Emicizumab in People with Moderate or Mild Haemophilia A Aged ≥40 Years, with and without Comorbidities

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Summary

There is a paucity of data on **older people with non-severe haemophilia A** (HA), particularly those with **comorbidities**, and in people with moderate or mild HA.

The safety and efficacy of emicizumab in people **aged ≥40** years with **non-severe HA** without inhibitors were evaluated in a post hoc analysis of the **HAVEN 6 trial** (NCT04158648).

However, the number of people aged ≥40 years in this analysis (N=16) is small; thus, firm conclusions are precluded, and **further studies are warranted.**

The safety and efficacy of emicizumab in these participants **did not differ** notably from those observed in the overall HAVEN 6 population (people with moderate or mild HA).

Background

- Emicizumab is a bispecific antibody licensed by the European Medicines Agency and other regulatory authorities for prophylaxis in people of all ages with haemophilia A (HA) with factor (F)VIII inhibitors, and in those without FVIII inhibitors who have severe disease (FVIII activity <1%) or moderate disease (FVIII activity ≥1%–≤5%) with severe bleeding phenotype (label varies by country).[1]
- Few data exist on the use of emicizumab in older people with HA (PwHA), particularly those with comorbidities, such as cardiovascular (CV) conditions, hepatitis, and human immunodeficiency virus (HIV), and in people with moderate or mild HA.
- We present a post hoc analysis of PwHA aged ≥40 years from the HAVEN 6 trial (NCT04158648), which was conducted to evaluate the safety and efficacy of emicizumab in people with non-severe HA without FVIII inhibitors.

Methods

- HAVEN 6 is a global, multicentre, open-label, single-arm, Phase III trial conducted in individuals of all ages with a diagnosis of moderate (FVIII activity ≥1%–≤5%) or mild (FVIII >5%–<40%) HA without FVIII inhibitors, warranting prophylaxis as assessed by the investigator.[2]
- The emicizumab loading dose was administered subcutaneously at 3mg/kg once weekly, for 4 weeks
  - This was then followed by the participant's choice of maintenance dose, which included the options of 1.5mg/kg weekly, 3mg/kg every 2 weeks, or 6mg/kg every 4 weeks.
- The primary objective was safety, including thromboembolic events (TEs) and thrombotic microangiopathy (TMA), and the primary efficacy endpoint was the annualized bleed rate (ABR) for treated bleeds.
- An age cut-off of ≥40 years was selected for this exploratory analysis in order to obtain a population with a high proportion of comorbidities in PwHA
  - In this analysis, comorbidities included CV risk factors (history of CV disease; hypertension; hyperlipidaemia; diabetes; body mass index [BMI] ≥30kg/m^2), HIV, and current or previous history of hepatitis C virus (HCV) infection.

Results

- At data cut-off (30 October 2021), 72 participants had been treated in HAVEN 6; 16 were aged ≥40 years and were included in this analysis.
- Demographics and characteristics for participants aged ≥40 years are shown in **Table 1**.

Table 1. Demographics and characteristics

	Participants aged ≥40 years
Total, N (%)	16 (100)
Median (range) age, years	50.5 (41–71)
Aged ≥50 years	8 (50.0)
Male, n (%)	16 (100)
Median (range) emicizumab treatment duration, years	1.1 (0.6–1.7)
Haemophilia severity at study entry, n (%)	
Mild	6 (37.5)
Moderate	10 (62.5)
CV risk factors, n (%)	
≥1 CV risk factor	9 (56.3)*
≥2 CV risk factors	5 (31.3)
HIV and/or HCV infection, n (%)	
HIV infection only	1 (6.3)
HCV infection only	3 (18.8)
HCV+HIV coinfection	2 (12.5)

*Of the nine participants who had CV risk factors, seven had hypertension, four had past medical history events (these included atrial fibrillation, coronary artery disease, mitral valve incompetence, and one participant having both sinus tachycardia and pelvic venous thrombosis), two had a baseline BMI ≥30kg/m^2, and one had diabetes.

There were no fatal adverse events (AEs), AEs leading to treatment withdrawal/modification/interruption, or thrombotic microangiopathies

- The median (range) duration of emicizumab exposure was 1.1 (0.6–1.7) years.
- Fifteen (93.8%) of the 16 participants experienced ≥1 AE during the study. Three (18.8%) experienced a serious AE and 1 (6.3%) a Grade 3–4 AE; these were deemed unrelated to emicizumab (**Table 2**).
- One individual, who had no CV risk factors or HIV/HCV infection, experienced a TE (Grade 1 thrombosed haemorrhoids); this was deemed unrelated to emicizumab.
- Three participants experienced a total of six treatment-related AEs: three injection-site reactions and one case each of fatigue, head discomfort, and accidental overdose.

