EU RISK MANAGEMENT PLAN FOR HEMLIBRA®/EMICIZUMAB

RMP version to be assessed as part of this application:

RMP version number: 5.0

Data lock point for this RMP: 15 November 2023

Date of final sign off: See latest date in date stamps below

Date and Time (UTC)	Reason for Signing	Name
08-Apr-2024 23:41:27	Company Signatory (PV)	PPD
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Table of Contents

List of Tables

List of Figures

List of Annexes

Rationale for Submitting an Updated RMP

This RMP (version 5.0) is updated to incorporate feedback received during assessment of parallel procedures. BO44691 was originally requested as a Category 3 PASS during variation EMEA/H/C/004406/II/0027 (extension of indication for moderate non-inhibitor patients) and is already included in the current EU RMP. The protocol has subsequently been developed and version 2.0 was approved by PRAC under post-authorization measure EMEA/H/C/004406/MEA/012.

Summary of Significant Changes in This RMP

This RMP has been updated to align study information for the non-interventional PASS study BO44691 with that included in the PRAC-approved protocol version 2. Additionally, Annex 2 and Annex 3 have been updated to reflect the latest information on this PASS. Milestones and study information have been updated where needed to align with recently updated protocols for the existing PASS studies. Furthermore, minor updates relating to the important identified and potential risks, and missing information have been made; these do not impact the characterization of any of the risks rather provide latest information (Part II, Module SVII.3).

Details of Currently Approved RMP

RMP Version Number: 4.7

Approved with Procedure Number: EMEA/H/C/004406/II/0027

Date of approval (opinion date): CHMP Approval, 15 December 2022.

See page 1 for signature and date

Delegate: Dr PPD (Deputy EU QPPV)	Date
PPD MD MHSc (PPD)	Date

PART I: PRODUCT OVERVIEW

Active substance(s) (INN or common name)	Emicizumab
Pharmacotherapeutic group(s) (ATC Code)	B02BX06
Marketing Authorization Holder	Roche Registration Limited
Medicinal products to which this RMP refers	One
Invented name(s) in the European Economic Area (EEA)	HEMLIBRA
Marketing authorization procedure	Centralized
Brief description of the product	**Chemical class** Emicizumab (also known as ACE910 and RO5534262) is a humanized monoclonal modified immunoglobulin G4 (IgG4) antibody with a bispecific antibody structure against activated factor IX (anti-FIXa) and factor X (anti-FX). **Summary of mode of action** Emicizumab bridges activated factor IX and factor X to restore the function of missing activated factor VIII that is needed for effective hemostasis. In patients with hemophilia A, hemostasis can be restored irrespective of the presence of FVIII inhibitors, as emicizumab shares no sequence homology with FVIII. **Important information about its composition** Emicizumab is produced by recombinant DNA technology in Chinese hamster ovary cells.
Hyperlink to the Product Information	Refer to the Product Information
Indication(s) in the EEA	**Current:** Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with hemophilia A (congenital factor VIII deficiency): • With factor VIII inhibitors • Without factor VIII inhibitors who have: - severe disease (FVIII < 1%). - moderate disease (FVIII ≥ 1% and ≤ 5%) with severe bleeding phenotype. Hemlibra can be used in all age groups.
	Proposed: Not applicable.
Dosage in the EEA	**Current:** Loading dose of 3 mg/kg subcutaneously (SC) every week (QW) for 4 weeks, followed by maintenance dose of either 1.5 mg/kg SC QW, 3 mg/kg SC once every 2 weeks (Q2W), or 6 mg/kg SC once every 4 weeks (Q4W).

	Proposed: Not applicable
Pharmaceutical form(s) and strengths	**Current:** Solution for injection. Single-use vials of 1.0 mL containing 30 mg or 150 mg of emicizumab at concentrations of 30 mg/mL or 150 mg/mL, respectively. Single-use vial of 0.7 mL containing 105 mg of emicizumab at a concentration of 150 mg/mL. Single-use vial of 0.4 mL containing 60 mg of emicizumab at a concentration of 150 mg/mL. Single-use vial of 0.4 mL containing 12 mg (30mg/mL). Single-use vial of 2 mL containing 300 mg (150mg/mL).
	Proposed: No changes.
Is or will the product be subject to additional monitoring in the EU?	No

ABBREVIATIONS

Abbreviation	Definition
ADA	anti-drug antibody
AE	adverse event
aPCC	activated prothrombin complex concentrate (FEIBA®)
aPTT	activated partial thromboplastin time
ATA	anti-therapeutic antibodies
BU	Bethesda units
BI	Barthel index
CI	confidence interval
DDI	drug-drug interaction
CVAD	central venous access device
FVIII	factor VIII
FVIIIa	activated factor VIII
FIX	factor IX
FIXa	activated factor IX
FX	factor X
FXa	activated factor X
HCP	Healthcare professional
HRQoL	Health-related quality of life
ICH	International Conference on Harmonisation
ICH	intracranial hemorrhage
IU	International Units
IV	Intravenous
ITI	immune tolerance induction
MABEL	minimal anticipated biological effect level
NE	not evaluable
NIS	non-interventional study
NSAIDS	non-steroidal anti-inflammatory drugs
PY	patient-years
QW	once weekly
Q2W	once every two weeks
Q4W	once every four weeks
rFVIIa	recombinant activated factor VII (NovoSeven®)
SAE	serious adverse event
SC	Subcutaneous
SD	standard deviation
SmPC	Summary of Product Characteristics
TMA	thrombotic microangiopathy
WFH	World Federation of Hemophilia

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION

SI.1 INDICATION

Hemlibra® (emicizumab) is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency):

- With factor VIII inhibitors
- Without factor VIII inhibitors who have:
  - Severe disease (FVIII $<$ 1%).
  - Moderate disease (FVIII $\geq$ 1% and $\leq$ 5%) with severe bleeding phenotype.

Hemlibra® (emicizumab) can be used in all age groups.

SI.1.1 EPIDEMIOLOGY OF THE DISEASE

1.1.1.1 Incidence

Hemophilia A is an X-linked recessive disorder with an incidence of approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 417 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27) (Eurostat 2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000 males with severe hemophilia A. In high-income countries, 45.52% of hemophilia A is severe, 14.64% is moderate and 39.52% mild and 0.31% unknown. The proportion of severe is similar in upper middle income (43.76% and lower middle and low-income countries (45.92%), although there is a larger proportion of unknown severity-11.25% in upper middle income and 22.28% in lower middle and low-income countries (WFH 2019).

Treatment of patients with hemophilia A commonly includes intravenous (IV) replacement therapy with FVIII concentrates. It is estimated that approximately 20–30% of the patients treated with FVIII for hemophilia A develop neutralizing alloantibodies (inhibitors) against FVIII during their lifetime (Franchini et al. 2012; Fischer et al. 2015; Peyvandi et al. 2016; Vepsäläinen 2016). Inhibitors bind to FVIII and neutralize its activity, thereby rendering FVIII replacement therapy ineffective (Franchini et al. 2012). In about 95% of patients with HA who develop inhibitors, it occurs within the first 75 exposure days to FVIII replacement (Jardim 2020). In severe hemophilia patients, most inhibitors develop during the first 50 exposure days with 50% of inhibitors present after 14-15 exposure days (van den Berg 2019). The overall incidence rate of inhibitor development was 2.06 per 1000 person-years in patients with severe or moderately

severe hemophilia A (Hassan 2018). The incidence of inhibitors in patients with non-severe hemophilia A is 5%-10%, lower than in those with severe hemophilia. These inhibitors typically occur at an older age and often after intensive FVIII exposure (Srivastava 2020).

1.1.1.2 Prevalence

The World Federation of Hemophilia (2019) estimates 157,517 people (87% males) with hemophilia A from 115 countries worldwide. The overall prevalence of hemophilia A reported in registry data from Australia, Canada, France, Italy, New Zealand, and the United Kingdom was estimated to be 17.1 per 100,000 for males. While, the prevalence of severe hemophilia A was estimated to be 6.0 per 100,000 for males (WFH 2019).

The estimated prevalence of hemophilia by country is reported annually from a survey by the WFH (WFH 2019). The number of patients with hemophilia A registered in 2019 in various regions across the world included 5,410 individuals in Japan (4.3 per 100,000 people); 13,915 in United States[4.2 per 100,000 people]; and 20,975 in five European nations (United Kingdom, France, Germany, Poland, and Belgium; 6.8 per 100,000 people (WFH 2019). The worldwide prevalence of hemophilia A was found to be 2.8 per 100,000 population (WFH 2019). There is variability in the reported prevalence across countries, including that observed across high-income countries (Table 1). No biological or environmental factors that could account for this variability have been identified, and it is unclear to what extent the variation in prevalence is genuine or impacted by geographic variations in diagnosis sensitivity and in the completeness of the reporting systems (Stonebraker et al. 2010). Available data appear to indicate an increase in prevalence over time in a majority of countries (Stonebraker et al. 2010).

Table 1 Prevalence Estimates of Hemophilia A in 2019 in Selected Countries

Country	Prevalence (per 100,000 people)
UK	10.2
France	10.0
Australia	8.7
Germany	4.5
Russia	4.5
USA	4.2
Japan	4.3

Source: Annual Global Survey of the World Federation of Hemophilia (WFH 2019)

1.1.1.3 Demographics and Risk Factors

The majority of male participants across all severity levels and hemophilia types had a family history of hemophilia. Of the male participants with hemophilia A, a family history of hemophilia was present in 71%, not present in 23%, and unknown in 6%. Comparing the distribution of hemophilia A with respect to race and ethnicity in the US population, Caucasians are more common, followed by African-American, while Asian ancestry are less commonly affected. A large proportion (31%) of people with hemophilia A in Europe are in the 45+ age category, compared to 13% in Africa, 7% in South East Asia and 8% in the Eastern Mediterranean (AGS 2019). In high-income countries, 29% of hemophilia A patients were over 45 years old, whereas in low-income countries, only 4% were over 45 years old, showing a positive relationship between older age (45+) and Gross National Income (GNI) (AGS 2019) per capita.

The presence of a *F8* gene (encodes for coagulation factor VIII) mutation is the most important determinant, or risk factor, of hemophilia A and the resulting clinical phenotype. Numerous different mutations throughout the *F8* gene have been described in patients with hemophilia A resulting in loss of FVIII expression or function. Patients with null mutations tend to have a modestly more severe phenotype (Carcao et al 2013), but importantly are at higher risk of developing inhibitors compared to individuals who have residual expression of non-functional FVIII protein. Interestingly, significant inter-patient variability of FVIII expression was observed in non-severe hemophilia A patients carrying the same mutation (Loomans et al 2017).

1.1.1.4 Treatment Options

The standard of care for all patients with severe hemophilia is regular replacement therapy (prophylaxis) with clotting factor concentrates, or other hemostasis products to prevent bleeding, started early in life (before age 3) to prevent musculoskeletal complications from recurrent joint and muscle bleeds.

A coordinated hemophilia care program, administered through a designated agency and integrated within the existing healthcare system, improves outcomes for people with hemophilia (Srivastava et al. 2020).

In the non-interventional study (NIS) BH29768, prescribed medication for hemophilia A was analyzed; all patients without inhibitors receiving at least one episodic or prophylactic treatment were prescribed FVIII (Table 2).

Table 2 Prescribed Medication for Hemophilia A in the Non-interventional Study BH29768

	Patients Without FVIII Inhibitors		Patients With FVIII Inhibitors	
	Episodic (n = 45)	Prophylactic (n = 49)	Episodic (n = 75)	Prophylactic (n = 28)
Total number of patients with at least one treatment	44	49	75	28
FVIII	44 (100.0%)	49 (100.0%)	5 (5.3%)	5 (17.9%)
aPCC	0	0	47 (62.7%)	25 (89.3%)
rFVIIa	0	0	45 (60.0%)	10 (35.7%)
Prothrombin NOS	0	0	11 (14.7%)	0
Tranexamic acid	3 (6.8%)	3 (6.1%)	9 (12.0%)	3 (10.7%)

aPCC = activated prothrombin complex concentrate; FVII = factor VII; FVIII = factor VIII; NOS = not otherwise specified.

Multiple uses of a specific medication for a patient were counted once in the frequency for that medication. Patients could receive more than one type of medication.

Source: NIS BH29768 (Mahlangu et al. 2016; BH29768 final clinical study report available on request)

Prophylaxis has conventionally been defined as the regular intravenous (IV) infusion of the missing clotting factor VIII (FVIII) in people with hemophilia A, given in order to increase the FVIII level with the intent to prevent bleeding. The focus of this conventional definition of prophylaxis has been on preventing joint bleeds and maintaining musculoskeletal health. (Srivastava et al. 2020)

Non-factor replacement therapy (emicizumab, a FVIII mimetic) differs from conventional types of prophylaxis as it does not replace the missing coagulation factor, is administered subcutaneously, and in some cases can be administered as infrequently as once every 2 or 4 weeks. The first, and at the time of this publication, the only licensed non-factor replacement therapy for hemophilia A is emicizumab. Emicizumab is not associated with the peak and trough curves of protection. Emicizumab has the advantage of early prophylaxis (without the need of central venous access devices) and can be beneficial in reducing the risk of bleeding in young children prior to the commencement of prophylaxis.

The development of inhibitors has been reported as the most serious complication of FVIII replacement therapy in patients with hemophilia A as these antibodies can neutralize FVIII activity and render this treatment ineffective, consequently posing a great challenge to treating the underlying disease (Coppola et al. 2016). These FVIII inhibitors typically develop very early during the course of FVIII therapy (after a median of 13 exposure days), with half of all cases occurring before the age of 5 years (Fischer 2015a).

Inhibitor development occurs more frequently in severe disease than in non-severe hemophilia. Inhibitors to FVIII in hemophilia A pose a greater challenge in controlling bleeds and is associated with a higher disease burden, including increased risk of musculoskeletal complications, pain, physical limitations, and treatment challenges, all of which may impact a patient's physical functioning, capacity for physical activities, and quality of life. For patients with hemophilia A and inhibitors who have acute bleeds, FVIII concentrate can be used for those with low-responding inhibitors, and a bypassing agent (recombinant factor VIIa [rFVIIa] or activated prothrombin complex concentrate [aPCC]) for those with high-responding inhibitors. In those receiving non-factor therapy for prophylaxis (e.g., emicizumab), rFVIIa is preferred over aPCC because of the risk of thrombotic microangiopathy when aPCC is used with emicizumab. For patients with hemophilia A who develop persistent low-responding inhibitors, immune tolerance induction (ITI) is to be considered. For patients with hemophilia A and persistent inhibitors who fail ITI or never underwent ITI, emicizumab prophylaxis is recommended over bypass agent prophylaxis (rFVIIa or aPCC). Emicizumab is more effective in bleed prevention and simpler to administer, it is given weekly and subcutaneously.

Patients with severe FVIII gene defects (e.g., large deletions, nonsense mutations, intron-22 inversion) and no endogenous FVIII synthesis are reported to have a 7–10 times higher inhibitor prevalence than patients with defects that result in a loss of FVIII function but retain some FVIII production (e.g., small deletions, missense mutations) (Oldenburg et al. 2002; Witmer et al. 2013). Accordingly, severity of disease is an important risk factor, with patients with severe disease having the highest risk of developing inhibitors compared to patients with non-severe disease who have residual endogenous FVIII expression (Fischer 2015a and 2015b). The intensity of FVIII treatment is also perceived to be a risk factor for inhibitor development. Significant cell injury or inflammation, for example after surgery, leads to immunologic ‘danger signals’ that activate antigen-presenting cells and amplify immunologic responses, which could promote formation of inhibitors to FVIII (Witmer et al. 2013; Gouw et al. 2007).

The role of treatment product in inhibitor development has been disputed in the literature. A randomized clinical trial found that patients treated with plasma-derived FVIII containing von Willebrand factor had a lower incidence of inhibitors than those treated with recombinant FVIII (Peyvandi 2016).

Lastly, African-American racial origin and Hispanic ethnicity may be risk factors for development of inhibitors to FVIII products (Ragni et al 2009, Leissinger et al 2011a).

Before the introduction of emicizumab, alternative treatment options were limited in patients with hemophilia A who develop inhibitors to FVIII, and even those limited options have limited effectiveness. This was a population with unmet need and high treatment burden and re-enabling the use of FVIII replacement through permanent eradication of inhibitors was an important goal. This can be accomplished by intensive FVIII administration (doses between 50 International Units [IU] FVIII/kg 3 times weekly

and 200 IU/kg/d) over 1–2 years which achieve ITI in approximately 60% to 80% of patients with inhibitors (Kempton and White 2009; Santagostino et al. 2009; Hay and DiMichele 2012). However, hemostatic management with bypassing agents may be challenging while ITI is ongoing. Furthermore, ITI is not a viable option for patients with inhibitors in many countries, owing to its high cost, the scarce local supply of FVIII concentrates, potential complications associated with central venous access devices, and psychological stress on patients and their families for this highly demanding therapeutic endeavor. Finally, even with successful implementation, ITI will fail to eliminate inhibitors in 21 to 44% of patients (Mariani et al. 2003).

For patients with a history of a high-titer (≥5 Bethesda units [BU]/mL) inhibitor following a re-challenge with FVIII administration (i.e., a high-responding inhibitor), the only hemostatic options available before the introduction of emicizumab were prothrombotic coagulation factors that augment other parts of the coagulation cascade (i.e., “bypassing agents”). Bypassing agents include FEIBA® (factor eight inhibitor bypassing activity, an activated prothrombin complex concentrate [aPCC]; FEIBA® will be referred to as aPCC throughout this document), and NovoSeven® (recombinant activated human FVIIa [rFVIIa]; NovoSeven® will be referred to as rFVIIa throughout this document) (Srivastava et al. 2013). In NIS BH29768, the most common medication prescribed for hemophilia A patients with inhibitors was aPCC, followed by rFVIIa (Table 2).

The hemostatic effect of bypassing agents is less reliable in comparison with that of FVIII concentrates. Patients receiving prophylactic treatment with bypassing agents still have frequent bleeding; in the NIS BH29768 which included 28 hemophilia A patients with inhibitors receiving prophylactic bypassing agents, the annualized bleed rate was 14.7 for treated bleeds (Mahlangu et al. 2016; BH29768 final clinical study report available on request). Furthermore, there is inter-individual variability in response to different bypassing agents; some patients with inhibitors will have bleeds that respond better to rFVIIa while others will respond better to aPCC. Several publications evaluating the efficacy of prophylactic therapy in adults and children with the bypassing agents rFVIIa (Konkle et al. 2007) and aPCC (Leissinger et al. 2007; Ettingshausen and Kreuz 2010; Leissinger et al. 2011b; Antunes et al. 2014) showed decreased bleeding rates compared with episodic therapy, and aPCC has been approved in the US and EU for prophylactic use in patients with inhibitors. However, prophylactic rFVIIa and aPCC were still associated with an average of 2.2–3.0 bleeds/month and a median annualized bleed rate of 7.9, respectively (Konkle et al. 2007; Antunes et al. 2014).

In addition, as opposed to the 8-12-hour half-life and 15-20-minute infusion time of FVIIIC, rFVIIa has a half-life of only 2-3 hours and aPCC needs 30-45 minutes to infuse, requiring frequent and extended IV infusions, respectively, and further adding to treatment burden. Treatment with bypassing agents has also been associated with increased risk of thrombotic complications and consumption coagulopathy (Pruthi et al. 2007, Makris 2012, Negrier et al. 2016, Rocino et al. 2017).

In conclusion, the therapies available before emicizumab to prevent and control bleeding episodes in hemophilia A patients both with or without inhibitors have limited efficacy and their administration is associated with iatrogenic morbidity and high treatment burden.

1.1.1.5 Mortality and Morbidity

Natural History of the Indicated Condition in the Untreated Population

The vast majority of patients with moderate and severe hemophilia A receive treatment during their lifetimes. Patients with untreated severe disease may be at high risk of frequent and prolonged bleeding, leading to long-term complications and increased morbidity and mortality.

Newborns with hemophilia are at risk of intracranial hemorrhage (ICH), extracranial hemorrhage, and other bleeding complications. It is likely that ICH is more common in newborns with severe hemophilia, as compared to those with moderate disease and is usually associated with permanent morbidity. Extracranial hemorrhage is equally common and can, when severe, result in life-threatening anemia. Bleeding at the sites of heel pokes, intramuscular injections, and venipunctures is possible. Bleeding in the oral mucosa becomes more common after 30 days of age (Moorehead 2018).

In milder forms, there is less frequent spontaneous bleeding, and the disorder might only be diagnosed after a surgery or serious injury (Loomans et al. 2017; Ljung. 2008). In severe cases, heavy bleeding occurs after minor injury or even when there is no injury (spontaneous bleeding). Bleeding into the joints, muscles, brain, or organs can cause pain and other serious complications. People with inherited hemophilia A require life-long care, preferably through a specialized hemophilia treatment center. Life expectancy may depend on the response to treatment and the presence of other health conditions (NIH 2021).

Morbidity in Target Indication

Hemophilia A often presents in infancy and becomes apparent during medical procedures, such as those incurred during childbirth, blood draws, or circumcision, or later from bruising or sustained bleeding following common injuries (CDC 2016). It is a heterogeneous disease due to the different underlying mutations and resultant variations in level of active clotting factor. Patients are classified as having severe hemophilia if their FVIII activity is $<1\%$, and moderate if it is 1-5% (Srivastava et al. 2013). All patients with high-titer (>5 BU) inhibitors are considered to have severe disease as they have no endogenous FVIII activity. In general, higher residual FVIII activity is associated with fewer bleeding episodes, less comorbidities such as arthropathy, and better health-related quality of life (HRQoL) (Collins et al. 2009). However, it has been accepted that plasma FVIII activity level does not necessarily correlate with bleeding phenotype (Jiménez-Yuste et al. 2014; Chitlur et al. 2008).Patients with severe hemophilia and

some patients with moderate hemophilia can experience bleeding episodes several times a month, which are often spontaneous (Srivastava et al. 2013). However, residual FVIII activity level accounts for only roughly 70% of the bleeding phenotype, the remaining 30% are potentially related to unexplained individual variables; thus, some patients do not exhibit a bleed phenotype as traditionally expected based on their FVIII level (Mancuso et al. 2018).

The main bleeding sites are intra-articular, intramuscular, subcutaneous, intraoral, intracranial, gastrointestinal, and intranasal. While external bleeding may be hard to control, the sequelae of internal bleeds into the joints, muscles, digestive tract, and brain often present a serious long-term health threat. In particular, the repeated injury due to hemarthrosis can cause permanent joint damage and deformity leading to significant pain, disability and reduced HRQoL (Riley et al. 2011; Gringeri et al. 2013). Joint replacement surgery at a relatively early age may be necessary (Riley et al. 2011).

In a cross-sectional study of patients with hemophilia from Bulgaria, France, Germany, Hungary, Italy, Spain, Sweden and the UK, for the disability score, 60% showed no disability (Barthel index (BI) score more than 91), 22% showed mild-to-moderate dependence (BI score from 90 to 61) and 8% severe/complete dependence (BI under 60). The average EuroQol 5-domain (EQ-5D) index score of people who have hemophilia is 0.69 lower than the HRQoL in the general population. The study found people with hemophilia consider their physical health and mental health impaired (Cavazza 2016).

Inhibitors are most commonly encountered in severe hemophilia A patients (overall 25-40% lifetime risk) compared to those with non-severe hemophilia A (overall 5-15% lifetime risk) (Inhibitors in Hemophilia, 2018).

Patients with inhibitors have consistently been shown to have increased mortality and morbidity (Franchini et al. 2012; Walsh et al. 2015) and poorer HRQoL (Gringeri et al. 2013) compared with patients without FVIII inhibitors. In a study evaluating burden of disease and treatment in 1285 patients with severe hemophilia receiving either prophylactic or episodic treatment, patients with inhibitors self-reported higher annual number of bleeds (8.3 vs 3.8), with a higher percentage of these being major bleeds (33% vs 22%), compared with patients without inhibitors. Ninety-three percent of the patients with inhibitors reported target joints (defined as sites of recurrent bleeds) (average number of target joints: 2.2), compared with 55% of patients without inhibitors (average number: 1) (CHESS 2015, additional analyses available on request). Patients with inhibitors also reported pain more frequently (54% vs 24%) and lower levels of QoL (mean EQ-5D: 0.5 vs. 0.8) (Oladapo, 2016).

