P2103

Emicizumab Prophylaxis in People with Hemophilia A (PwHA), Aged ≥50 Years, with Comorbidities – Pooled Data from Four Phase III Studies (HAVEN 1, 3, and 4, and STASEY)

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Summary

Cardiovascular (CV) risk factors are common among PwHA, particularly as they get older, with HIV and HCV infections also being more common in this older population

The efficacy and safety of emicizumab in older PwHA with CV risk factors or HIV and/or HCV infection were analyzed in pooled data from four phase III studies

HAVEN 1 | HAVEN 3 | HAVEN 4 | STASEY

ABR (95% CI)

Overall pooled population, **1.39** (0.08–6.23) N=504

PwHA ≥50 years **1.82** (0.19–6.93) n=96

p-values (0.2641–0.9997)

Safety outcomes were also similar to the overall study population: emicizumab prophylaxis was well tolerated in PwHA ≥50 years

ABRs for PwHA ≥50 years were similar to the overall population

No significant differences were seen between ABRs for PwHA ≥50 years and those ≥50 years with CV risk factors or HIV/HCV infection

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Background

- Emicizumab, a bispecific monoclonal antibody, bridges activated factor (F)IX and FX to restore hemostasis in people with hemophilia A (PwHA). It is indicated for routine prophylaxis in PwHA with/without FVIII inhibitors (exact label may vary by country)
  - Despite being indicated for all ages, the care of older people receiving emicizumab may be complicated by comorbidities.
- Prevalence and early onset of cardiovascular (CV) risk factors, including hypertension, are common among PwHA.[1–3]
- Human immunodeficiency virus (HIV), which is likely to be more common in older PwHA, is associated with increased risk of heart disease,[4] and co-infection of HIV with hepatitis C virus (HCV) increases the risk of end-stage liver disease and worsens HCV progression.[5]
- Data regarding emicizumab in older PwHA with comorbidities (CV risk factors or concomitant HIV and/or HCV infection) are limited
  - This post hoc analysis of PwHA in four phase III studies evaluated efficacy and safety of emicizumab in PwHA aged ≥50 years with CV risk factors or HIV and/or HCV infection.

Four phase III studies were included in the analysis

- For this post hoc analysis, four phase III studies were included: HAVEN 1, 3, and 4, and STASEY (**Figure 1**)
  - All studies enrolled **PwHA aged ≥12 years**.
- An age cut-off of **≥50 years** was selected for this analysis.
- PwHA were excluded from those studies if they had:
  - Severe hepatic disease, including history or clinical signs of cirrhosis;
  - HIV infection with a CD4 count <200 cells/μL;
  - Concurrent disease, treatment, or abnormality that could impact safe participation (as deemed by the investigator).

Figure 1. Summary of the phase III studies included in the analysis

HAVEN 1[6]	HAVEN 3[7]	HAVEN 4[8]	STASEY[9]
NCT02622321 Open-label, randomized study	NCT02847637 Open-label, randomized study	NCT03020160 Open-label, single-arm study	NCT03191799 Open-label, single-arm study
PwHA ≥12 years **with** FVIII inhibitors	PwHA ≥12 years **without** FVIII inhibitors	PwHA ≥12 years **with/without** FVIII inhibitors	PwHA ≥12 years **with** FVIII inhibitors
Emicizumab 1.5mg/kg QW	Emicizumab 1.5mg/kg QW 3.0mg/kg Q2W	Emicizumab 6mg/kg Q4W	Emicizumab 1.5mg/kg QW

QW, every week; Q2W, every 2 weeks; Q4W, every 4 weeks

Data were available for 504 PwHA across the four studies, of whom 96 were ≥50 years and eligible for this analysis

- PwHA were assessed for cardiovascular (CV) risk factors (past medical history of CV disease or current evidence of: hypertension, diabetes, hyperlipidemia, or obesity [body mass index ≥30 kg/m^2]), HCV infection (defined as prior/current infection), and HIV infection.

Table 1. Demographics and characteristics of PwHA ≥50 years

	PwHA ≥50 years
Total, n (%)	96 (100.0)
HAVEN 1	17 (17.7)
HAVEN 3	33 (34.4)
HAVEN 4	12 (12.5)
STASEY	34 (35.4)
Median age (range), years	57 (50–80)
50–64 years, n (%)	74 (77.1)
≥65 years, n (%)	22 (22.9)
Median emicizumab treatment duration (range), years	2.02 (0.14–4.25)
CV risk factors*, n (%)	
≥1 CV risk factor	70 (72.9)
≥2 CV risk factors	24 (25.0)
HIV and/or HCV infection†, n (%)	
HIV infection only	1 (1.0)
HCV infection only	48 (50.0)
HCV+HIV coinfection	22 (22.9)

*CV risk factors included past medical history of CV disease or current evidence of: hypertension, diabetes, hyperlipidemia, or obesity (body mass index ≥30kg/m^2); †HCV infection was defined as prior/current infection;
Bleeds were defined per the HAVEN 1, 3 and 4 and STASEY study protocols.
CV, cardiovascular; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwHA, people with hemophilia A

