3173	0.18 (-0.16, 0.52) 0.3173
Deterioration	3/11/27.27	3/11/27.27 (6.02, 60.97)	1.00 (0.20, 4.95) 1.0000	1.00 (0.20, 4.95) 1.0000	0.00 (-0.44, 0.44) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Dealing with Hemophilia Domain Score

Baseline Steatosis Grade Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference	
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g] P value [h]	
Post-Treatment Month 12	Improvement	1.40		1.40		0.08	0.9763
	Deterioration	23.79	@	17.53	@	0.52 @	NA @
Post-Treatment Month 24	Improvement	0.33		0.33		-0.18	0.2945
	Deterioration	2.67		2.25		0.20	0.3144

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20. Hem-A-QoL-Score (15 % MCID) – Hem-A-QoL (Behandlung) – Subgruppenanalysen – Studie HOPE-B – Monat 24

Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Race Group: White (N=40)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
			- - -	- - -	- - -
(n: 40/35/34/40/39/34)	[d]				
(nb: 40/40/40/40/40/36)	[e]				
Improvement	7/40/17.50	19/39/48.72 (32.42, 65.22)	3.40 (1.25, 9.22) 0.0105	2.71 (1.22, 6.02) 0.0105	0.31 (0.09, 0.52) 0.0105
Deterioration	5/40/12.50	2/39/5.13 (0.63, 17.32)	0.40 (0.08, 2.06) 0.2568	0.40 (0.08, 2.06) 0.2568	-0.08 (-0.21, 0.05) 0.2568
Post-Treatment Month 24					
Improvement	7/40/17.50	17/34/50.00 (32.43, 67.57)	3.00 (1.09, 8.25) 0.0253	2.43 (1.09, 5.42) 0.0253	0.29 (0.06, 0.53) 0.0253
Deterioration	5/40/12.50	4/34/11.76 (3.30, 27.45)	1.00 (0.25, 4.00) 1.0000	1.00 (0.25, 4.00) 1.0000	0.00 (-0.16, 0.16) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of

Life Index (Hem-A-QoL) by Subgroups
Analysis
Set: Modified Intent to Treat Population [N=52]

Race Group: Non-White or Not Specified (N=12)		Domain: Treatment Domain Score				
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 12/8/8/12/9/12) [d]						
(nb:12/12/12/12/11/12)	[e]					
Improvement	4/12/33.33	4/9/44.44 (13.70, 78.80)	1.33 (0.30, 5.96) 0.7055	1.33 (0.30, 5.96) 0.7055	0.11 (-0.46, 0.68) 0.7055	
Deterioration	1/12/8.33	1/9/11.11 (0.28, 48.25)	1.00 (0.06, 15.99) 1.0000	1.00 (0.06, 15.99) 1.0000	0.00 (-0.31, 0.31) 1.0000	
Post-Treatment Month 24						
Improvement	4/12/33.33	5/12/41.67 (15.17, 72.33)	1.33 (0.30, 5.96) 0.7055	1.25 (0.39, 3.99) 0.7055	0.08 (-0.35, 0.51) 0.7055	
Deterioration	1/12/8.33	2/12/16.67 (2.09, 48.41)	2.00 (0.18, 22.06) 0.5637	2.00 (0.18, 22.06) 0.5637	0.08 (-0.20, 0.36) 0.5637	

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Race Group Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	2.56	2.04	0.20	0.3238
Deterioration	0.40	0.40	-0.08	0.4431
Post-Treatment Month 24				
Improvement	2.26	1.94	0.21	0.2312
Deterioration	0.50	0.50	-0.08	0.5597