Mortality in Target Indication

Hemophilia A is generally not immediately life-threatening for patients living in developed countries. In some developed countries, the mean life expectancy in patients with hemophilia A without HIV approaches that of the general population (Tagliaferri et al. 2010; Lövdahl et al. 2013), as detailed below for individual countries. Older studies consistently report mortality rates in the overall hemophilia population to be approximately twice that of the general population (Plug et al. 2006; Darby et al. 2007; Tagliaferri et al. 2010). Historically, AIDS and hepatitis C have been the most common cause of hemophilia-related deaths (approximately 60% of all deaths), with hemorrhage accounting for approximately 20% of the deaths (Soucie et al. 2000; Plug et al. 2006; Darby et al. 2007; Tagliaferri et al. 2010).

Studies indicated that severe hemophilia A is correlated with poorer clinical outcomes and an increased risk of mortality compared with non-severe disease. From six observational studies crude mortality rates for Persons with Hemophilia A (PwHA) or combined populations of hemophilia A and hemophilia B of all severities ranged from 2.0 to 10.0/1000 person-years. The mortality rate of hemophilia A in Europe, Australia and America was found to be similar and calculated as 2.0/1000 PY (Hay 2021). An Italian study found mortality rates of 5.0 per 1000 person-years for moderate hemophilia, and for severe hemophilia, a mortality rate of 9.0 per 1000 person-years was reported (Tagliaferri et al 2010).

The US, ATHN dataset (collected between 2010 and 2018) included 6624 non-serious HA patients observed for a total of 56,119 patient-years. At the end of an average follow-up period of 8.5 years, 136 deaths were reported, occurring at a median age of 63 years (SD: 1.5). The overall all-cause mortality rate was 2.4 per 1000 person-years. The age-adjusted mortality rates for inhibitor and non-inhibitor participants were 2.6 (95% CI, 2.7, 1.0-4.1) and 3.3 (95% CI, 2.7-3.9) per 1000 person-years, respectively. Mortality risk increased two-fold with each additional decade of age. Persons with hepatitis C were at twice the risk of death and persons with HIV had almost 4 times the risk of death compared with persons without these conditions. The most common causes of mortality were malignancy (19.9%), liver disease (14%) and cardiovascular disease (8.1%) (Lim 2020).

A retrospective study indicated that mortality may be further increased in patients with hemophilia A who had active inhibitors (Walsh et al. 2015): data from 7386 patients with hemophilia A, including 627 (8.5%) patients with current inhibitors, were collected over a 13-year period. Patients with inhibitors had 70% increased risk of death, compared to patients without inhibitors (odds ratio: 1.7, p-value <0.01), after adjustment for risk factors including: demographics (age, race, body mass index, insurance status), medical history (prior intracranial hemorrhage, liver disease, HIV, and HCV status), and disease and treatment characteristics (number of bleeds in the last 6 months, decreased activity, and bypass agents treatment).

A further study conducted in the UK from 1977 – 2000 with 6018 patients with hemophilia who were not infected with HIV, demonstrated no significant difference in mortality rate between hemophilia A and B (Darby et al. 2007). The mortality rate did not change significantly over the duration of the study, and it was 2.69 and 1.19 times higher than that of the general population for patients with severe and non-severe disease, respectively. Table 3 shows mortality rate estimates in the UK of male patients with hemophilia (of any type) by disease severity.

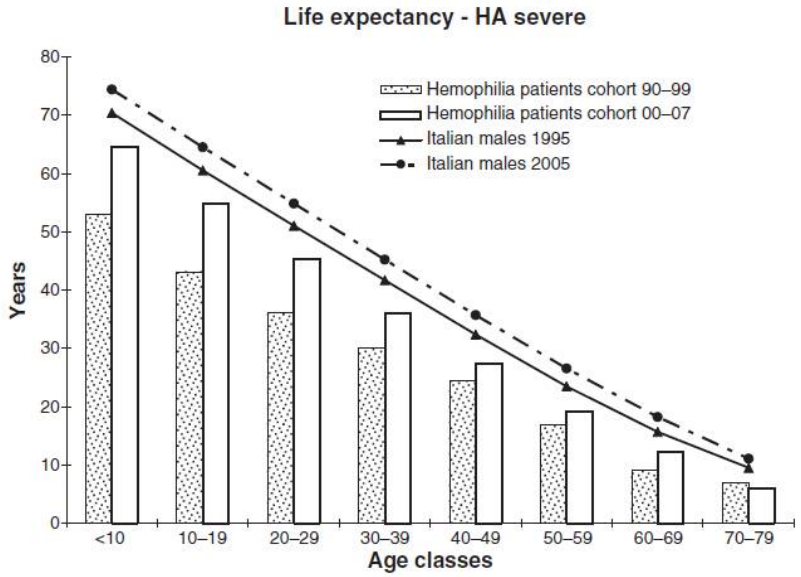
Table 3 Mortality rate in male patients with hemophilia (of any type) in the UK

	Severe hemophilia 1977-1999			Non-severe hemophilia 1985-1999			All men in the UK, 1999
	No. of deaths	Death rate per 1000 PY	95%CI	No. of deaths	Death rate per 1000 PY	95%CI	Death rate per 1000 PY
Age, y							
0-4	13	5.1	3.0-8.8	6	2	0.9-4.6	1.5
5-14	4	0.7	0.2-1.7	4	0.5	0.2-1.3	0.1
15-24	15	2.6	1.6-4.4	9	1.1	0.6-2.0	0.7
25-34	28	5.8	4.0-8.4	16	1.7	1.1-2.8	1
35-44	28	8	5.6-11.7	16	2	1.2-3.3	1.6
45-54	41	17.8	13.1-24.1	35	5.8	4.2-8.1	4.1
55-64	51	39.2	29.8-51.5	71	15.4	12.2-19.5	11.2
65-74	41	66.7	49.1-90.5	135	43	36.3-50.9	32.3
75-84	25	133	89.9-196.8	122	91.7	76.8-109.5	81.1

PY = patient-years; y = years
Source Darby et al. 2007

A study including 252 Italian patients with hemophilia A who died between 1980 – 2007 found an overall death rate of 5.7 per 1000 PY at risk (95%CI: 5.2-6.4) (Tagliaferri et al. 2010). Median age at death was 39, and 49 years old for patients with severe and moderate disease, respectively. Age-specific life expectancy in patients with severe disease increased from 1990 – 1999 to 2000 – 2007, approaching but not reaching that of the general population in the recent cohort (Figure 1).

Figure 1 Age-specific life expectancy in Italian patients with severe hemophilia A, 1990–2007



Source Tagliaferri et al. 2010

Another recent observational study (Hassan 2021) of 1031 Dutch hemophilia A patients, reported an overall crude death rate of 8.9 deaths per 1000 person-years (incidence proportion of 13%) during a follow-up period between 2001 and 2018. The standardized mortality (all-cause) ratio was 1.4. From 2001 to 2018, frequent causes of death were non-hepatic malignancies (26%) and intracranial bleeding (14%). Acquired immunodeficiency syndrome (AIDS; 2%), chronic liver disease (7%), and hepatocellular carcinoma (7%) were less frequent causes of death. Mortality in patients with severe hemophilia was higher than moderate hemophilia. The mortality rates based on severity and age is described in Table 4.

Table 4 Mortality rates based on severity and age (2001-2018)

Groups	Crude Mortality Rate (per 1000 patient-years)
Stratified by Severity	
All patients	8.9
Moderate hemophilia	8.2
Severe hemophilia	10.2
Stratified by Age	
0-14 years	0
15-29 years	0.8
30-44 years	2.3
45-59 years	8.1
60+ years	33.7

(Hassan 2021)

In a prospective cohort study that included 796 Dutch patients living with hemophilia A in 1992 (Plug et al. 2006), the standardized mortality ratio was 2.3. Life expectancy in the entire cohort was 68 years and increased to 70 years when limited to HIV-negative patients. In patients followed from 1992-2001, the most common causes of death were AIDS (26%) and hepatitis C (21%), while hemorrhages accounted for 10% of all deaths.

A Swedish study (Lövdahl et al. 2013) reported that the risk of death was increased 2.2 times in patients with hemophilia, compared with matched, hemophilia-free controls. This effect was reduced to 1.6 times when HIV-infected patients were excluded. Median age of death in the entire cohort increased from 60 years old in 1990 – 2000 to 69 years old in 2001-2008 but remained lower than that in the control group (76 years, in 2001 – 2008). The most common cause of death in patients with hemophilia was malignancy, with a similar proportion to that found in the general population (22% and 23%, respectively). Hemorrhage accounted for 14% of deaths, ischemic heart disease for 13% (29% in the general population control), and HIV for 8% (31% in patients with severe hemophilia).

AEs Expected in the Target Population

Inhibitor development is the most significant and life-changing adverse event (AE) of FVIII treatment. As previously described, inhibitors can neutralize FVIII activity and make treatment with FVIII replacement ineffective (Coppola et al. 2016; Franchini et al. 2017).

Treatment with bypassing agents has been associated, although rarely, with thromboembolic complications, with reported incidence ranging between 1.1% and 4.3% (Pruthi et al. 2007; Makris 2012; Negrier et al. 2016; Rocino et al. 2017). Reported events include deep vein thrombosis, pulmonary embolism, disseminated intravascular coagulation, stroke and myocardial infarction. For aPCC, the risk of thrombotic events

appears to be related to the dose and treatment duration of bypassing agents, and it is increased in patients with thrombotic risk factors and patients who receive aPCC and rFVIIa in combination (Rocino et al. 2017, Pruthi et al. 2007).

Hypersensitivity reactions (including severe and systemic reactions such as anaphylaxis with urticaria and angioedema, bronchospasm, and circulatory shock) have also been observed in patients receiving aPCC, as well as rises in the inhibitor titer, potentially due to anamnestic response (Aledort 2008). The incidence of hypersensitivity reactions (include urticaria, allergic reactions, injection-site reactions) ranged between 0.93% and 5.5% in congenital HA patients (Montalvao et al. 2015) (Atunes et al. 2014). Anaphylaxis after concentrate infusion is extremely rare, but minor allergic reactions represent the most common nonthrombotic, non-inhibitor AEs associated with hemophilia treatment. A systematic review of all prospective registration studies in patients with hemophilia A identified only a single anaphylactic episode in the last 20 years. The overall number of adverse events was 732, with 240 allergic reactions reported, including site reactions, nausea, vomiting, and headache. No difference between plasma-derived or recombinant products in terms of adverse event association was reported. On the whole, the total rate of adverse events was calculated at 0.13%, confirming the high degree of safety of the products currently used for replacement therapy (Franchini 2012). No evidence related to acquired HA population was found in the literature. Majorly adolescent and adults aged (12-70 years) were included in the literature. Among children with congenital HA, a phase III trial reported an incidence of 5.5% for hypersensitive reaction with recombinant factor VIII (Santagostino et al. 2020), while an open-label study reported an incidence of 2.9% for allergic edema and 1.5% each for severe allergic reaction and urticarial (Trakymienė et al. 2020).

For patients who receive ITI, the most common AEs are infections associated with the use of central venous access devices. In a randomized clinical trial evaluating ITI treatment in patients with severe hemophilia A (Hay and DiMichele 2012), 99 of the 115 patients randomized (86%) had catheters inserted. Among those, 41 patients (41%, or 36% of all patients receiving ITI) developed a total of 124 infections associated with the use of central venous access devices. There was no evidence that infections affected the outcomes of the ITI.

1.1.1.6 Concomitant Medication(s) Not Administered for Hemostasis in the Target Population

In the NIS BH29768 in patients with hemophilia A (Mahlangu et al. 2016; BH29768 final clinical study report available on request), the most commonly administered medication classes for conditions other than hemophilia A in patients with hemophilia A with inhibitors were (in patients on episodic or prophylactic treatment, respectively):

- Non-steroidal anti-inflammatory drugs (NSAIDs; 20.0% and 28.6%)
- Analgesics (33.3% and 14.3%)

- Antiviral agents not elsewhere classified (11.1% and 14.3%)

Similarly, in patients with inhibitors, the most commonly administered medication classes were (in patients on episodic or prophylactic treatment, respectively):

- Analgesics (26.7% and 21.4%)
- NSAIDs (22.7% and 17.9%)
- Opioid analgesics (14.7% and 14.3%)

A study utilizing US insurance claims data from commercially insured US residents identified 3698 patients with at least one claim for hemophilia A (both patients with or without inhibitors) who were followed for a median of approximately 3 years. This study analyzed concomitant medication not related to hemophilia, and also demonstrated frequent use of analgesia (e.g., acetaminophen/hydrocodone [28.6%]), as well as antibiotic, antiviral, and antifungal treatments (e.g., amoxicillin 30%); procoagulation products (e.g., aminocaproic acid [24.9%]) and anticoagulation products (warfarin [6.9%], heparin [6.5%]); steroids (e.g., prednisolone [14.3%]); respiratory agents (albuterol sulfate [13.4%]); and antiemetics (ondansetron [13%]) (Roche internal data, report available on request).

Combined evidences from the two studies indicate that analgesics (non-opioid and opioid), anti-inflammatory agents (non-steroidal and steroidal), and antibiotics are the most commonly administered non-hemophilia medication. The high use of analgesic possibly reflects the need of the patients to control pain associated with hemophilia, both acute pain from bleeding and chronic pain that characterizes joint deterioration and arthritis.

1.1.1.7 Important Comorbidities Found in the Target Population

The following clinically relevant comorbidities are reported in the target population (see Annex 7a for details):

- HIV infection
- Hepatitis C infection
- Hemophilic arthropathy
- Renal disease
- Malignancies (related to transmission of infectious agents from contaminated blood products [HIV and HCV])
- Hematologic abnormalities
- Neurologic abnormalities

PART II: MODULE SII - NONCLINICAL PART OF THE SAFETY SPECIFICATION

Key safety findings from nonclinical studies with emicizumab are summarized in Table 5.

The cynomolgus monkey was considered the most appropriate model for nonclinical safety studies, as emicizumab is known to only bind to human and non-human primate FIXa and FX. All but one toxicology study were performed according to Good Laboratory Practice regulations.

Emicizumab was well tolerated by cynomolgus monkeys with a variety of dosing regimens including 4-week IV QW, 4-week SC QW, 13-week SC QW, and 26-week SC QW at dose levels up to 100 mg/kg IV and 30 mg/kg SC.

Table 5 Key Safety Findings from Nonclinical Studies

<table>
<tr><th>Key Safety findings (from nonclinical studies)</th><th>Relevance to human usage</th></tr>
<tr><td>Acute Toxicity:
Acute toxicity was evaluated as part of 4-week IV, 4-week SC and 13-week SC toxicity studies. No toxicological changes attributable to emicizumab at doses of 10, 30 and 100 mg/kg/week (IV) and of 1, 6, and 30 mg/kg/week (SC) were noted.</td><td>No specific toxicities were identified in cynomolgus monkeys; therefore, none are expected to occur in human patients.</td></tr>
<tr><td>Repeat-dose Toxicity:
Repeat-dose toxicity was evaluated in IV and SC studies in cynomolgus monkeys with once per week dosing.
Summary of Repeat-dose Toxicity Studies
<table>
<tr><th>Type of study</th><th>Species</th><th>Dose (mg/kg/week)</th><th>GLP compliance</th></tr>
<tr><td>4-Week IV</td><td>Cynomolgus Monkey</td><td>10, 30, 100</td><td>Yes</td></tr>
<tr><td>4-Week SC</td><td>Cynomolgus Monkey</td><td>1, 6, 30</td><td>No</td></tr>
<tr><td>13-Week SC</td><td>Cynomolgus Monkey</td><td>1, 6, 30</td><td>Yes</td></tr>
<tr><td>26-Week SC</td><td>Cynomolgus Monkey</td><td>1, 6, 30</td><td>Yes</td></tr>
</table>
No toxicological changes attributable to IV or SC administration of emicizumab were observed; the NOAEL was the highest tested dose in each study (i.e., 100 mg/kg for IV dosing and 30 mg/kg for SC dosing).
In the 4-week IV toxicity study and 4-week and 13-week SC toxicity studies, hematology examinations revealed shortening of the activated partial thromboplastin time (aPTT) in all emicizumab-treated groups, which was attributed to the pharmacological action of emicizumab. There were no abnormalities in the other related parameters and no corresponding pathological findings.
In the 13-week SC toxicity study in cynomolgus monkeys, polyarthritis was noted in one female in the 1 mg/kg/week group after the first dose (out of a total of 88 monkeys that received emicizumab in the general toxicity studies), and the animal was sacrificed after the seventh dose. The underlying mechanism of the polyarthritis is unclear. However, the polyarthritis was judged to be an incidental change.</td><td>No repeat-dose toxicity was observed in cynomolgus monkeys. The NOAEL was the highest tested dose in each study (100 mg/kg for IV dosing and 30 mg/kg for SC dosing).
aPTT shortening was observed in both IV and SC toxicity studies, but this was attributed to the pharmacological action of emicizumab.
One cynomolgus monkey developed polyarthritis, but this was judged to be due to incidental change and not expected in humans. The change was only seen in one female in the 1 mg/kg low-dose group. In addition, spontaneously occurring polyarthritis has been reported in macaques.
There were no AEs reported for polyarthritis in the Phase III Studies BH29884, BH29992, BH30071, and BO39182, BO41423 or the Phase I/II Study ACE002JP; therefore this risk was not categorized as an important risk.
One cynomolgus monkey developed localized swelling/hemorrhage/vasculitis, considered an Arthus reaction (a local type III hypersensitivity reaction). In the CDP, the study protocols excluded hemophilia patients with a history of hypersensitivity associated with mAb therapies or components of the emicizumab injection. For clinical data, refer to Table 17 and Table 19.
There were no adverse events reported for events of vasculitis in the clinical studies. Therefore this risk was not categorized as important.
One cynomolgus monkey developed periarteritis in several organs. The</td></tr>
</table>

Key Safety findings (from nonclinical studies)	**Relevance to human usage**
In the 26-week SC toxicity study one male cynomolgus monkey dosed with 6 mg/kg/week developed localized swelling/hemorrhage/vasculitis at the administration site which was considered an Arthus reaction triggered by administration of a heteroprotein. The animal was prematurely necropsied in week 23. In the 4-week IV toxicity study in cynomolgus monkeys, polyarteritis (diagnosed based on histopathological findings of periateritis in the liver, pancreas, stomach, and spleen) was observed in 1 female in the 100 mg/kg group after the third dose. The pathomechanism of the polyarteritis remained unclear and the finding was considered to be a spontaneous case of polyarteritis.	cause of this polyarteritis was unclear, but was considered to be incidental and not related to emicizumab and not expected in humans. The risk of anaphylaxis, anaphylactoid and systemic hypersensitivity reactions are described as an important potential risk in this RMP.
Genotoxicity Per ICH S6 (R1) Guidance on the Nonclinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals, genotoxicity studies routinely performed for small molecules are not applicable to biotechnology-derived large molecules, such as emicizumab	A direct genotoxic effect of emicizumab is unlikely given that emicizumab is a large molecule and is therefore not expected to possess DNA damaging properties based on its physico-chemical properties.
Carcinogenicity No carcinogenicity studies have been conducted with emicizumab and none are planned. Classical lifetime rodent bioassays, which are commonly used to assess carcinogenesis risk for small molecules, are considered inappropriate for biotherapeutics in general as these assays have largely been validated with genotoxic compounds and protein therapeutics are considered to have low genotoxic potential. Furthermore, lifetime studies in rodents with emicizumab are not viable given the lack of cross-reactivity. None of the cynomolgus monkeys treated with emicizumab developed any malignant or non-malignant tumors.	The carcinogenic potential of emicizumab, a mAb, is considered low.
Reproductive and Developmental Toxicity The effects of emicizumab on fertility were assessed in the repeat-dose toxicity studies in cynomolgus monkeys (including mature animals). Emicizumab did not cause any toxicological changes on male or female reproductive organs, on testicular size, sperm analysis and menstrual cyclicity. No data are available with respect to potential effects of emicizumab on embryofetal development.	The available data on the pharmacological action of emicizumab and the absence of relevant systemic toxicity in general toxicity studies do not suggest that emicizumab would interfere with embryofetal development. In addition, as the vast majority of hemophilia A patients are males, the potential for embryofetal development toxicities is relevant for only a small subset of patients, therefore the risk is low. Moreover, the risk of transmission of drug from semen is low. The margin

Key Safety findings (from nonclinical studies)	**Relevance to human usage**
	between the MABEL plasma concentration (7 ng/mL) and the estimated maternal C_{max} (at 3 mg/kg/week emicizumab dosing regimens, which is the highest exposure tested in clinics) is greater than 10-fold (Banholzer et al. 2012). At this time, very small proportion of emicizumab is thought to transfer into semen, and there are no known reproductive risks to female partners of male patients treated with emicizumab. Condom use will not be required in male patients.
Studies in juvenile animals The available 13-week SC toxicity study in monkeys of 3 years of age with QW dosing supports treatment of adolescent humans at 12 years of age and older. Toxicology studies in juvenile animals have not been conducted and are not considered meaningful for emicizumab.	Safety in pediatric patients has been established in clinical trials. Analysis in this population continues.
Local Tolerance Evaluation of local tolerance at the administration site in the repeat-dose SC toxicity studies revealed reversible hemorrhage related to the SC injection technique, perivascular mononuclear cell infiltration due to the SC injection of a protein formulation and degeneration/ necrosis of subcutis and swelling of endothelium.	Injection-site reactions are a non-important identified risk related to treatment with emicizumab and are fully reversible.
Safety Pharmacology Emicizumab did not have any effects on the central nervous, respiratory, or cardiovascular systems based on assessments performed in the repeat-dose general toxicity studies.	No indication of adverse effects. There were no findings in nonclinical toxicity studies and no findings in clinical studies to date. Antibodies are unable to enter hERG channels and PK/QT analyses in ACE002JP study revealed no QT prolongation with increased emicizumab concentration. Therefore there were no cardiovascular concerns.
Other toxicity studies In an in vitro study of cytokine release that used the whole blood of healthy adults the levels of cytokine induced by emicizumab were comparable to those induced by panitumumab, a reference antibody with low clinical risk. In a tissue cross-reactivity assay in normal human tissue staining of intracytoplasmic granules was observed in a number of tissues.	The safety profile of emicizumab has been established in clinical trials based on the experience in human patients. It is considered unlikely that serious adverse drug reactions related to cytokine release will develop in humans because it is unlikely that emicizumab will cross the cell membrane.
Mechanism for laboratory coagulation test interference: All standard assays based on aPTT reagents, such as one-stage single-factor assays, are not	Coagulation laboratory tests (including but not limited to aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) do

Key Safety findings (from nonclinical studies)	**Relevance to human usage**
appropriate for testing plasma samples containing emicizumab, because emicizumab will affect the results (see SmPC section 4.4). Emicizumab replaces the tenase cofactor activity of FVIIIa. However, coagulation laboratory tests based on intrinsic clotting time (e.g., aPTT) assume that non-activated FVIII is present and so the tests will overestimate the activity of FVIIIa or molecules with similar mechanism such as emicizumab, due to more rapid clotting times.	not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. There may be a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab. This risk may be most relevant when a patient is treated by HCPs other than the emicizumab-prescribing HCP for a serious bleed in settings such as an emergency room or in an acute care setting. Therefore, the risk was categorized as an important potential risk.
Mechanisms for drug interactions: based on PK The potential for PK drug interactions with emicizumab and other drugs was not investigated. Emicizumab is not expected to show interactions with other drugs on the metabolizing P450 enzymes since the clearance pathways of IgGs are distinct from those of small molecules. Likewise it is not expected to show interaction with drug transporters. Furthermore, emicizumab has no effect on interferon or cytokine levels in the body (changes in interferon/cytokine levels can lead to an altered cytochrome P450 expression).	No formal DDI clinical studies have been conducted with emicizumab, as no PK based DDIs are expected via cytochrome P450 enzymes or other metabolizing enzymes or drug transporters for a mAb like emicizumab. Emicizumab has also no effect on cytokines that modify cytochrome P450 expression. Since emicizumab is administered by SC infusion, drug-food interactions are also not anticipated. The occurrence of unexpected drug-drug interactions will be monitored via routine pharmacovigilance activities.
Mechanisms for drug interactions: based on PD (Enhanced Prothrombotic potential) In combination with either rFVIIa or aPCC, emicizumab further enhanced thrombin generation in vitro suggesting a potential drug interaction. The nonclinical data suggests that the thrombogenic potential of emicizumab monotherapy is not substantially greater than that of FVIII or bypassing agents rFVIIa and aPCC alone. In combinations at clinically relevant exposure conditions, a relative small additive effect was noted for the rFVIIa-emicizumab combination but a disproportionate synergistic increase was observed for the aPCC-emicizumab combination. An increased hemostatic potency for combinations of emicizumab with rFVIIa or aPCC versus emicizumab alone has also been suggested in the in vivo provoked thrombus formation study in cynomolgus monkeys. The data suggest the emicizumab-aPCC combination has a higher potential than emicizumab-rFVIIa to induce	The results with cynomolgus model suggested that the risk of thrombus formation following co-administration of emicizumab plus rFVIIa or aPCC should not markedly exceed that seen with bypassing agents alone. However, pharmacodynamic interactions (enhanced prothrombotic potential) between emicizumab and FVIII, aPCC or rFVIIa cannot be ruled out based on nonclinical study data. Clinical evidence currently indicates that there is a DDI between emicizumab and aPCC. Thromboembolic/TMA events were reported in a clinical trial with concomitant treatment with emicizumab and average cumulative doses of aPCC $>$ 100 U/kg/24 hours for 24 hours or more. Both events were categorized as important identified

Key Safety findings (from nonclinical studies)	**Relevance to human usage**
thrombosis when aPCC is administered at clinically established doses (estimated clinical dose of 100 U/kg) and especially when repeat aPCC doses are administered. Prothrombotic potential was evaluated for rFVIIa or aPCC in combination with emicizumab and compared with emicizumab alone in a venous stasis model in FVIII depleted cynomolgus monkeys. A potential interaction was observed for the drug combinations, as the thrombus weight observed at the stasis sites in these co-administration groups was numerically higher than the maximum weight in the aPCC-only group in some vessels; however, it was not significantly different from that in the rFVIIa or aPCC-only groups. In an in vitro thrombin generation assay, the combination of emicizumab and low concentrations (0.01 or 0.1 IU/mL) of FVIII showed greater peak height of thrombin than either agent alone, but emicizumab caused little to no increase in peak height above that seen with 1 IU/mL FVIII alone. In a normo-coagulative cynomolgus monkey venous stasis model, a similar degree of thrombus formation was seen with single agent administration of emicizumab, rFVIIa, or FVIII, indicating that the addition of emicizumab to normal levels of endogenous FVIII has a similar potential for increased net hemostatic potential as the addition of FVIII. However, despite these findings in the provoked venous stasis model, no evidence of spontaneous thrombosis has been observed during any of toxicology studies in normo-coagulative cynomolgus monkeys.	risks. Based on the in vitro and in vivo thrombin generation studies, the prothrombotic potential with emicizumab and FVIII is less than that of emicizumab with rFVIIa or aPCC. Competition for targets (FIXa and FX) exists between FVIII and emicizumab, which could explain this lower thrombotic potential.

aPCC = activated prothrombin complex concentrate; aPTT = activated partial thromboplastin time; ADA = anti-drug antibody; CDP = clinical development plan; DDI = drug-drug interaction; FVIIa = factor VIIa; GLP = good laboratory practice; HCP = healthcare professional; ICH = International Conference on Harmonisation; IV = intravenous; PK = pharmacokinetic; mAb = monoclonal antibody; MABEL = minimal anticipated biological effect level; NOAEL = no-observed-adverse-effect-level; rFVIIa = recombinant factor VIIa; SAE = serious adverse event; SC = subcutaneous; TMA = thrombotic microangiopathy

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

Emicizumab is being developed for the treatment of adults and children with hemophilia A, with and without FVIII inhibitors.

