Roche

HEMLIBRA®
emicizumab-kxwh
injection for subcutaneous use
150 mg/mL

HEMLIBRA®
Monograph-Non-inhibitors

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1. OVERVIEW OF HEMOPHILIA A

1.1. PATHOPHYSIOLOGY

Hemophilia A is an X linked recessive bleeding disorder (Figure 1) characterized by congenital underproduction or dysfunction of blood coagulation factor VIII (FVIII). FVIII, which is usually produced in liver sinusoidal cells and endothelial cells outside the liver throughout the body, is a component of the intrinsic pathway in the coagulation cascade and essential for promoting clot formation. It is a cofactor for activated factor IX (FIXa) that forms a complex activating factor X (FXa), which in turn cleaves prothrombin to generate thrombin. Hemophilia A results from mutations or defects in the gene that encodes FVIII. Due to the fact that hemophilia A is passed along by X linked recessive inheritance, the vast majority (approximately 90%) of identified patients are males (WFH. 2016).

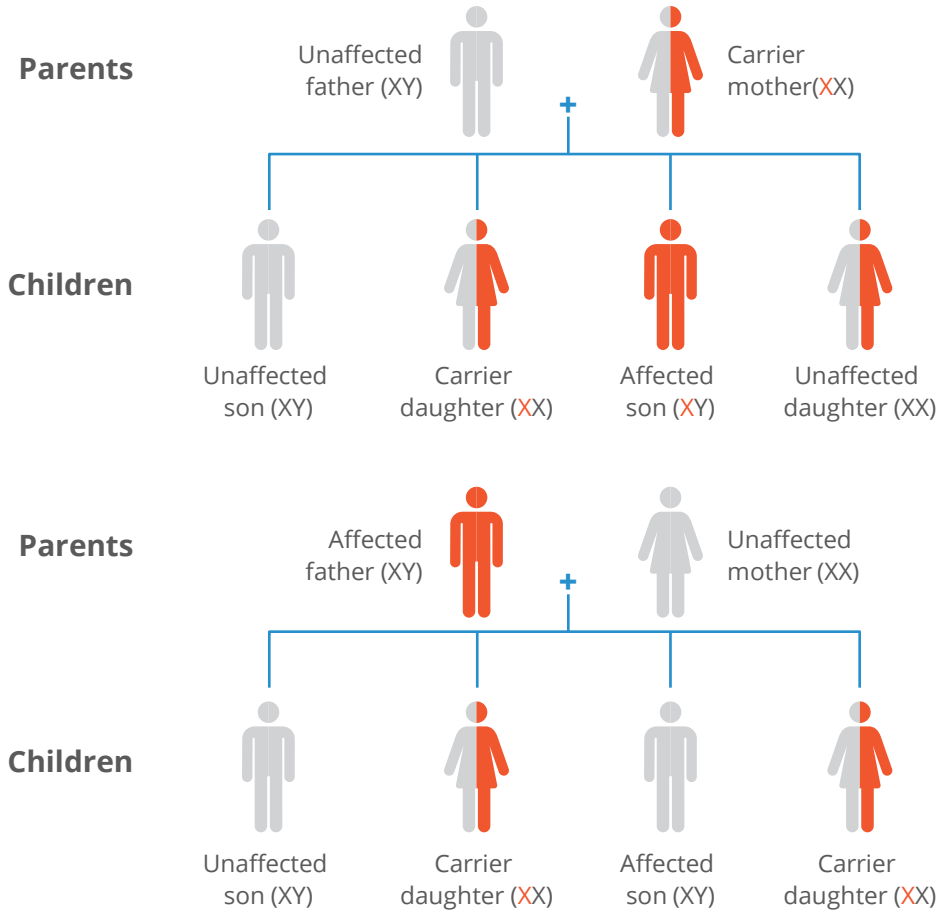


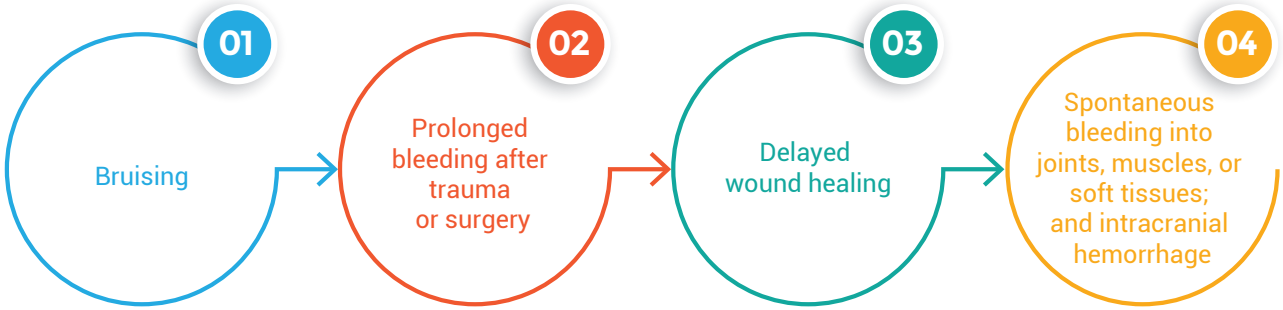
Figure 1: Hemophilia A X-linked recessive inheritance

Hemophilia A results in a lifelong bleeding tendency and is a serious chronic disease that can be fatal. Some patients who are born with normal FVIII develop autoantibodies directed against FVIII.

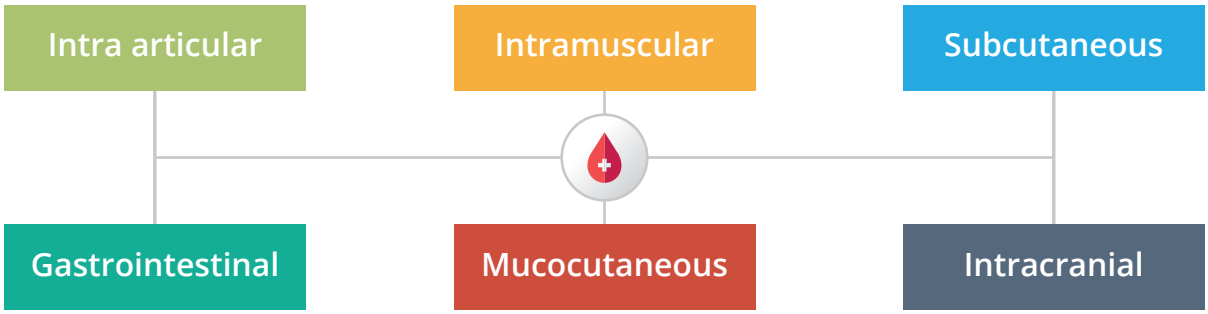
2. CLINICAL FEATURES OF HEMOPHILIA A

Underproduction or dysfunction of FVIII leads to a lifelong bleeding tendency.

Common clinical signs of hemophilia A include:



The main types of bleeding are as follows:



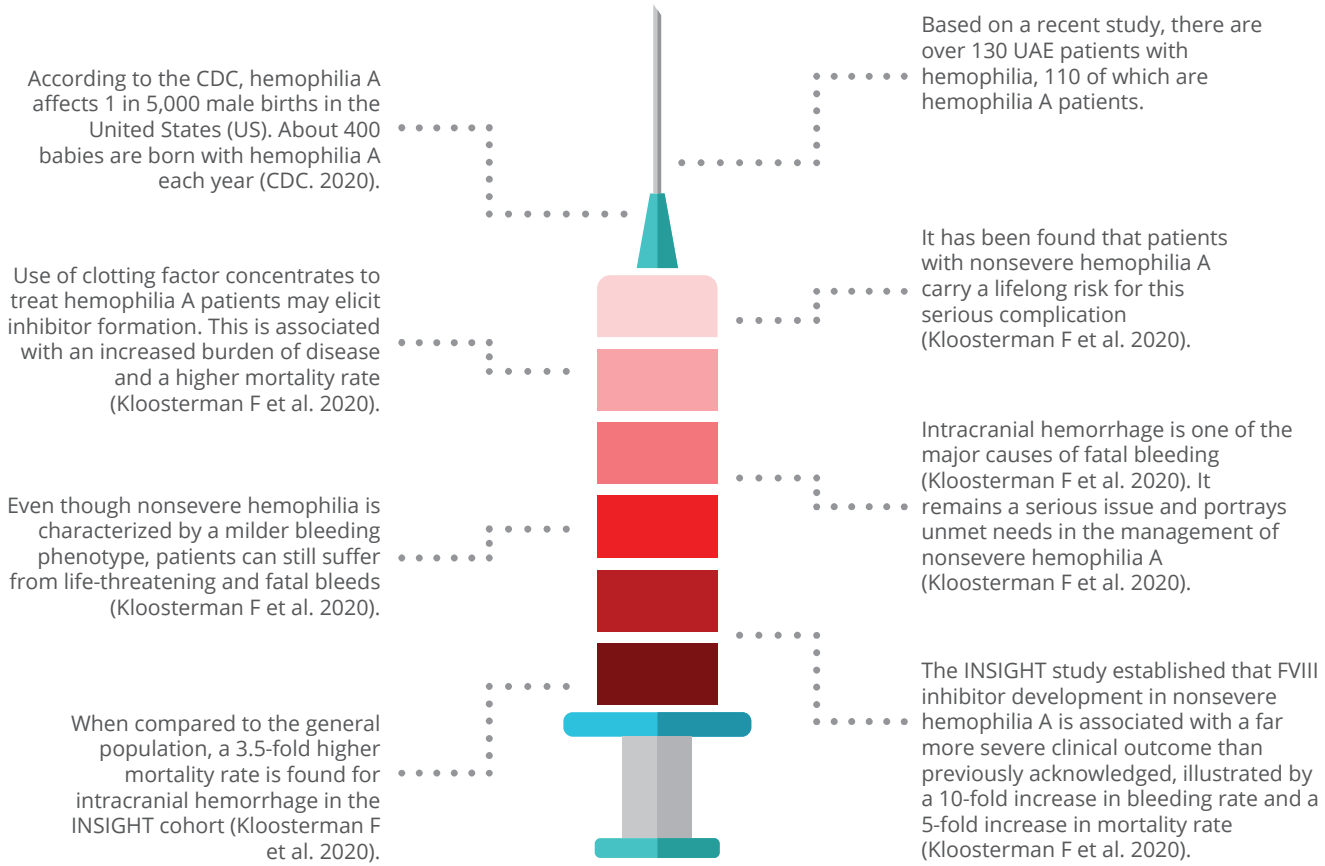
3. DISEASE BURDEN

Although hemophilia A is a rare disease, it exerts a substantial humanistic, societal, and economic burden on individuals, caregivers, and healthcare systems. Hemophilia affects interpersonal relationships and educational, career and lifestyle choices. Patients with hemophilia experience diminished quality of life as a result of bleeding events, chronic pain, and other disease complications and parents of children with hemophilia have decreased HRQoL compared with the general population.

3.1. HUMANISTIC BURDEN

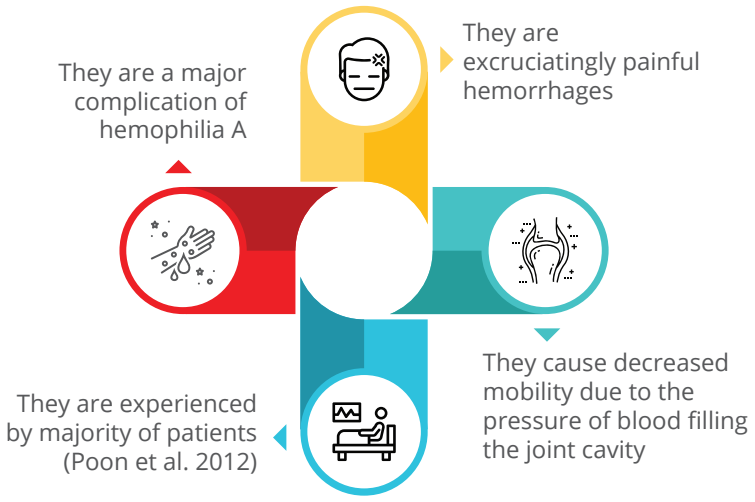
The complications associated with spontaneous and prolonged bleeding lead to increased morbidity in patients with hemophilia A, especially in patients with severe disease. Severe hemophilia has lower levels of FVIII and is associated with a significantly higher number of annual bleeding episodes compared with mild hemophilia (Zhou et al. 2015). Severe hemophilia is characterized by recurrent spontaneous bleeds typically into joints, muscles, or subcutaneously, and potentially life threatening gastrointestinal or intracranial hemorrhages.