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Protocol: CT-AMT-061-02

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Geographic Region: Europe (N=33)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
			- - -	- - -	- - -
(n: 33/27/26/33/30/30)	[d]				
(nb: 33/33/33/33/32/31)	[e]				
Improvement	6/33/18.18	15/30/50.00 (31.30, 68.70)	3.25 (1.06, 9.97) 0.0290	2.50 (1.07, 5.86) 0.0290	0.30 (0.05, 0.55) 0.0290
Deterioration	4/33/12.12	2/30/6.67 (0.82, 22.07)	0.50 (0.09, 2.73) 0.4142	0.50 (0.09, 2.73) 0.4142	-0.07 (-0.22, 0.09) 0.4142
Post-Treatment Month 24					
Improvement	6/33/18.18	13/30/43.33 (25.46, 62.57)	2.75 (0.88, 8.64) 0.0707	2.17 (0.92, 5.12) 0.0707	0.23 (-0.01, 0.47) 0.0707
Deterioration	4/33/12.12	3/30/10.00 (2.11, 26.53)	1.00 (0.20, 4.95) 1.0000	1.00 (0.20, 4.95) 1.0000	0.00 (-0.16, 0.16) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Geographic Region: USA (N=19)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 19/16/16/19/18/16)	[d]				
(nb: 19/19/19/19/19/17)	[e]				
Improvement	5/19/26.32	8/18/44.44 (21.53, 69.24)	2.00 (0.60, 6.64) 0.2482	2.00 (0.60, 6.64) 0.2482	0.22 (-0.14, 0.59) 0.2482
Deterioration	2/19/10.53	1/18/5.56 (0.14, 27.29)	0.50 (0.05, 5.51) 0.5637	0.50 (0.05, 5.51) 0.5637	-0.06 (-0.24, 0.13) 0.5637
Post-Treatment Month 24					
Improvement	5/19/26.32	9/16/56.25 (29.88, 80.25)	2.00 (0.60, 6.64) 0.2482	1.80 (0.65, 4.95) 0.2482	0.25 (-0.16, 0.66) 0.2482
Deterioration	2/19/10.53	3/16/18.75 (4.05, 45.65)	1.50 (0.25, 8.98) 0.6547	1.50 (0.25, 8.98) 0.6547	0.06 (-0.21, 0.33) 0.6547

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Geographic Region Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	1.63	1.25	0.08	0.4439
Deterioration	1.00	1.00	-0.01	0.9821
Post-Treatment Month 24				
Improvement	1.38	1.21	-0.02	0.9613
Deterioration	0.67	0.67	-0.06	0.4823

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

		Domain: Treatment Domain Score					
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and		Post Treatment vs Lead-In Risk Ratio, 95% CI, and		Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 39/30/29/39/35/35)	[d]						
(nb: 39/39/39/39/38/37)	[e]						
Improvement	7/39/17.95	17/35/48.57 (31.38, 66.01)	2.83	(1.12, 7.19)	2.83	(1.12, 7.19)	0.31 (0.07, 0.56)
Deterioration	6/39/15.38	1/35/2.86 (0.07, 14.92)	0.17	(0.02, 1.38)	0.17	(0.02, 1.38)	-0.14 (-0.28, -0.00)
Post-Treatment Month 24							
Improvement	7/39/17.95	16/35/45.71 (28.83, 63.35)	2.50	(0.97, 6.44)	2.29	(0.98, 5.34)	0.26 (0.02, 0.50)
Deterioration	6/39/15.38	5/35/14.29 (4.81, 30.26)	1.00	(0.29, 3.45)	1.00	(0.29, 3.45)	0.00 (-0.18, 0.18)

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups

Analysis Set: Modified Intent to Treat Population [N=52]

		Domain: Treatment Domain Score				
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,	
(n: 13/13/13/13/13/11)	[d]					
(nb: 13/13/13/13/13/11)	[e]					
Improvement	4/13/30.77	6/13/46.15 (19.22, 74.87)	2.00 (0.37, 10.92) 0.4142	1.50 (0.56, 4.00) 0.4142	0.15 (-0.21, 0.51) 0.4142	
Deterioration	0/13/0.00	2/13/15.38 (1.92, 45.45)	5.87 (0.25, 135.15) 0.2301 @	5.00 (0.26, 95.02) 0.2301 @	0.14 (-0.08, 0.37) 0.2301 @	
Post-Treatment Month 24						
Improvement	4/13/30.77	6/11/54.55 (23.38, 83.25)	2.00 (0.37, 10.92) 0.4142	1.50 (0.56, 4.00) 0.4142	0.18 (-0.24, 0.60) 0.4142	
Deterioration	0/13/0.00	1/11/9.09 (0.23, 41.28)	3.86 (0.14, 104.65) 0.4036 @	3.50 (0.16, 78.19) 0.4036 @	0.09 (-0.12, 0.30) 0.4036 @	

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Lead-in Bleeding Episode Count Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference	
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]	
						P value [h]	
Post-Treatment Month Improvement	12	1.42		1.89		0.16	0.4091
		0.03	@	0.03	@	-0.28	NA @
Post-Treatment Month Improvement	24	1.25		1.53		0.08	0.7249
		0.26	@	0.29	@	-0.09	NA @
Deterioration							