Clinical trial exposure in the target population is based on two Phase I and I/II studies (ACE001JP and ACE002JP) and five ongoing Phase III studies. The Phase III studies either include patients with hemophilia A with inhibitors (BH29884 and BH29992) or without inhibitors exclusively (BH30071), patients with mild or moderate hemophilia A without inhibitors (BO41423), or hemophilia A patients regardless of inhibitor status (BO39182).

For this RMP, patient safety data from ACE001JP and ACE002JP studies have been analyzed collectively up to a clinical cut-off date of 31 August 2017 and are referred to as “Study ACE002JP” (ACE002JP is an extension of ACE001JP, i.e. the patients participated in both studies). Additionally, safety data are included from the following Phase III studies:

- Study BH29884–last patient last visit (LPLV): 1 December 2020
- Study BH29992– LPLV 11 November 2020
- Study BH30071–LPLV 12 May 2022
- Study BO39182–LPLV 29 June 2022
- Study BO41423–CCOD 30 October 2021

Studies ACE002JP, BH29884, BH30071, and BO39182 included adults and adolescents ($\geq$12 years) while Study BH29992 included patients $<$12 years and patients between 12 and 17 years who weighed $<$40kg. In Study BO41423, patients of all age groups were enrolled. The dose received by the patients was not the same among the Phase I/II and Phase III studies. However, an analysis of all studies and doses has been conducted in order to maximize exposure to assess the overall safety of emicizumab, regardless of the dosing regimen and length of the exposure, received by the patient. Only data while patients were receiving emicizumab were included in this analysis.

The emicizumab safety population provides data from 489 patients with 1335.2 patient-years (PY) of exposure (Table 6, Table 7, Table 8, Table 9, Table 10); this includes 399 patients from Studies BH29884, BH29992, BH30071, and BO39182 with 1199.5 PY of exposure, and 18 patients from Study ACE002JP with 59.4 PY of exposure, and 72 patients from Study BO41423 with 76.3 PY exposure. Exposure data for HAVEN 6 are presented separately to the exposure data from the HAVEN 1 to 4 and ACE002JP studies for comparison of patients with mild or moderate HA with populations involving patients with severe HA.

SIII.1 DURATION OF EXPOSURE

Table 6 Duration of Exposure

Patients with hemophilia A with or without factor VIII inhibitors[a]		
Duration of exposure in weeks	Patients (N = 417)	PY (total 1258.8)
0–4	1	0.1
5–12	3	0.3
13–24	4	1.2
25–36	3	1.9
37–52	1	0.9
> 52	405	1254.5
Patients with hemophilia A with factor VIII inhibitors[a]		
Duration of exposure in weeks	Patients (N = 219)	PY (total 219.4)
0–4	1	0.1
5–12	2	0.2
13–24	2	0.7
25–36	3	1.9
37–52	1	0.9
> 52	210	505.1
Patients with hemophilia A without factor VIII inhibitors[a]		
Duration of exposure in weeks	Patients (N = 198)	PY (total 750.1)
0–4	0	0.0
5–12	1	0.1
13–24	2	0.5
25–36	0	0.0
37–52	0	0.0
> 52	195	749.5

Table 6 Duration of Exposure (cont.)

Patients with mild or moderate hemophilia A without factor VIII inhibitors (Study BO41423)		
Duration of exposure in weeks	Patients (N = 72)	PY (total 76.3)
0–4	0	NE
5–12	1	0.2
13–24	1	0.4
25–36	2	1.2
37–52	24	22.9
> 52	44	51.6

[a]Data are included from completed Studies BH29884, BH29992, BH30071, BO39182 (N = 399), and ACE002JP (N = 18).

[b]Data are included from ongoing Study BO41423 (N = 72)

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.

A dose is a day with injection of emicizumab. A dose can be given with one or more injections.

Patient-years is the sum over patients of the time intervals between the start and end of emicizumab treatment.

PY = patient-years

Adapted from: t_ex_paty_durwk_SAF.out, ACE002JP Interim CSR, t_ex_paty_inhib_DUREXPW_P1_TRT_30OCT2021_41423.out

SIII.2 AGE GROUP AND GENDER

Table 7 Age Group and Gender

Patients with hemophilia A with or without factor VIII inhibitors[a]		
Age Group (years)[1]	Patients (N = 417)	PY (total 1258.8)
0 – < 2	8	12.9
2 – < 6	24	40.4
6 – < 12	53	109.4
12 – < 18	50	135.4
18 – < 65	269	914.7
≥ 65[2]	13	46.1
Patients with hemophilia A with factor VIII inhibitors[a]		
Age Group (years)[1]	Patients (N = 219)	PY (total 508.8)
0 – < 2	8	12.9
2 – < 6	24	40.4
6 – < 12	53	109.4
12 – < 18	39	96.0
18 – < 65	89	233.5
≥ 65[2]	6	16.6
Patients with hemophilia A without factor VIII inhibitors[a]		
Age Group (years)[1]	Patients (N = 198)	PY (total 750.1)
0 – < 2	0	0
2 – < 6	0	0
6 – < 12	0	0
12 – < 18	11	39.4
18 – < 65	180	681.2
≥ 65[2]	7	29.5

Table 7 Age Group and Gender (cont.)

Patients with mild or moderate hemophilia A without factor VIII inhibitors[b]		
Age Group (years)[3]	Patients (N = 72)	PY (total 76.3)
0 – < 2	0	NE
2 – < 6	5	5.7
6 – < 12	11	12.3
12 – < 18	14	15.1
18 – < 65	40	41.2
≥ 65[2]	2	2.1

[a]Data are included from Studies BH29884, BH29992, BH30071, BO39182 (N = 399), and ACE002JP (N = 18).

[b]Data are included from Study BO41423 (N=72)

[1] Only male patients. No female patients with hemophilia A were enrolled in the studies ACE002JP, BH29884, BH29992, BH30071 and BO39182 because of the rarity of the disease in females.

[2] Elderly patients were grouped in one category due to the small number of patients ≥ 65 years enrolled

[3] Three female patients were enrolled in Study BO41423

Patient-years is the sum over patients of the time intervals between the start and end of emicizumab treatment.

NE = not evaluable; PY = patient-years

Adapted from: t_ex_paty_age_SAF.out, ACE002JP Interim CSR, and t_ex_paty_inhib_AGE_P1_TRT_30OCT2021_41423.out

SIII.3 EXPOSURE BY DOSE

Table 8 Exposure by Dose

Patients with hemophilia A with or without factor VIII inhibitors[a]		
Original maintenance dose level and regimen	Patients (N = 417)	PY (total 1258.8)
0.3 mg/kg QW (Study ACE002JP)	6	25.6
1 mg/kg QW (Study ACE002JP)	6	16.9
1.5 mg/kg QW (Studies BH29884, BH29992 and BH30071)	279	792.7
3 mg/kg Q2W (Study BH30071)	62	219.9
3 mg/kg QW (Study ACE002JP)	6	16.9
6 mg/kg Q4W (Study BO39182)	58	186.8

Table 8 Exposure by Dose (cont.)

Patients with hemophilia A with factor VIII inhibitors[a]		
Original maintenance dose level and regimen	Patients (N = 219)	PY (total 508.8)
0.3 mg/kg QW (Study ACE002JP)	4	17.1
1 mg/kg QW (Study ACE002JP)	4	11.6
1.5 mg/kg QW (Studies BH29884, BH29992 and BH30071)	180	413.3
3 mg/kg Q2W (Study BH30071)	10	16.8
3 mg/kg QW (Study ACE002JP)	3	10.0
6 mg/kg Q4W (Study BO39182)	18	40.0
Patients with hemophilia A without factor VIII inhibitors[a]		
Original maintenance dose level and regimen	Patients (N = 198)	PY (total 750.1)
0.3 mg/kg QW (Study ACE002JP)	2	8.5
1 mg/kg QW (Study ACE002JP)	2	5.3
1.5 mg/kg QW (Studies BH29884, BH29992 and BH30071)	99	379.4
3 mg/kg Q2W (Study BH30071)	52	203.1
3 mg/kg QW (Study ACE002JP)	3	7.0
6 mg/kg Q4W (Study BO39182)	40	146.8
Patients with mild or moderate hemophilia A without factor VIII inhibitors (Study BO41423)[b]		
Original maintenance dose level and regimen	Patients (N = 72)	PY (total 76.3)
1.5mg/kg/week	25	25.8
3mg/kg/2 weeks	39	42.9
6mg/kg/4 weeks	8	7.6

[a]Data are included from Studies BH29884, BH29992, BH30071, BO39182 (N = 399), and ACE002JP (N = 18).

[b]Data are included from Study BO41423 (N=72)

In studies BH29884, BH29992, BH30071 and BO39182, the four initial loading doses were

3 mg/kg/week. In study ACE001JP, only one loading dose was given at 3 mg/kg except for the 6 patients (Arm C-1) that had the loading dose at 1 mg/kg/week (followed by subsequent maintenance doses at 0.3 mg/kg/week). All patients treated with emicizumab in ACE001JP (Arm C) were enrolled in ACE002JP.

Treatment duration is the date of the last dose of study medication minus the date of the first dose plus one day.

A dose is a day with injection of emicizumab. A dose can be given with one or more injections.

Patient-years is the sum over patients of the time intervals between the start and end of emicizumab treatment.

A total of 26 patients were up-titrated to 3 mg/kg/week emicizumab, two of whom later down-titrated, and a total of seven patients had at least one change of dosing regimen. In ACE002JP studies, three patients in the 0.3 mg/kg/week group and one patient in the 1 mg/kg/week group up–titrated to 3 mg/kg/week. In Study BH29884, seven patients were up–titrated to 3 mg/kg/week. In Study BH29992, three patients were up–titrated to 3 mg/kg/week. In Study BH30071, nine patients were up–titrated to 3 mg/kg/week and six other patients had a change in dosing regimen (patients received the same overall dose delivered at a different frequency). In Study BO39182, four patients were up–titrated to 3 mg/kg/week, two of whom were later down–titrated, and one other patient had a change of dosing regimen twice.

PY = patient-years

Adapted from: t_ex_paty_dose_SAF.out, ACE002JP Interim CSR, and t_ex_paty_inhib_DOSE_P1_TRT_30OCT2021_41423.out

SIII.4 EXPOSURE STRATIFIED BY OTHER PARAMETERS

Table 9 By Ethnic or Racial Origin

Patients with hemophilia A with or without factor VIII inhibitors[a]		
Racial origin	Patients (N = 417)	PY (total 1258.8)
American Indian or Alaska Native	1	2.1
Asian	93	255
Black or African American	32	93.6
Native Hawaiian or Other Pacific Islander	2	6.4
White	266	827.3
Multiple	2	2.9
Unknown	21	71.6
Patients with hemophilia A with factor VIII inhibitors[a]		
Racial origin	Patients (N = 219)	PY (total 508.8)
American Indian or Alaska Native	1	2.1
Asian	48	123.2
Black or African American	23	57.7
Native Hawaiian or Other Pacific Islander	1	4.2
White	113	295.5
Multiple	2	2.9
Unknown	11	23.1
Patients with hemophilia A without factor VIII inhibitors[a]		
Racial origin	Patients (N = 198)	PY (total k750.1)
American Indian or Alaska Native	0	0
Asian	45	131.8
Black or African American	9	35.9
Native Hawaiian or Other Pacific Islander	1	2.2
White	133	531.7
Multiple	0	0
Unknown	10	48.5

Table 9 By Racial Origin (cont.)

Patients with mild or moderate hemophilia A without factor VIII inhibitors[b]		
Racial origin	Patients (N = 72)	PY (total 76.3)
American Indian or Alaska Native	0	0
Asian	3	2.4
Black or African American	6	7.5
Native Hawaiian or Other Pacific Islander	0	0
White	61	64.3
Multiple	0	0
Unknown	2	2.2

[a]Data are included from Studies BH29884, BH29992, BH30071, BO39182 (N = 399), and ACE002JP (N = 18).

[b]Data are included from Study BO41423 (N=72)

Patient-years is the sum over patients of the time intervals between the start and end of emicizumab treatment.

NE = not evaluable; PY = patient-years

Adapted from: t_ex_paty_inhib_race_SAF, dm11_sp.out and adperiy_sp.out and t_ex_paty_inhib_RACE_P1_TRT_30OCT2021_41423.out

Table 10 Special Population Exposure

Patients with hemophilia A with or without factor VIII inhibitors[a]		
	Patients (N = 417)	PY
Renal impairment (mild or moderate)[1]	30	102.4
Renal impairment (severe)	0	0
Liver impairment (mild or moderate)	60	195.7
Liver impairment (severe)	0	0
Patients with hemophilia A with factor VIII inhibitors[a]		
	Patients (N = 219)	PY
Renal impairment (mild or moderate)[1]	9	26.7
Renal impairment (severe)	0	0
Liver impairment (mild or moderate)	30	75.7
Patients with hemophilia A without factor VIII inhibitors		
	Patients (N = 198)[1]	PY
Renal impairment (mild or moderate)[1]	21	75.6
Renal impairment (severe)	0	0
Liver impairment (mild or moderate)	30	120.1
Patients with mild or moderate hemophilia A without factor VIII inhibitors[b]		
	Patients (N = 72)	PY
Renal impairment (mild or moderate)	4	4.5
Renal impairment (severe)	0	0
Liver impairment (mild or moderate)	8	9.6
Liver impairment (severe)	0	0

Table 10 Special Population Exposure (Cont.)

[a]Data are included from Studies BH29884, BH29992, BH30071, BO39182 (N =399), and ACE002JP (N =18).

[b]Data are included from Study BO41423 (N=72)

[1] Renal impairment defined using Creatine clearance (CLcr) derived from Cockcroft Gault formula as follows: Normal > 90 mL/min; Mild: 60-89 mL/min; Moderate 30-59 mL/min; Severe < 30 mL/min. CLcr in children <12 years was determined using the Bedside Schwartz formula.

[2] Hepatic impairment defined by NCI score based on aspartate aminotransferase (AST) and total bilirubin (TB) as follows: Normal: TB & AST ≤ upper limit of normal (ULN); Mild Garcinia bioflavonoid 1(GB1): TB < ULN, AST > ULN; Mild GB2: TB 1-1.5xULN; Moderate: TB >1.5-3xULN; Severe: TB > 3xULN (Mild GB1, Mild GB2, and Moderate were grouped into one category)

At the time of the clinical data cut-offs of the previous RMP versions, the upper reference range for total bilirubin was lower. This led to a change in the liver impairment classification for one patient, which now falls into the 'normal' category instead of being assigned to "Mild GB2"

Due to inclusion criteria, only patients with adequate renal function or hepatic function were enrolled in the study (see Part II: Module SV - Post-authorization experience). As a result of inclusion criteria and limited number of patients, no patients with severe renal or liver impairment were enrolled.

Patient-years is the sum over patients of the time intervals between the start and end of emicizumab treatment.

PY = patient-years

Adapted from: t_ex_paty_imp_SAF, ACE002JP Interim CSR, t_ex_paty_inhib_RENIMP_P1_TRT_30OCT2021_41423.out, t_ex_paty_inhib_LIVIMP_P1_TRT_30OCT2021_41423.out

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program

Criteria	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
History of hypersensitivity associated with monoclonal antibody therapies or components of the emicizumab injection	This is a contraindication.	No	Contraindication minimizes potential anaphylaxis events. Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions are important potential risks.
Ongoing ITI therapy (Studies BH29884, BH29992 and BO39182 only)	High doses of FVIII could confound safety and efficacy assessments in patients with FVIII inhibitors.	No*	The safety of emicizumab in patients receiving ITI is unknown
Thromboembolic disease: treatment in the last 12 months or current signs	Patients who have current signs of thromboembolic disease or who were treated in the last 12 months are at greater risk of recurrence or exacerbation of thromboembolic disease due to the potential risk associated with emicizumab.	No	No evidence for a risk of thromboembolic disease with emicizumab alone in clinical trials.
Use in patients who are at high risk for TMA (e.g., have a previous medical or family history of TMA), in the investigator's judgement	The exclusion criterion was added to the clinical development program after the occurrence of TMA events in BH29884.	No	Based on the totality of current available data, patients with a previous medical history of TMA or who have hereditary predispositions to TMA, such as ADAMTS13 deficiency or

Criteria	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	Nearly all patients in Study BH29884 enrolled prior to addition of this exclusion criterion, and the criterion was added during enrollment in Study BH29992, BH30071, and BO39182. No patients on any study failed screening due to this exclusion criterion.		complement pathway mutation, would be unlikely to have increased susceptibility to TMA mediated by the drug-drug interaction between emicizumab and aPCC. Past medical history and family history of TMA are included in W&P; however, no further specific clinical actions are recommended and no additional PV activities are planned.
Conditions such as autoimmune or cardiovascular diseases that may increase the risk of bleeding or thrombosis	Conditions that may increase the risk of bleeding could confound efficacy assessments (bleeding rates). Conditions that may increase the risk of thrombosis could confound safety assessments.	No	No evidence for a risk of thromboembolic disease with emicizumab alone in clinical trials. Only the increased risk of thromboembolism associated with emicizumab and aPCC will be a W&P.
Use of systemic immunomodulators (e.g., interferon or corticosteroids)	Concerns that the addition of systemic immunomodulators may confound the safety profile of emicizumab	No	Based on MOA, there is no anticipated reason to expect emicizumab to lead to immunosuppression. There was no evidence of any increased risk of immunosuppression in patients treated with emicizumab.
Planned surgery	Surgery could	No*	There is limited

Criteria	Reason for Exclusion	Is it to be included as missing information? (Yes/No)	Rationale
	confound safety assessments		experience with surgical procedures in the clinical studies (see SVII.3.2). The available data are insufficient to provide specific dosing guidance for the use of FVIII or bypassing agents in the peri-operative setting. Therefore, peri-operative management of patients on emicizumab was included as missing information. Under-treatment with FVIII or bypassing agents may result in uncontrolled peri-operative bleeding that may result in poor outcomes.
Adult female only: Pregnancy or lactation, or intent to become pregnant during treatment. Use highly effective contraception methods	No data available, no animal reproduction study done	No*	Prevalence of severe hemophilia in females is ≤2.4% (See SIV.3). There is no scientific evidence to expect that emicizumab will affect reproductive capacity, cause harm to the fetus when administered to pregnant women or whether it is excreted in human milk.

Table 11 Important Exclusion Criteria in Pivotal Studies in the Development Program (Cont.)

aPCC = activated prothrombin complex concentrate; FVIII = factor VIII; ITI = immune tolerance induction therapy; MOA = mode of action; TMA = thrombotic microangiopathy; W&P = warnings and precautions.

*EU RMP v2.6 was submitted to address recommendations identified during review of the previously submitted EU RMP (v2.5) as per the Pharmacovigilance Risk Assessment Committee (PRAC) Updated Preliminary Assessment Report for procedure EMEA/H/C/004406/II/0021 regarding the removal of the following safety concerns assessed as missing information upon confirmation that they were not in line with GVP Module V (R2): use in female patients, pregnancy and lactation, long-term use of emicizumab, peri-operative management of patients on emicizumab and the safety of emicizumab in patients receiving ITI therapy.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Limitations of adverse drug reaction (ADR) detection in the clinical development program in hemophilia A are discussed in Table 12.