MORTALITY



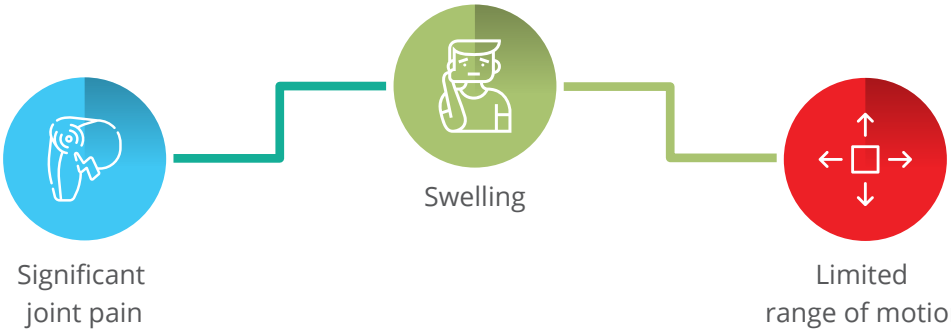
JOINT BLEEDS

The following points are true of joint bleeds:



Historically, about 90% patients with severe hemophilia experience such chronic degenerative changes (hemophilic arthropathy) in one to six major joints (e.g., ankles, elbows, knees) by the second or third decade of life (Rodriguez Merchan 2010).

Repeated intra articular bleeds into the same joints:



Hemophilic arthropathy may ultimately require surgical intervention, including joint replacement at young age (Riley et al. 2011). Increased functional disability due to hemophilia symptoms is a major burden for patients, affecting daily life activities (Tlacuilo Parra et al. 2010; Witkop et al. 2015). Costs of care are especially high with joint bleeds and hemophilic arthropathy.

HEALTH-RELATED QOL

The symptom and treatment burden associated with hemophilia A can have a major impact on HRQoL of hemophilic patients through the following:

- Pain has been shown to have a considerable impact on patient's HRQoL and interferes with patient's activities (Forsyth et al. 2015).
- Worse physical HRQoL has been reported for patients with hemophilia A compared with the general population (Poon et al. 2012; Pollmann et al. 2013; St Louis et al. 2016), with physical HRQoL decreasing significantly with increasing severity of the disease (Poon et al. 2012; Pollmann et al. 2013).
- Repeated intra articular bleeding in the same joints (target joints) is a major contributor to decreased HRQoL in patients with hemophilia A, because the joint damage associated with multiple hemarthroses may progress to hemophilic arthropathy (Klamroth et al. 2011; Riley et al. 2011; Gringeri et al. 2013).

While physical limitations are a key cause of diminished HRQoL, the psychological impact, coping strategies, and emotional reactions to a life restricting disease vary with life stage and by person, and are important consequences beyond the physical problems the condition can cause (Cassis 2007).

3.2. CAREGIVER BURDEN

Having a family member with hemophilia inevitably increases the burden on the caregivers and the family (Khair and von Mackenson 2017).

Hemophilia has intangible costs, including reduced QoL, pain and suffering of the individual and family, and emotional and physical toll on the patient and caregivers.

Hemophilia negatively impacts the caregiver's HRQoL, especially when a child is affected (Khair and von Mackenson 2017). Pain, emotional stress, and financial burden have been reported as the most burdensome domains among caregivers of children as well as adult patients with hemophilia A (Dekoven et al. 2014) (Dekoven et al. 2013).

The emotional and practical aspects of caregiver burden are specifically high when the patient requires frequent infusions of hemophilia treatment. A large study including hemophilia caregiver reported worse social, physical, emotional, financial, and lifestyle impact with more infusions per week (Schwartz et al. 2018).

Cooperation is needed among the key stakeholders (Sheh-Li Chen. 2016):

Healthcare professionals

Patients and their caregivers

Managed care professionals

Benefits of cooperation among the stakeholders (Sheh-Li Chen. 2016):

Individualized treatment strategies for patients with hemophilia

Individualized strategies designed to prevent complications

Optimized clinical and economic outcomes while enhancing patient QoL

3.3. ECONOMIC BURDEN

The management of hemophilia is associated with high medical expenses and high indirect costs that can vary widely depending on disease severity, frequency of bleeds, presence or absence of inhibitors to FVIII, and treatment regimen.

Direct medical costs for hemophilia include:

- Outpatient drug acquisition claims (drug acquisition claims for prophylaxis treatment)
- Inpatient admission claims (drug acquisition claims needed to manage the bleeding episodes)

Non drug related direct costs for hemophilia include:

- Hematologist and other specialist consultations
- Medical tests and examinations
- Bleed-related management (medications, hospitalization, physiotherapy, radiotherapy, outpatient consultation, outpatient nursing, etc.)

Mean annual indirect costs for hemophilia include:

- Loss of earnings
- Transfer payments
- Over the counter medications
- Devices
- Personal aids
- Alternative therapies
- Transport

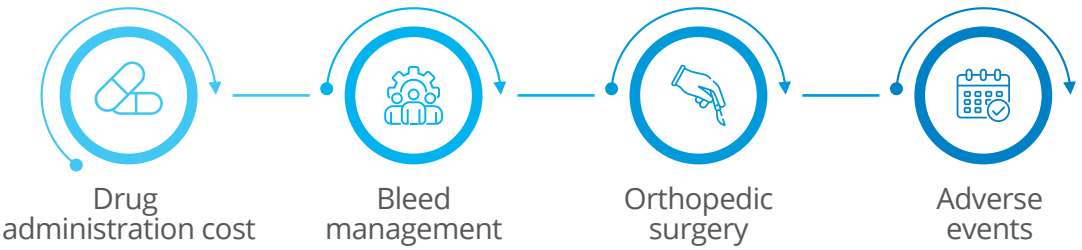
COST OF ILLNESS

Local data was generated by a 'burden of disease model' for hemophilia A patients in UAE. The cost of illness study which was designed to assess the clinical, economic and humanistic burden of hemophilia A in UAE, suggests that:

- The management of hemophilia in UAE is estimated to be 93,926,563 AED annually
- 75.14% of which (70,575,427 AED) is spent on drug acquisition cost
- 24.86% of which (23,351,136 AED) is spent on non-drug acquisition costs, mainly to manage the bleeds resulting from insufficient protection for the patient using factor replacement therapy

More than 23.3 million AED is spent on the management of bleeds, despite the high rate of adequate prophylaxis with factor replacement. Prophylaxis rate is estimated to be 96%.
In 5 years' time horizon, more than 116 million AED are spent on the management of bleeds, that are not captured in the drug acquisition cost.

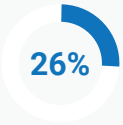
Non-drug acquisition costs include:



Reports have shown that UAE has 68 hemophilia A patients without inhibitors (which represents 92% of the total hemophilia A patients in UAE).

The management of hemophilia A without inhibitors in UAE is estimated to be 83.822,027 AED annually

74% of which (62,241,855 AED) is spent on drug acquisition costs



26% of which (21,580,171 AED) is spent on non-drug acquisition cost

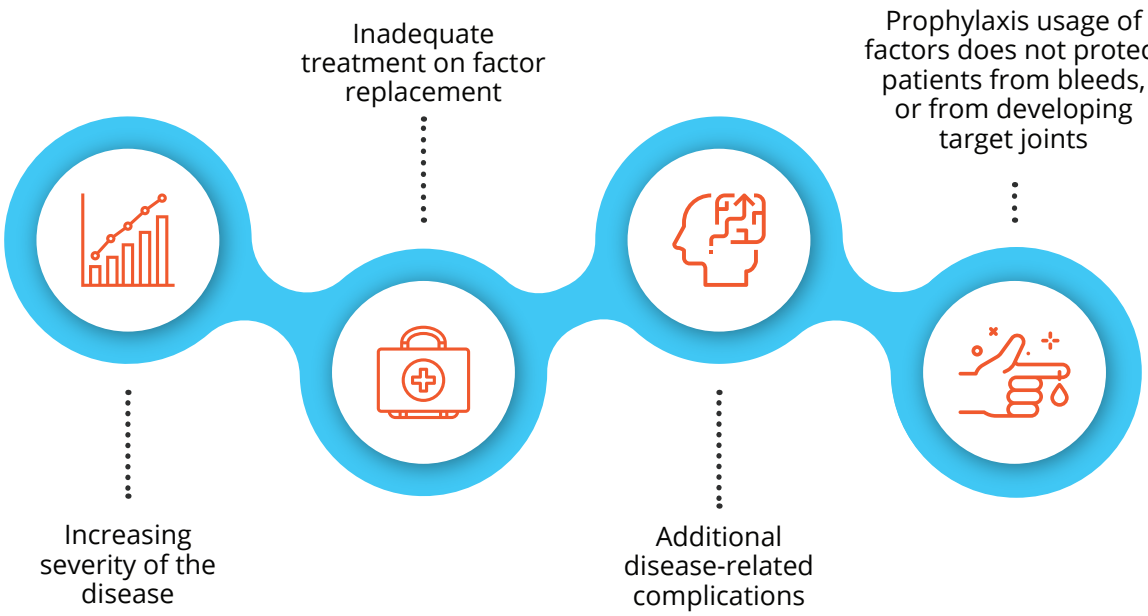
More than 21.5 million AED are spent on the management of bleeds, despite the high rate of adequate prophylaxis with factor replacement. Prophylaxis rate is estimated to be 96%.

In 5 years' time horizon, more than 108 million AED are spent on the management of bleeds, that are not captured in the drug acquisition cost.

In 5 years' time horizon, each patient costs around 1.6 million AED which are not related to the prophylaxis drug cost and are spent on the management of bleeds and surgeries.

Non−drug-related direct costs should not be underestimated. A substantial proportion of hemophilia A patients have at least one visit to the emergency department (approximately 30%) or undergo at least one hospitalization (approximately 15% to 20%) per year (Guh et al. 2012a; Zhou et al. 2015).

Reasons behind an increase in the non−drug-related costs:



E.g., significantly higher costs in patients with target joints than for patients without target joints

4. CLINICAL MANAGEMENT OF THE DISEASE OR HEALTH CONDITION

4.1. UNMET MEDICAL NEED

Replacement therapy with recombinant FVIII:

01

Recombinant FVIII is a widely used treatment for patients with hemophilia A with and without inhibitors to FVIII (Castaman and Linari. 2018)

02

Limitations of recombinant VIII are:

- Inadequate efficacy due to incomplete coverage
- High treatment burden and low patient compliance (Castaman and Linari. 2018)

Given these challenges, there is need for therapeutics with the following characteristics:

HIGH TREATMENT BURDEN WITH FVIII PROPHYLAXIS

Lack of sustained therapeutic drug levels:

- The therapeutic drug levels are not sustained with FVIII prophylaxis (Figure 2) (Castaman G. 2018).

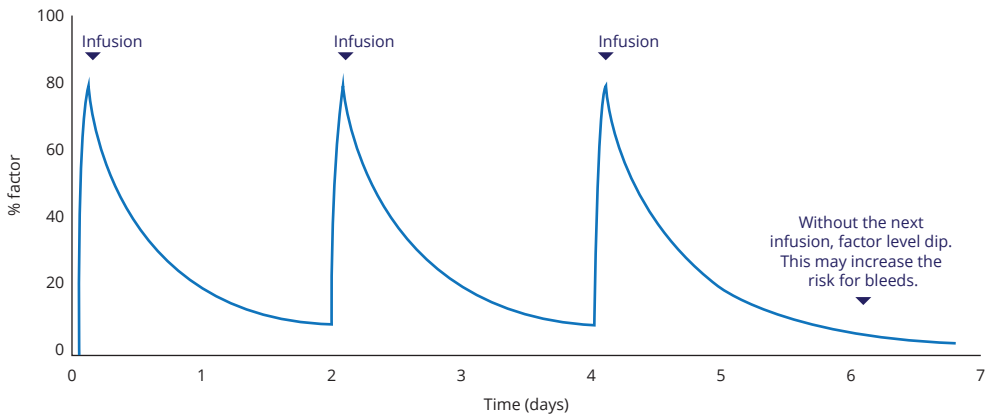


Figure 2: Therapeutic drug levels with FVIII prophylaxis

- The half-life of FVIII is short
    - o 8 to 18 hours for current plasma derived concentrates
    - o 21 hours for certain (half-life extended) recombinant products
- Thus, the current prophylaxis regimens aim at maintaining FVIII levels at a trough of 1% to partially restore hemostasis (Valentino et al. 2012)
- However, this target coverage does not provide complete protection
- The development of extended half-life FVIII products results in only a modestly increased half-life by 1.5-fold (Mahlangu et al. 2014; Giangrande et al. 2017; Konkle et al. 2015)
- Patients on FVIII prophylaxis still experience microbleeds resulting in
    - o progressive arthropathy and long-term joint damage, even in the absence of clinical bleeds (Kraft et al. 2012; Olivieri et al. 2012)

Lifetime requirement of intravenous infusion:

- Adequate prophylaxis requires a lifetime of self-administered intravenous infusion of FVIII at least QW to 4 times per week
    - o It is time consuming (Shapiro et al. 2001)
    - o It can put considerable strain on patients, caregivers, and families, including frequent absences from school or work (Shapiro et al. 2001)

Patients should have venous cannulation skills:

- The routine intravenous administration of FVIII relies on venous cannulation skills of patients and their care providers (Hacker et al. 2001)
- Intravenous administration of FVIII may be a problem because because of the following reasons
    - o Patients may not be able to administer the drug due to lack of skill especially in children and elders
    - o It may be associated with complications contributing to hemophilia associated long-term morbidity
- Over time, peripheral venous access may prove to become more difficult due to (Guillon et al. 2015)
    - o Scar formations on the skin and vessels walls
    - o Leakage
    - o Injection site bruising
    - o Vessel thrombosis

BREAKTHROUGH BLEEDS AND BLEEDING EPISODES WITH FVIII PROPHYLAXIS

More than half of patients experience bleeds with FVIII prophylaxis:

Patients who comply with their prophylactic FVIII regimens may still experience a certain number of bleeds per year and related morbidity (e.g., chronic arthropathy).