Table 2. Summary of safety outcomes by comorbidities and risk factors

		Participants aged ≥40 years					
	Participants aged <40 years (N=56)	Participants aged ≥40 years (N=16)	No CV risk factor (n=7)	≥1 CV risk factor (n=9)	≥2 CV risk factors (n=5)	No HCV or HIV (n=10)	HCV and/or HIV (n=6)
Number of AEs, n	192	56	26	30	22	39	17
Participants with ≥1 AE, n (%)							
Any AE	45 (80.4)	15 (93.8)	7 (100.0)	8 (88.9)	4 (80.0)	9 (90.0)	6 (100.0)
Serious AE	5 (8.9)	3 (18.8)	2 (28.6)	1 (11.1)	1 (20.0)	3 (30.0)	0
Fatal AE	0	0	0	0	0	0	0
AE leading to withdrawal	0	0	0	0	0	0	0
AE leading to dose modification/interruption	0	0	0	0	0	0	0
Grade 3–4 AE	3 (5.4)	1 (6.3)	0	1 (11.1)	1 (20.0)	1 (10.0)	0
Treatment-related AE	12 (21.4)	3 (18.8)	2 (28.6)	1 (11.1)	1 (20.0)	3 (30.0)	0
Injection-site reaction	10 (17.9)	2 (12.5)	1 (14.3)	1 (11.1)	1 (20.0)	2 (20.0)	0
Thromboembolic event	0	1 (6.3)	1 (14.3)	0	0	1 (10.0)	0
Thrombotic microangiopathy	0	0	0	0	0	0	0

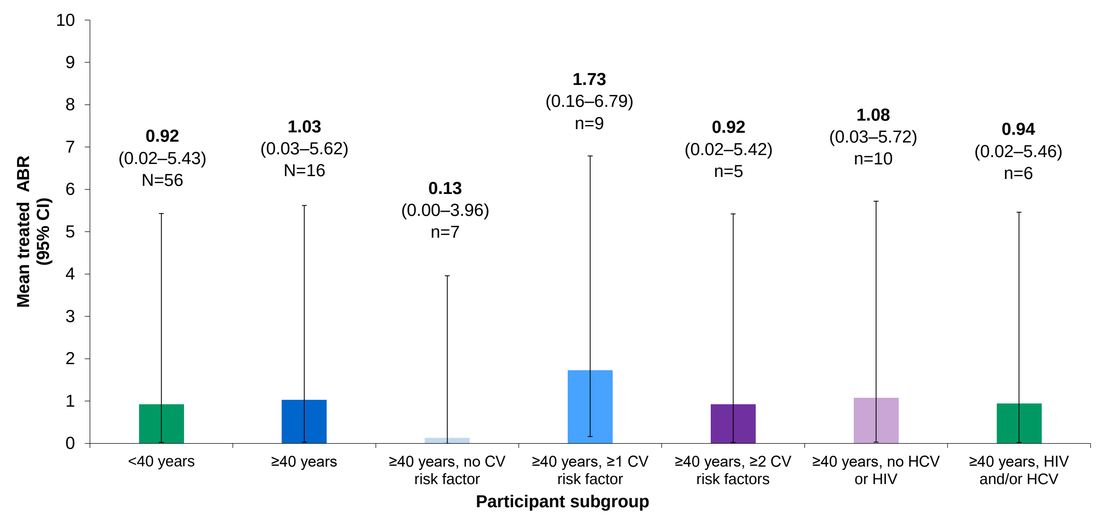
Bleed outcomes in the ≥40 years subgroup were similar to those for the overall HAVEN 6 population, and to those aged <40 years

- During the study, the mean (95% confidence interval [CI]) and median ABR for treated bleeds for the 16 participants aged ≥40 years were 1.03 (0.03–5.62) and 0, respectively (**Table 3**)
  - Mean (95% CI) ABRs were similar to that of the overall population of HAVEN 6 (0.94 [0.02–5.48]) and the population aged <40 years (0.92 [0.02–5.43]; **Figure 1**).[2]
- A total of 11 participants (68.8%) had zero bleeds during the study, which is comparable with the 66.7% reported for the total population[2] and 66.1% reported for participants aged <40 years.

Table 3. Summary of bleed outcomes by comorbidities and risk factors

		Participants aged ≥40 years					
	Participants aged <40 years (N=56)	Participants aged ≥40 years (N=16)	No CV risk factor (n=7)	≥1 CV risk factor (n=9)	≥2 CV risk factors (n=5)	No HCV or HIV (n=10)	HIV and/or HCV (n=6)
Total number of treated bleeds, n	54	17	1	16	5	11	6
Participants with zero treated bleeds, n (%)	37 (66.1)	11 (68.8)	6 (85.7)	5 (55.6)	3 (60.0)	6 (60.0)	5 (83.3)
Median ABR	0	0	0	0	0	0	0

Figure 1. Mean ABR for treated bleeds by age, comorbidities, and risk factors



Conclusions

- This post hoc analysis of the HAVEN 6 trial helps to address the existing data gap of the safety and efficacy of emicizumab in older PwHA, particularly those with comorbidities, and in people with moderate or mild HA.
- Overall, emicizumab prophylaxis appeared to be well tolerated in PwHA ≥40 years with comorbidities (CV risk factor or HIV and/or HCV infection).
- The safety and efficacy of emicizumab in these participants did not differ notably from those observed in the overall population of people with moderate or mild HA in HAVEN 6, or from those aged <40 years.
- However, the small number of individuals aged ≥40 years included in the current analysis (N=16) is a limitation that precludes drawing firm conclusions from the data; further studies and data from real-world evidence are therefore warranted in older PwHA with comorbidities.

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