Table 12 Limitations of ADR Detection Common to Clinical Trial Development Programs

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
Which are rare	The emicizumab safety population provides data from -489 patients with 1335.2 PY of exposure from studies BH29884, BH29992, BH30071, BO39182 (N = 399; 1199.5 PY), BO41423 (N=72; 76.3 PY) and ACE002JP (N = 18; 59.4 PY). There is the potential that rare and very rare ADRs have not been observed within the emicizumab clinical trial program.	The number of patients exposed is insufficient to detect uncommon (frequency of ≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000) serious adverse events. There is a potential that a patient treated with emicizumab could experience a rare or uncommon ADR, which has not previously been seen within the clinical trial program. Rare AEs may emerge with increasing use of emicizumab. Routine and additional PV activities are in place to monitor AEs experienced by patients in the post-marketing setting.
Due to prolonged exposure	A total of 399 patients were exposed to emicizumab in studies BH29884, BH29992, BH30071 and BO39182. Mean (SD) duration of exposure was 156.9 (78.4) weeks. Median duration of exposure was 130.7 weeks of exposure (range 3.4 – 287.1). In these phase III studies, 97.5% of patients (389/399) had > 52 weeks of exposure to emicizumab. The mean (SD) duration of exposure in Study ACE002JP was 172.24 (68.76) weeks and the median duration of exposure was 196.79 (range 4.1 – 225.1) weeks. All 16 patients from ACE001JP who entered the extension Study ACE002JP were still on emicizumab at the time of study completion and, therefore, were exposed for more than 3 years.	As hemophilia A is a chronic disease, there is an expectation that patients may receive treatment with emicizumab for a period of years. There is a potential that patients treated with emicizumab for prolonged period could experience ADRs either not previously seen within the clinical trial program, or known ADRs at an increased frequency. Rare AEs may emerge with increasing use of emicizumab. Routine and additional PV activities are in place to monitor AEs experienced by patients in the post-marketing setting.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	In Study BO41423, 72 patients were exposed to emicizumab, with a mean (SD) exposure period of 55.28 (11.71) weeks and a median of 54.29 (range 8.1 - 89.1) weeks.	
Due to cumulative effects	The mean (SD) number of emicizumab doses administered in studies BH29884, BH29992, BH30071 and BO39182 was 126.4 (73.9) doses and the median was 108.0 (range 4–288) doses. The mean (SD) total cumulative dose was 17931 (12651) mg. The median total cumulative dose was 13344 (range 839 – 70875) mg. In Study ACE002JP, the mean (SD) number of emicizumab doses administered was 176.8 (64.3) doses and the median was 194.5 (range 4 – 225) doses. The mean (SD) total cumulative dose was 18,271.2 (13,314.2) mg and the median total cumulative dose was 15,863.6 (range 313.6 – 40,349.6) mg. In Study BO41423, 72 patients were exposed to emicizumab with the mean (SD) total cumulative dose was 6430.97 (2973.56) mg and the median total cumulative dose was6466.50 (range 1230.0 - 14349.0) mg.	There is a potential that a hemophilia A patient treated with emicizumab could experience ADRs either not previously seen within the clinical trial program or known ADRs at an increased frequency due to cumulative effects of repeated exposure to emicizumab.
Which have a long latency	A total of 471 patients were exposed to emicizumab in the studies BH29884, BH29992, BH30071, BO39182 and BO41423. In Study ACE002JP, a total of 18 patients were exposed to emicizumab, 16 of whom were included in the study extension and thus had longer exposures. Due to the difference of emicizumab treatment period between the studies, the latency data are	There is a potential that a hemophilia A patient treated with emicizumab with an exposure longer than that of the currently available data could experience an ADR with a long latency which has not yet been observed at a true rate within the clinical trial program.

Ability to detect adverse reactions	Limitation of trial program	Discussion of implications for target population
	presented by study. In BH29884, 112 patients were exposed to emicizumab, with a mean (SD) exposure period of 127.99 (53.01) weeks and a median of 110.64 (range 3.4 – 249.1) weeks. In BH29992, 88 patients were exposed to emicizumab, with a mean (SD) exposure period of 101.86 (42.13) weeks and a median of 91.64 (range 15.0 – 187.7) weeks. In BH30071, 151 patients were exposed to emicizumab, with a mean (SD) exposure period of 201.28 (79.72) weeks and a median of 249.14 (range 6.1 – 287.1) weeks. In BO39182, 48 patients were exposed to emicizumab, with a mean (SD) exposure period of 185.28 (84.14) weeks and a median of 242.14 (range 71.9 – 272.3) weeks. In ACE002JP, the median administration period was 222.14 (range 220.3 – 225.1) weeks, 196.79 (range 4.1 – 204.1) weeks, and 173.57 (range 12.1 – 178.4) weeks for the 0.3, 1, and 3 mg/kg/week groups, respectively. In BO41423, 72 patients were exposed to emicizumab, with a mean (SD) exposure period of 55.28 (11.71) weeks and a median of 54.29 (range 8.1 - 89.1) weeks.	

Serious adverse events frequency: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000), or very rare (< 1/10,000)

ADR = adverse drug reaction; AE = adverse event; SD = standard deviation; PY = patient-years.

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAM

Limitations in respect to populations not studied or understudied in the clinical development program in hemophilia A are discussed below and summarized in Table 13. No studies were performed in special populations.

Table 13 List of Populations included or not in clinical trial development program

Type of special population	Any included in pre-authorization clinical development program?	Exposure
Pregnant women	No	N/A
Breastfeeding women	No	N/A
Patients with relevant comorbidities[1]		
Patients with liver impairment (mild GB1 and GB2)	Yes	60 patients, 182.9 PY
Patients with liver impairment (moderate)	Yes	8 patients, 22.7 PY
Patients with renal impairment (mild)	Yes	31 patients, 96.9 PY
Patients with renal impairment (moderate)	Yes	3 patients, 10.0 PY
Patients with cardiac impairment	No	N/A
Patients with a disease severity different from inclusion criteria in clinical trials	No	N/A
Population with relevant different ethnic origin[2]	Yes	See Table 9

Data are included from Studies BH29884, BH29992, BH30071, BO39182 (N = 399), StudyACE002JP (N = 18), and Study BO41423 (N=72).

[1] Renal impairment defined using Creatine clearance derived from Cockcroft Gault formula as follows: Normal > 90 mL/min; Mild: 60-89 mL/min; Moderate 30-59 mL/min; Severe < 30 mL/min. CLcr in children <12 years was determined using the Bedside Schwartz formula.

Hepatic impairment defined by NCI score based on aspartate aminotransferase (AST) and total bilirubin (TB) as follows: Normal: TB & AST ≤ Upper limit of normal; Mild Garcinia biflavonoid 1 (GB1): TB < ULN, AST > ULN; Mild GB2: TB 1-1.5xULN; Moderate: TB > 1.5-3xULN; Severe: TB > 3xULN.

[2] All ethnicities were represented and the efficacy and safety profiles are not expected to be different between ethnicities.

PY = patient-years

Use in Female Patients, Pregnancy and Lactation

Hemophilia A is extremely rare in women. According to the most recent global hemophilia survey (WFH 2017), 3% of patients with hemophilia A (congenital disease and acquired hemophilia A) were reported to be female. This would equate to a prevalence in developed countries of approximately 0.2 to 0.6 per 100,000 women. Furthermore, when presenting in women, hemophilia A tends to exhibit a mild phenotype

due to heterozygosity of the aberrant FVIII gene. The WFH reports that, in developed countries (where ascertainment is highest), 86.7% of cases in women are mild, 2.1% moderate, 2.4% severe, and 5.1% unknown (WFH 2017).

Although female patients could be enrolled in the studies (except those who were pregnant, lactating, or intending to become pregnant), no female patients with hemophilia A were enrolled in the Studies BH29884, BH29992, BH30071, BO39182 or ACE002JP because of the rarity of the disease in women. Three female patients were enrolled in BO41423.

It is not known whether emicizumab can cross the placenta or cause harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. As with other IgG antibodies, emicizumab is however thought to be able to cross the placenta. Therefore, emicizumab should not be administered to pregnant women. Women of childbearing potential who are receiving or have received emicizumab prophylaxis should use effective contraception during, and for at least 6 months after cessation of emicizumab treatment. Although embryofetal development studies are not available, condom use will not be required in male patients as the margin between the minimal anticipated biological effect level (MABEL) plasma concentration (7 ng/mL) and the estimated maternal $C_{max,}$ as a consequence of seminal fluid-related exposure at 3 mg/kg/week dosing regimens (which provided the highest exposure tested in clinics), is greater than 10-fold (Banholzer et al. 2012).

It is not known whether emicizumab is excreted in human milk. However, IgG is generally known to be excreted in breast milk. Because many drugs are excreted in human milk and because of the potential for serious ADRs in nursed infants, emicizumab should not be administered to nursing mothers.

Data on this special population will be monitored as part of routine pharmacovigilance activities; however, it is anticipated, for reasons related to the underlying genetics of hemophilia A (as described earlier), that the number of patients at-risk is too small to collect meaningful data.

Neonates and Infants

Across Studies BH29884, BH29992, BH30071, BO39182, BO41423 and ACE002JP, there were no patients <1 year of age included. Available data from 10 patients ≤ 2 years of age from Study BH29992, including 5 patients aged 1 to <2 years of age, demonstrated no effect of age on the pharmacokinetics or the safety and efficacy profile of emicizumab, and no dose adjustment was required in these patients.

The investigation of the safety and efficacy of emicizumab in neonates and infants is currently ongoing in Study MO41787 (HAVEN 7), a Phase IIIb, multicenter, open-label, single-arm study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in patients from birth to ≤12 months of age with

severe hemophilia A without FVIII inhibitors. As of 22 May 2023, data from 55 patients has shown that the safety profile of emicizumab in patients ≤12 months is similar to that in adolescent and adult patients. Patients enrolled in Study MO41787 will undergo long-term safety follow-up for seven years. Thus safety data in neonates and infants is still considered missing information at this time.

Hemophilia A is a bleeding disorder that is attributable to a congenital absence or hypofunction of FVIII, regardless of age. Therefore emicizumab is expected to be efficacious irrespective of the patient's age.

Elderly Patients

Emicizumab has not been investigated in a dedicated study in elderly patients. Fifteen patients ≥ 65 years have been enrolled and treated in the phase III studies (BH29884, N = 5; BH30071, N = 5; BO39182, N = 3; BO41423, N = 2). Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients < 65 years and patients ≥ 65 years. No dose adjustment is suggested or required in patients aged 65 years and older. No differences in efficacy or safety were observed compared to patients < 65 years of age.

Renal Impairment

Emicizumab is a monoclonal antibody; therefore, it is cleared via catabolism rather than renal excretion. Only a few patients with mild or moderate renal impairment (31 and 3 patients, respectively; based on creatinine clearance) have been enrolled in the studies BH29884, BH29992, BH30071, BO39182, BO41423 and ACE002JP. No patients with severe renal impairment have been enrolled in the studies. Mild or moderate renal impairment did not affect emicizumab pharmacokinetics. Emicizumab has not been investigated in a dedicated study in patients with renal impairment, as there are no specific anticipated risks to this population related to prophylaxis with emicizumab. No dose adjustments are recommended in patients with mild or moderate renal impairment.

Liver Impairment

Emicizumab has not been investigated in a dedicated study in patients with liver impairment, as there are no specific anticipated risks to this population related to prophylaxis with emicizumab.

Emicizumab is a monoclonal antibody; therefore, it is not metabolized by the liver. There is no target-mediated disposition of emicizumab. A reduced hepatic production of several coagulation factors, including FIX and FX, is expected with liver impairment. Such a reduction of hepatic production does not affect the metabolism of emicizumab but may affect its pharmacodynamics.

A total of 68 patients with mild or moderate liver impairment based on NCI criteria have been enrolled in the Studies BH29884, BH29992, BH30071, BO39182, BO41423 and ACE002JP. Mild or moderate liver impairment did not affect emicizumab

pharmacokinetics. Pharmacokinetic profiles in patients with mild or moderate liver impairment did not differ from the rest of the population. Likewise, there were no unique safety signals in this population. No dose adjustments are recommended in patients with mild or moderate liver impairment.

Cardiac Impairment

Emicizumab has not been investigated in a dedicated study in patients with cardiac impairment, as there are no specific anticipated risks to this population related to prophylaxis with emicizumab. Inclusion of patients with cardiovascular disease was only allowed if the cardiovascular condition would not increase the risk of bleeding or thrombosis. A limited number of patients with cardiovascular disease were enrolled in Studies BH29884, BH29992, BH30071, BO39182, BO41423 and ACE002JP. Data on this special population will be monitored as part of routine pharmacovigilance activities.

Patients With a Disease Severity Different from the Inclusion Criteria in the Clinical Trial Population

All patients enrolled in BH29884, BH29992, BH30071 and BO39182 were considered to have severe hemophilia A (11 patients were mild and moderate at diagnosis; however, all of these patients had inhibitors and therefore had severe phenotypes). Patient populations with low and high inhibitor titers at baseline were included in the studies BH29884, BH29992 and BO39182. Patients with inhibitors included in studies BH29884 and BH29992 were required to have a documented history of high-titer inhibitors ($\geq$ 5 BU). All patients enrolled in BO41423 had mild or moderate hemophilia A without inhibitors (21 patients were mild and 51 patients were moderate at diagnosis). All patients had a documented history of prophylactic or episodic FVIII treatment in the 24 weeks prior to study entry. In ACE002JP, all but one patient had severe hemophilia and all patients with inhibitors had history of titers $\geq$ 5 BU.

Sub-populations Carrying Known and Relevant Polymorphisms

Information regarding patients' *F8* genotypes was not collected in the emicizumab studies. Patients were included based on documented diagnosis of congenital hemophilia A. It is expected that the efficacy and safety profiles of patients with emicizumab prophylaxis will not be affected by *F8* genotype differences, as its mechanism of action is independent of FVIII.

Patients of Different Racial and/or Ethnic Origin

Despite the overall small number of patients treated with emicizumab, most races and ethnicities were represented in the clinical studies. No appreciable differences were observed in the AE profile of emicizumab as a function of race.

CONCLUSIONS ON MISSING INFORMATION FROM THE CLINICAL TRIAL PROGRAM

Table 14 Missing information*^

Safety concerns due to limitations of the clinical trial program		Outstanding concern?
Safety Concern	**Comment**	
Use in Neonates and Infants	Based on recruitment feasibility limitations: interim data on children was needed before opening enrollment to patients <2 years of age using the same dosing regimen used for children, adolescents, and adults. Enrollment to Study BH29992 was opened to patients <2 years on 7 December 2016; data are available from 5 patients <2 years of age. No patients <1 year of age were included. The investigation of the safety and efficacy of emicizumab in neonates and infants is currently ongoing in Study MO41787 (HAVEN 7), a Phase IIIb, multicenter, open-label, single-arm study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in patients from birth to ≤12 months of age with severe hemophilia A without FVIII inhibitors. As of 22 May 2023, data from 55 patients has shown that the safety profile of emicizumab in patients ≤12 months is similar to that in adolescent and adult patients. Patients enrolled in Study MO41787 will undergo long-term safety follow-up for seven years. Thus safety data in neonates and infants is still considered missing information at this time.	Yes, included in this RMP as missing information

*In EU RMP v2.4, Use in elderly patients, was removed as missing information in accordance with a request as part of Type II variation (EMEA/H/C/004406/II/0002) and the following changes in the level of scientific evidence for the causal association or benefit-risk impact: Thirteen

patients ≥65 years have been enrolled and treated in the Phase III studies (BH29884 n=5; BH30071 n=5; BO39182 n=3). There are no data in patients over 77 years old. Relative bioavailability decreased with older age, but no clinically important differences were observed in the pharmacokinetics of emicizumab between patients <65 years and patients ≥65 years. No dose adjustment is suggested or required in patients aged 65 years and older. No differences in efficacy or safety were observed compared to patients < 65 years of age. There is no anticipated risk in the elderly patient population.

^ EU RMP v2.6 was submitted to address recommendations identified during review of the previously submitted EU RMP (v2.5) as per the Pharmacovigilance Risk Assessment Committee (PRAC) Updated Preliminary Assessment Report for procedure EMEA/H/C/004406/II/0021 regarding the removal of the following safety concerns assessed as missing information upon confirmation that they were not in line with GVP Module V (R2): use in female patients, pregnancy and lactation, long-term use of emicizumab, peri-operative management of patients on emicizumab and the safety of emicizumab in patients receiving ITI therapy.

PART II: MODULE SV - POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method Used to Calculate Exposure

Emicizumab was first approved on 16 November 2017 (IBD).

Information on methodology used to calculate exposure is provided in the Periodic Benefic–Risk Evaluation Report 1126611 (PBRER) Section 5.2.1. For all territories, patient exposure is defined as summation of new and maintenance patient number whereas cumulative patient exposure includes new, maintenance as well as patients who have discontinued emicizumab.

Sources of patient counts are still different among regions as the goal is to utilize the methodology, which gives the most reliable regional estimates.

- Chugai utilizes field force reports for Japan, Taiwan, and South Korea
- US reports the patient numbers via sales data analysis, consistent with the EU approach, and this is evidenced by secondary claims data through the brand's market patient share. In addition, the US uses claims data for the latest assumptions.
- EEA and ROW countries excluding Russia utilize volume sales to estimate the patient numbers in the vast majority of countries it represents.

SV.1.2 Exposure

Emicizumab was first approved on 16 November 2017 (IBD). Since the IBD of 16 November 2017 an estimated total of 27,675 patients have received emicizumab from marketing experience; see Annex 7d for further details.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 POTENTIAL FOR MISUSE FOR ILLEGAL PURPOSES

No dedicated studies on the potential for emicizumab to cause dependence have been performed. However, from the available data, there is no evidence that emicizumab treatment results in dependence. Distribution studies were not performed. However, it is expected that only traces of emicizumab can cross the blood-brain barrier, as immunoglobulins have limited ability to cross this barrier (endogenous IgG levels in cerebrospinal fluid are approximately 0.1 to 1% of serum levels) (Roskos et al. 2004). On the basis of its pharmacological and pharmacokinetic properties, the risk of abuse or misuse of emicizumab is low.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

SVII.1.1 Risks Not Considered Important for Inclusion in the List of Safety Concerns in the RMP

Reason for NOT including an identified or potential risk in the list of safety concerns in the RMP:

The following risk included in the SmPC is expected to have minimal impact on patients in relation to the severity of hemophilia A:

- Injection-site reactions.

Adverse reactions with clinical consequences, even serious, but occurring with a low frequency and are considered to be acceptable in relation to the severity of the indication treated:

- Thromboembolic events associated with concomitant use of rFVIIa.

SVII.1.2 Risks Considered Important for Inclusion in the List of Safety Concerns in the RMP

Important Identified Risk: Thromboembolic Events (Associated With Emicizumab and APCC)

Risk-benefit impact: Out of the 141 patients exposed to emicizumab, 1.4% (2/141) experienced at least one thromboembolic event following treatment with aPCC. Overall, out of the 34 patients who received aPCC while on emicizumab prophylaxis, 5.88% (2/34) experienced at least one thromboembolic event. Average cumulative doses of aPCC $>$ 100 U/kg/24 hours for 24 hours or more were administered prior to the onset of these events in both patients. In both patients (and in all 3 events), the thromboembolic events were reported as SAEs (with a severity grade $\leq$ 3). One patient had a dose interruption and the other had a dose discontinuation. The thromboembolic events were not life-threatening or fatal in either patient. Neither patient required anticoagulation therapy.

Important Identified Risk: Thrombotic Microangiopathy (Associated With Emicizumab and APCC)

Risk-benefit impact: At the data cut-off date used for this RMP, out of the 141 patients exposed to emicizumab, 1.4% (2/141) experienced a TMA event following treatment with aPCC. Overall, out of the 34 patients who received aPCC while on emicizumab prophylaxis, 5.88% (2/34) experienced a TMA event. Both TMA events were assessed as SAEs (Grade 3 and Grade 4 in intensity, and related to study treatment). One patient had a dose interruption and the other had a dose discontinuation.

After the data cut-off date used for this RMP, a third patient experienced a TMA event. In this case, the patient also experienced rectal hemorrhage with a fatal outcome. The

investigator assessed the patient's death as related to the SAE of rectal hemorrhage and unrelated to emicizumab, and the TMA as related to emicizumab and aPCC.

For all three patients who experienced a TMA event (including the patient with the event occurring after the clinical cut-off date), average cumulative doses of aPCC $>$ 100 U/kg/24 hours for 24 hours or more were administered prior to the onset of these events.

Important Potential Risk: Life-threatening Bleeding Due to Misinterpretation of the Standard Coagulation Tests, Which Are Unreliable in Patients Treated With Emicizumab

Risk-benefit impact: Multiple coagulation laboratory tests (including, but not limited to, aPTT, FVIII activity, and FVIII inhibitor measurement by Bethesda assay; see SmPC) are unreliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis. Laboratory coagulation test interference by emicizumab is an issue for *in vitro* testing for all standard assays (approved for diagnostic use) based on aPTT reagents.

The risk was well-managed in emicizumab clinical trials due to adequate training of the investigators. There have been no reports of bleeding events that were not treated because of laboratory test interference in emicizumab clinical trials.

It is anticipated that, in the market setting, there is a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests and inhibitor assays, which are unreliable in the setting of emicizumab if a patient is treated by healthcare professionals (HCPs) other than the emicizumab-prescribing HCP in settings such as the emergency room or in an acute care setting. Therefore, this risk was categorized as an important potential risk.

Important Potential Risk: Anaphylaxis, Anaphylactoid and Systemic Hypersensitivity Reactions

Risk-benefit impact: Across the studies, 2 cases (one patient in Study BH29884) were identified using a systemic search based on Sampson criteria. However, medical review of these cases determined that these events were not indicative of an anaphylactic, anaphylactoid, or systemic hypersensitivity reaction. No cases were reported through expedited reporting of SAEs and/or AESIs in the pivotal Phase III studies (BH29884 and BH29992) and the supportive study (ACE002JP). Therefore, the frequency for AEs/SAEs related to development of anaphylaxis, anaphylactoid and systemic hypersensitivity events was 0.0% (0 AEs /141 patients).

Systemic hypersensitivity reactions, including fatal or life-threatening anaphylactic reactions, may occur with biological products such as emicizumab. Therefore, it is as an important potential risk due to the class effect of subcutaneously administered monoclonal antibodies.

Important Potential Risk: Immunogenicity

Risk-benefit impact: Across the studies, 4 patients (all in ACE002JP) developed anti-therapeutic antibodies (ATAs); however, they were all non-neutralizing. There were no AEs/SAEs reported related to developing ATAs. Therapeutic proteins have the potential to elicit unwanted immune responses, which may affect pharmacokinetics, pharmacodynamics, safety, and/or efficacy of the molecule to various degrees. The presence of ATAs is not always of clinical relevance but may also result in the formation of circulating immune complexes with generalized hypersensitivity reactions (Types 1 or 3) and/or tissue deposition with consequences for specific organs.

Immunogenicity is a class effect of subcutaneously administered monoclonal antibodies. Therefore, it is categorized as an important potential risk.

Missing Information: Use in Female Patients, Pregnancy and Lactation

Risk-benefit impact: It is not known whether emicizumab crosses the placenta or causes harm to the fetus when administered to pregnant women or whether it affects reproductive capacity. As with other IgG antibodies, emicizumab is thought to be able to cross the placenta. It is not known whether emicizumab is excreted in human milk. However, IgG is generally known to be excreted in breast milk. Emicizumab should not be administered to pregnant women. Women of childbearing potential who are receiving or have received emicizumab prophylaxis should use effective contraception during, and for at least 6 months after cessation of emicizumab treatment. Because many drugs are excreted in human milk, emicizumab should not be administered to nursing mothers.

Data on this special population will be monitored as part of routine pharmacovigilance activities; however, it is anticipated that the number of patients at-risk is too small to collect meaningful data.

Missing Information: Use in Neonates and Infants

Risk-benefit impact: The investigation of the safety and efficacy of emicizumab in children aged $\leq$2 years old with hemophilia A with FVIII inhibitors is currently ongoing and data are not yet available. Data on patients below 2 years old should be available upon completion of the ongoing study in children (BH29992).

Missing Information: Use in Elderly Patients

Risk-benefit impact: Emicizumab has not been investigated in a dedicated study in elderly patients. Pharmacokinetic profiles in elderly patients (3 patients$\geq$65 years) did not differ from the rest of the population. Age had no relevant effect on emicizumab pharmacokinetics. Likewise, safety and efficacy data in this small number of elderly patients were similar to patients $<$ 65 years. No dose adjustment is suggested or required in patients aged 65 years or older.

Missing Information: Long-term Use of Emicizumab

Risk-benefit impact: There is no exposure of patients to emicizumab longer than 177 weeks. Additional information will be obtained by routine PV activities

Missing Information: Peri-operative Management of Patients on Emicizumab

Risk-benefit impact: There is a gap of knowledge in the peri-operative management of patients on emicizumab. The available data are insufficient to provide specific dosing guidance for the use of aPCC or other bypassing agents in the peri-operative setting. Therefore, peri-operative management of patients on emicizumab was included as missing information. Under-treatment with bypassing agents may result in peri-operative bleeding that may result in poor outcom

Missing Information: Safety of Emicizumab in Patients Receiving ITI

Risk-benefit impact: ITI is used in the general practice setting. The available data are insufficient to provide safety information in patients receiving ITI. Therefore, this is included as missing information. Additional information will be obtained by routine PV activities.