Subgroup populations of PwHA aged ≥50 years were identified according to CV risk factors and HIV/HCV infection status

Table 2. Demographics and characteristics of PwHA by age, comorbidities, and risk factors

	PwHA ≥50 years				
	≥1 CV risk factor (n=70)	≥2 CV risk factors (n=24)	HIV positive only (n=1)	HCV positive only (n=48)	HIV+HCV positive (n=22)
Median age (range), years	58 (50–80)	61 (50–77)	50 (50–50)	56.5 (50–76)	53.5 (50–67)
Participants with FVIII inhibitors, n (%)	33 (47.1)	12 (50.0)	0 (0.0)	28 (58.3)	2 (9.1)
Median (range) bleeds in 24 weeks prior to study	6.5 (0–84)	8.0 (0–35)	5.0 (5–5)	7.0 (0–63)	6.0 (0–49)
Median (range) emicizumab treatment duration, years	2.02 (0.14– 3.69)	1.98 (0.14–3.69)	2.96 (2.96, 2.96)	2.07 (0.46–4.25)	1.92 (0.14–3.61)
Target joints at baseline, n (%)					
1 joint	12 (17.1)	4 (16.7)	1 (100.0)	9 (18.8)	1 (4.6)
≥1 joints	45 (64.3)	16 (66.7)	1 (100.0)	32 (66.7)	12 (54.6)
Hemophilic arthropathy at baseline, n (%)					
1 joint	34 (48.6)	11 (45.8)	0	23 (47.9)	14 (63.6)
≥1 joints	39 (55.7)	12 (50.0)	0	25 (52.1)	17 (77.3)

CV, cardiovascular; F, factor; HCV, hepatitis C virus; HIV, human immunodeficiency virus; PwHA, people with hemophilia A

Emicizumab prophylaxis resulted in ABRs for PwHA ≥50 years with comorbidities that were similar to the overall study population

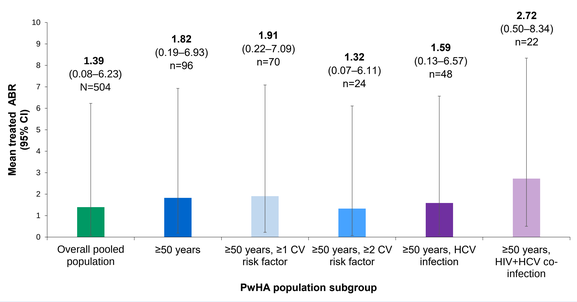
- The mean (95% CI) treated annualized bleeding rate (ABR) for the **overall population** (N=504) was 1.39 (0.08–6.23)
  - For PwHA aged **≥50 years** (n=96), mean treated ABR was 1.82 (0.19–6.93; **Table 3 and Figure 2**).
- Mean treated ABR was **consistent** in participants with CV risk factors and HCV infection.
- PwHA aged ≥50 years with HIV+HCV co-infection (n=22) had a **numerically higher treated ABR** of 2.72 (0.50–8.34), however this was not statistically significant (p=0.4593) and may have been skewed by one participant with an ABR of 21 and three others with ABRs ≥5 (**Table 4**).

Table 3. Mean treated ABRs of PwHA ≥50 years with or without FVIII inhibitors by subgroup

		PwHA ≥50 years				
	Overall pooled population (N=504)	Total (n=96)	≥1 CV risk factor (n=70)	≥2 CV risk factors (n=24)	HCV positive only (n=48)	HIV+HCV positive (n=22)
All participants						
Mean treated ABR, (95% CI)	1.39 (0.08–6.23)	1.82 (0.19–6.93)	1.91 (0.22–7.09)	1.32 (0.07–6.11)	1.59 (0.13–6.57)	2.72 (0.50–8.34)
Participants with FVIII inhibitors						
n (%)	283 (56.2)	49 (51.0)	33 (47.1)	12 (50.0)	28 (58.3)	2 (9.1)
Mean treated ABR, (95% CI)	1.41 (0.09–6.27)	1.22 (0.05–5.95)	1.15 (0.04–5.84)	0.55 (0–4.77)	1.63 (0.14–6.63)	2.65 (0.48–8.24)
Participants without FVIII inhibitors						
n (%)	221 (43.8)	47 (49.0)	37 (52.9)	12 (50.0)	20 (41.7)	20 (90.9)
Mean treated ABR, (95% CI)	1.36 (0.08–6.18)	2.44 (0.39–7.91)	2.59 (0.45–8.15)	2.08 (0.27–7.35)	1.54 (0.12–6.48)	2.72 (0.5–8.35)

Data from the one patient with HIV infection only have been omitted.
ABR, annualized bleeding rate; CI, confidence interval; CV, cardiovascular; F, factor; HCV, hepatitis C virus; HIV, human immunodeficiency virus; NE, not evaluable

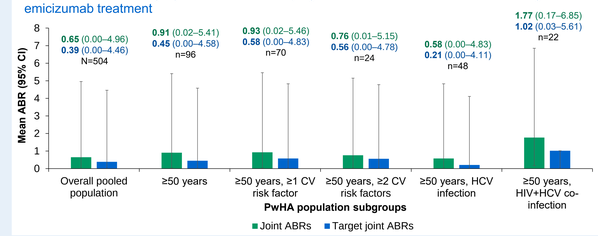
Figure 2. Mean treated ABR by age, comorbidities, and risk factors during emicizumab treatment



95% CI derived from exact Poisson distribution. N/n represents the number of participants. Data from the one patient with HIV infection only have been omitted.