- 62% of 66 pediatric patients with severe hemophilia A still had bleeds over a period of 6 months (Mullins et al. 2017)
- Approximately 70% of 272 patients had bleeds over 1 year in routine clinical practice (Khair et al. 2018)

Real-world data highlight the increase in ABR despite prophylaxis:

- *Prospective non-interventional study (NIS)*

Results from a prospective non-interventional study (NIS) in a real-world setting showed that persons with hemophilia A (PwHA) without inhibitors continue to bleed on prophylaxis **(Figure 3)**, and require treatment for breakthrough bleeds.

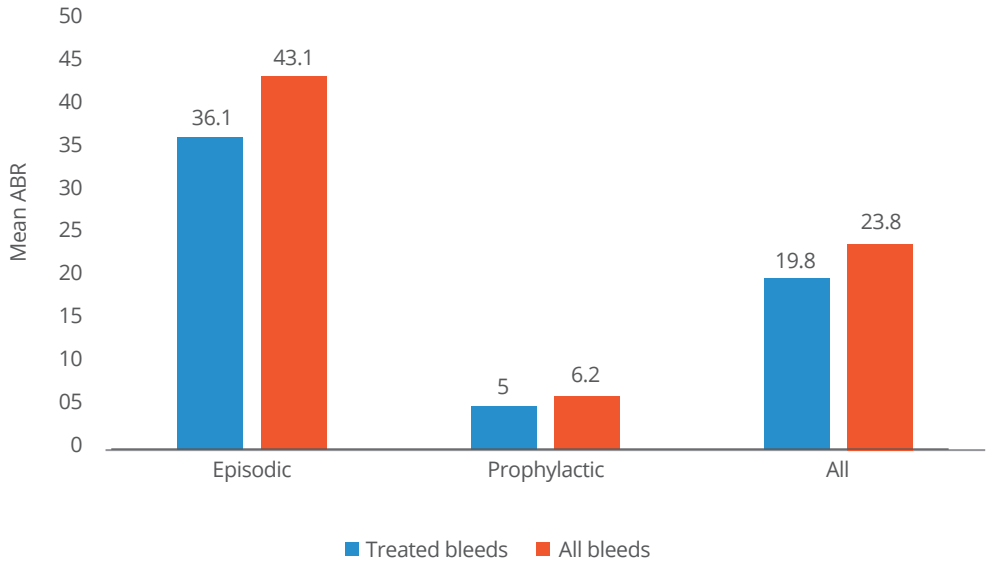


Figure 3: ABR in adult/adolescent PwHA without FVIII inhibitors

The study demonstrated the need for more efficacious hemostatic approaches (Kruse-Jarres R et al. 2019).

- *Advate® Hemophilia A Outcome Database (AHEAD) cohort study*

The global prospective long-term AHEAD cohort study collected real-world data from patients with severe and moderate hemophilia. The cohort included 522 patients enrolled from 21 countries. The details of the median ABR in the prophylaxis group and on-demand group are given in **Table 1**.

	Median ABR in prophylaxis group	Median ABR in ondemand group
Year 1 visit	1.7	8.9
Year 2 visit	1.6	13.0
Year 3 visit	2.2	10.3

Table 1: Median ABR in the prophylaxis group and on-demand group

The study concluded that though the goal of zero bleed is achievable, patients still bleed (Khair K et al. 2018).

• *THUNDER Study*

The THUNDER study analyzed the treatment patterns and outcomes in UK patients with severe or moderate hemophilia A (SHA/MHA) in 2015. Inhibitors were present in 159 (8.8%) SHA patients and 34 (3.9%) MHA patients. Of 717 non-inhibitor patients with SHA or MHA reporting HT-compliant data during the study period, 563 (78.5%) had SHA, and 154 (21.5%) MHA. The median (IQR) ABR in patients with SHA on prophylaxis was 2.0 (0.0-7.0) and 6.5 (2.0-17.8) on-demand. The study showed that the ABR increased with age in both the prophylaxis and on-demand groups (Figure 4) (Scott MJ, et al. 2019).

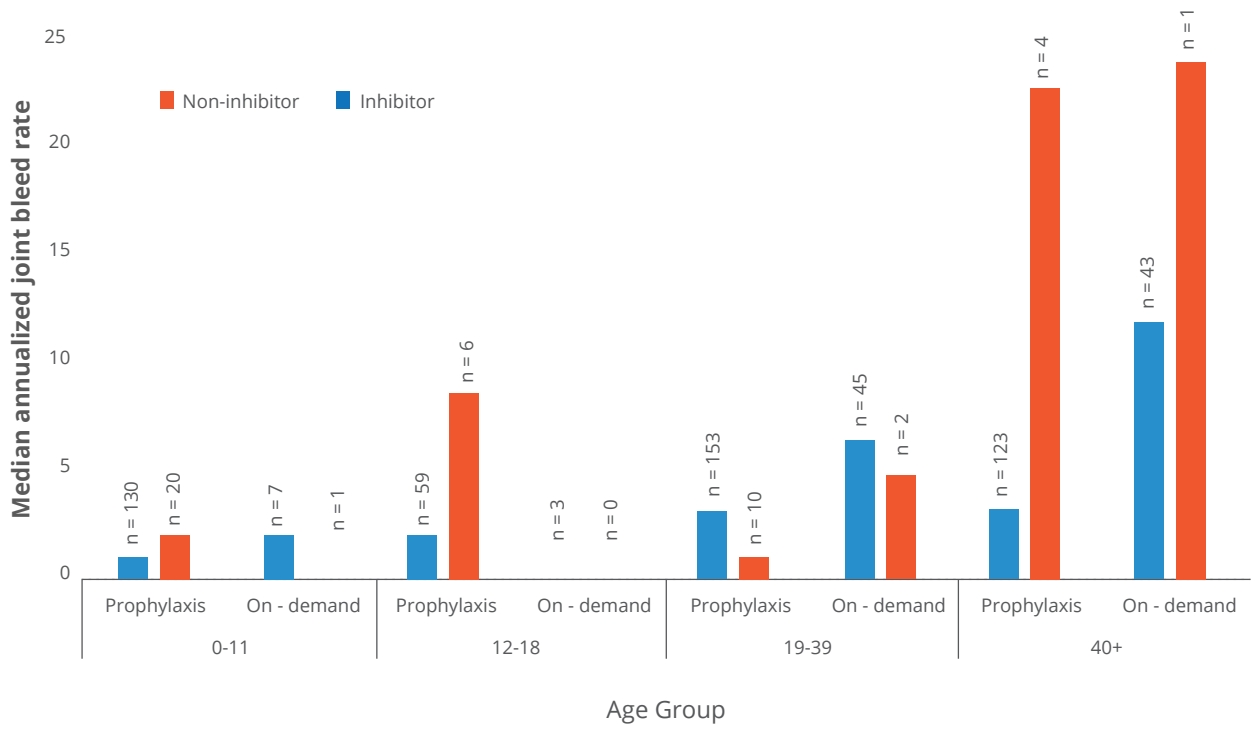


Figure 4: Median ABR for Haemtrack-compliant patients with severe haemophilia A using prophylaxis and on-demand treatment, categorized according to age and inhibitor status

JOINT BLEEDS WITH FVIII PROPHYLAXIS

Patients with hemophilia A experience permanent joint damage. This is because many patients with hemophilia A without FVIII inhibitors still have breakthrough bleeds despite FVIII prophylaxis.

• *AHEAD Study*

About 42% of patients on prophylaxis vs 12% of patients on on-demand therapy had zero AJBR (Khair K et al. 2018).

• *THUNDER Study*

AJBR increased with age in both the prophylaxis and on-demand groups (Figure 5) (Scott MJ, et al. 2019).

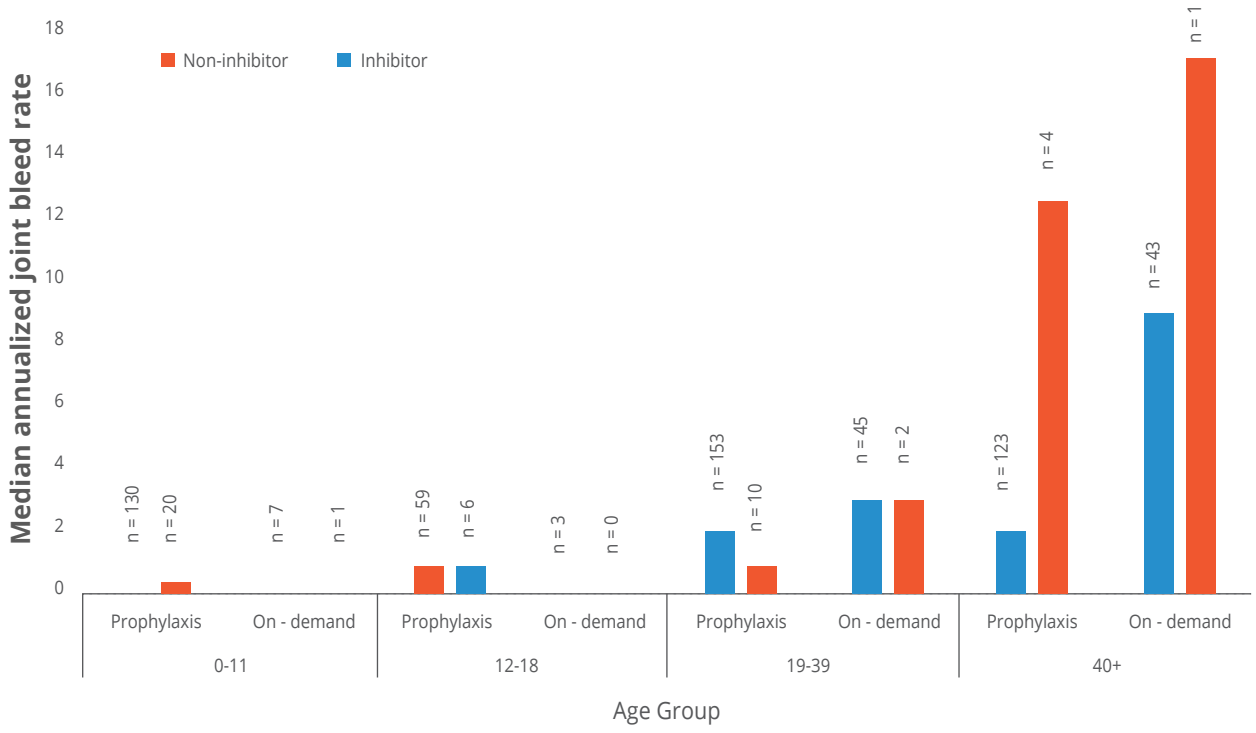


Figure 5: Median AJBR for Haemtrack-compliant patients with severe haemophilia A using prophylaxis and on-demand treatment, categorized according to age and inhibitor status

The median (IQR) AJBR in patients with SHA on prophylaxis was 1.0 (0.0-4.0) and on-demand was 3.5 (0.0-12.8). Among patients with SHA, around 38% patients in the prophylaxis groups and 28% in the on-demand group were joint-bleed-free.

Median hemophilia joint health score (HJHS) (n = 453) increased with age in SHA and MHA. The median (IQR) HJHS in patients treated on-demand was 0.0 (0.0-0.0), 0-18 years and 56.5 (53.0-60.0), aged >60 years (Figure 6) (Scott MJ, et al. 2019).