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

Not applicable.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED AND POTENTIAL RISKS AND MISSING INFORMATION

SVII.3.1 Presentation of Important Identified Risks and Important Potential Risks

Table 15 Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC)

Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC)	
Potential mechanisms	The leading hypothesis is that both thromboembolic and thrombotic microangiopathy events have been mediated by temporarily increased FIXa-emicizumab-FXa ternary complex formation on the surface of a phospholipid bilayer and excessive thrombin generation, with localization to certain microvascular beds (see Table 16).
Evidence source and strength of evidence	Evidence is based on the Phase III studies (BH29884, BH29992, BH30071, and BO39182; N = 399), BO41423 (N=72) and the Phase I/II study (ACE002JP; N = 18) of emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors. Overall, 6.25% of patients (2/32) who received aPCC while on emicizumab prophylaxis across the Phase III studies had at least one event for this important identified risk of thromboembolic event (associated with emicizumab and aPCC); there were no patients (0/5; 0%) with such an event in Study ACE002JP.
Characterization of the risk	A total of 489 patients were exposed to emicizumab in the Phase III studies BH29884, BH29992, BH30071, BO39182 and the Phase I/II Study ACE002JP. In Studies BH29884, BH29992, BH30071, and BO39182, out of 399 patients receiving emicizumab, 0.5% (2/399) had at least one thromboembolic event associated with the concomitant use of emicizumab and aPCC. There were no thromboembolic events associated with aPCC reported from Study BO41423* (N=72) as of CCOD (30 Oct 2021). Overall, out of the 32 patients who received at least 1 dose of aPCC while on emicizumab prophylaxis in Studies BH29884 and BH29992 (no patients received aPCC in BH30071 or BO39182), 6.25% (2/32) had at least one thromboembolic event associated with emicizumab and aPCC. Both patients were enrolled in Study BH29884. The investigator assessed the thromboembolic events as related to the use of emicizumab and aPCC. The 2 patients that experienced thromboembolic events associated with emicizumab and aPCC did so when on average a cumulative dose of > 100 U/Kg/24 hours of aPCC for 24 hours or more was administered during a treatment episode. In the Phase III studies, there were 86 instances of aPCC treatment[1], of which 82 were in Studies BH29884 and 4 were in Study BH29992. Of these, 8 instances consisted of on

Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC)	
	average a cumulative aPCC dose of > 100 U/kg/24 hours for 24 hours or more, all of which occurred in Study BH29884. In Study ACE002JP, 5/18 patients receiving emicizumab received at least 1 dose of aPCC while on emicizumab prophylaxis, and no patients experienced a thromboembolic event associated with the concomitant use of aPCC. In Study ACE002JP, no patients received a dose of aPCC > 100 U/kg/24 hours while receiving emicizumab. No cases of thromboembolic events have been observed in patients who received emicizumab and concomitant rFVIIa alone or FVIII alone, or who were treated with single doses of aPCC up to 100 U/kg per infusion. In both patients experiencing thromboembolic events associated with emicizumab and aPCC, the AEs were reported as SAEs. Out of the 2 patients who experienced at least one thromboembolic event associated with emicizumab and aPCC: • One patient had dose interruption and the other discontinued. • Neither patient received anticoagulation (only supportive care) to treat their thromboembolic event. • At the time of data cut-off, these events had resolved and both patients were reported to have recovered. The thromboembolic events associated with emicizumab and aPCC were not life-threatening or fatal in either patient. A summary of these two patients is provided below: • One patient experienced 2 SAEs contemporaneously, the SAEs were skin necrosis (severity: Grade 3) and thrombophlebitis superficial (severity: Grade 2); the events were diagnosed after the patient received 101 units/kg/day of aPCC on 2 consecutive days to treat a spontaneous right knee hemarthrosis (onset Study Day 145) and a spontaneous shin bleed (onset Study Day 146). Emicizumab treatment was permanently discontinued, and aPCC was discontinued. The patient received supportive therapy and did not receive anticoagulation and, at the time of the data cut-off, the events had resolved and the patient had recovered. • In the second patient, the SAE of cavernous sinus thrombosis (severity: Grade 3) was diagnosed on Study Day 134 after the patient received aPCC for 4 consecutive days to treat a knee joint bleed, during which he used > 200 units/kg/day of aPCC for 2 consecutive days. Emicizumab prophylaxis was interrupted, and aPCC was discontinued. The event resolved without anticoagulation on Study Day 151. Emicizumab treatment was restarted on Study Day 162, and there was no recurrent thromboembolic event.

Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC)	
Risk groups or risk factors	Both patients who experienced thromboembolic events associated with emicizumab and aPCC received multiple doses of aPCC for the treatment of breakthrough bleeds just prior to developing symptoms. From additional analyses including data on thromboembolic and TMA events, the Sponsor concludes that there is sufficient evidence to support a DDI between aPCC and emicizumab (see Table 16). This interaction is primarily based on the dose and time interval over which aPCC is administered, with average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more associated with an increased risk for developing thromboembolic and TMA events.
Preventability	This risk is manageable and can be minimized by providing guidance for use of bypassing agents including aPCC (see below). This risk has only been observed in patients that have received average cumulative doses of aPCC exceeding 100 U/kg/24 hours for 24 hours or more. Patients receiving emicizumab prophylaxis should be monitored for the development of thromboembolism when administering aPCC. The physician should immediately discontinue aPCC and interrupt emicizumab therapy if clinical symptoms, imaging, and/or laboratory findings consistent with thrombotic events occur, and manage as clinically indicated. Physicians and patients/caregivers should weigh the benefits and risks of resuming emicizumab prophylaxis following resolution of thrombotic events on a case-by-case basis. In case a bypassing agent is indicated in a patient receiving emicizumab prophylaxis, see below for dosing recommendations for use of bypassing agents. ***Guidance on the use of bypassing agents in patients receiving emicizumab prophylaxis:*** Treatment with bypassing agents should be discontinued the day before starting emicizumab therapy. Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving emicizumab prophylaxis. Emicizumab increases the patient's coagulation potential. The bypassing agent dose required may therefore be lower than that used without emicizumab prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding, and on the patient's clinical condition. Use of aPCC should be avoided unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving emicizumab prophylaxis, the initial dose should not exceed 50 U/kg and laboratory monitoring is recommended (including but not restricted to renal monitoring, platelet testing and evaluation of thrombosis). If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision with consideration made to laboratory monitoring and verification of

Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC)	
	bleeds prior to repeated dosing. The total aPCC dose should not exceed 100 U/kg in the first 24-hours of treatment. Treating physicians must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24-hours. In clinical trials, no cases of thrombotic microangiopathy or thrombotic events were observed with use of rFVIIa or FVIII alone in patients receiving emicizumab prophylaxis. If patients require bypassing agents in the peri-operative setting, it is recommended that the dosing guidance above for aPCC be followed. Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of emicizumab prophylaxis. In addition to routine risk minimization activities, additional risk minimization measures to include (see Part V for details): • Guide for Healthcare Professionals. • Patient Card. • Patient/Carer Guide. Effectiveness of the risk mitigations measures monitored via educational material distribution metrics and Study BO40853 (completed) (see Part V.2).
Impact on the benefit-risk balance of the product	Thromboembolic events encompass a broad scope of events. In clinical trials, patients have reported SAEs, such as cavernous sinus thrombosis and thrombophlebitis superficial, related to thromboembolic events. In both patients who experienced at least one thromboembolic event the AEs were reported as SAEs • One patient had dose interruption. • One patient discontinued treatment. Based on the review of these events: • A dosing guide for use of bypassing agents was included in the SmPC. • and the following educational materials were prepared: o Guide for Healthcare Professionals o Patient Card. o Patient/Carer Guide.
Public health impact	The incidence of hemophilia A is estimated to be approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 417 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27)

Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC)	
	(Eurostat2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000 males with severe hemophilia A. The current estimated number of patients with hemophilia A is 320,000 globally and 21,780 in the EU-5 countries. It is estimated that there are between 6400 and 16,000 hemophilia A patients with inhibitors worldwide. Due to the rarity of hemophilia A patients with FVIII inhibitors, who are almost exclusively the only patient population likely to receive aPCC and emicizumab, no impact on public health is expected.

[1] An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break. It includes all instances of aPCC treatment excluding those in the first 7 days and those that occurred 30 days after the discontinuation of emicizumab.

AE = adverse event; aPCC = activated prothrombin complex concentrate; DDI = drug-drug interaction; EUHASS = European Haemophilia Safety Surveillance; FVIII = factor VIII; MAH = market authorization holder; MOA = mode of action; rFVIIa = recombinant factor VIIa; SAE = serious adverse event; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy.

*BO41423: is a study in patients with hemophilia A without inhibitors. These patients are not treated with aPCC.

Table 16 Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
Potential mechanisms	The pathophysiological mechanism(s) by which the posited drug-drug interaction between emicizumab and aPCC results in thrombotic microangiopathy events has not yet been fully elucidated. The leading hypothesis is that both thromboembolic and thrombotic microangiopathy events have been mediated by temporarily increased FIXa-emicizumab-FXa ternary complex formation on the surface of a phospholipid bilayer and excessive thrombin generation, with localization to certain microvascular beds. Emicizumab likely has a unique interaction with aPCC, due to the inclusion of emicizumab's substrates within aPCC, as well as other coagulation factors with long half-lives (e.g., prothrombin) that accumulate with repeated dosing (Sørensen et al. 2011). It is conceivable that, in addition to the independent, procoagulant effects of aPCC, the presence of FIX, FIXa, FX, and FXa (included at low levels in aPCC, which primarily contains prothrombin complex zymogens) may increase the frequency and concentration of enzyme (FIXa)-cofactor (emicizumab)-substrate (FX) complex formation in a dose-dependent manner, resulting in an increase in emicizumab's cofactor activity and capacity to generate thrombin. In contrast, rFVIIa does not directly impact emicizumab's potential to form the intrinsic tenase complex, which is in agreement with clinical results showing that thromboembolic and thrombotic microangiopathy events were associated with high cumulative doses of concomitant aPCC treatment but not rFVIIa treatment. This hypothesized coagulation-mediated mechanism of action is further supported by in vitro and in vivo studies which showed enhanced thrombin generation (in vitro) or enhanced provoked thrombus formation (in vivo) with the concomitant use of emicizumab with either rFVIIa or aPCC. The clinical course of the thromboembolic and thrombotic microangiopathy events in Study BH29884 is not consistent with that of typical thromboembolism (e.g., deep vein thrombosis [DVT]/pulmonary embolism [PE]) and thrombotic microangiopathy events; the thromboembolic events did not require treatment with anticoagulation and the thrombotic microangiopathy events started to resolve within 1 week following discontinuation of aPCC. The latter finding argues against mechanistic processes that involve autoantibodies against von Willebrand factor cleaving proteases (i.e., thrombotic thrombocytopenic purpura) or dysregulation of the alternative complement pathway (i.e., atypical hemolytic uremic syndrome), both of which are generally associated with prolonged systemic therapeutic interventions before remission can be achieved.

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
	Other potential mechanisms of action of thrombotic microangiopathy associated with the use of aPCC and emicizumab cannot be completely ruled out as an explanation for the interaction between emicizumab with aPCC at this time.
Evidence source and strength of evidence	Evidence is based on the Phase III studies (BH29884, BH29992, BH30071, and BO39182; N = 399), BO41423 (N=72) and the Phase I/II study (ACE002JP; N = 18) of emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors. Overall, 9.4% of patients (3/32) who received at least 1 dose of aPCC while on emicizumab prophylaxis across the Phase III studies had an event for this important identified risk of TMA (associated with emicizumab and aPCC); there were no patients (0/5; 0%) with such an event in Study ACE002JP.

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
Characterization of the risk	Of the 399 patients exposed to emicizumab in the Phase III studies BH29884, BH29992, BH30071, and BO39182, 0.75% (3/399) experienced a TMA event associated with the concomitant use of emicizumab and aPCC. There were no TMA events reported from Study BO41423* (N=72) as of the study CCOD (30 Oct 2021). Overall, out of the 32 patients who received at least 1 dose of aPCC while on emicizumab prophylaxis in Studies BH29884 and BH29992 (no patients received aPCC in BH30071 or BO39182), 9.4% (3/32) had at least one TMA event associated with aPCC and emicizumab. All 3 patients were enrolled in Study BH29884. In BH29884, the 3 patients who experienced TMA events associated with emicizumab and aPCC did so when on average a cumulative dose of > 100 U/Kg/24 hours of aPCC for 24 hours or more was administered during a treatment episode. In the Phase III studies, there were 86 instances of aPCC treatment[1], of which 82 were in Studies BH29884 and 4 were in Study BH29992. Of these, 8 instances consisted of on average a cumulative aPCC dose of > 100 U/kg/24 hours for 24 hours or more, all of which occurred in Study BH29884. In Study ACE002JP, out of 18 patients receiving emicizumab, 5 received at least 1 dose of aPCC while on emicizumab prophylaxis, and no patients (0%) experienced a TMA event associated with the concomitant use of aPCC. In Study ACE002JP, no patients received a dose of aPCC > 100 U/kg/24 hours while receiving emicizumab. No cases of TMA have been observed in patients who received emicizumab and rFVIIa alone or FVIII alone, or who were treated with single doses of aPCC up to 100 U/kg per infusion. In two cases, the TMA AEs were assessed as SAEs (Grade 3 and Grade 4 in intensity, and related to study treatment). Both TMA SAEs reported the PT of Thrombotic microangiopathy. One patient had dose interruption and the other had dose discontinuation. Both patients had an outcome of "Recovered/Resolved". In the third case, the patient experienced the event of rectal hemorrhage with a fatal outcome. The investigator assessed the patient death as related to the SAE of rectal hemorrhage and unrelated to emicizumab, and the thrombotic microangiopathy (grade 4 in intensity) as related to emicizumab and aPCC. A summary of these three patients is provided below: • One patient received 1 dose of aPCC 94 U/kg to treat a traumatic left knee hemarthrosis on Study Day 48. Sixteen and a half hours later, on Study Day 49, the patient received 1 dose of aPCC 94 U/kg to treat a spontaneous left elbow bleed. On Study Day 50, the

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
	patient reported having a bleed in his lower back, for which he received 2 doses of rFVIIa 85 μg/kg, his scheduled dose of emicizumab, followed by 2 doses of aPCC 94 U/kg. The following day, Study Day 51, the patient presented to the hospital with thrombocytopenia (platelet count: 17 x 10^9/L), hyperbilirubinemia (total bilirubin: 7.5 mg/dL), and acute renal failure (creatinine: 4.08 mg/dL). He was diagnosed with TMA and treated with therapeutic plasma exchange, hemodialysis, and supportive care. Emicizumab prophylaxis was permanently discontinued, and aPCC treatment was discontinued. The patient's condition improved (during which he received a total of 5 doses of rFVIIa, each 85-94 μg/kg), and TMA resolved on Study Day 65. The investigator assessed the event as being related to emicizumab and bypassing agents, aPCC and rFVIIa. • Another patient received one dose of aPCC 74 U/kg for a traumatic right ankle hemarthrosis and his scheduled dose of emicizumab on Study Day 218. On Study Day 219, he received 2 doses of aPCC 74 U/kg, and on Study Day 220, he received an additional 2 doses of aPCC 74 U/kg to treat the same bleed, after which the patient developed abdominal pain and emesis. On Study Day 222, the patient presented to the hospital with thrombocytopenia (platelet count: 35 x 10^9/L), acute renal failure (creatinine: 6.31 mg/dL), hemolysis (lactate dehydrogenase: 830 units/L), and a peripheral smear that showed 3–4 schistocytes per high-power field. The patient was diagnosed with TMA and admitted to the intensive care unit for supportive care. Emicizumab prophylaxis was held, and aPCC treatment was discontinued. Of note, the patient's laboratory values improved without any interventions, such as therapeutic plasma exchange or hemodialysis. On Study Day 230, the patient was discharged from the hospital. On Study Day 239, TMA resolved, and the patient was restarted on emicizumab prophylaxis without recurrence of TMA as of the data cut-off date. The investigator assessed the event as being related to emicizumab and a concomitant medication. • In the third TMA case, the patient presented to the hospital complaining of rectal bleeding, postural dizziness, and exertional dyspnea on Study Day 238. Of note, the patient declined receipt of blood and blood products throughout his entire hospital course despite experiencing an SAE of rectal hemorrhage. He received 11 doses of rFVIIa 87 μg/kg over 3 consecutive days and underwent multiple interventions (hemostatic powder application, absorbable hemostat

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
	packing, and embolization of rectal arteries) in attempts to control the bleeding. Despite these, the patient continued to have rectal hemorrhage. On Study Day 240, the patient's bypassing agent treatment was changed to aPCC (first day: 98 units/kg × 1 and 65 units/kg × 2, followed by 3 days of 65 units/kg × 3), with temporary cessation of bleeding by Study Day 241. On Study Day 243 (4 days following the start of aPCC), the patient was diagnosed with TMA after being found to have microangiopathic hemolytic anemia (peripheral blood smear showed schistocytes, lactate dehydrogenase: 2746 U/L), thrombocytopenia (platelet count: 33 x 10^9/L), and acute renal failure (creatinine: 490 μmol/L). Emicizumab prophylaxis was permanently discontinued, and aPCC was discontinued. The patient underwent 2 sessions of therapeutic plasma exchange with albumin as the replacement fluid. On Study Day 246, the patient had recurrent rectal hemorrhage, for which additional arterial embolization and surgery were deemed not to be feasible. At the time of the patient's last laboratory assessment (3 days after discontinuing aPCC), the patient's platelet count (114 x 10^9/L) and LDH (775 U/L) were improving, and the investigator assessed the patient's TMA to be recovering/resolving. The patient continued to decline receipt of blood and blood products and was placed on comfort care before passing away the same day. The investigator assessed the patient's death as related to the SAE of rectal hemorrhage and unrelated to emicizumab, and the TMA as related to emicizumab and aPCC.
Risk groups or risk factors	No specific risk factors for TMA in hemophilia A patients were identified in the literature. However, all cases in the emicizumab clinical program occurred in patients who had taken average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more while receiving emicizumab prophylaxis. Negative re-challenge for one patient restarting emicizumab after resolution of TMA without recurrence support the aforementioned observation as a potential etiology. From additional analyses including data on thromboembolic and TMA events, the Sponsor concludes that there is sufficient evidence to support a DDI between aPCC and emicizumab (see Table 15). This interaction is primarily based on the dose and time interval over which aPCC is administered, with

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
	average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more associated with an increased risk for developing thromboembolic and TMA events.
Preventability	This risk is manageable and can be minimized by providing guidance for use of bypassing agents including aPCC (see below). This risk has only been observed in patients that have received average cumulative doses of aPCC exceeding > 100 U/kg/24 hours for 24 hours or more. Patients receiving emicizumab prophylaxis should be monitored for the development of TMA when administering aPCC. The physician should immediately discontinue aPCC and interrupt emicizumab therapy if clinical symptoms and/or laboratory findings consistent with TMA occur, and manage as clinically indicated. Physicians and patients/caregivers should weigh the benefits and risks of resuming emicizumab prophylaxis following resolution of TMA on a case-by-case basis. In case a bypassing agent is indicated in a patient receiving emicizumab prophylaxis, see below for dosing recommendations for use of bypassing agents. ***Guidance on the use of bypassing agents in patients receiving emicizumab prophylaxis:*** Treatment with bypassing agents should be discontinued the day before starting emicizumab therapy. Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving emicizumab prophylaxis. Emicizumab increases the patient's coagulation potential. The bypassing agent dose required may therefore be lower than that used without emicizumab prophylaxis. The dose and duration of treatment with bypassing agents will depend on the location and extent of bleeding, and on the patient's clinical condition. Use of aPCC should be avoided unless no other treatment options/alternatives are available. If aPCC is indicated in a patient receiving emicizumab prophylaxis, the initial dose should not exceed 50 U/kg and laboratory monitoring is recommended (including but not restricted to renal monitoring, platelet testing, and evaluation of thrombosis). If bleeding is not controlled with the initial dose of aPCC up to 50 U/kg, additional aPCC doses should be administered under medical guidance or supervision with consideration made to laboratory monitoring and verification of bleeds prior to repeated dosing. The total aPCC dose should not exceed 100 U/kg in the first 24-hours of treatment. Treating physicians must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment beyond a maximum of 100 U/kg in the first 24-hours. In clinical trials, no cases of thrombotic microangiopathy or thrombotic events were observed with use of activated recombinant human FVII (rFVIIa) or FVIII alone in patients

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
	receiving emicizumab prophylaxis. If patients require bypassing agents in the peri-operative setting, it is recommended that the dosing guidance above for aPCC be followed. Bypassing agent dosing guidance should be followed for at least 6 months following discontinuation of emicizumab prophylaxis. In addition to routine risk minimization activities, additional risk minimization measures to include (see Part V for details): • Guide for Healthcare Professionals. • Patient Card. • Patient/Carer Guide. Effectiveness of the risk mitigation measures will be monitored via educational material distribution metrics and Study BO40853 (completed) (see Part V.2).
Impact on the benefit-risk balance of the product	TMA is potentially life-threatening disorder and is characterized by intravascular (involving small blood vessels) thrombi of aggregated platelets leading to thrombocytopenia and organ ischemia and anemia. Three hemophilia A patients with FVIII inhibitors developed TMA while receiving emicizumab and bypassing agents during Study BH29884: • One patient recovered after plasmapheresis and hemodialysis and was discontinued from emicizumab treatment. • Another patient recovered with supportive care only and restarted emicizumab treatment. • In the third patient, TMA occurred in context of treating the event of rectal hemorrhage, with a fatal outcome attributed to rectal hemorrhage and not TMA. The severity grades for the 3 patients with TMA were as follows: • In 2 patients, the severity grade was 4. • In 1 patient, the severity grade was 3. Out of the 3 patients who experienced a TMA event, 1 patient had emicizumab dose interruption and 2 patients permanently discontinued emicizumab (1 as a result of fatality). Based on the review of these events: • A dosing guide for use of bypassing agents was included in the SmPC. • And the following educational materials were prepared:

Important Identified Risk: Thrombotic microangiopathy (associated with emicizumab and aPCC)	
	○ Guide for Healthcare Professionals. ○ Patient Card. ○ Patient/Carer Guide.
Public health impact	The incidence of hemophilia A is estimated to be approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 417 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27) (Eurostat 2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000, males with severe hemophilia A. There are currently 6306 patients living with hemophilia A with clinically identified inhibitors globally, and 467 newly identified cases in 2019. The proportion of patients currently living with inhibitors is about 4% of all hemophilia A patients (Section 1.1.1.2). Due to the rarity of hemophilia A patients with FVIII inhibitors, who are almost exclusively the only patient population likely to receive aPCC and emicizumab, no impact on public health is expected.

[1] An instance of aPCC treatment is defined as all doses of aPCC received by a patient, for any reason, until there was a 36-hour treatment-free break. It includes all instances of aPCC treatment excluding those in the first 7 days and those that occurred 30 days after the discontinuation of emicizumab.

AE = adverse event; aPCC = activated prothrombin complex concentrate; DDI = drug-drug interaction; EUHASS = European Haemophilia Safety Surveillance; FVIII = factor VIII; FXa = activated factor X; MAH = market authorization holder; MOA = mode of action; rFVIIa = recombinant factor VIIa; SAE = serious adverse event; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy.

*BO41423: is a study in patients with hemophilia A without inhibitors. These patients are not treated with aPCC.

Table 17 Important Identified Risk: Loss of efficacy due to anti-emicizumab antibodies

Important Identified Risk: Loss of efficacy due to anti-emicizumab antibodies	
Potential mechanisms	All therapeutic proteins have the potential to elicit unwanted immune responses, which may affect pharmacokinetics or pharmacodynamics, which in turn may lead to loss of efficacy of the molecule to various degrees primarily through the development of ADAs (FDA Guidance for Industry 2014; EMA Guideline 2017). While the presence of ADAs is not always of clinical relevance, it may lower efficacy by increasing drug clearance or by neutralizing drug effect, which in turn, may result in loss of efficacy.