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Status of Target Joint at Screening Category: Presence (N=9)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
			- - -	- - -	- - -
(n: 9/7/6/9/9/8) [d]					
(nb: 9/9/9/9/9/9) [e]					
Improvement	1/9/11.11	5/9/55.56 (21.20, 86.30)	5.00 (0.58, 42.80) 0.1025	5.00 (0.58, 42.80) 0.1025	0.44 (-0.00, 0.89) 0.1025
Deterioration	1/9/11.11	0/9/0.00	0.30 (0.01, 8.35) 0.4675 @	0.33 (0.02, 7.24) 0.4675 @	-0.10 (-0.36, 0.16) 0.4675 @
Post-Treatment Month 24					
Improvement	1/9/11.11	5/8/62.50 (24.49, 91.48)	NC (NC, NC) 0.0455	5.00 (0.87, 28.86) 0.0455	0.50 (0.15, 0.85) 0.0455
Deterioration	1/9/11.11	1/8/12.50 (0.32, 52.65)	1.00 (0.06, 15.99) 1.0000	1.00 (0.06, 15.99) 1.0000	0.00 (-0.35, 0.35) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Status of Target Joint at Screening Category: Absence (N=43)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 43/36/36/43/39/38)	[d]				
(nb: 43/43/43/43/42/39)	[e]				
Improvement	10/43/23.26	18/39/46.15 (30.09, 62.82)	2.29 (0.94, 5.56) 0.0606	2.00 (0.96, 4.19) 0.0606	0.23 (0.00, 0.46) 0.0606
Deterioration	5/43/11.63	3/39/7.69 (1.62, 20.87)	0.60 (0.14, 2.51) 0.4795	0.60 (0.14, 2.51) 0.4795	-0.05 (-0.19, 0.09) 0.4795
Post-Treatment Month 24					
Improvement	10/43/23.26	17/38/44.74 (28.62, 61.70)	1.88 (0.79, 4.42) 0.1444	1.70 (0.83, 3.50) 0.1444	0.18 (-0.06, 0.42) 0.1444
Deterioration	5/43/11.63	5/38/13.16 (4.41, 28.09)	1.25 (0.34, 4.65) 0.7389	1.25 (0.34, 4.65) 0.7389	0.03 (-0.13, 0.18) 0.7389

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Status of Target Joint at Screening Category Interactions

			Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference	
			Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction	
			Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g] P value [h]	
Post-Treatment Improvement	Month	12	2.18		2.50		0.21	
			0.50	@	0.55	@	-0.05	@
Post-Treatment Improvement	Month	24	NC		2.94		0.32	
			0.80		0.80		-0.03	
Deterioration							0.9964	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Baseline anti AAV5 NAb Titer Category: Positive (N=19)

		Post-Treatment									
		Lead-In [a]	Improvement or Post Treatment vs				Post Treatment vs		Post Treatment vs		
		Improvement or Deterioration		Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk							
		Deterioration	n/N1/Proportion 95% CI, and		95% CI, and		Difference, 95% CI,				
		n/N1/Proportion (95% CI*)	P-value [b]		P-value [b]		and P-value [b]				
(n: 19/16/16/19/18/17)		[d]									
(nb: 19/19/19/19/18/17)		[e]									
Improvement		3/19/15.79	8/18/44.44	2.67	(0.71, 10.05)	2.67	(0.71, 10.05)	0.28	(-0.06, 0.62)		
			(21.53, 69.24)	0.1317		0.1317		0.1317			
Deterioration		3/19/15.79	0/18/0.00	0.13	(0.01, 2.65)	0.15	(0.01, 2.72)	-0.15	(-0.33, 0.03)		
				0.1310 @		0.1310 @		0.1310 @			
Post-Treatment Month 24											
Improvement		3/19/15.79	7/17/41.18	3.00	(0.61, 14.86)	2.33	(0.70, 7.82)	0.24	(-0.07, 0.54)		
			(18.44, 67.08)	0.1573		0.1573		0.1573			
Deterioration		3/19/15.79	2/17/11.76	0.67	(0.11, 3.99)	0.67	(0.11, 3.99)	-0.06	(-0.32, 0.20)		
			(1.46, 36.44)	0.6547		0.6547		0.6547			