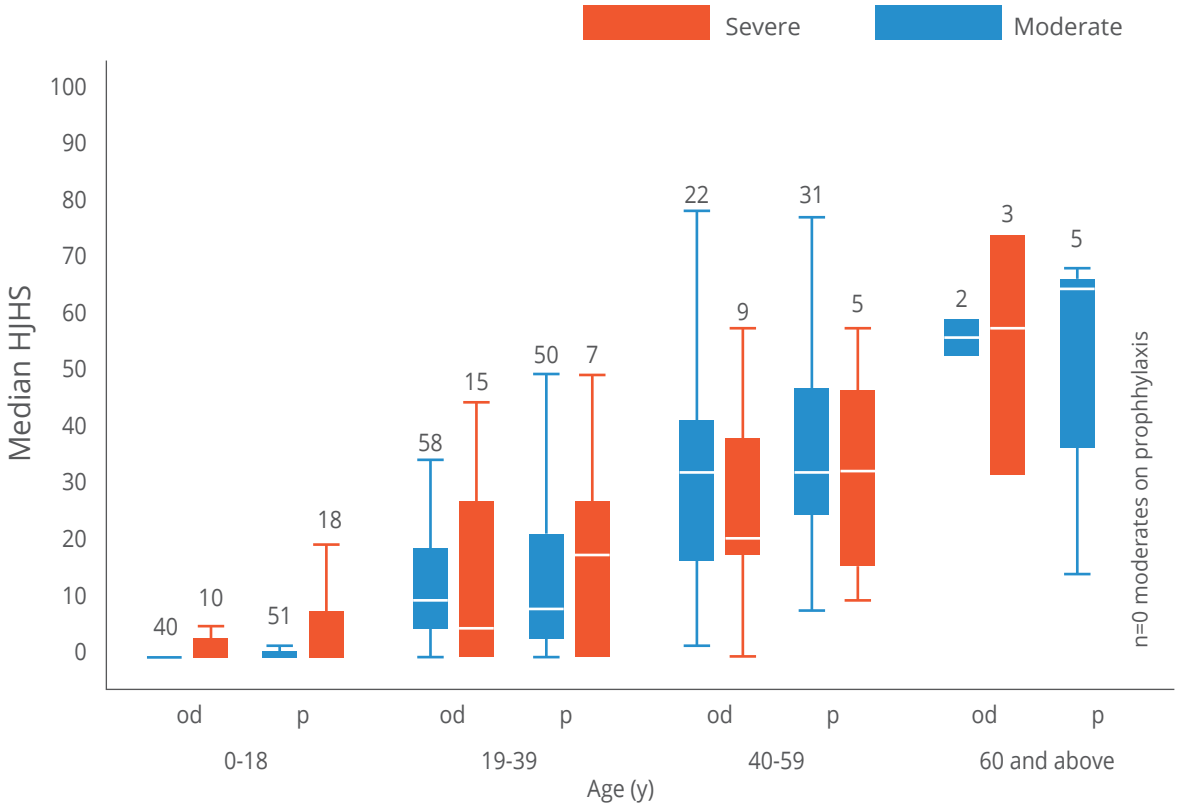


Figure 6: Median haemophilia joint health score for patients with severe haemophilia A and moderate haemophilia A, categorized according to treatment type and age.

The line represents the median value; the box interquartile range and the whiskers the lowest data still within 1.5 IQR of the lower quartile, and the highest data still within 1.5 IQR of the upper quartile.

- *Other studies*

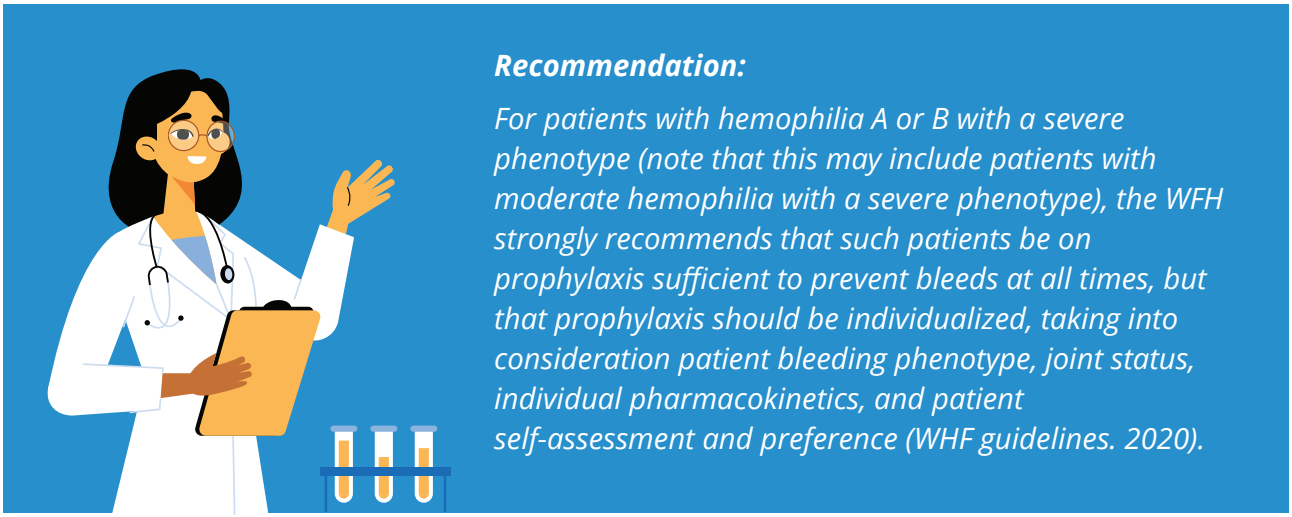
Evidence supports the occurrence of progressive arthropathy in up to two third of patients who receive an adequate primary prophylaxis regimen. These changes begin within the first decade of life and involve clinically bleed free joints (Kraft et al. 2012; Olivieri et al. 2012), indicating that FVIII prophylaxis delays, but does not completely prevent, long term skeletal morbidity (Oldenburg et al. 2015).

5. STANDARD-OF-CARE: PROHYLAXIS VS ON-DEMAND TREATMENT FOR HEMOPHILIA A PATIENTS

PROPHYLAXIS VS EPISODIC THERAPY IN HEMOPHILIA (WHF guidelines. 2020)

- Prophylaxis in hemophilia consists of regular administration of therapeutic products aimed at maintaining hemostasis to prevent bleeding, especially joint hemorrhages, which would lead to arthropathy and disability. Prophylaxis should enable people with hemophilia to lead healthy and active lives including participation in most physical and social activities (at home, school, work, and in the community), similar to the non-hemophilic population.
- Prophylaxis with clotting factor concentrates (CFCs) is referred to as regular replacement therapy; it stands in contrast to episodic replacement therapy (also known as on-demand therapy), which is defined as the administration of CFCs only at the time of a bleed.

- Episodic therapy, regardless of the doses used, while essential in reducing the pain and debilitating impact of individual bleeds, does not alter the bleeding profile significantly and hence does not change the natural history of hemophilia leading to musculoskeletal damage and other complications due to bleeding.
- Therefore, the use of prophylaxis is always recommended over episodic therapy. In countries with healthcare constraints and for patients with limited access to CFCs, less intensive prophylaxis regimens may be used. Still, in all countries the ideal is for patients to not experience any bleeds (i.e., achieve "zero" bleeds).
- With the ***advent of innovative non-factor replacement therapies (e.g. emicizumab)***, which for the most part can be administered subcutaneously, prophylaxis is being redefined as the regular administration (intravenously, subcutaneously, or otherwise) of a hemostatic agent/agents to enhance hemostasis and effectively prevent bleeding in people with hemophilia.



Recommendation:

For patients with hemophilia A or B with a severe phenotype (note that this may include patients with moderate hemophilia with a severe phenotype), the WFH strongly recommends that such patients be on prophylaxis sufficient to prevent bleeds at all times, but that prophylaxis should be individualized, taking into consideration patient bleeding phenotype, joint status, individual pharmacokinetics, and patient self-assessment and preference (WHF guidelines. 2020).

STANDARD OF CARE IN HEMOPHILA (WHF guidelines. 2020)

- According to WFH, the standard of care for all patients with severe hemophilia is regular replacement therapy (prophylaxis) with CFCs, or other hemostasis products (emicizumab) to prevent bleeding, started early in life (before age 3) to prevent musculoskeletal complications from recurrent joint and muscle bleeds.
- Episodic ("on demand") clotting factor replacement therapy should no longer be considered to be a long-term treatment option.
- Implementation of home-based prophylaxis programs increases compliance and allows people with hemophilia to live relatively normal lives. These programs should be accompanied by education of patients, families, and healthcare providers on the benefits of prophylaxis and the importance of adherence to treatment regimens.
- Prophylaxis in young children may be the best way for a country to begin implementing universal prophylaxis for people with hemophilia.

BENEFITS OF PROPHYLAXIS

PROPHYLAXIS USING CLOTTING FACTOR CONCENTRATES (WHF guidelines. 2020).

- All forms of prophylaxis (high/intermediate/low dose with CFCs or prophylaxis with non-factor replacement agents, e.g., emicizumab) provide superior benefits over episodic therapy. Conventional high-dose and intermediate-dose prophylaxis, initiated early in life, have been associated with over 90% reduction in joint bleeding rates, annualized joint bleeding rates (AJBRs) below 3 per year, and a significant reduction in joint deterioration and degenerative joint disease.
- Prophylaxis also provides protection from other types of hemorrhages in hemophilia, including preventing or substantially reducing the risk of intracranial hemorrhage.
- Longer-term benefits include reduction of chronic musculoskeletal pain, functional limitations and disability, need for orthopedic surgery, hospitalization, emergency room visits, and reduced length of hospital stays; all of this leads to greater participation (i.e., regular attendance) in educational, recreational, and professional activities, with improved quality of life.
- Because of these benefits, the World Health Organization (WHO), the WFH, and many national and international hemophilia organizations have endorsed early prophylaxis as the standard of care for children with a severe phenotype hemophilia and recommend that prophylaxis be continued lifelong. Additionally, adults with severe phenotype hemophilia (if not already on prophylaxis) should initiate prophylaxis as well.

PROPHYLAXIS USING NON-¬FACTOR REPLACEMENT THERAPIES (WHF guidelines. 2020).

- Emicizumab prophylaxis in a number of clinical trials has been shown to be associated with very low rates of bleeding (an annualized bleeding rate [ABR] of 1.5) and ABRs lower than what patients previously reported while on prophylaxis with CFCs.
- More research is needed regarding long-term outcomes with emicizumab.
- Data on the use of other non-factor therapies for prophylaxis are at present much more limited.

Details on emicizumab will be discussed in the following section.

6. OVERVIEW OF HEMLIBRA®(EMICIZUMAB)

HEMLIBRA® (Emicizumab) is a humanized bispecific antibody that recognizes FIX/IXa and FX/Xa. It accelerates FIXa-catalyzed FX activation by bridging FIXa and FX in a manner similar to FVIIIa (Kitazawa T, et al. 2017).

FIXa-catalyzed FX activation is a crucial step in the blood clotting process and is facilitated by FVIII which links FIXa and FX together. However, this process is hampered due to FVIII deficiency in patients with hemophilia A (Kitazawa T et al. 2017). Thus, HEMLIBRA® helps to restore the natural hemostatic process in people with hemophilia A (HEMLIBRA® SmPC). However, HEMLIBRA® has no structural relationship or sequence homology to FVIII and does not induce or enhance the development of direct inhibitors to FVIII. Thus, HEMLIBRA® can be used in hemophilia A patients with and without inhibitors.

Apart from the novel mechanism of action, HEMLIBRA® has improved efficacy over the standard of care FVIII concentrates. HEMLIBRA® is administered subcutaneously, obviating the need for venous access. Due to high subcutaneous bioavailability, it has the potential to significantly change the treatment of patients with hemophilia A. Phase III randomized controlled trials confirm the favorable PK properties of HEMLIBRA®. It also allows for weekly (QW), every 2 weeks (Q2W), or every 4 weeks (Q4W) dosing of HEMLIBRA® , which is an advantage over the frequent dosing of intravenous FVIII therapies. Thus, HEMLIBRA® is expected to substantially improve upon current treatment options, allowing for a more convenient mode of administration and addressing the major issues with current prophylactic intravenous regimens, while fulfilling a strong medical need.

Clinical trials suggest that patients with severe hemophilia A should be given the sustained protection of HEMLIBRA®. This is because:

- The half-life of HEMLIBRA® lasts for weeks and not hours (HEMLIBRA® SmPC; Elocta® SmPC)
- It has convenient subcutaneous dosing with sustained protection (HEMLIBRA® SmPC; Elocta® SmPC)
- HEMLIBRA® results is 68% fewer bleeds as compared to prior FVIII prophylaxis as observed over ≥24 weeks (HEMLIBRA® SmPC; Mahlangu J et al. 2018)
- It has proven safety without risk of FVIII inhibitors (HEMLIBRA® SmPC)
- It is trusted by more than 6100 patents worldwide (Callaghan M. 2019; HEMLIBRA® SmPC)
- About 98% patients preferred HEMLIBRA® over FVIII prophylaxis after switching (Mahlangu J et al. 2018)

HEMLIBRA® is widely available globally (Bloomberg. 2019). UAE was granted the approval for using HEMLIBRA® in hemophilia A patients with inhibitors in June, 2018. The approval for its use in patients with non-inhibitors was received in October, 2018 (Roche. Data on file).