Important Identified Risk: Loss of efficacy due to anti-emicizumab antibodies	
Evidence source and strength of evidence	Evidence is based on data from eight Phase III studies (BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881, and MO39129) and the Phase I/II study (ACE002JP) of emicizumab in hemophilia A patients, both with and without FVIII inhibitors.
Characterization of the risk	In the Phase I/II Study ACE002JP, 4 out of 18 patients tested positive for anti-emicizumab antibodies (3 patients in the 0.3 mg/kg/week group and 1 patient in the 1 mg/kg/week group). There were no clinically relevant changes in the pharmacokinetics and pharmacodynamics of emicizumab in these patients with hemophilia A. All anti-emicizumab antibodies were considered non-neutralizing. The overall incidence rate of anti-emicizumab antibodies across the eight Phase III studies was low (4.9%; 36 of 739 patients tested) as is expected for humanized mAbs. In 19 patients (2.6%), anti-emicizumab antibodies were neutralizing in vitro. Of these 19 patients, the neutralizing anti-emicizumab antibodies did not appear to have a clinically meaningful impact on the pharmacokinetics or efficacy of emicizumab in 15 patients.Four patients (0.5%) had neutralizing anti-emicizumab antibodies associated with decreasing emicizumab concentrations, further supported by reduced PD effects (e.g., prolonged aPTT, reduced FVIII activity, decreased thrombin generation). One patient (0.1%) with neutralizing anti-emicizumab antibodies and decreased emicizumab plasma concentrations experienced loss of efficacy after 5 weeks of treatment and discontinued emicizumab treatment.
Risk groups or risk factors	There is no single risk factor for the development of ADAs (Shankar et al. 2007). ADA may be a risk factor as it could lead to loss of efficacy due to decreasing plasma concentration of emicizumab.
Preventability	No measures to prevent the development of anti-emicizumab antibodies have been identified. Development of clinically important anti-emicizumab antibodies may impact systemic emicizumab plasma concentration, which could lead to a higher rate of bleeding events in a small proportion of patients. Thus, it is recommended that healthcare providers consider anti-emicizumab antibodies as a potential cause of loss of efficacy manifesting as breakthrough bleeding events, despite adherence to emicizumab dosing. In case of clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events), prompt evaluation by a physician should be sought to assess the etiology and a possible change in treatment should be considered.
Impact on the benefit-risk balance of the product	In Phase III studies, 4.9% of patients (36 of 739 total patients) who received treatment with emicizumab (1.5 mg/kg QW, 3 mg/kg Q2W, and 6 mg/kg Q4W) developed anti-emicizumab antibodies. Of the 4.9% of patients (n=36) that tested positive for anti-emicizumab antibodies, 2.6% (n=19) had nAbs. Less than

Important Identified Risk: Loss of efficacy due to anti-emicizumab antibodies	
	1% of all patients (n=4) had neutralizing anti-emicizumab antibodies associated with decreasing emicizumab concentrations; of these, one patient discontinued treatment due to loss of efficacy. Based on the rarity of the event of loss of efficacy due to anti-emicizumab antibodies and the consistency with previous results, there was no change to the benefit-risk profile, which remains favorable.
Public health impact	The incidence of hemophilia A is estimated to be approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 417 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27) (Eurostat 2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000, males with severe hemophilia A. There are currently 6306 patients living with hemophilia A with clinically identified inhibitors globally, and 467 newly identified cases in 2019. The proportion of patients currently living with inhibitors is about 4% of all hemophilia A patients (Section 1.1.1.2). Due to the rarity of hemophilia A patients, as well as the low frequency of loss of efficacy due to anti-emicizumab antibodies, no impact on public health is expected.

ADA=anti-drug antibody; aPTT=activated partial thromboplastin time; FVIII=factor VIII

The Immunogenicity Report V4 was used as the source document for this table which includes the Phase III studies BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881 and MO39129, and the Phase I/II study (ACE002JP).

Table 18 Important Potential Risk: Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab

Important Potential Risk: Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	
Potential mechanisms	Emicizumab exhibits activity in any assay based on the intrinsic coagulation pathway because it replaces the tenase cofactor activity of activated FVIII (FVIIIa). However, coagulation laboratory tests based on intrinsic clotting time (e.g., aPTT, ACT) assume that non-activated FVIII is present, and so the tests will overestimate the activity of FVIIIa or molecules with similar mechanism such as emicizumab, due to more rapid clotting times. Therefore, aPTT and all single-factor coagulation laboratory tests based on aPTT (including one-stage FVIII activity) are not reliable in the emicizumab setting and do not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. In addition, emicizumab drives clotting even in the presence of inhibitors against FVIII, leading to false negative results in Bethesda assays for functional FVIII inhibitors. Finally, emicizumab exhibits no activity in FVIII chromogenic activity assays containing bovine coagulation proteins because it is specific for human coagulation proteins. Due to the long half-life of emicizumab, these effects on coagulation assays may persist for up to 6 months after the last dose. There is a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab if a patient is treated by HCPs other than the emicizumab-prescribing HCP in settings such as the emergency room or in an acute care setting.

Important Potential Risk: Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	
Evidence source and strength of evidence	In vitro: Emicizumab's mechanism of action and resulting interference was clearly demonstrated in the aPTT and in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials: Data from emicizumab clinical trials (Phase III studies BH29884, BH29992, BH30071, BO39182, BO41423 and the Phase I/II Study ACE002JP) also demonstrated the effects of emicizumab on laboratory assays. However, no instances of under-treatment of bleeding events due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab, were observed.
Characterization of the risk	Due to its mechanism of action, emicizumab interference in laboratory coagulation assays occurs for all patients. However, there have been no instances of under-treatment of bleeding events reported in emicizumab clinical trials (BH29884, BH29992, BH30071, BO39182, BO41423 and ACE002JP) due to misinterpretation of the standard coagulation tests in patients treated with emicizumab.
Risk groups or risk factors	Standard coagulation laboratory tests based on intrinsic clotting (including but not limited to aPTT, one-stage FVIII activity and FVIII inhibitor measurement by Bethesda assay) are not reliable and do not accurately reflect the patient's underlying hemostatic status while receiving emicizumab prophylaxis. These tests should not be used to monitor for emicizumab activity, determine need for factor replacement dosing, or measure FVIII inhibitors. There is a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab if a patient is treated by HCPs other than the emicizumab-prescribing HCP in settings such as an emergency room or in an acute care setting.
Preventability	Although the effect of emicizumab on laboratory assays is a direct result of its mechanism of action and cannot be changed, the resulting risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab, can be reduced through appropriate educational activities. Such additional risk mitigation measures (see Part V for details) include: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide • Laboratory Professional Guide Effectiveness of the risk mitigations measures will be monitored via educational material distribution metrics.

Important Potential Risk: Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	
Impact on the benefit-risk balance of the product	Multiple coagulation laboratory tests (including but not limited to aPTT, FVIII activity, and FVIII inhibitor measurement by Bethesda assay, see SmPC) are not reliable in the emicizumab setting and do not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. There is a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab if a patient is treated by HCPs other than the emicizumab-prescribing HCP in settings such as the emergency room or an acute care setting. Based on the evaluation of this important potential risk, the following educational materials are available: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide • Laboratory Professional Guide
Public health impact	The incidence of hemophilia A is estimated to be approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 417 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27) (Eurostat 2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000, males with severe hemophilia A. There are currently 6,306 patients living with hemophilia A with clinically identified inhibitors globally, and 467 newly identified cases in 2019. The proportion of patients currently living with inhibitors is about 4% of all hemophilia A patients (Section 1.1.1.2). Due to the rarity of hemophilia A patients, no impact on public health is expected.

aPTT = activated partial thromboplastin time; FVIII = factor VIII; HCP = healthcare professional; SmPC = Summary of Product Characteristics

Table 19 Important Potential Risk: Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions

Important Potential Risk: Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions[1]	
Potential mechanisms	Hypersensitivity reactions include Gell and Coombs Classification Types I to IV reactions. These may or may not be associated with ADAs. Anaphylaxis is a severe, potentially fatal event. It is an acute onset systemic Type I hypersensitivity reaction which may present with flushing, hypotension, urticaria, angioedema and bronchospasm. Anaphylactic reactions associated with drugs can be due to IgE antibody–mediated immunological reactions to the drug or to a metabolite or excipient. Reactions with similar symptoms, however, can be non-immunologically mediated. This condition was formerly called non-immunological anaphylaxis (Faria et al. 2014). Type II hypersensitivity reactions are antibody–mediated cytotoxicity reactions involving specific IgG or IgM antibodies directed at drug-hapten coated cells leading to cell or tissue injury. Clinical manifestations include hemolytic anemia, neutropenia, or thrombocytopenia. In addition, ADAs may lead to the formation of circulating immune complexes resulting in generalized hypersensitivity reactions and/or tissue deposition with consequences for specific organs including serum sickness (Type III reactions). (Shankar et al. 2014, Steenholdt et al. 2011). Type IV hypersensitivity reactions are cell-mediated, often have delayed onset, and involve the skin.
Evidence source and strength of evidence	Evidence is based on data from the Phase III studies (BH29884, BH29992, BH30071, BO39182, BO41423, YO39309, MO39129, JO39881 and Phase I/II Study ACE002JP of emicizumab in hemophilia A patients, both with and without FVIII inhibitors. Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions are typical potential class effects of all therapeutic protein products including subcutaneously administered monoclonal antibodies such as emicizumab.
Characterization of the risk	There have been no cases of anaphylaxis, anaphylactoid and systemic hypersensitivity reactions related to emicizumab treatment in Phase III Studies BH29884, BH29992, BH30071, BO39182, BO41423, YO39309, MO39129, JO39881 and Phase I/II Study ACE002JP*. • In the Phase I/II Study ACE002JP, 4 out of 18 patients tested positive for anti-emicizumab antibodies (3 patients in the 0.3 mg/kg/week group and 1 patient in the 1

[1] Section 4.8/Undersirable effects of the SmPC includes post-marketing adverse drug reactions of rash, urticaria and angioedema.

Important Potential Risk: Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions[1]	
	mg/kg/week group). • The overall incidence rate of anti-emicizumab antibodies across the eight Phase III studies was low (4.9%; 36/739 patients) as is expected for humanized mAbs. The presence of anti-emicizumab antibodies was not associated with any safety concerns including hypersensitivity reactions. • No cases of anaphylactic reactions or severe hypersensitivity reactions were reported, nor were any events indicative of potential immune complex deposition, in patients with positive results for anti-emicizumab antibodies. This important potential risk will be characterized through the ongoing additional pharmacovigilance activities: the EUHASS and PedNET registries.
Risk groups or risk factors	Patients with previous history of anaphylaxis and atopic individuals are risk groups. Older age is a risk factor for death from drug-induced anaphylaxis; 73% of all such deaths occurred in patients aged 55 to 85 years old (Liew WK et al. 2009). There is no single risk factor for the development of ADAs in the formation of circulating immune complexes resulting in generalized hypersensitivity reactions (Shankar et al. 2014, Steenholdt et al. 2011).
Preventability	Patients with a history of a severe allergic reaction to a biologic agent or known hypersensitivity should be closely monitored. If any systemic hypersensitivity symptoms are observed, administration of emicizumab must be stopped and appropriate action taken immediately in accordance with the symptoms and the treating physician's medical judgement. Patients should be educated to recognize signs/symptoms of systemic hypersensitivity and instructed to seek medical attention if they experience symptoms outside of the clinic. If symptoms suggesting a severe hypersensitivity reaction are observed, treatment with emicizumab should be stopped and appropriate treatment should be started immediately. No re-challenge should be performed in patients who experience a severe hypersensitivity, anaphylactic or anaphylactoid reaction. No measures to prevent the development of anti-emicizumab antibodies have been identified.

Important Potential Risk: Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions[1]	
Impact on the benefit-risk balance of the product	Acute hypersensitivity reactions to administration may lead to the following symptoms: skin symptoms such as urticaria, digestive symptoms such as abdominal pain and vomiting, respiratory symptoms such as difficulty breathing, and shock related symptoms such as clouding of consciousness due to sudden drop in blood pressure. These symptoms may become life-threatening and require emergency medical intervention. Systemic hypersensitivity reactions manifesting clinically with shock, decreased blood pressure, or difficulty breathing may include fatal or life-threatening anaphylactic reactions and may occur with biological products such as emicizumab (potential class effect).
Public health impact	The incidence of hemophilia A is estimated to be approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 417 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27) (Eurostat 2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000, males with severe hemophilia A. There are currently 6306 patients living with hemophilia A clinical identified inhibitors globally, and 467 newly identified cases in 2019. The proportion of patients currently living with inhibitors is about 4% of all hemophilia A patients (Section 1.1.1.2). Due to the rarity of hemophilia A patients, no impact on public health is expected.

AE = adverse event; AESI = adverse event of special interest; ADA = anti-drug antibody; EUHASS = European Haemophilia Safety Surveillance; FVIII = factor VIII; SAE = serious adverse event

* The Immunogenicity Report V4.0 was used as the source document for this table which includes the Phase III studies BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881 and MO39129, and the Phase I/II study (ACE002JP).

Table 20 Important Potential Risk: Thromboembolic events not associated with concomitant use of aPCC

Important Potential Risk: Thromboembolic events not associated with concomitant use of aPCC	
Potential mechanisms	With an increase in hemostatic potential as achieved with emicizumab, and as coagulation levels approach that of the general population, there is hypothetical plausibility that thrombotic risk might mirror that of the general population more closely (Barg et al. 2019). Additionally, some studies suggest that in the context of an aging hemophilia A population, with increased comorbidities, that there is a risk of cardiovascular disease (and thus thrombotic risk) similar to that of the general population (Wang 2016, Faghmous et al. 2019, Hofstede et al. 2008). Nonetheless, while emicizumab improves hemostasis closer to normal in a hemophilia A patient; hemostasis is not completely restored and remains below that of a healthy individual (e.g. typically restores to a mid-mild hemophilia phenotype).
Evidence source and strength of evidence	Cumulated experience indicates that there is insufficient evidence for a causal relationship between emicizumab without concomitant use of aPCC and thromboembolic events. • In the context of a cumulative post-marketing and clinical trial estimated exposure of 28,847 patients worldwide*, a cumulative search of the Roche Global Safety database** (excluding events associated with aPCC and in unapproved indications) yielded 78 cases comprising 90 thromboembolic events. Cases reporting adequate clinical information were all reported in patients with predisposing comorbidities and would not be unexpected in the hemophilia A or general populations. • The incidence proportion, and rate of thromboembolic events in clinical trials with emicizumab remain within the background incidence in the hemophilia A population (e.g., an incidence rate of 0.17 serious events per 100 patient-years and 0.38 all grade events per 100 patient-years in clinical trials with emicizumab vs. 0.51 events per 100 patient-years[1]). The nonclinical data do not exclude the risk of thromboembolic events with emicizumab alone but suggest that the risk is not higher from emicizumab administration. The effect of emicizumab on thrombus formation was compared with the effect of rFVIIa and FVIII treatment in a model of venous stasis in normo-coagulative cynomolgus monkeys (Study PHM11-0008). Provoked thrombus formation by emicizumab was equal to the thrombus formation induced by either rFVIIa or FVIII. These results suggest that the risk of emicizumab causing thrombosis does not markedly exceed the risk of rFVIIa preparations or FVIII preparations causing thrombosis. In a second study of data from co-administration of

Important Potential Risk: Thromboembolic events not associated with concomitant use of aPCC	
	emicizumab and bypassing agents (rFVIIa and aPCC) on thrombus formation in a cynomolgus monkey model of FVIII-deficient hemophilia A/venous stasis (Study PHM12-0023), no thrombosis formation was seen with emicizumab monotherapy. The available data from nonclinical studies, clinical trials, literature, and real-world data sources do not support establishing a causal relationship. However with an increase in hemostatic potential as achieved with emicizumab, and as coagulation levels approach that of the general population, there is hypothetical plausibility that thrombotic risk might mirror that of the general population more closely (Barg et al. 2019). Additionally, some studies suggest that in the context of an aging hemophilia A population, with increased comorbidities, that there is a risk of cardiovascular disease (and thus thrombotic risk) similar to that of the general population (Wang 2016, Faghmous et al. 2019, Hofstede et al. 2008). Nonetheless, while emicizumab improves hemostasis closer to normal in a hemophilia A patient; hemostasis is not completely restored and remains below that of a healthy individual (e.g. typically restores to a mid-mild hemophilia phenotype). Since all thromboembolic events are closely monitored as part of additional pharmacovigilance activities, thromboembolic events not associated with concomitant use of aPCC have been formally reclassified as an important potential risk for completeness. This reclassification of the potential risk since the first RMP does not reflect a worsening of the benefit-risk profile of emicizumab.
Characterization of the risk	Based on the assessments provided above (see Evidence source and strength of evidence), there is insufficient evidence for a causal relationship between emicizumab without concomitant use of aPCC and thromboembolic events. Consistent with commitments related to PSUR/PBRER reporting, thromboembolic events not associated with concomitant use of aPCC have been monitored under the Important Identified Risk: Thromboembolic events (associated with emicizumab and aPCC) via post-authorization safety studies additional pharmacovigilance activities. The ongoing post-authorization safety studies with emicizumab which aim to further characterize the thromboembolic events and TMA risks in association with concomitant emicizumab and aPCC could be sources of additional relevant data, in addition to other ongoing studies and hemophilia registries.
Risk groups or risk factors	Unique risk groups or risk factors have not been determined to date. The observed thromboembolic events (arterial, venous, device related) occurred in patients with relevant past medical history (e.g., underlying cardiovascular risk factors) and/or other contributing comorbidities.

Important Potential Risk: Thromboembolic events not associated with concomitant use of aPCC	
	Without sufficient evidence to establish a causal relationship, the weighting of potential risk factors or group characteristics cannot yet be determined.
Preventability	Since this risk has no impact on the benefit-risk profile of emicizumab (no causal relationship has been established), there are no additional risk minimization activities. To maximize clarity and risk minimization messages for patients, carers and HCPs, risk minimization activities for emicizumab are focused on the risks associated with concomitant use of aPCC.
Impact on the benefit-risk balance of the product	At this time, this potential risk has no impact on the benefit-risk balance of emicizumab.
Public health impact	The incidence of hemophilia A is estimated to be approximately 1 in 5,000 liveborn male infants or 1 out of every 10,000 live births (Franchini and Mannucci 2013; CDC 2017). In the European Union (EU-27), this equates to approximately 416 newborns with hemophilia A in 2019 (based on an estimated 4.17 million children born in EU-27) (Eurostat 2020). The prevalence at birth is estimated to be 24.6 per 100,000 males with 9.5 per 100,000, males with severe hemophilia A. There are currently 6,306 patients living with hemophilia A with clinically identified inhibitors globally, and 467 newly identified cases in 2019. The proportion of patients currently living with inhibitors is about 4% of all hemophilia A patients (Section 1.1.1.2). Due to the rarity of hemophilia A patients, no impact on public health is expected.

[1] Sponsor assessment of claims database, methodology as described in Faghmous et al. 2019

*Worldwide cumulative post-marketing and clinical trial estimated exposure as of 15 November 2023 Source: PBRER 1126611 (Data Lock Point 15 November 2023).

**Cumulative search up to 01 August 2023.

aPCC = activated prothrombin complex concentrate; TMA = thrombotic microangiopathy

SVII.3.2 Presentation of the Missing Information

Table 21 Missing Information: Use in neonates and infants

Missing Information: Use in Neonates and Infants	
Evidence source	The investigation of the safety and efficacy of emicizumab in neonates and infants is currently ongoing in Study MO41787 (HAVEN 7), a Phase IIIb, multicenter, open-label, single-arm study to evaluate the efficacy, safety, pharmacokinetics, and pharmacodynamics of emicizumab in patients from birth to ≤12 months of age with severe hemophilia A without FVIII inhibitors. As of 22 May 2023, data from 55 patients has shown that the safety profile of emicizumab in patients ≤12 months is similar to that in adolescent and adult patients. Patients enrolled in Study MO41787 will undergo long-term safety follow-up for seven years. Thus safety data in neonates and infants is still considered missing information at this time.
Anticipated risk/consequence of the missing information	There is no anticipated risk/consequence of the missing information**:** • Hemophilia A is a bleeding disorder that is attributable to a congenital absence or hypofunction of FVIII, • There are no specific pediatric safety concerns from existing toxicity studies in young monkeys or from the pharmaceutical target/mode of action of emicizumab. Because of the similarity of the disease between adults/adolescents and children, as well as similar response to available treatments, emicizumab is expected to perform in the same way in adults and adolescents and in very young children, and the Sponsor does not anticipate differences in the long-term safety of emicizumab in neonates and infants compared with adults and older children.

FVIII = factor VIII

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 22 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• **Thromboembolic events (associated with emicizumab and aPCC)** • **Thrombotic microangiopathy (associated with emicizumab and aPCC)** • **Loss of efficacy due to anti-emicizumab antibodies**
Important potential risks	• **Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab** • **Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions** • **Thromboembolic events not associated with concomitant aPCC**
Missing information	• **Use in Neonates and Infants**

aPCC = activated prothrombin complex concentrate

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

Routine Pharmacovigilance Activities Beyond Adverse Reactions Reporting and Signal Detection:

Specific adverse reaction follow-up questionnaires for Thromboembolic events (associated with emicizumab and aPCC) and Thrombotic microangiopathy (associated with emicizumab and aPCC):

Specific guided questionnaires will be sent to HCPs reporting thromboembolic events or thrombotic microangiopathy events. The purpose of this routine pharmacovigilance activity is to obtain structured information on the reported events including dose and timing of concomitant medication use (including procoagulant agents, e.g., aPCC, rFVIIa, FVIII), timing of the adverse events. The questionnaires are provided in Annex 4.

Other Forms of Routine Pharmacovigilance Activities

Table 23 Other forms of routine pharmacovigilance activities: Safety concerns to be assessed as part of routine monitoring and special PSUR/PBRER reporting

Safety concerns	Objectives/Milestones
Thromboembolic events (associated with emicizumab and aPCC)[1]	Monitor and assess the frequency of thromboembolic events with respect to that experienced in the ongoing emicizumab clinical trials. PSUR/PBRER will be completed on a periodic basis.
Thrombotic microangiopathy (associated with emicizumab and aPCC)[1]	Monitor and assess the frequency of thrombotic microangiopathy events with respect to that experienced in the ongoing emicizumab clinical trials. PSUR/PBRER will be completed on a periodic basis.
Loss of efficacy due to anti-emicizumab antibodies	Monitor and assess the frequency of loss of efficacy due to suspected anti-emicizumab antibodies. PSUR/PBRER will be completed on a periodic basis.
Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	Monitor and assess the frequency of life- threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab. PSUR/PBRER will be completed on a periodic basis.
Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions	Monitor and assess the frequency of anaphylaxis, anaphylactoid and systemic hypersensitivity reactions. PSUR/PBRER will be completed on a periodic basis.
Thromboembolic events not associated with concomitant aPCC	Monitor and assess the frequency of thromboembolic events not associated with concomitant aPCC. PSUR/PBRER will be completed on a periodic basis.

Safety concerns	Objectives/Milestones
Use in Neonates and Infants	Monitor and assess the use in neonates and infants. PSUR/PBRER will be completed on a periodic basis.

[1] Results from the specific guided questionnaires will be reviewed on a routine basis
aPCC = activated prothrombin complex concentrate.

The Roche standard pregnancy follow-up process was implemented for all products to request additional information on the medication history of the exposed parent, relevant medical history for the mother and father, previous obstetric history, the current pregnancy, fetal and infant conditions, and results of tests and investigations for any pregnancy complication or congenital abnormality during pregnancy or within the first year of the infant's life.

Cumulative data will be presented in Periodic Safety Update Reports (PSURs)/PBRERs.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 24 Analysis of the EUHASS pharmacovigilance registry (PASS)

Study/activity title: Surveillance of emicizumab-treated patients with hemophilia A: an analysis of the EUHASS pharmacovigilance registry (PASS; Study GO40162)
Rationale and Study Objectives: The Sponsor participates in the EUHASS pharmacovigilance program in order to further characterize the safety profile of patients exposed to emicizumab. The primary objective for this study is as follows: • To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products. The secondary objectives for this study are as follows: • To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and in combination with each of the following drugs: aPCC, recombinant factor VII activate (rFVIIa), and FVIII product. • To describe individual cases of TE and TMA identified in EUHASS. • To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab. • To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information.
Study design: Prospective surveillance program for patients with inherited bleeding disorders in Europe. Patients are treated according to their regular standard of care. Individual reporting of target adverse events is done by the treating centers at three-month intervals or on an ongoing basis. Number of patients exposed to emicizumab, as well as number of patients treated with emicizumab and each bypassing agent, are provided annually and used to calculate incidence of the adverse events. Single case reports, based on the information available for each case of thromboembolic events, thrombotic microangiopathy and anaphylaxis, are provided. Anticipated sample size: The sample size will depend on the approval and uptake of emicizumab in the countries with centers participating in the EUHASS registry. As per last data available (1 January 2021–31 December 2021), 1,319 patients were treated with emicizumab alone, 71 patients were treated with emicizumab and NovoSeven, 490 patients were treated with emicizumab and other FVIII (other than Obizur), and 3 patients were treated with emicizumab and factor eight inhibitor bypassing activity (FEIBA).