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Baseline anti AAV5 NAb Titer Category: Negative (N=33)

		Post-Treatment				
		Lead-In [a]	Improvement or Post Treatment vs		Post Treatment vs	Post Treatment vs
		Improvement or Deterioration	Lead-In Odds Ratio, Lead-In Risk Ratio, Lead-In Risk			
		Deterioration	n/N1/Proportion 95% CI, and		95% CI, and	Difference, 95% CI,
		n/N1/Proportion (95% CI*)	P-value [b]		P-value [b]	and P-value [b]
(n: 33/27/26/33/30/29)		[d]				
(nb: 33/33/33/33/33/31)		[e]				
Improvement		8/33/24.24	15/30/50.002.60 (0.93, 7.29)	2.14 (0.95, 4.82)	0.27 (0.01, 0.53)	
			(31.30, 68.70) 0.0593	0.0593	0.0593	
Deterioration		3/33/9.09	3/30/10.001.00 (0.20, 4.95)	1.00 (0.20, 4.95)	0.00 (-0.16, 0.16)	
			(2.11, 26.53) 1.0000	1.0000	1.0000	
Post-Treatment	Month 24					
Improvement		8/33/24.24	15/29/51.722.17 (0.82, 5.70)	1.88 (0.86, 4.09)	0.24 (-0.04, 0.52)	
			(32.53, 70.55) 0.1083	0.1083	0.1083	
Deterioration		3/33/9.09	4/29/13.792.00 (0.37, 10.92)	2.00 (0.37, 10.92)	0.07 (-0.09, 0.23)	
			(3.89, 31.66) 0.4142	0.4142	0.4142	

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Baseline anti-AAV5 NAb Titer Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference	
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]	
						P value [h]	
Post-Treatment Month Improvement	12	1.03		1.25		0.01	0.7452
		0.13	@	0.15	@	-0.15	NA @
Post-Treatment Month Improvement	24	1.38		1.24		0.00	0.9107
		0.34		0.34		-0.13	0.5219
Deterioration							

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Hepatitis B or C Category: Yes (N=31)							
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and		Post Treatment vs Lead-In Risk Ratio, 95% CI, and		Post Treatment vs Lead-In Risk Difference, 95% CI,
			-	-	-	-	-
(n: 31/25/27/31/29/28)	[d]						
(nb: 31/31/31/31/30/28)	[e]						
Improvement	7/31/22.58	13/29/44.83 (26.45, 64.31)	2.20	(0.76, 6.33)	1.86	(0.82, 4.22)	0.21 (-0.05, 0.47)
Deterioration	3/31/9.68	2/29/6.90 (0.85, 22.77)	0.67	(0.11, 3.99)	0.67	(0.11, 3.99)	-0.03 (-0.19, 0.12)
			0.6547		0.6547		0.6547
Post-Treatment Month 24							
Improvement	7/31/22.58	15/28/53.57 (33.87, 72.49)	3.00	(0.97, 9.30)	2.14	(1.00, 4.61)	0.29 (0.03, 0.54)
Deterioration	3/31/9.68	2/28/7.14 (0.88, 23.50)	0.67	(0.11, 3.99)	0.67	(0.11, 3.99)	-0.04 (-0.19, 0.12)
			0.6547		0.6547		0.6547

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Hepatitis B or C Category: No							
(N=21)							
	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and		Post Treatment vs Lead-In Risk Ratio, 95% CI, and		Post Treatment vs Lead-In Risk Difference, 95% CI,
			-	-	-	-	-
(n: 21/18/15/21/19/18)	[d]						
(nb: 21/21/21/21/21/20)	[e]						
Improvement	4/21/19.05	10/19/52.63 (28.86, 75.55)	3.33	(0.92, 12.11)	3.33	(0.92, 12.11)	0.37 (0.04, 0.70)
Deterioration	3/21/14.29	1/19/5.26 (0.13, 26.03)	0.33	(0.03, 3.20)	0.33	(0.03, 3.20)	-0.11 (-0.31, 0.10)
			0.3173		0.3173		0.3173
Post-Treatment Month 24							
Improvement	4/21/19.05	7/18/38.89 (17.30, 64.25)	1.75	(0.51, 5.98)	1.75	(0.51, 5.98)	0.17 (-0.19, 0.52)
Deterioration	3/21/14.29	4/18/22.22 (6.41, 47.64)	2.00	(0.37, 10.92)	2.00	(0.37, 10.92)	0.11 (-0.15, 0.37)
			0.4142		0.4142		0.4142