7. CLINICAL EFFECTIVENESS, EFFICACY, AND SAFETY OF HEMLIBRA®

7.1. HAVEN CLINICAL TRIAL PROGRAMME

The HAVEN clinical trial programme by Roche is one of the largest pivotal clinical trial programmes in hemophilia. It is designed to assess the efficacy and safety of HEMLIBRA® in people with and without FVIII inhibitors. The programme also assesses the potential of HEMLIBRA® to help overcome current clinical challenges:

- the short-lasting effects of existing treatments
- the development of FVIII inhibitors
- the need for frequent venous access (Roche release. 2019)

	Study type	Objective	Study population	HEMLIBRA® regimen/dosage
HAVEN 1	Randomized,-multicenter, open-label, phase III study	Evaluate the efficacy, safety and pharmacokinetics of HEMLIBRA® prophylaxis compared to no prophylaxis	Adults and adolescents (12 years of age and older) with hemophilia A with inhibitors to FVIII, who were previously treated with bypassing agents on-demand or as prophylaxis	Once-weekly
HAVEN 2	Multicenter, open-label, clinical study	Evaluate the efficacy, safety and pharmacokinetics of HEMLIBRA®	Children younger than 12 years of age with hemophilia A with FVIII inhibitors	Once weekly, every two weeks or every four weeks
HAVEN 3	Randomized, multicenter, open-label, phase III study	Evaluate the efficacy, safety and pharmacokinetics of HEMLIBRA® versus no prophylaxis (episodic/on-demand factor VIII treatment)	Once weekly or every two weeks	Once weekly, every two weeks or every four weeks
HAVEN 4	Single-arm, multicenter, open-label, phase III study	Evaluate the efficacy, safety and pharmacokinetics of HEMLIBRA®	Adults and adolescents (12 years of age or older) with hemophilia A with or without FVIII inhibitors who were previously treated with either FVIII or bypassing agents, on-demand or as prophylaxis	Every four weeks

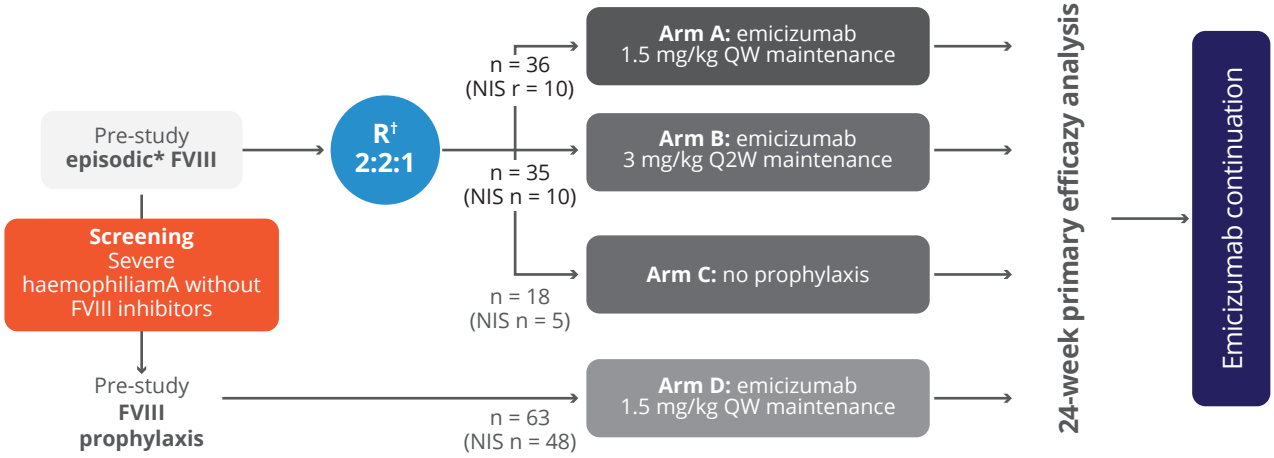
7.2. EFFICACY OF HEMLIBRA®

HAVEN 3 (Mahlangu J et al. 2018)

The HAVEN clinical trial programme by Roche is one of the largest pivotal clinical trial programmes in hemophilia. It is designed to assess the efficacy and safety of HEMLIBRA® in people with and without FVIII inhibitors. The programme also assesses the potential of HEMLIBRA® to help overcome current clinical challenges:

- the short-lasting effects of existing treatments
- the development of FVIII inhibitors
- the need for frequent venous access (Roche release. 2019)

Study design



*24-week bleed rate 5 for participants receiving episodic FVIII

†Randomisation stratified based on 6-month bleed rate of <9 or 9

F, factor; NIS, non-interventional study; QW, once weekly; Q2W, every 2 weeks; R, randomised

Primary efficacy outcomes

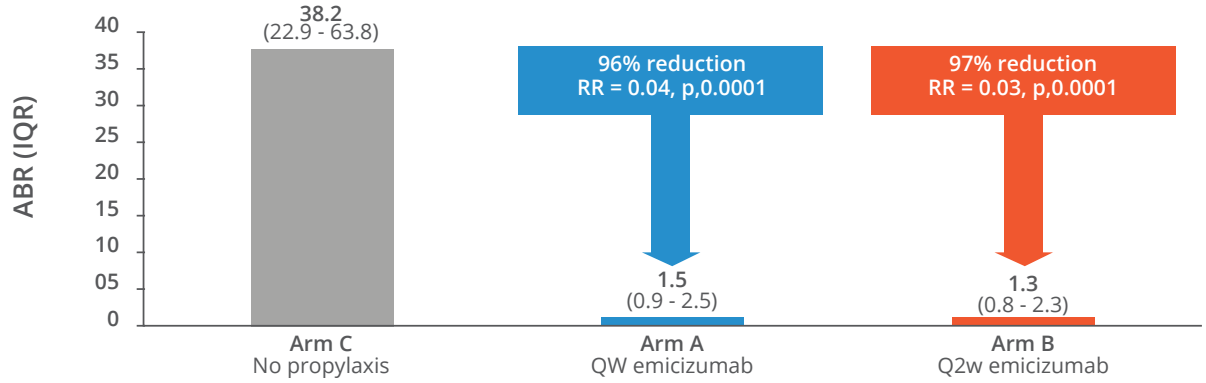
	Arm A emicizumab QW prophylaxis n = 36	Arm B emicizumab Q2W prophylaxis n = 35	Arm C no prophylaxis n = 18
Duration of efficacy period, weeks Median (min–max)	29.6 (17.3–49.6)	31.3 (7.3–50.6)	31.3 (7.3–50.6)
Treated bleeds (with FVIII)			
ABR, model based* (95% CI)	1.5 (0.9–2.5)	1.5 (0.9–2.5)	1.5 (0.9–2.5)
% risk reduction† RR, p-value	96% 0.04, p<0.0001	97% 0.03, p<0.0001	
Median ABR, calculated (IQR)	0.0 (0.0–2.5)	0.0 (0.0–1.9)	40.4 (25.3–56.7)
Participants with zero bleeds, % (95% CI)	55.6 (38.1–72.1)	60.0 (42.1–76.1)	0 (0.0–18.5)
Participants with 0–3 bleeds, % (95% CI)	91.7 (77.5–98.2)	94.3 (80.8–99.3)	0 (0.0–18.5)

*Data from 48 participants in Arm D who participated in the non-interventional study

†The ABR was calculated with the use of a negative binomial-regression model

ABR, annualised bleed rate; CI, confidence interval; IQR, interquartile range; NIS, non-interventional study; QW, once weekly; RR, rate ratio

Primary efficacy endpoint – treated bleeds



Secondary bleed-related endpoints

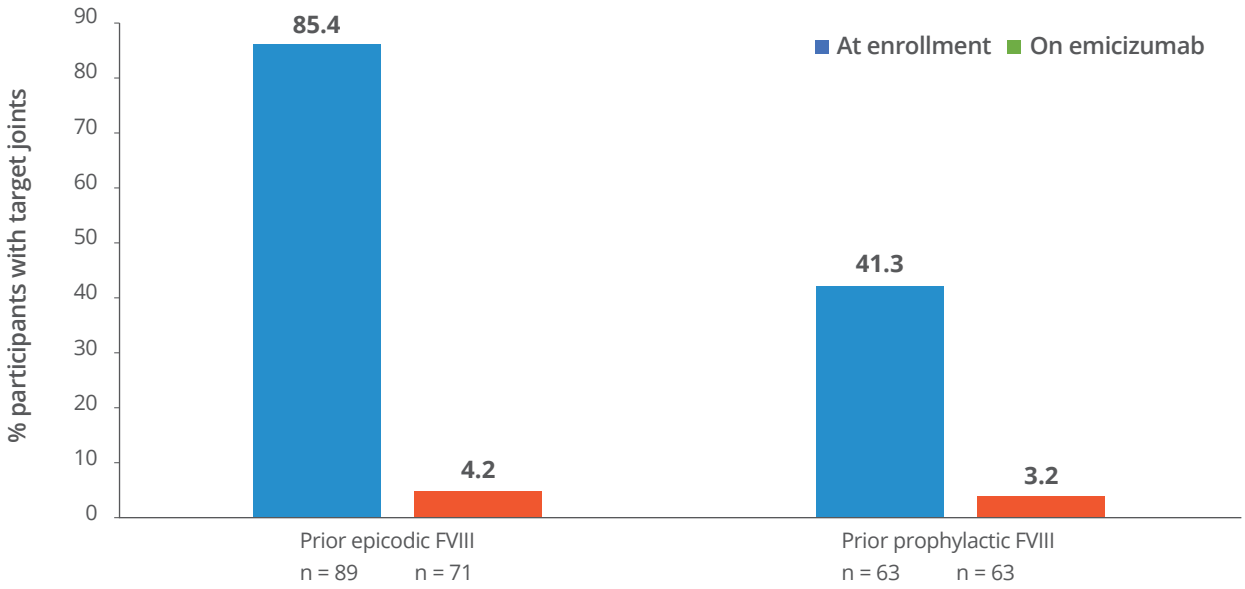
	Arm A emicizumab QW prophylaxis n = 36	Arm B emicizumab Q2W prophylaxis n = 35	Arm C no prophylaxis n = 18
All bleeds (treated or not treated with FVIII)			
ABR, model based* (95% CI)	2.5 (1.6–3.9)	2.6 (1.6–4.3)	47.6 (28.5–79.6)
% risk reduction† p-value	**95%** p<0.0001	**94%** p<0.0001	
Participants with zero bleeds, % (95% CI)	50.0 (32.9–67.1)	40.0 (23.9–57.9)	0 (0.0–18.5)
Median ABR, calculated (IQR)			
ABR, model based* (95% CI)	1.0 (0.5–1.9)	0.3 (0.1–0.8)	15.6 (7.6–31.9)
% risk reduction† p-value	**94%** p<0.0001	**98%** p<0.0001	
Participants with zero bleeds, % (95% CI)	66.7 (49.0–81.4)	88.6 (73.3–96.8)	22.2 (6.4–47.6)
Treated joint bleeds			
ABR, model based* (95% CI)	1.1 (0.6–1.9)	0.9 (0.4–1.7)	26.5 (14.7–47.8)
% risk reduction† p-value	**96%** p<0.0001	**97%** p<0.0001	
Participants with zero bleeds, % (95% CI)	58.3 (40.8–74.5)	74.3 (56.7–87.5)	0.0 (0.0–18.5)
Treated target joint bleeds‡			
ABR, model based* (95% CI)	0.6 (0.3–1.4)	0.7 (0.3–1.6)	13.0 (5.2–32.3)
% risk reduction† p-value	**95%** p<0.0001	**95%** p<0.0001	
Participants with zero bleeds, % (95% CI)	69.4 (51.9–83.7)	77.1 (59.9–89.6)	27.8 (9.7–53.5)

*The ABR was calculated with the use of a negative binomial-regression model; †Reduction in emicizumab groups compared with Arm C
‡Treated bleeds in joints pre-defined as target joints based on bleeding in 24 weeks prior to study entry
ABR, annualised bleed rate; CI, confidence interval; IQR, interquartile range; QW, once weekly; Q2W, every 2 weeks

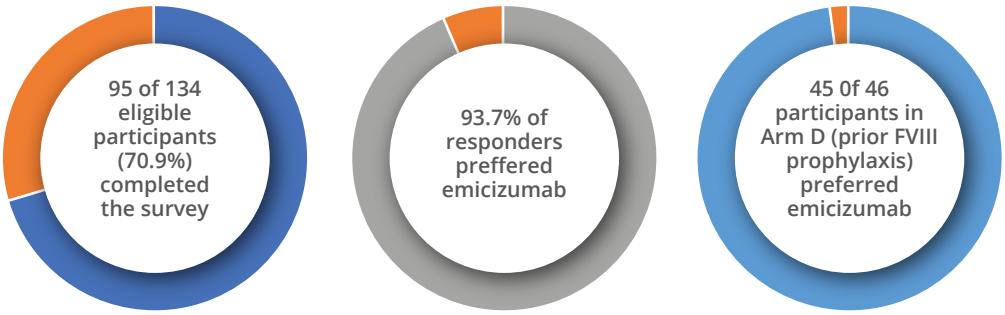
Intra-individual comparison – Arm D

	Arm A emicizumab QW prophylaxis n = 36	Arm B emicizumab Q2W prophylaxis n = 35
Duration of efficacy period, weeks Median (Min–max)	33.7 20.1–48.6	30.1 5.0–45.1
ABR, model based† (95% CI)	1.5 (1.0–2.3)	4.8 (3.2–7.1)
% risk reduction RR, p-value	68% 0.32, p<0.0001	
Median ABR, calculated (IQR)	0.0 (0.0–2.1)	1.8 (0.0–7.6)
Participants with zero bleeds, % (95% CI)	58.3 (40.8–74.5)	74.3 (56.7–87.5)
Participants with 0–3 bleeds, % (95% CI)	91.7 (80.0–97.7)	72.9 (58.2–84.7)