Study population: Patients treated with emicizumab (treatment group) will be identified from the larger EUHASS population, which consists of patients treated for inherited bleeding disorders in Europe, including hemophilia A patients with all disease severities.
Milestones: PASS annual report (generated by Roche, based on the emicizumab-specific annual report produced by EUHASS): Submission of First annual report: January 2021 Submission of annual reports yearly thereafter (final data collection Dec 2024) Submission of Final study report: By July 2026, following availability of final CSR June 2026

EUHASS = European Haemophilia Safety Surveillance

Table 25 Analysis of the PedNet registry (PASS)

Study/activity title: Emicizumab use in pediatric patients in the real world: an analysis of the PedNet registry (PASS; Study MO40685)
Rationale and Study Objectives: The Sponsor collaborates with the PedNet registry in order to generate information regarding the safety, efficacy and utilization of emicizumab in the pediatric population in the post-authorization setting. Safety endpoints of interest are thromboembolic events, thrombotic microangiopathy (TMA) and anaphylaxis, but all adverse events reported to the PedNET registry in patients treated with emicizumab are summarized. The primary objective for this study is as follows: • To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors. Primary safety endpoints: Frequency and incidence of thromboembolic events, TMA, anaphylaxis The secondary objectives for this study are as follows: • To evaluate frequency and incidence of any adverse events reported to the PedNet Registry in patients treated with emicizumab, in all patients and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors Secondary safety endpoints: Any AEs reported to PedNet Registry • To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors Secondary effectiveness endpoints: - Annual bleeding rate (ABR) for treated bleeds and percentage of patients with zero treated bleeds. - ABR for joint bleeds and major bleeds. - Bleeds count for soft tissue bleeds and minor bleeds.
Study design: This study will rely on data collected by PedNet registry. PedNet is a multicenter observational research database, which includes patients with FVIII/IX levels < 25 IU/dL, born after 1 January 2000 and treated in one of the participating Haemophilia

Study/activity title: Emicizumab use in pediatric patients in the real world: an analysis of the PedNet registry (PASS; Study MO40685)
Treatment Centers. Patients are treated according to the standard of care; therefore the registry data reflects patients experience in the real world. PedNet includes full cohorts of all consecutive patients diagnosed and treated in each center, on which information on treatment and outcomes is collected from hemophilia diagnosis or time of first treatment. To prevent selection bias, patients referred to a center after development of inhibitors are not included in the database. Participating centers report patient-specific data using electronic case report forms. For patients treated with coagulation factor concentrate products, detailed information on treatment and outcomes, including inhibitor development and bleeds, is collected during the first 50 days of exposure and at least yearly thereafter, until the patient reaches adulthood. Additional information is collected regarding surgeries, hospitalizations and adverse events. Similar level of detail is expected to be collected for patients treated with emicizumab prophylaxis, including information on concomitant use of coagulation products. PedNet performs annual data extractions in January of each year. Following each data extraction, PedNet group will analyze the data according to this PASS analytic protocol and provide the Sponsor with Annual Emicizumab-Specific Reports for the duration of the study.
Study population: PedNet is a disease registry, enrolling patients diagnosed with inherited bleeding disorders including hemophilia A patients with all disease severities, regardless of the treatment received. Patients treated with emicizumab (treatment group) will be identified from the larger PedNet population. **Target sample size:** The study sample size will depend on the approval and uptake of emicizumab in the countries with centers participating in the PedNet. Assuming a constant sample size of patients with severe disease in the registry (N=1173 with severe disease regardless of FVIII inhibitor and N=351 with inhibitor), and assuming that at least 50% of these patients receive emicizumab during the 6 years of the study, the anticipated sample size is expected to be n=587 for patients with severe disease and n=176 for patients with inhibitor at the end of this 6-year study. **Actual sample size:** As of 31 December 2022, a total of 428 patients have started treatment with emicizumab; of these 372 patients have had a minimum follow-up of 6 months.
Milestones: PASS annual report (generated by Roche, based on the emicizumab-specific annual report produced by PedNet): Submission of First annual report: January 2021 Submission of annual reports yearly thereafter (final data collection Dec 2024) Submission of Final study report: By October 2025, following availability of final CSR September 2025.

ABR = annual bleeding rate; TMA = Thrombotic microangiopathy

Table 26 Analysis of Planned Multi-registry Study (PASS)

Study/activity title: **Long-term non-interventional safety study of emicizumab treatment in patients with moderate hemophilia A and severe bleeding phenotype (PASS; Study BO44691)**.
Rationale and Primary Study Objectives: To evaluate the long-term safety profile of emicizumab (with focus on thromboembolic events) in patients with moderate congenital hemophilia A (1%≤ Factor VIII ≤5%), without FVIII inhibitors and with severe bleeding phenotype, who are exposed to emicizumab in real-world settings. The primary objective for this study is to determine the incidence of thromboembolic events. The secondary objectives for this study are: • To determine the incidence of serious adverse events (SAEs). • To determine the incidence of thrombotic microangiopathy (TMA) events. • To determine the incidence of serious systemic hypersensitivity reactions, including anaphylaxis. • To characterize the risk profile in terms of pre-defined risk factors of TE events in the patient population.
Study design: Prospective, observational, multicenter, multi-country registry based on national disease registries, monitored over a period of at least 4 years, in addition to a 2-year recruitment period. **Study populations:** The study will collect longitudinal data in approximately 200 patients treated with emicizumab, diagnosed with moderate congenital haemophilia A (1% ≤ Factor VIII ≤5%), without FVIII inhibitors and with a severe bleeding phenotype in a real-world environment. The study will include patients of all ages.
Milestones: Following initiation of the study, an update on recruitment status will be provided yearly. The first interim study report is expected in Q4 2025 and a second interim report is expected in Q4 2027. Submission of Final study report: Expected Q2 2031

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 27 Table of ongoing and planned additional PhIV studies/activities in the Pharmacovigilance Plan

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization				
This section is not applicable because there are no specific requirements.				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances				
This section is not applicable because there are no specific requirements.				
Category 3 - Required additional pharmacovigilance activities				
PASS based on the EUHASS registry (GO40162) Ongoing	To assess the incidence of thromboembolism, thrombotic microangiopathy, and anaphylaxis in real-world conditions, in patients exposed to emicizumab and treated at centers participating to the European Haemophilia Safety Surveillance System (EUHASS) in all disease severities.	• Thromboembolic events (associated with emicizumab and aPCC) • Thrombotic microangiopathy (associated with emicizumab and aPCC) • Thromboembolic events not associated with concomitant use of aPCC • Systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Loss of efficacy due to anti-emicizumab antibodies	PASS annual report (generated by Roche, based on the emicizumab -specific annual report from EUHASS) Submission of First PASS annual report Submission of annual reports yearly thereafter (final data collection Dec 2024) Submission of Final study report	 January 2021 By July 2026 (report finalized June 2026)

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
PASS based on the PedNet registry (MO40685) Ongoing	Evaluation of the incidence of thromboembolic events, TMA, and anaphylaxis in the pediatric population in the post-authorization setting in all disease severities.	• Thromboembolic events (associated with emicizumab and aPCC) • Thrombotic microangiopathy (associated with emicizumab and aPCC) • Thromboembolic events not associated with concomitant use of aPCC • Systemic hypersensitivity, anaphylaxis, and anaphylactoid events • Loss of efficacy due to anti-emicizumab antibodies • Use in Neonates and Infants	PASS annual report (generated by Roche, based on the emicizumab -specific annual report from PedNet) Submission of First PASS annual report Submission of annual reports yearly thereafter (final data collection Dec 2024) Submission of Final study report	 January 2021 By October 2025 (report finalized September 2025)
PASS based on national disease registries (BO44691) Planned	To evaluate the long-term safety of emicizumab treatment (with focus on thromboembolic events) in patients with moderate hemophilia A and severe bleeding phenotype.	• Thromboembolic events not associated with concomitant use of aPCC	Following initiation of the study, an update on recruitment status will be provided yearly. The first interim study report is expected Q4 2025 and a second	 Final Study Report expected Q2 2031

Study Status	Summary of Objectives	Safety concerns addressed	Milestones	Due dates
			interim report is expected in Q4 2027.	

aPCC = activated prothrombin complex concentrate; EUHASS = European Haemophilia Safety Surveillance; HCP = healthcare professional;
*EUHASS/PedNet data collection may be extended further, depending on reimbursement timelines for moderate HA.

PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

This section is not applicable because there are no specific requirements for post-authorization efficacy studies with emicizumab.

PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

RISK MINIMIZATION PLAN
V.1 ROUTINE RISK MINIMIZATION MEASURES

Table 28 Routine Risk Minimization Measures

Safety concern	Routine risk minimization activities
Thromboembolic events (associated with emicizumab and aPCC)	**Routine risk communication:** Proposed text is provided in SmPC: • 4.4 Special warnings and precautions for use • 4.5 Interaction with other medicinal products and other forms of interaction • 4.8 Undesirable effects Proposed text is provided in Package Leaflet: • Section 2 What you need to know before you use Hemlibra • Section 4 Possible side effects with Hemlibra **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring for the development of thromboembolism are included in SmPC section 4.4 **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription
Thrombotic microangiopathy (associated with emicizumab and aPCC)	**Routine risk communication:** Proposed text is provided in SmPC: • 4.4 Special warnings and precautions for use • 4.5 Interaction with other medicinal products and other forms of interaction • 4.8 Undesirable effects Proposed text is provided in Package Leaflet: • Section 2 What you need to know before you use Hemlibra • Section 4 Possible side effects with Hemlibra

Safety concern	Routine risk minimization activities
	Routine risk minimization activities recommending specific clinical measures to address the risk: Recommendation for monitoring for the development of TMA are included in SmPC section 4.4 **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription
Loss of efficacy due to anti-emicizumab antibodies	**Routine risk communication:** Proposed text is provided in SmPC: • 4.4 Special warnings and precautions for use • 4.8 Undesirable effects • 5.1 Pharmacodynamic properties Proposed text is provided in Package Leaflet: • 2. What you need to know before you use Hemlibra • 4. Possible side effects with Hemlibra **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations to alert prescribers on the use and management of emicizumab in case of loss of efficacy due to suspected anti-emicizumab antibodies are included in SmPC section 4.4. **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription
Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	**Routine risk communication:** Proposed text is provided in SmPC: • 4.4 Special warnings and precautions for use • 4.5 Interaction with other medicinal products and other forms of interaction Proposed text is provided in Package Leaflet: • Section 2 What you need to know before you use Hemlibra **Routine risk minimization activities recommending specific clinical measures to address the risk:** N/A **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription
Anaphylaxis, anaphylactoid and systemic	**Routine risk communication:** Proposed text is provided in SmPC:

Safety concern	Routine risk minimization activities
hypersensitivity reactions	• 4.3 Contraindications Proposed text is provided in Package Leaflet: • Section 2 What you need to know before you use Hemlibra **Routine risk minimization activities recommending specific clinical measures to address the risk:** N/A **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription
Thromboembolic events not associated with concomitant aPCC	**Routine risk communication:** No specific text in the SmPC **Routine risk minimization activities recommending specific clinical measures to address the risk:** N/A **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription
Use in Neonates and Infants	**Routine risk communication:** Proposed text is provided in SmPC: • 4.2 Posology and method of administration (special populations) **Other routine risk minimization measures beyond the Product Information:** **Legal status:** Emicizumab is on restricted prescription

aPCC = activated prothrombin complex concentrate; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy

V.2. ADDITIONAL RISK MINIMIZATION MEASURES

Table 29 Additional Risk Minimization Measures

Additional Risk Minimization Measures	• **Guide for Healthcare Professionals** • **Patient/Carer Guide** • **Patient Card** • **Guide for Laboratory Professionals**[1]
Objectives	• Intensify communication and medical and patient education around the important identified risks of TMA (associated with emicizumab and aPCC) and thromboembolic events (associated with emicizumab and aPCC). o The end goal is to reduce the occurrence of thromboembolic events and TMA by educating patients and medical providers on these important identified risks • Intensify communication and medical and patient education around the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab o The goal is to educate patients and medical providers that multiple coagulation laboratory tests (including but not limited to aPTT, one-stage FVIII activity, and FVIII inhibitor measurement by Bethesda assay) are not reliable in the emicizumab setting and do not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. o The aim is to reduce the risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab
Rationale for the additional risk minimization activity	• A patient on emicizumab can use bypassing agents to treat episodic or break through bleeds based on the guidance on the use of bypassing agents provided in the prescribing information. • Coagulation laboratory tests based on intrinsic clotting (including but not limited to aPTT, one-stage FVIII activity and FVIII inhibitor measurement by Bethesda assay) are not reliable in the emicizumab setting and do not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. These tests should not be used to routinely monitor for emicizumab activity, determine need for factor replacement dosing, or measure FVIII inhibitors.
Target audience and planned distribution path	• Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders. • In the event that hemophilia A patients on emicizumab are receiving health care by HCPs other than their prescribing specialist physicians, these patients have both a Patient/Carer Guide and an

Additional Risk Minimization Measures	• **Guide for Healthcare Professionals** • **Patient/Carer Guide** • **Patient Card** • **Guide for Laboratory Professionals**[1]
	alert card to communicate emicizumab risks.
Plans for evaluating the effectiveness of the interventions and criteria for success	• Metrics of distribution channels of materials to patients, laboratory professionals, and healthcare professionals. • Study BO40853 Emicizumab survey to prescribers and patients/carers: Effectiveness measure to evaluate awareness and compliance to the additional risk minimization measures (Category 3 PASS, completed 2021).

[1] Guide for Laboratory Professionals applies only to important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab.

aPCC = activated prothrombin complex concentrate; aPTT = activated partial thromboplastin time; EUHASS = European Haemophilia Safety Surveillance; HCP = healthcare professional; TMA = Thrombotic microangiopathy; PASS = Post Authorization Safety Study

Removal of Additional Risk Minimization Activities

This section is not applicable because no additional risk minimization measures have been removed since the previous version of the RMP.

V.3 SUMMARY TABLE OF PHARMACOVIGILANCE AND RISK MINIMIZATION ACTIVITIES BY SAFETY CONCERN

Table 30 Summary table of Pharmacovigilance and Risk Minimization activities by Safety Concern

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Identified risks		
Thromboembolic events (associated with emicizumab and aPCC)	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction section • SmPC section 4.8: Undesirable effects • Package Leaflet Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide	Routine pharmacovigilance activities: • Specific guided questionnaires • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry

Safety concern	Risk minimization measures	Pharmacovigilance activities
Thrombotic microangiopathy (associated with emicizumab and aPCC)	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction section • SmPC section 4.8: Undesirable effects • Package Leaflet Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide	Routine pharmacovigilance activities: • Specific guided questionnaires • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry
Loss of efficacy due to anti-emicizumab antibodies	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.8: Undesirable effects • SmPC section 5.1: Pharmacodynamic properties • Package Leaflet section 2: What you need to know before you use Hemlibra • Package Leaflet section 4: Possible side effects with Hemlibra Additional risk minimization measures: N/A	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry.

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important Potential risks		
Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab	Routine risk minimization measures: • SmPC section 4.4: Special warnings and precautions for use • SmPC section 4.5: Interaction with other medicinal products and other forms of interaction section • Package Leaflet section 2 What you need to know before you use Hemlibra • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide • Guide for Laboratory Professionals	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: N/A
Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions	Routine risk minimization measures: • SmPC section 4.3: Contraindications • Package Leaflet section 2 What you need to know before you use Hemlibra Additional risk minimization measures: N/A	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry

Safety concern	Risk minimization measures	Pharmacovigilance activities
Thromboembolic events not associated with concomitant aPCC	Routine risk minimization measures: • No specific text in the SmPC • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: N/A	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNet registry • PASS based on multinational registry study BO44691
Missing Information		
Use in neonates and infants	• SmPC section 4.2: Posology and method of administration (special populations) Additional risk minimization measures: N/A	Routine pharmacovigilance activities: • Assess as part of routine PSUR/PBRER reporting Additional pharmacovigilance activities: PASS based on the PedNET registry

aPCC = activated prothrombin complex concentrate; EUHASS = European Haemophilia Safety Surveillance; SmPC = Summary of Product Characteristics

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PART VI: SUMMARY OF THE RISK-MANAGEMENT PLAN

SUMMARY OF RISK MANAGEMENT PLAN FOR HEMLIBRA (EMICIZUMAB)

This is a summary of the risk management plan (RMP) for Hemlibra. The RMP details important risks of Hemlibra, how these risks can be minimized, and how more information will be obtained about Hemlibra's risks and uncertainties (missing information).

Hemlibra's Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Hemlibra should be used.

This summary of the RMP for Hemlibra should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the EPAR.

Important new concerns or changes to the current ones will be included in updates of Hemlibra's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

Hemlibra is authorized for use in adults and children with hemophilia A, with and without factor VIII inhibitors (see SmPC for the full indication). It contains emicizumab as the active substance and it is given by subcutaneous injection.

Further information about the evaluation of Hemlibra’s benefits can be found in Hemlibra’s EPAR, including in its plain-language summary, available on the EMA website, under the medicine’s webpage.

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMISE OR FURTHER CHARACTERIZE THE RISKS

Important risks of Hemlibra, together with measures to minimize such risks and the proposed studies for learning more about Hemlibra’s risks, are outlined below.

Measures to minimize the risks identified for medicinal products can be:

- Specific Information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals;
- Important advice on the medicine’s packaging;
- The authorized pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly;
- The medicine’s legal status — the way a medicine is supplied to the public (e.g., with or without prescription) can help to minimize its risks.

Together, these measures constitute *routine risk minimization* measures. In the case of Hemlibra these measures are supplemented with *additional risk minimization* measures mentioned under relevant risks, below.

- Guide for Healthcare Professionals
- Patient Card
- Patient/Carer Guide
- Guide for Laboratory Professionals

In addition to these measures, information about adverse events is collected continuously and regularly analyzed, including PSUR assessment so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Hemlibra is not yet available; it is listed under 'missing Information' below.

II.A List of Important Risks and Missing Information

Important risks of Hemlibra are risks that need special risk-management activities to further investigate or minimize the risk, so that the medical product can be safely administered. Important risks can be regarded as either identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Hemlibra. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information about the safety of the medicinal product that is currently missing and needs to be collected (e.g., on the long-term use of the medicine).

List of important risks and missing information	
Important identified risks	• Thromboembolic events (associated with emicizumab and aPCC) • Thrombotic microangiopathy (associated with emicizumab and aPCC) • Loss of efficacy due to anti-emicizumab antibodies
Important potential risks	• Life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab • Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions • Thromboembolic events not associated with concomitant use of aPCC
Missing information	• Use in neonates and infants

II.B Summary of Important Risks

Important Identified Risks:
Thromboembolic Events (Associated With Emicizumab and APCC):

Evidence for linking the risk to the medicine	Evidence is based on the Phase III studies (BH29884, BH29992, BH30071, and BO39182; N = 399), BO41423 (N=72) and the Phase I/II study (ACE002JP; N = 18) of emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors. In Studies BH29884, BH29992, BH30071, and BO39182, out of 399 patients receiving emicizumab, 0.5% (2/399) had at least one thromboembolic event associated with the concomitant use of emicizumab and aPCC. There were no thromboembolic events associated with aPCC reported from Study BO41423 as of CCOD (30 Oct 2021). Overall, 6.45% of patients (2/32) who received aPCC while on emicizumab prophylaxis across the Phase III studies had at least one event for this important identified risk of thromboembolic event (associated with emicizumab and aPCC); there were no patients (0/5; 0%) with such an event in Study ACE002JP.
Risk factors and risk groups	There were two patients who experienced thromboembolic events in clinical trials while receiving emicizumab prophylaxis. Both patients received multiple doses of aPCC for the treatment of breakthrough bleeds just prior to developing symptoms. From additional analyses including data on thromboembolic and TMA events, the Sponsor concludes that there is sufficient evidence to support a DDI between aPCC and emicizumab. This interaction is primarily based on the dose and time interval over which aPCC is administered, with average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more associated with an increased risk for developing thromboembolic and TMA events.

Risk minimization measures	Routine risk minimization measures:
	• Provide text In the SmPC regarding this risk
	  ○ Section 4.4: Special warnings and precautions for use
	  ○ Section 4.5: Interaction with other medicinal products and other forms of interaction section
	  ○ Section 4.8: Undesirable effects
	• Provide text in the Package Leaflet regarding this risk Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects
	• Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders
	Additional risk minimization measures:
	• Guide for Healthcare Professionals

	• Patient Card • Patient/Carer Guide
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry See Section II.C of this summary for an overview of the post-authorization development plan.

aPCC = activated prothrombin complex concentrate; DDI = drug-drug interaction; EUHASS = European Haemophilia Safety Surveillance; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy

Thrombotic Microangiopathy (Associated With Emicizumab and APCC)

Evidence for linking the risk to the medicine	Evidence is based on the Phase III studies (BH29884, BH29992, BH30071, and BO39182; N = 399), BO41423 (N=72) and the Phase I/II study (ACE002JP; N = 18) of emicizumab, including adults, adolescents, and children with hemophilia A, both with and without FVIII inhibitors. Of the 399 patients exposed to emicizumab in the Phase III studies BH29884, BH29992, BH30071, and BO39182, 0.75% (3/399) experienced a TMA event associated with the concomitant use of emicizumab and aPCC. There were no TMA events reported from Study BO41423* (N=72) as of the study CCOD (30 Oct 2021). Overall, 9.4% of patients (3/32) who received aPCC while on emicizumab prophylaxis across the Phase III studies experienced this important identified risk of TMA (associated with emicizumab and aPCC); there were no patients (0/5; 0%) with such an even in Study ACE002JP.
Risk factors and risk groups	No specific risk factors for TMA in hemophilia A patients were identified in the literature. However, all cases in the emicizumab clinical program occurred in patients who had taken average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more while receiving emicizumab prophylaxis. Negative re-challenge for one patient restarting emicizumab after resolution of TMA without recurrence support the aforementioned observation as a potential etiology. From additional analyses including data on thromboembolic and TMA events, the Sponsor concludes that there is sufficient evidence to support a DDI between aPCC and emicizumab. This interaction is primarily based on the dose and time interval over which aPCC is administered, with average cumulative doses of aPCC > 100 U/kg/24 hours for 24 hours or more associated with an increased risk for developing thromboembolic and TMA events.

Risk minimization measures	Routine risk minimization measures:
	• Provide text In the SmPC regarding this risk
	  ○ Section 4.4: Special warnings and precautions for use
	  ○ Section 4.5: Interaction with other medicinal products and other forms of interaction section
	  ○ Section 4.8: Undesirable effects
	• Provide text in the Package Leaflet regarding this risk: Section 2 What you need to know before you use Hemlibra and Section 4 Possible side effects
	• Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders
	Additional risk minimization measures:
	• Guide for Healthcare Professionals
	• Patient Card
	• Patient/Carer Guide

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry See Section II.C of this summary for an overview of the post-authorization development plan.

aPCC = activated prothrombin complex concentrate; DDI = drug-drug interaction; EUHASS = European Haemophilia Safety Surveillance; SmPC = Summary of Product Characteristics; TMA = thrombotic microangiopathy

Loss of Efficacy Due to Anti-emicizumab Antibodies

Evidence for linking the risk to the medicine	Evidence is based on data from eight Phase III studies (BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881, and MO39129) and the Phase I/II study (ACE002JP) of emicizumab in hemophilia A patients, both with and without FVIII inhibitors*. A total of 36 out of 739 patients tested positive for anti-emicizumab antibodies, of which one patient experienced loss of efficacy.
Risk factors and risk groups	There is no single risk factor for the development of ADAs (Shankar et al. 2007).

Risk minimization measures	Routine risk minimization measures:
	• Provide text In the SmPC regarding this risk
	  ○ 4.4: Special warnings and precautions for use
	  ○ 4.8: Undesirable effects
	  ○ 5.1: Pharmacodynamic properties
	• Provide text in the Package Leaflet regarding this risk:
	  ○ Section 2 What you need to know before you use Hemlibra
	  ○ Section 4 Possible side effects with Hemlibra
	Routine risk minimization activities recommending specific clinical measures to address the risk:
	Recommendations to alert prescribers on the use and management of emicizumab in case of loss of efficacy due to suspected anti-emicizumab antibodies are included in SmPC section 4.4.

Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry. • PASS based on the PedNET registry. See Section II.C of this summary for an overview of the post-authorization development plan.

ADA = anti-drug antibody; aPTT = activated partial thromboplastin time; FVIII = factor VIII; SmPC = Summary of Product Characteristics

* The Immunogenicity Report V4 was used as the source document for this table which includes the Phase III studies BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881 and MO39129, and the Phase I/II study (ACE002JP).