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Table GHТА_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Hepatitis B or C Category Interactions

	Between-subgroup ratio of	Between-subgroup ratio of	Between-subgroup difference	
	Post Treatment vs Lead-In	Post Treatment vs Lead-In	of Post Treatment vs Lead-In Interaction	
	Odds Ratio [f]	Risk Ratio [f]	Risk Difference [g]	P value [h]
Post-Treatment Month 12				
Improvement	0.66	0.56	-0.16	0.5651
Deterioration	2.03	2.03	0.08	0.6321
Post-Treatment Month 24				
Improvement	1.71	1.22	0.12	0.6834
Deterioration	0.34	0.34	-0.15	0.4913

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Baseline Steatosis Grade Category: <S2 (N=27)

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
			- - -	- - -	- - -
(n: 27/23/22/27/25/24)	[d]				
(nb: 27/27/27/27/27/26)	[e]				
Improvement	7/27/25.93	11/25/44.002.00 (24.40, 65.07) 0.1967	(0.68, 5.85)	1.83 (0.72, 4.67) 0.1967	0.20 (-0.09, 0.49) 0.1967
Deterioration	4/27/14.81	3/25/12.000.75 (2.55, 31.22) 0.7055	(0.17, 3.35)	0.75 (0.17, 3.35) 0.7055	-0.04 (-0.25, 0.17) 0.7055
Post-Treatment Month 24					
Improvement	7/27/25.93	11/24/45.831.67 (25.55, 67.18) 0.3173	(0.61, 4.59)	1.57 (0.64, 3.84) 0.3173	0.17 (-0.15, 0.49) 0.3173
Deterioration	4/27/14.81	3/24/12.501.00 (2.66, 32.36) 1.0000	(0.20, 4.95)	1.00 (0.20, 4.95) 1.0000	0.00 (-0.20, 0.20) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Baseline Steatosis Grade Category: ~~>=S2 (N=11)~~

	Lead-In [a] Improvement or Deterioration n/N1/Proportion	Post-Treatment Improvement or Deterioration n/N1/Proportion (95% CI*)	Post Treatment vs Lead-In Odds Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Ratio, 95% CI, and	Post Treatment vs Lead-In Risk Difference, 95% CI,
(n: 11/9/9/11/9/11) [d]					
[e]					
(nb:11/11/11/11/10/11)					
Improvement	2/11/18.18	5/9/55.56 (21.20, 86.30)	4.00 (0.45, 35.79) 0.1797	2.50 (0.63, 10.00) 0.1797	0.33 (-0.10, 0.77) 0.1797
Deterioration	1/11/9.09	0/9/0.00	0.37 (0.01, 10.18) 0.5516 @	0.40 (0.02, 8.78) 0.5516 @	-0.08 (-0.31, 0.16) 0.5516 @
Post-Treatment Month 24					
Improvement	2/11/18.18	6/11/54.55 (23.38, 83.25)	5.00 (0.58, 42.80) 0.1025	3.00 (0.75, 12.00) 0.1025	0.36 (-0.02, 0.74) 0.1025
Deterioration	1/11/9.09	1/11/9.09 (0.23, 41.28)	1.00 (0.06, 15.99) 1.0000	1.00 (0.06, 15.99) 1.0000	0.00 (-0.25, 0.25) 1.0000

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Table GHTA_2.3.8.30 Proportion of Subjects with Improvement or Deterioration of 15% Threshold for Hemophilia Specific Quality of Life Index (Hem-A-QoL) by Subgroups
Analysis Set: Modified Intent to Treat Population [N=52]
Domain: Treatment Domain Score

Baseline Steatosis Grade Category Interactions

		Between-subgroup ratio of		Between-subgroup ratio of		Between-subgroup difference	
		Post Treatment vs Lead-In		Post Treatment vs Lead-In		of Post Treatment vs Lead-In Interaction	
		Odds Ratio [f]		Risk Ratio [f]		Risk Difference [g]	
						P value [h]	
Post-Treatment Month	12	0.50		0.73		-0.13	0.4379
	Improvement	2.03	@	1.88	@	0.04	NA @
Post-Treatment Month	24	0.33		0.52		-0.19	0.4855
	Improvement	1.00		1.00		0.00	0.9076

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