Bleed-related endpoints: reduction in percentage of participants with target joints

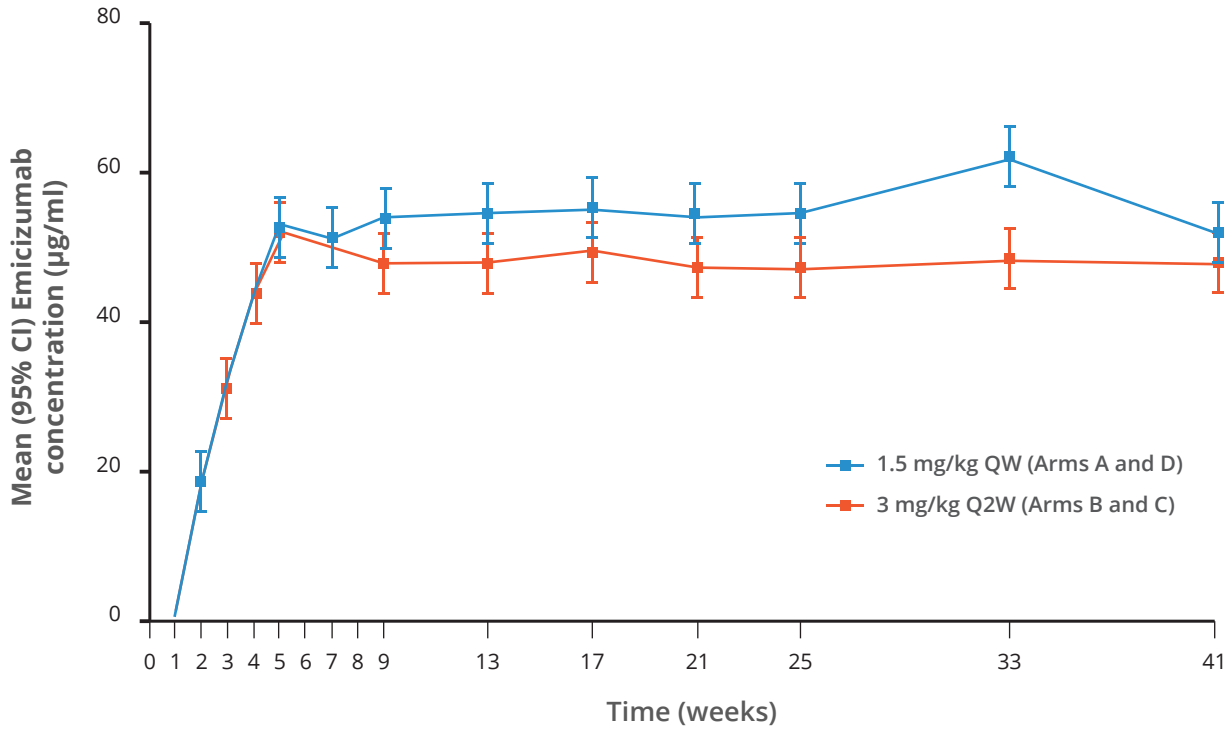


Exploratory outcome – treatment preference survey



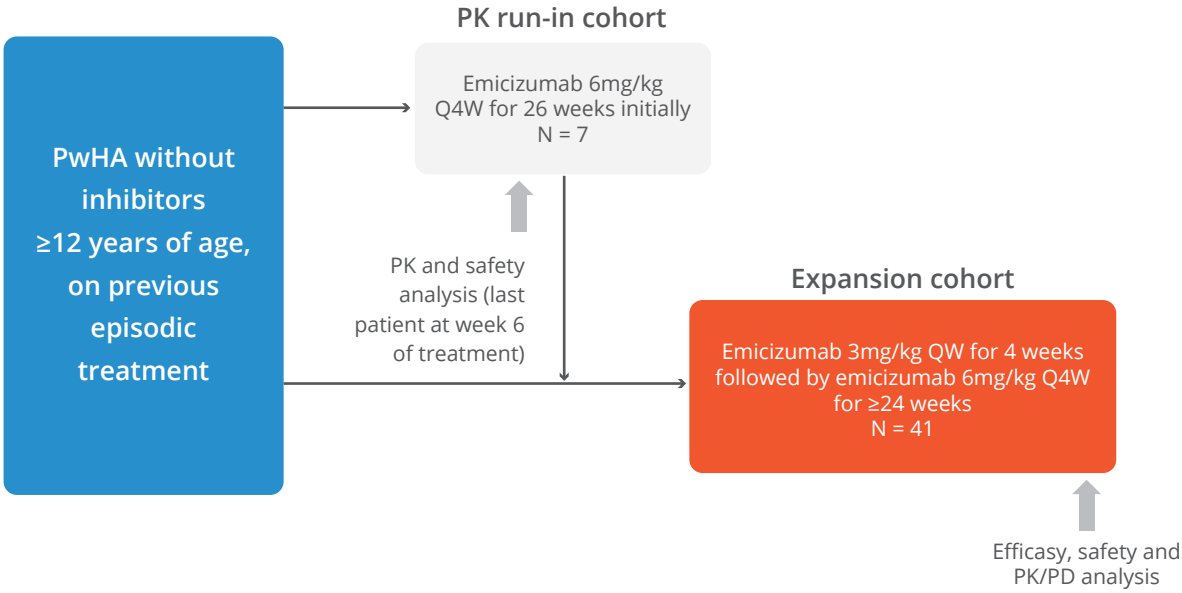
Pharmacokinetics

Effective emicizumab trough plasma concentrations were sustained with both maintenance doses for the duration of the trial.



HAVEN 4 (Jiménez-Yuste et al. ASH 2017)

Intra-individual comparison – Arm D



PK run-in: bleed-related endpoints

There were zero treated bleeds. The majority of participants (85.7%) had no bleeds (treated or untreated) on emicizumab 6 mg/kg Q4W. One participant with inhibitors experienced three spontaneous nose bleeds; no coagulation product or treatment/procedure was required for these bleeds

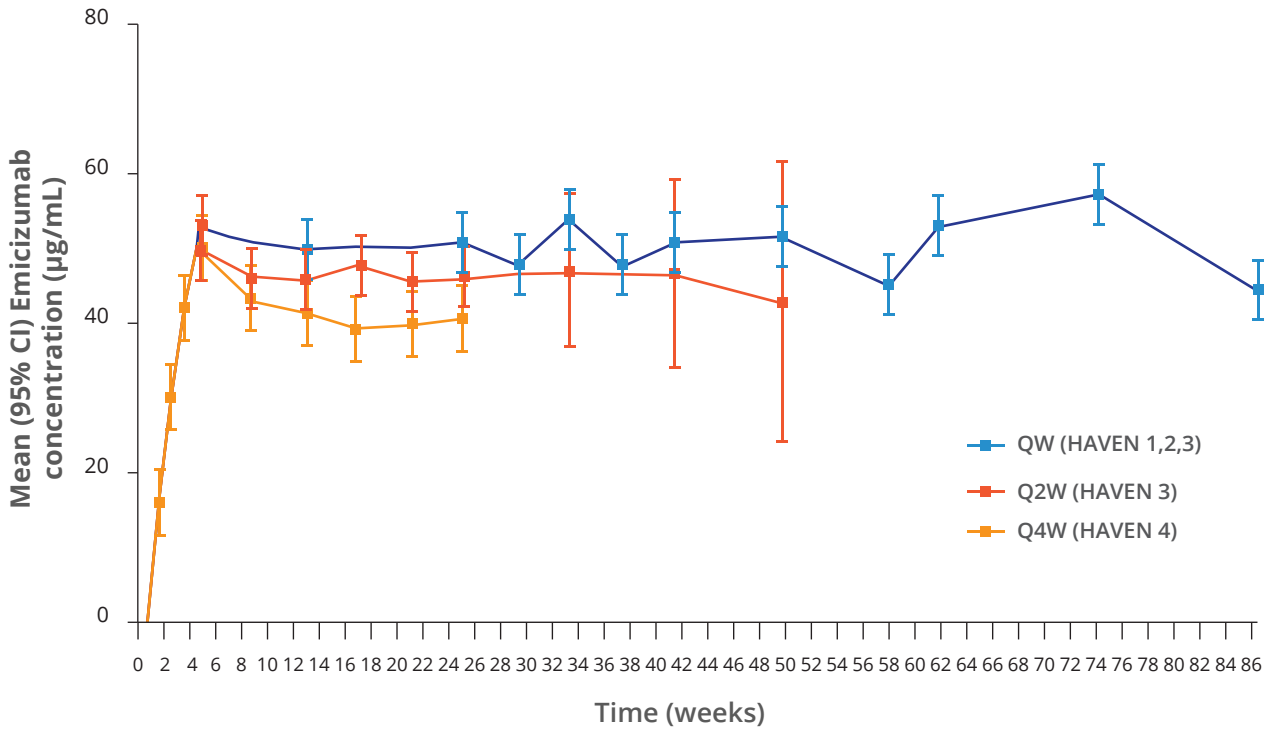
Expansion phase: bleed-related endpoints

	ABR* (95% CI)	Median ABR (IQR)	Participants with zero bleeds, % (95% CI)	Participants with 0–3 bleeds, % (95% CI)
Treated bleeds	2.4 (1.4–4.3)	0.0 (0.0–2.1)	56.1 (39.7–71.5)	90.2 (76.9–97.3)
All bleeds	4.5 (3.1–6.6)	2.1 (0.0–5.9)	29.3 (16.1–45.5)	80.5 (65.1–91.2)
Treated spontaneous bleeds	0.6 (0.3–1.5)	0.0 (0.0–0.0)	82.9 (67.9–92.8)	97.6 (87.1–99.9)
Treated joint bleeds	1.7 (0.8–3.7)	0.0 (0.0–1.9)	70.7 (54.5–83.9)	95.1 (83.5–99.4)
Treated target joint bleeds	1.0 (0.3–3.3)	0.0 (0.0–0.0)	85.4 (70.8–94.4)	97.6 (87.1–99.1)

*based on a negative binomial-regression model
Data cut-off: 15 December 2017
ABR, annualized bleed rate; BTB, breakthrough bleeds; CI, confidence interval; IQR, interquartile range

Expansion phase: PK profiles

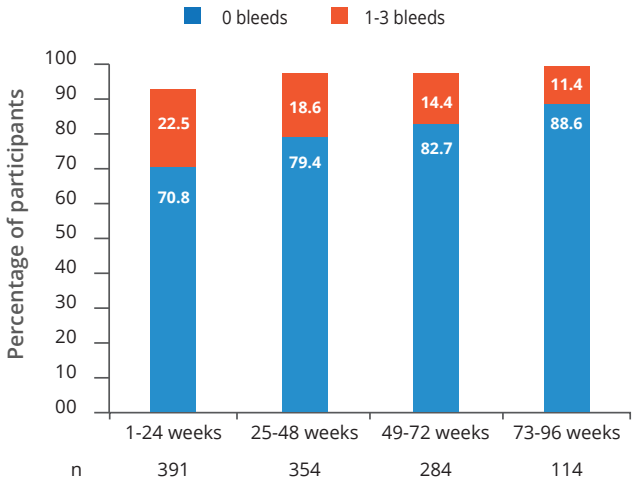
Clinically efficacious concentrations were obtained with all three dosing regimens (consistent with PK model predictions). For Q4W, emicizumab mean trough concentrations were maintained at ~41 µg/mL from Week 13 to Week 25.