Joint and target joint treated ABRs were consistent across the overall PwHA population and PwHA ≥50 years with comorbidities

Figure 3. Joint and target joint treated ABRs by age, comorbidities, and risk factors during emicizumab treatment



Data from the one patient with HIV infection only have been omitted.

No significant difference in treated ABR was identified in comparisons between PwHA ≥50 years with comorbidities and the rest of the cohort

- When PwHA ≥50 years with CV risk factors, HIV infection, or HCV infection were compared with those without, **no significant effects on ABR** were observed (**Table 4**).

Table 4. Annual adjusted treated ABR in PwHA ≥50 years with comorbidities versus PwHA ≥50 years without comorbidities

	PwHA with comorbidity		PwHA without comorbidity		Rate ratio	
	n	Lsmean (95% CI)	n	Lsmean (95% CI)	Lsmean (95% CI)	p-value*
≥1 CV risk factor	70	1.48 (0.91–2.40)	26	2.28 (1.00–5.23)	0.65 (0.25–1.68)	0.3721
≥2 CV risk factors	24	1.07 (0.46–2.52)	72	1.85 (1.16–2.97)	0.58 (0.22–1.51)	0.2641
HCV infection only	48	1.71 (0.92–3.16)	48	1.63 (0.90–2.92)	1.05 (0.45–2.48)	0.9100
HCV or HIV	71	1.78 (1.11–2.85)	25	1.27 (0.53–3.03)	1.41 (0.53–3.71)	0.4903
HCV and HIV coinfection	22	2.20 (0.92–5.28)	74	1.47 (0.87–2.47)	1.50 (0.51–4.42)	0.4593

Data from the one patient with HIV infection only have been omitted.
*p-values were obtained via negative binomial regression adjusting for the effects of study and baseline bleed levels.
Lsmean, least-squares mean

Rates of adverse events and serious adverse events were similar in PwHA ≥50 years and the overall study population

- Adverse events (AEs), serious AEs, Grade 3–4 AEs and injection-site reaction rates were **similar among PwHA in the overall population and PwHA ≥50 years (Table 5)**.
- In the overall population, thrombotic events (TEs) and thrombotic microangiopathies (TMAs) occurred in 6 (1.2%) and 3 (0.6%) PwHA, respectively. In PwHA ≥50 years, one TE each occurred in two participants who both had ≥1 risk factor, one of whom also had HCV infection; **no TMAs were observed**.
- AEs leading to withdrawal occurred in 1.0% (n=5) of the overall study population, and 1.0% (n=1) of PwHA ≥50 years.

Table 5. Summary of safety outcomes by age, comorbidities, and risk factors

		PwHA ≥50 years				
Outcome, n (%)	Overall pooled population (N=504)	Total (n=96)	≥1 CV risk factor (n=70)	≥2 CV risk factors (n=24)	HCV positive only (n=48)	HIV+HCV positive (n=22)
Any AE	462 (91.7)	89 (92.7)	66 (94.3)	22 (91.7)	45 (93.8)	21 (95.5)
Serious AE	97 (19.2)	23 (24.0)	16 (22.9)	2 (8.3)	11 (22.9)	5 (22.7)
Grade 3–4 AE	107 (21.2)	25 (26.0)	18 (25.7)	5 (20.8)	13 (27.1)	4 (18.2)
Local ISR	102 (20.2)	12 (12.5)	9 (12.9)	3 (12.5)	2 (4.2)	6 (27.3)
TE	6 (1.2)	2 (2.1)	2 (2.9)	0	1 (2.1)	0
TMA	3 (0.6)	0	0	0	0	0

Data from the one patient with HIV infection only have been omitted.
AE, adverse event; ISR, injection-site reaction; TE, thrombotic event; TMA, thrombotic microangiopathy

Conclusions

- ABRs for PwHA ≥50 years with CV risk factors, or with HIV and/or HCV infection, receiving emicizumab prophylaxis were similar to the overall study populations receiving emicizumab prophylaxis
- Safety outcomes were similar to the overall study populations; emicizumab prophylaxis was well tolerated in PwHA ≥50 years with comorbidities
- Despite the small number of patients, this analysis suggests that the efficacy and safety of emicizumab prophylaxis are not adversely affected by age or common comorbidities seen in older PwHA

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Emicizumab is subject to additional safety monitoring requirements in many countries. Healthcare professionals are asked to report any suspected adverse reactions to the regulatory authorities in your country according to your national requirements.

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