Important Potential Risks:
Life-threatening Bleeding Due to Misinterpretation of the Standard Coagulation Tests, Which Are Unreliable in Patients Treated With Emicizumab

Evidence for linking the risk to the medicine	In vitro: Emicizumab's mechanism of action and resulting interference was clearly demonstrated in the aPTT and in a wide variety of coagulation laboratory tests approved for in vitro diagnostic use. Clinical trials: Data from emicizumab clinical trials (Phase III studies BH29884, BH29992, BH30071, and BO39182, BO41423 and the Phase I/II Study ACE002JP) also demonstrated the effects of emicizumab on laboratory assays. However, no instances of under-treatment of bleeding events due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab, were observed.

Risk factors and risk groups	Standard coagulation laboratory tests based on intrinsic clotting (aPTT, one-stage FVIII activity, including functional (clotting-based) assays for FVIII inhibitors (e.g., Bethesda assays)) are not reliable in the emicizumab setting and do not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. There is a risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests, which are unreliable in patients treated with emicizumab if a patient is treated by HCPs other than the emicizumab-prescribing HCP in settings such as an emergency room or in an acute care setting.
Risk minimization measures	Routine risk minimization measures: • Provide text In the SmPC regarding this risk o Section 4.4: Special warnings and precautions for use o Section 4.5: Interaction with other medicinal products and other forms of interaction section • Provide text in the Package Leaflet regarding this risk: Section 2 What you need to know before you use Hemlibra • Treatment should be initiated under the supervision of a physician experienced in the treatment of hemophilia and/or bleeding disorders Additional risk minimization measures: • Guide for Healthcare Professionals • Patient Card • Patient/Carer Guide • Laboratory Professional Guide
Additional pharmacovigilance activities	None

aPTT = activated partial thromboplastin time; FVIII = factor VIII; HCP = healthcare professional; SmPC = Summary of Product Characteristics

Anaphylaxis, Anaphylactoid and Systemic Hypersensitivity Reactions

Evidence for linking the risk to the medicine	Evidence is based on data from the Phase III studies (BH29884, BH29992, BH30071 BO39182. BO41423, YO39309, MO39129, JO39881) and Phase I/II Study ACE002JP of emicizumab in hemophilia A patients, both with and without FVIII inhibitors*. Anaphylaxis, anaphylactoid and systemic hypersensitivity reactions are typical potential class effects of subcutaneously administered monoclonal antibodies such as emicizumab. In the Phase I/II Study ACE002JP, 4 out of 18 patients tested positive for anti-emicizumab antibodies. A total of 36 patients from the Phase III studies had developed

	anti-emicizumab antibodies. There were neither anaphylaxis events nor severe hypersensitivity reactions related to development of anti-emicizumab antibodies across studies. Overall, the safety profile of emicizumab was similar between those patients with anti-emicizumab antibodies and those without. Therefore, these were categorized as important potential risks.
Risk factors and risk groups	Patients with previous history of anaphylaxis and atopic individuals are risk groups. Older age is a risk factor for death from drug-induced anaphylaxis; 73% of all such deaths occurred in patients aged 55 to 85 years old (Liew WK et al. 2009). There is no single risk factor for the development of ADAs in the formation of circulating immune complexes resulting in generalized hypersensitivity reactions (Shankar et al. 2014, Steenholdt et al. 2011).
Risk minimization measures	Routine risk minimization measures: • Provide text in the SmPC regarding this risk o SmPC section 4.3: Contraindications • Provide text in the Package Leaflet regarding this risk: • Section 2 What you need to know before you use Hemlibra *No additional measures*
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry See Section II.C of this summary for an overview of the post-authorization development plan.

EUHASS = European Haemophilia Safety Surveillance; FVIII = factor VIII; SmPC = Summary of Product Characteristics

* The Immunogenicity Report V4 was used as the source document for this table which includes the Phase III studies BH29884, BH29992, BH30071, BO39182, YO39309, BO41423, JO39881 and MO39129, and the Phase I/II study (ACE002JP).

Thromboembolic Events Not Associated With Concomitant Use of APCC

Evidence for linking the risk to the medicine	Cumulated experience indicates that there is insufficient evidence for a causal relationship between emicizumab without concomitant use of aPCC and thromboembolic events. • In the context of a cumulative post-marketing and clinical trial estimated exposure of 28,847 patients worldwide*, a cumulative search of the Roche Global Safety database** (excluding events associated with aPCC) yielded 78 cases comprising 90 thromboembolic events. These cases were all reported in patients with predisposing comorbidities and would not be unexpected in the hemophilia A or general

	populations. • The incidence, proportion, and rate of thromboembolic events in clinical trials with emicizumab remain within the background incidence in the hemophilia A population (e.g., an incidence rate of 0.17 serious events per 100 patient-years and 0.38 all grade events per 100 patient-years in clinical trials with emicizumab vs. 0.51 events per 100 patient-years[1]). The nonclinical data do not exclude the risk of thromboembolic events with emicizumab alone, but suggest that the risk is not higher from emicizumab administration. The effect of emicizumab on thrombus formation was compared with the effect of rFVIIa and FVIII treatment in a model of venous stasis in normo-coagulative cynomolgus monkeys (Study PHM11-0008). Provoked thrombus formation by emicizumab was equal to the thrombus formation induced by either rFVIIa or FVIII. These results suggest that the risk of emicizumab causing thrombosis does not markedly exceed the risk of rFVIIa preparations or FVIII preparations causing thrombosis. In a second study of data from co-administration of emicizumab and bypassing agents (rFVIIa and aPCC) on thrombus formation in a cynomolgus monkey model of FVIII-deficient hemophilia A/venous stasis (Study PHM12-0023), no thrombosis formation was seen with emicizumab monotherapy. The available data from nonclinical data, clinical trials, literature, and real-world data sources do not support establishing a causal relationship. However with an increase in hemostatic potential as achieved with emicizumab, and as coagulation levels approach that of the general population, there is hypothetical plausibility that thrombotic risk might mirror that of the general population more closely (Barg et al. 2019). Additionally, some studies suggest that in the context of an aging hemophilia A population, with increased comorbidities, that there is a risk of cardiovascular disease (and thus thrombotic risk) similar to that of the general population (Wang 2016, Faghmous et al. 2019, Hofstede et al. 2008). Nonetheless, while emicizumab improves hemostasis closer to normal in a hemophilia A patient; hemostasis is not completely restored and remains below that of a healthy individual (e.g. typically restores to a mid-mild hemophilia phenotype). Since all thromboembolic events are closely monitored as part of additional pharmacovigilance activities, thromboembolic events not associated with concomitant use of aPCC have been formally reclassified as an important potential risk for completeness. This reclassification of the potential risk since the first RMP does not reflect a worsening of the benefit-risk profile of emicizumab.
Risk factors and risk groups	Unique risk groups or risk factors have not been determined to date. The observed thromboembolic events (arterial, venous, device related) occurred in patients with relevant past medical history (e.g., underlying cardiovascular risk factors) and/or other contributing comorbidities. Without sufficient evidence to establish a causal relationship, the weighting of potential risk factors or group characteristics cannot

	yet be determined.
Risk minimization measures	None
Additional pharmacovigilance activities	Additional pharmacovigilance activities: • PASS based on the EUHASS registry • PASS based on the PedNET registry • PASS based on multinational registry study BO44691 See Section II.C of this summary for an overview of the post-authorization development plan.

[1] Sponsor assessment of claims database, methodology as described in Faghmous et al. 2019

*Worldwide cumulative post-marketing and clinical trial estimated exposure as of 15 November 2023 Source: PBRER 1126611 (Data Lock Point 15 November 2023).

**Cumulative search up to 01 August 2023.

aPCC = activated prothrombin complex concentrate

Missing Information:
Use in Neonates and Infants

Risk minimization measures	Routine risk minimization measures: **Use in neonates and infants** • SmPC section 4.2: Posology and method of administration (special populations)
Additional pharmacovigilance activities	**Use in neonates and infants** • PASS based on the PedNET registry

II.C Post-authorization Development Plan

II.C.1 Studies Which Are Conditions of the Marketing Authorization

There are no studies which are conditions of the marketing authorization or specific obligation of Hemlibra.

II.C.2 Other Studies in Post-authorization Development Plan

Study/activity title: Surveillance of emicizumab-treated patients: an analysis of the EUHASS pharmacovigilance registry (PASS; Study GO40162)

Purpose of the study:

The Sponsor participates in the European Haemophilia Safety Surveillance (EUHASS) pharmacovigilance program in order to further characterize the safety profile of patients exposed to emicizumab.

The primary objective for this study is as follows:

- To estimate the incidence of TE, TMA, and anaphylaxis in patients exposed to emicizumab, with or without coagulation factor products.

The secondary objectives for this study are as follows:

- To estimate the incidence of TE and TMA in patients exposed to emicizumab alone and in combination with each of the following drugs: aPCC, recombinant factor VII activate (rFVIIa), and FVIII product.
- To describe individual cases of TE and TMA identified in EUHASS.
- To summarize the frequency of other adverse events collected by EUHASS in patients exposed to emicizumab.
- To describe individual cases of “unexpected poor efficacy” reported to EUHASS based on the available information.

Study/activity title: Emicizumab use in pediatric patients in the real world: an analysis of the PedNet registry (PASS; Study MO40685)

Purpose of the study:

The Sponsor collaborates with the PedNet registry in order to generate information regarding the safety, efficacy and utilization of emicizumab in the pediatric population in the post-authorization setting. Safety endpoints of interest are thromboembolic events, thrombotic microangiopathy (TMA) and anaphylaxis, but all adverse events reported to the PedNET registry in patients treated with emicizumab are summarized.

Primary study objective is as follows:

To evaluate the overall safety and tolerability of emicizumab administration, in all patients and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors

Primary safety endpoints:

– Frequency and incidence of thromboembolic events, thrombotic microangiopathy (TMA), anaphylaxis.

Secondary study objectives are as follows:

To evaluate frequency and incidence of any adverse events reported to the PedNet Registry inpatients treated with emicizumab, in all patients and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors.

Secondary safety endpoints:

– Any AEs reported to PedNet Registry.

To describe the bleeding profile of patients treated with emicizumab, overall and in subgroups determined by age and status of inhibitor as well as by severity for patients without inhibitors.

Secondary effectiveness endpoints:

- ABR for treated bleeds and percentage of patients with zero treated bleeds.
- ABR for joint bleeds and major bleeds.
- Bleed counts for soft tissue bleedsand minor bleeds.

Study/activity title: Long-term safety study of emicizumab treatment in patients with moderate HA and severe bleeding phenotype (BO44691) (PASS)

Purpose of the study:

The aim of the study is to evaluate the long-term safety profile of emicizumab in patients with moderate congenital HA (1% ≤ FVIII ≤ 5%) without FVIII inhibitors and with severe bleeding phenotype and who are exposed to emicizumab in real-world settings, with a specific focus on TE events.

The primary objective for this study is to determine the incidence of TE events.

The secondary objectives for this study are:

- To determine the incidence of serious adverse events (SAEs).
- To determine the incidence of thrombotic microangiopathy (TMA) events.
- To determine the incidence of serious systemic hypersensitivity reactions, including anaphylaxis.
- To characterize the risk profile in terms of pre-defined risk factors of TE events in the patient population.

ANNEX 4

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

ANNEX 4:

SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of Contents

Specific adverse reactions follow-up forms/questionnaires

Emicizumab adverse event information will be collected using the following guided questionnaires:

- Guided Questionnaire Thromboembolic Events
- Guided Questionnaire Thrombotic Microangiopathy (TMA)

Guided Questionnaire Thromboembolic Events

AER:	
Site No:	
Patient ID/Initials:	
Patient Gender:	❑ M ❑ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy):	

Serious thromboembolic events have been observed in some patients treated with emicizumab who received concomitant treatment with aPCC (FEIBA®) for breakthrough bleeds.

This request does not convey a company assessment that the adverse event was associated with the use of emicizumab. By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information

Name of reporter completing this form **(if other than addressee, provide contact information below)**:		
Health Care Provider? ❑Yes ❑ No:	If Yes, please specify: ❑ Hematologist/Oncologist ❑ ER MD ❑ General MD ❑ Other specialty MD	
Phone Number:	Fax Number:	Email:

Drug Indication (Disease History)

Date of Diagnosis of Indication:		Indication for Emicizumab:
Factor VIII Inhibitor Status:	❑ Negative	❑ Positive Date of Diagnosis: _____
Treatment for Hemophilia (Prior to Emicizumab):	❑ Episodic ❑ Prophylactic	❑ rFVIIa (eptacog alfa/NovoSeven®) ❑ activated prothrombin complex concentrate (aPCC/FEIBA®) ❑ Other
List any major complications of the disease the patient has experienced		
Please summarize the history of the disease		

Adverse Event:

Please state the current diagnosis:		
Date of Diagnosis:	Date of Last dose of Emicizumab:	
Did the patient have any of the following signs or symptoms:		
Pain/ache	❑ Yes	❑ No
Shortness of breath	❑ Yes	❑ No
Headache	❑ Yes	❑ No
Location of thrombosis		
Other: *Please list*		

Was Factor VIII administered within 30 days prior to the onset of symptoms?	❑ Yes	❑ No
Was a Bypassing Agent administered within 30 days prior to the onset of symptoms?	❑ Yes	❑ No
What was the reason for the Bypass Agent or Factor VIII use?		
If Bypassing Agent or Factor VIII was given:	Type: ……	Date/Time: ……
	Type: ……	Date/Time: ……
	Type: ……	Date/Time: ……
	Type: ……	Date/Time: ……

Did the patient require:	❑ anticoagulation	❑ Other therapy (please describe)_____
Was it effective? ❑Yes ❑ No	If Yes, please describe:	

What was the Outcome:	❑ Not Recovered	
	❑ Recovering	Date: ……..
	❑ Recovered	Date: ……..
	❑ Unknown	

Autopsy Data - If Applicable, please provide the following information:
If the patient has expired, was an autopsy performed?
❑ Yes
❑ No
❑ Unknown
If yes, please provide the autopsy results including the cause of death:

Relevant Imaging Data:
(If multiple Imaging results are collected, please provide all available information)

Diagnostic	Baseline (pre-event onset)	At Event Onset	Following Event Resolution
	Date/Results	Date/Results	Date/Results
CT			
MRI			
USN			
Other			

Other Relevant Laboratory/Diagnostic Data:
(If multiple laboratory results are collected, please provide all available information)

Diagnostic	Baseline (pre-event onset)	At Event Onset	Following Event Resolution
	Date/Results	Date/Results	Date/Results
PT/INR			
PTT			
Platelets			
Creatinine			
BUN			
Fibrinogen			
D-dimer			
Hemoglobin			
White count			
Total Bilirubin			
LDH			
Other:			

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

Roche

Guided Questionnaire Thrombotic Microangiopathy (TMA)

AER:	
Site No:	
Patient ID/Initials:	
Patient Gender:	❑ M ❑ F

Local Case ID:	
Patient Date of Birth (dd-MMM-yyyy):	

Thrombotic Microangiopathy has been observed in some patients treated with emicizumab who received concomitant treatment with aPCC (FEIBA®) for breakthrough bleeds.

This request does not convey a company assessment that the adverse event was associated with the use of emicizumab. By filling in this questionnaire, you will help us to understand more fully the risk factors for this condition.

Reporter Information

Name of reporter completing this form **(if other than addressee, provide contact information below)**:		
Health Care Provider? ❑Yes ❑ No:	If Yes, please specify: ❑ Hematologist/Oncologist ❑ ER MD ❑ General MD ❑ Other specialty MD	
Phone Number:	Fax Number:	Email:

Drug Indication (Disease History)

Date of Diagnosis of Indication:		Indication for Emicizumab:
Factor VIII Inhibitor Current Status:	❑ Negative	❑ Positive Date of Diagnosis: _____
Treatment for Hemophilia (Prior to Emicizumab):	❑ Episodic ❑ Prophylactic	❑ rFVIIa (eptacog alfa/NovoSeven®) ❑ activated prothrombin complex concentrate (aPCC/FEIBA®) ❑ Other
List any major complications of the disease the patient has experienced		
Please summarize the history of the disease		

Adverse Event:

Please state the current diagnosis:		
Date of Diagnosis:	Date of Last dose of Emicizumab:	
Did the patient have any of the following signs or symptoms:		
Microangiopathy Hemolytic Anemia (MAHA)	❑ Yes	❑ No
Thrombocytopenia	❑ Yes	❑ No
Acute Renal Failure	❑ Yes	❑ No
Hyperbilirubinemia	❑ Yes	❑ No
LDH		
Other: *Please list*		

Was Factor VIII administered within 30 days prior to the onset of symptoms?	❑ Yes	❑ No
Was a Bypassing Agent administered within 30 days prior to the onset of symptoms?	❑ Yes	❑ No
What was the reason for the Bypass Agent or Factor VIII use?		
If Bypassing Agent or Factor VIII was given:	Type: ……	Date/Time: ……
	Type: ……	Date/Time: ……
	Type: ……	Date/Time: ……
	Type: ……	Date/Time: ……

Did the patient require:	❑ Plasma Therapy (ie. Plasma exchange/plasmapheresis)	❑ Hemodialysis ❑ other
Was it effective? ❑Yes ❑ No	If Yes, please describe:	

What was the Outcome:	❑ Not Recovered	
	❑ Recovering	Date: ……..
	❑ Recovered	Date: ……..
	❑ Unknown	

Autopsy Data - If Applicable, please provide the following information:
If the patient has expired, was an autopsy performed?
❑ **Yes**
❑ **No**
❑ **Unknown**
If yes, please provide the autopsy results including the cause of death:

Relevant Imaging Data:
(If multiple Imaging results are collected, please provide all available information)

Diagnostic	**Baseline** (pre-event onset)	**At Event Onset**	**Following Event Resolution**
	Date/Results	Date/Results	Date/Results
CT			
MRI			
USN			
Other			

Other Relevant Laboratory/Diagnostic Data:
(If multiple laboratory results are collected, please provide all available information)

Diagnostic	**Baseline** (pre-event onset)	**At Event Onset**	**Following Event Resolution**
	Date/Results	Date/Results	Date/Results
Peripheral Blood Smear			
PT/INR			
PTT			
Platelets			
Creatinine			
BUN			
Fibrinogen			
D-dimer			
Hemoglobin			
White count			
Total Bilirubin			
LDH			
Other (e.g. ADAMTS13, complement levels, shiga-toxin, please specify):			

Completed by:

Name: _____ Position: _____

Signature: _____ Date: _____

E-mail: _____

ANNEX 6

DETAILS OF PROPOSED ADDITIONAL RISK-MINIMIZATION ACTIVITIES (if applicable)

ANNEX 6: DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Draft key messages of the additional risk minimisation measures

TABLE OF CONTENTS

1. ADDITIONAL RISK MINIMISATION MEASURES

Prior to launch of Hemlibra in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing communication and medical and patient education around the important identified risks of thromboembolic events and thrombotic microangiopathy associated with the concomitant use of emicizumab and activated prothrombin complex concentrate (aPCC), and the important potential risk of life-threatening bleeding due to misinterpretation of the standard coagulation tests (unreliable in patients treated with emicizumab) and provide information on how to manage them.

The MAH shall ensure that in each Member State where Hemlibra is marketed, all healthcare professionals, patients/carers who are expected to prescribe, dispense or use Hemlibra, and laboratory professionals, have access to/are provided with the following educational package:

- Physician educational material
- Patient/Carer educational material
- Laboratory professionals educational material
- Patient Card

The physician educational material should contain:

- The Summary of Product Characteristics
- Guide for healthcare professionals

1.1 GUIDE FOR HEALTHCARE PROFESSIONALS

The guide for healthcare professionals shall contain the following key elements:

- Brief introduction to emicizumab (chemical class, mode of action, pharmacodynamics and indication)
- Relevant information (e.g. seriousness, severity, frequency, time to onset, reversibility as applicable) of the following safety concerns associated with the use of Hemlibra:

– thromboembolic events associated with the concomitant use of emicizumab and activated prothrombin complex concentrate (aPCC),

– thrombotic microangiopathy associated with the concomitant use of emicizumab and aPCC
– life-threatening bleeding due to misinterpretation of the standard coagulation tests (unreliable in patients treated with emicizumab)

- Guidance on the use of bypassing agents concomitantly with emicizumab, including the following information:

– Treatment with prophylactic bypassing agents should be discontinued the day before starting emicizumab therapy;
– Physicians should discuss with all patients and/or caregivers the exact dose and schedule of bypassing agents to use, if required while receiving emicizumab prophylaxis;
– Emicizumab increases the patient's coagulation potential and the dose and duration of treatment with bypassing agents may require adjustment depending on the location and extent of bleeding and on the patient's clinical conditions;
– For all coagulation agents (aPCC, rFVIIa, FVIII, etc.), consideration should be given to verifying bleeds prior to repeated dosing;
– Use of aPCC should be avoided unless no other treatment options/alternatives are available and aPCC dosing recommendations in case aPCC is the only option.
– Treating physicians must carefully weigh the risk of TMA and thromboembolism against the risk of bleeding when considering aPCC treatment.

- Information on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability in the emicizumab setting and warning that these tests should not be used to monitor for emicizumab activity, determine need for factor replacement dosing, or measure FVIII inhibitors.
- Information on assays and methods not affected by emicizumab that may be used to assess coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays;
- Listing of laboratory tests unaffected by emicizumab;
- Reminder that all patients receiving treatment with emicizumab should be given a Patient Card and reminded to carry it at all times and show it to any healthcare professionals who may treat them and to laboratory professionals that will perform their coagulation testing;
- Reminder to report any adverse events associated with the use of emicizumab.

1.2 PATIENT/CARER EDUCATION MATERIAL

The patient/carer educational material should contain:

- The package leaflet
- Guide for patients/carers

- **The guide for patients/carers** shall contain the following key messages:

  - What is emicizumab, how emicizumab has been tested, and how to use emicizumab;

  - Warning on the risks associated with the concomitant use of bypassing agents and Hemlibra and to discuss with their doctor if they are receiving activated prothrombin complex concentrate (aPCC) when being prescribed or while receiving Hemlibra;

  - Description of the signs and symptoms of the following safety concerns and reminder of the importance of immediately stopping Hemlibra and aPCC and notifying their treating physician if symptoms occur:

    - Destruction of red blood cells (thrombotic microangiopathy)

    - Blood clots (thromboembolism)

  - Information that they should be given a Patient Card and reminder to carry it at all times and to show it to any healthcare professionals who may treat them;

  - Information on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability and on the importance to show the Patient Card to any healthcare professionals who may treat them and to laboratory professionals that will perform their coagulation testing;

  - Reminder to report any adverse events to their treating doctor.

1.3 LABORATORY PROFESSIONALS

The laboratory professional educational material should contain:

- The Summary of Product Characteristics
- Guide for Laboratory Professionals

- **The guide for laboratory professionals** shall contain the following key messages:

  - Chemical class, mode of action, pharmacodynamics and indication for emicizumab

  - Information on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability and not accurately reflect the patient's underlying hemostatic status during emicizumab prophylaxis. Warning that these tests should not be used to monitor for emicizumab activity, determine need for factor replacement dosing, or measure FVIII inhibitors;

  - Information on assays and methods not affected by emicizumab and that may be used to assess coagulation parameters during treatment, with specific considerations for FVIII chromogenic activity assays;

  - Listing of laboratory tests unaffected by emicizumab;

  - Recommendation that the laboratory director contact the patient's treating physician to discuss any abnormal test results.

1.4 PATIENT CARD

The Patient Card shall contain the following key messages:

- Instructions for patients to carry the card at any time, including in conditions of emergency and to present the card at visits to doctors, hospital clinics, carers, laboratory professionals or pharmacists to inform on emicizumab treatment and risks;
- Information on serious, life-threatening thromboembolic events or TMA events that have been observed with the concomitant use of emicizumab with aPCC in patients on emicizumab prophylaxis;
- Guidance on the use of bypassing agents concomitantly with emicizumab and on the dosing recommendations for patients requiring treatment with bypassing agents in the perioperative setting;
- Warning on emicizumab's interference with certain laboratory coagulation tests which will affect their reliability and information that single-factor assays utilizing chromogenic or immuno-based methods are not affected by emicizumab and may be used to assess coagulation parameters during treatment, with specific consideration for factor VIII chromogenic activity assays;
- Contact details of the patient's emicizumab prescriber.