POOLED DATA FROM FOUR HAVEN STUDIES (Callaghan M et al. 2019)

HAVEN 1–4: bleed rates

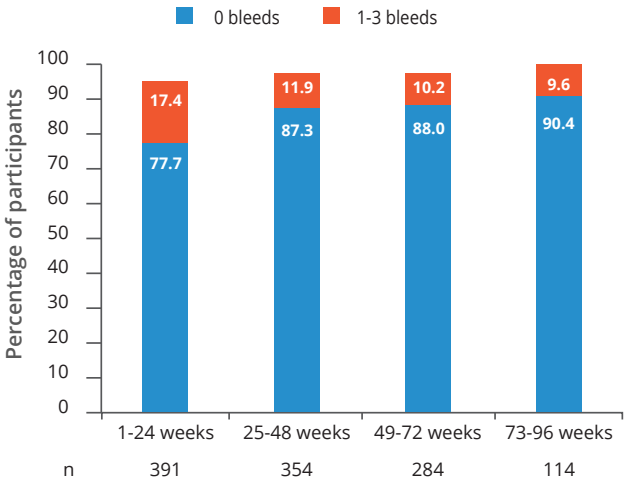
Model-based ABR*	Treated bleeds over time
Treated bleeds: 1.5 (95% CI, 1.20-1.84)	Proportion of participants with 0 or 1-3 traeted bleeds over time (n=400)
Spontaneous bleeds: 0.6 (95% CI, 0.5-0.8)	
Joint bleeds: 1.0 (95% CI, 0.8-1.3)	



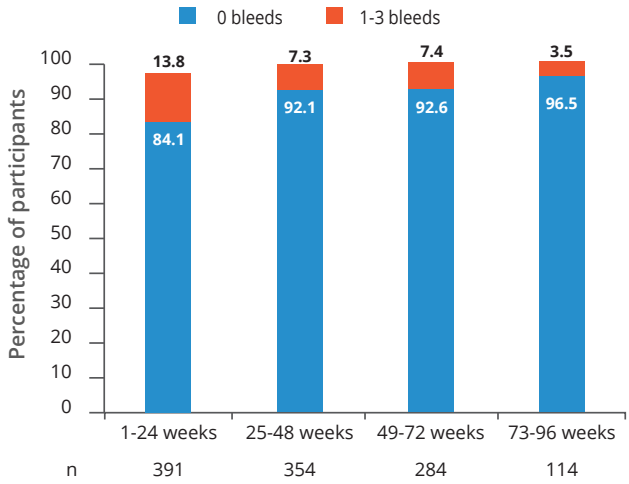
*Calculated using negative binomial regression over a median of 83 weeks' duration of exposure.

HAVEN 1–4: joint and spontaneous bleeds over time

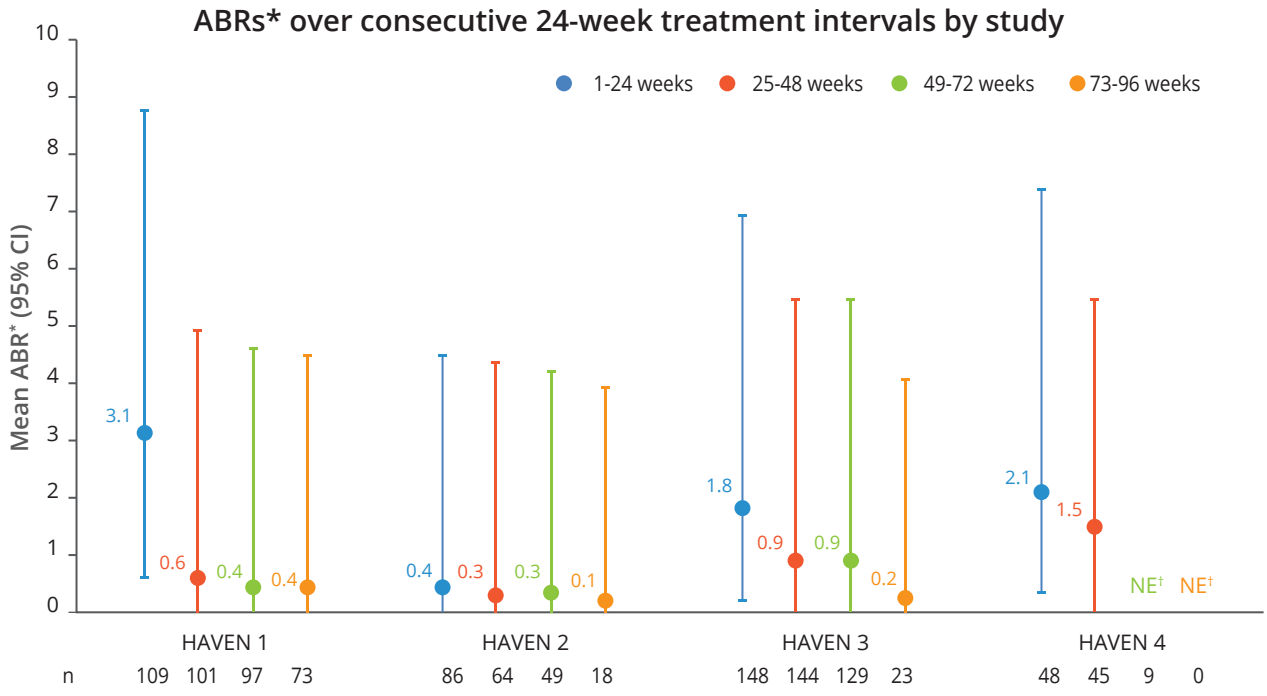
Proportion of participants with 0 or 1-3 joints bleeds over time (N=400)



Proportion of participants with 0 or 1-3 spontaneous bleeds over time (N=400)



HAVEN 1–4: mean ABRs over time

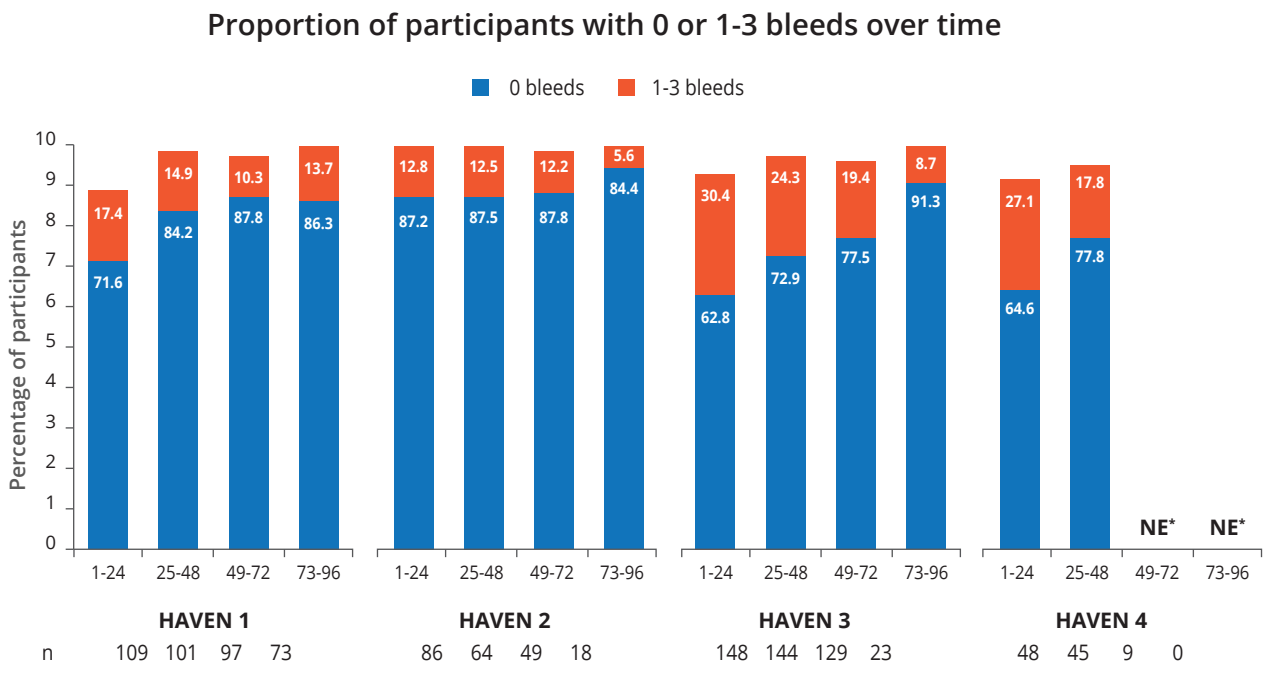


*Based on the calculated annualized bleed rate for bleeds treated with coagulation factors. †Only data for time intervals with ≥10 participants are reported.

There was a trend for decreasing ABR in each study over time.

With longer follow-up, the adult inhibitor/non-inhibitor ABRs decreased to be closer to the rates of paediatric patients, who tend to have lower ABR due to less damaged joints.

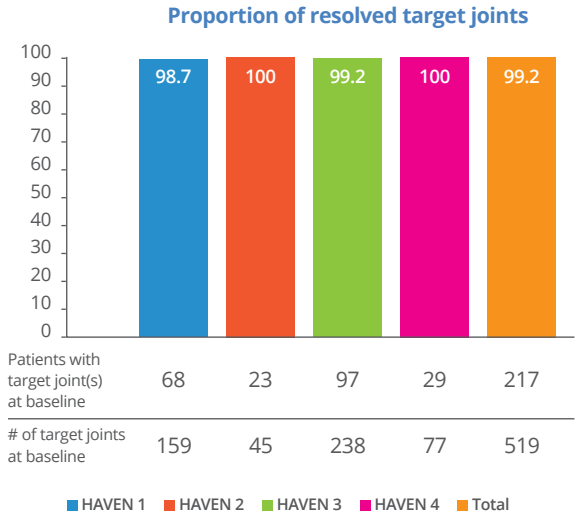
HAVEN 1–4: zero bleeds over time

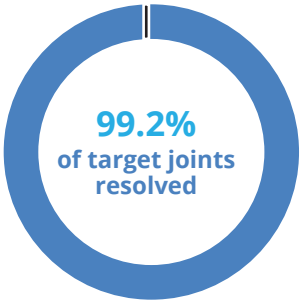


*Only data for time intervals with ≥10 participants are reported.

‡Bleeds treated with coagulation factors.

HAVEN 1–4: target joint resolution





- 195 of 217 (90%) participants had no spontaneous or traumatic bleeding into a target joint while on emicizumab
- For 498 of 519 (96%) baseline target joins, 2 spontaneous or traumatic bleeding events occured while on emicizumab

This depiction of data focuses attention on the high percentage of patients with target joint resolution across studies (no difference by age, inhibitor status, regimen, etc.)*Target joints were defined as major joints (e.g. hip, elbow, wrist, shoulder, knee, and ankle) in which ≥3 bleeding events occurred over a 24-week period. Target joint resolution was defined as ≤2 bleeding events in a 52-week period in a joint previously defined as a target joint.

7.3. SAFETY PROFILE OF HEMLIBRA®

HAVEN 3 (Mahlangu J et al. 2018)

	Arm A: emicizumab QW prophylaxis n = 36	Arm B: emicizumab Q2W prophylaxis n = 35	Arm C: no prophylaxis* n = 16	Arm D: emicizumab QW prophylaxis n = 63	Total N = 150
Total number of AEs, n	143	145	19	236	543
Total patients with ≥1 AE, n (%)	34 (94.4)	30 (85.7)	8 (50.0)	55 (87.3)	127 (84.7)
Number of serious AEs	1	3	0	10	14
Emicizumab-related serious AEs	0	0	0	0	0
Injection-site reaction‡	9 (25.0)	7 (20.0)	2 (12.5)	20 (31.7)	38 (25.3)
Upper respiratory tract infection	4 (11.1)	4 (11.4)	0	8 (12.7)	16 (10.7)
Patients with AE leading to withdrawal, n (%)	0	1 (2.9)§	0	0	1 (0.7)

- Of 215 events of co-exposure to FVIII and emicizumab in 64 patients, 43 included an average FVIII dose ≥50 IU/kg/24 hours, of which 8 events lasted >24 hours; co-exposure to emicizumab and FVIII was not related to serious AEs, thrombotic microangiopathy or thromboembolic event
- No deaths
- No ADAs detected; no patients on emicizumab developed de novo FVIII inhibitors

HAVEN 4 (Jiménez-Yuste et al. ASH 2017)

PK run-in: safety summary

	Emicizumab 6 mg/kg Q4W (N = 7)
Total number of AEs	14
Total participants experiencing ≥1 AE, n (%)	5 (71.4)
Serious AE	1 (14.3)
Grade ≥3 AE	1 (14.3)
Related AE	0
Local injection-site reaction	0

- No AEs led to treatment withdrawal or dose modification/interruption
- No unexpected changes in vital signs (except elevated blood pressure in 1 patient*) or electrocardiogram
- No haematology findings and only mild (grade 1) changes in blood chemistry
- No anti-drug antibodies were detected
- Grade 3 serious AE was a worsening of pre-existing hypertension, which was not considered related to emicizumab treatment

*The participants had elevated blood pressure at study entry and experienced another episode of grade 2 (moderate) hypertension

Expansion phase: safety summary

	Emicizumab 6 mg/kg Q4W (N = 41)
Total number of AEs	148
Total participants experiencing ≥1 AE, n (%)	30 (73.2)
Serious AE	1 (2.4)
Grade ≥3 AE	1 (2.4)
Related AE	12 (29.3)
Local injection-site reaction	9 (22.0)
AEs of special interest	
Hypersensitivity	0
TE/TMA	0

- 73.2% of participants experienced ≥1 AE
- Only one serious (grade ≥3) AE was reported (rhabdomyolysis; unrelated to emicizumab)
- No AEs leading to emicizumab discontinuation or withdrawal from the study were reported
- Injection-site reactions were the most common emicizumab-related AE (22.0% of participants)
- consistent with other HAVEN studies
- No TEs, TMAs, or unexpected safety signals were reported
- No ADAs detected; no de novo FVIII inhibitors

POOLED DATA FROM FOUR HAVEN STUDIES

- No deaths, thrombotic, or thrombotic microangiopathy events were observed beyond those reported in the HAVEN 1 primary analysis (Oldenburg et al. 2017)
- 103 SAEs were reported in 71 participants (Callaghan M et al. 2019)
    - o serious adverse event (SAEs) reported by ≥5 participants were haemorrhage (n = 7, 1.8%) and hemarthrosis (n = 5, 1.3%)
- The most common treatment-related AEs were injection-site reaction† (n = 104; 26.1%) (Callaghan M et al. 2019)
- ADAs with neutralizing potential were observed in <1% (3/398) of participants (Callaghan M et al. 2019)

Long-term safety

	Total (N = 399)*
Total number of participants with ≥1 AE, n (%)	373 (93.5)
Total number of patients, n (%)	1 (0.3)
AE with fatal outcome	71 (17.8)
Serious AE	5 (1.3)
AE leading to withdrawal from treatment	73 (18.3)
Grade ≥3 AE	134 (33.6)
Related AE	107 (26.8)
Local injection-site reaction†	
Adverse events of special interest	1 (0.3)‡
Systemic hypersensitivity/anaphylactic/anaphylactoid reaction	3 (0.8)
TMA event related to concomitant aPCC and emicizumab	2 (0.5)
TE related to concomitant aPCC and emicizumab	1 (0.3)
Other TE (grade 1 device occlusion)	

*The safety population only included those patients who received emicizumab. One participant in HAVEN 1 discontinued prior to emicizumab treatment and was excluded from the safety analyses.

†All ISRs were mild in severity. ‡Assessed using the Sampson Criteria and including all participants that experienced indicative symptoms.

7.4. QUALITY OF LIFE (QoL): HAVEN 3 AND 4

PROPHYLAXIS VS EPISODIC THERAPY IN HEMOPHILIA (WHF guidelines. 2020)

The updated results of HAVEN 3 and HAVEN 4 came from the assessment of impact of prophylactic emicizumab on HRQoL of PwHA with/without FVIII inhibitors.

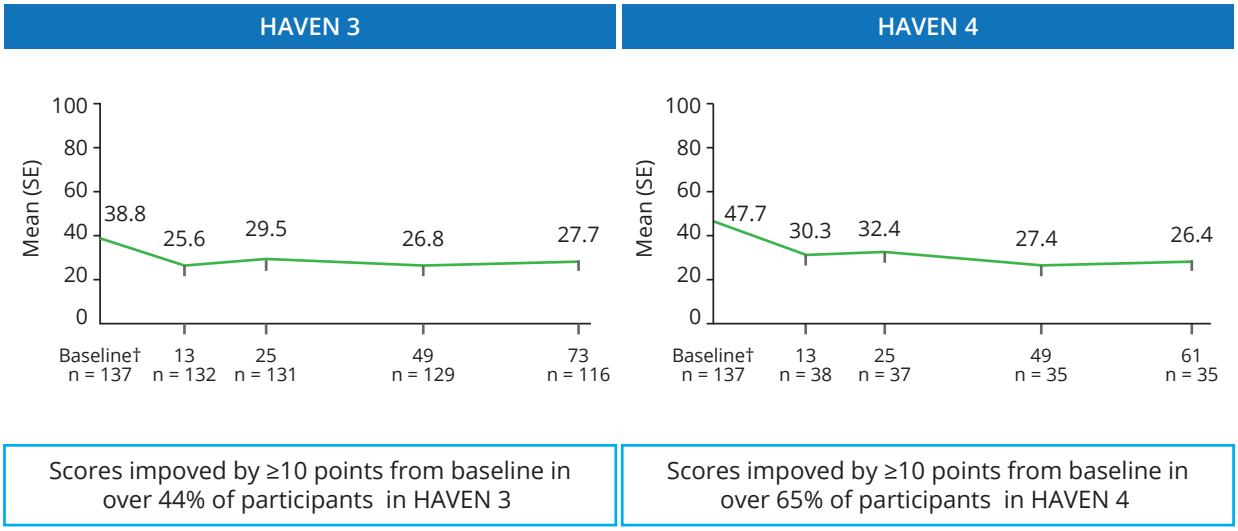
HRQoL was assessed by the Haem-A-QoL questionnaire, with 143 and 38 eligible respondents (aged ≥18 years) for HAVEN 3 and 4, respectively.

Methodology

- HRQoL data were pooled by study regardless of patient baseline characteristics or treatment

- For the 'physical health' score subscale, a ≥10-point change from baseline was considered clinically meaningful
- The proportion of missed work days was also collected
- The schedule of assessments for the Haem-A-QoL and the missed work day item for HAVEN 3 and HAVEN 4 (expansion cohort only) included: Weeks 1, 13, 25, 49, 61 (HAVEN 4 only), 73 (HAVEN 3 only), and study completion

Haem-A-QoL* physical health score



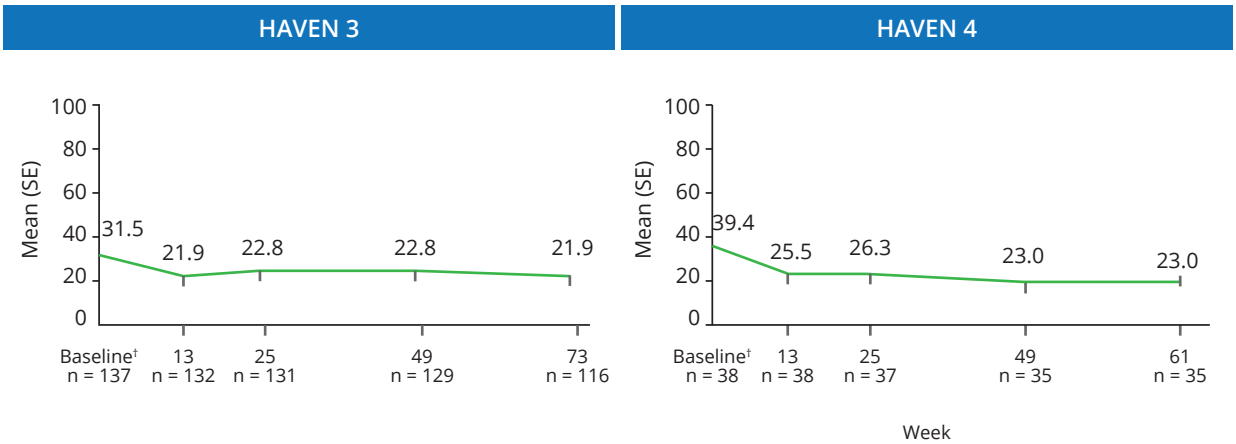
Scores impoved by ≥10 points from baseline in over 44% of participants in HAVEN 3

Scores impoved by ≥10 points from baseline in over 65% of participants in HAVEN 4

*Lower scores reflect better functioning; completed by participants aged ≥18 years only.

†Baseline assessment is the last valid assessment on or before study day 1.

Haem-A-QoL* total score



Scores impoved from 31.5 at baseline to 22.8 at week 25 in Haven3, with improvements maintained throughout follow up

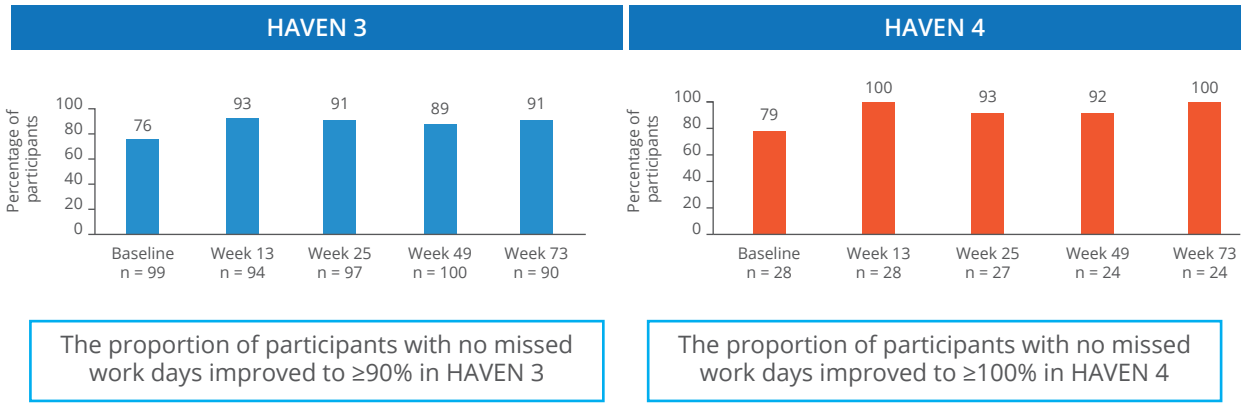
Scores impoved from 39.4 at baseline to 26.3 at Week 25 in HAVEN $, with improvements maintainte throughout follow up

*Lower scores reflect better functioning; completed by participants aged ≥18 years only.

†Baseline assessment is the last valid assessment on or before study day 1.

- For the 'physical health' score subscale, a ≥10-point change from baseline was considered clinically meaningful
- The proportion of missed work days was also collected
- The schedule of assessments for the Haem-A-QoL and the missed work day item for HAVEN 3 and HAVEN 4 (expansion cohort only) included: Weeks 1, 13, 25, 49, 61 (HAVEN 4 only), 73 (HAVEN 3 only), and study completion

QoL: Missed days of work



The proportion of participants with no missed work days improved to ≥90% in HAVEN 3

The proportion of participants with no missed work days improved to ≥100% in HAVEN 4

n is the number of participants enrolled in work at each time point.

*Reflects the work period 28 days prior to enrolment.

Summary

- Clinically meaningful improvements were observed in Haem-A-QoL physical health scores with emicizumab prophylaxis in ≥44% and ≥65% of participants in HAVEN 3 and HAVEN 4, respectively
    - o improvements were consistent with the demonstrated efficacy of emicizumab
    - o participants in HAVEN 3 and HAVEN 4 achieved similar physical health and total scores from week 13 onwards, regardless of baseline QoL scores
- The proportion of participants with no missed work days increased to ≥90% with emicizumab prophylaxis in both HAVEN 3 and HAVEN 4
- The HRQoL results seen here are consistent with those seen in the HAVEN 1 study, indicating that emicizumab improves aspects of HRQoL regardless of inhibitor status

8. ADMINISTRATION AND DOSING OF HEMLIBRA®

HEMLIBRA dosages and strengths'


Sky Blue: 30 mg/ml


Purple: 60 mg/0.4 ml


Turquoise: 105 mg/0.7 ml


Brown: 150 mg/ml

HEMLIBRA is available in 2 concentrations:

- 30 mgirl (30-mg vial)
- 150 mo/ml. (60-mg. 105-mg, and 150-mg vials)

Different vial concentrations should not be combined in the same syringe.

- Stable at room temperature (below 30"C) up to a cumulative total of 7 days
- No requirement for routine laboratory monitoring

Required injection supplies*

Transfer needle + Syringe + Injection needle

Following initial administration by a healthcare provider and sufficient training of the patient in medication preparation and subcutaneous injection technique, HEMLIBRA® is intended for self administration at home or administration by a caregiver at home. In contrast, plasma derived or recombinant FVIII concentrate is administered intravenously, usually by the patient or caregiver at home and current prophylactic regimens require the administration of multiple doses per week.

9. TAKE HOME MESSAGES

- Although currently available FVIII replacement therapies comprise the cornerstone of hemophilia A management, they provide only incomplete coverage and do not restore normal health and lifestyle to patients.
- Given the inadequate efficacy and the considerable management challenges in adults and children with hemophilia A, there is a true need for therapeutics that provide improved efficacy to prevent bleeding and minimize long term morbidity, along with a reduction in treatment burden.
- HEMLIBRA® is the first and only treatment for hemophilia A so far to show superior efficacy over FVIII prophylaxis, with a higher proportion of patients staying free of bleeds and significantly reduced bleed rates.
- HEMLIBRA® can be administered QW (or even less often) and subcutaneously, which provides a considerable reduction in treatment burden compared with the current standards of care and leaves the patient the choice for the most appropriate treatment regimen.
- HEMLIBRA®, with its consistent and clinically meaningful efficacy, an acceptable safety profile, and positive benefit risk profile, represents a substantial improvement over currently available treatment options and has the potential to address the current unmet needs of hemophilia A patients across age groups.

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