Risk Management Plan

Concizumab

Active substance(s)	**Concizumab**
RMP version number:	2.1
Data lock point for this RMP	30 Sep 2024
Date of final sign off:	See signature page
Rationale for submitting an updated RMP	The RMP has been updated from Version 2.0 to Version 2.1 in accordance with the Committee for Medicinal Products for Human Use (CHMP)/Pharmacovigilance Risk Assessment Committee (PRAC) Day 90 assessment report for the updated new therapeutic indications of haemophilia A or haemophilia B without inhibitors (HA or HB) and in alignment with updated Summary of Product Characteristics.
Summary of significant changes in this RMP	• Update indications of HA and HB • Update RMP relevant sections for HA and HB • Update data for clinical study NN7415-4307 (56-week data) • Update data for compassionate use
Other RMP versions under evaluation	None
Details of the currently approved RMP	RMP version 0.4 (EMEA/H/C/005938/0000)
QPPV Delegate	Wasim Anwar
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Abbreviations

ABR	annualised bleeding rate
ADA	anti-drug antibodies
ADR	adverse drug reaction
AE	adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
aPCC	activated prothrombin complex concentrates
AST	aspartate transaminase
ATHN	American Thrombosis and Haemostasis Network
BU	Bethesda units
CACO	confirmatory analysis cut-off
CNS	central nervous system
CUP	compassionate use programme
CVD	cardiovascular disease
DIC	disseminated intravascular coagulation
DLP	data lock point
DVT	deep vein thrombosis
eGFR	estimated glomerular filtration rate
EUHASS	European Haemophilia Safety Surveillance
F8	coagulation factor VIII gene
F9	coagulation factor IX gene
FVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
FIX	coagulation factor IX
FXa	activated coagulation factor X
HA	haemophilia A without inhibitors
HAwI	haemophilia A with inhibitors
HB	haemophilia B without inhibitors
HBV	hepatitis B virus
HBwI	haemophilia B with inhibitors
HCC	hepatocellular carcinoma
HCP	healthcare professional
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HTC	haemophilia treatment centre
ICH	intracranial haemorrhage
IgG	immunoglobulin G
INN	international non-propriety name
IPB	individual patient basis
ITI	Immune tolerance induction
i.v.	intravenous(-ly)
MedDRA	Medical dictionary for regulatory activities
MI	myocardial infarction
PACO	primary analysis cut-off
PE	pulmonary embolism
PPX	prophylaxis
PSUR	periodic safety update report
PT	preferred term

PWH	people with haemophilia
PYE	participant-years of exposure / patient-years of exposure
rFVIIa	activated recombinant coagulation factor VII
rFVIII	recombinant coagulation factor VIII
rFIX	recombinant coagulation factor IX
RMP	risk management plan
ROM	range of motion
SAE	serious adverse event
s.c.	subcutaneous(-ly)
SmPC	Summary of Product Characteristics
SMQ	standardised MedDRA query
TE	thromboembolic event
TF	tissue factor
TFPI	tissue factor pathway inhibitor
ULN	upper limit of normal
WFH	World Federation of Haemophilia

1 Product overview

Table 1-1 Product overview

Active substance(s) (INN or common name)	**Concizumab**
Pharmacotherapeutic group(s) (ATC Code)	Antihaemorrhagics – other systemic haemostatics: B02BX10
Marketing authorisation applicant	Novo Nordisk A/S Novo Allé DK-2880 Bagsværd Denmark
Medicinal products to which this RMP refers	All presentations of Alhemo® (concizumab)
Invented name(s) in the European Economic Area (EEA)	Alhemo®
Marketing authorisation procedure	Centralised procedure
Brief description of the product	**Chemical class** Biopharmaceutical – Recombinant monoclonal antibody
	Summary of mode of action Concizumab is a humanised recombinant monoclonal antibody directed against the tissue factor pathway inhibitor (TFPI). TFPI is involved in down-regulation of the initiation of coagulation. Concizumab binds specifically to the Kunitz 2 domain of TFPI and prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa). When the TFPI inhibitory activity is reduced, the FXa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex will result in sufficient generation of thrombin to achieve haemostasis. The novel mechanism of action of concizumab is independent of the presence or absence of FVIII or FIX.
	Origin of the active substance Concizumab is a humanised IgG4 monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells.
Hyperlink to the Product Information:	Alhemo® SmPC
Indication(s) in the EEA	**Current (if applicable)** Alhemo® is indicated for routine prophylaxis of bleeding in patients with: • haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and of age 12 years or more. • haemophilia B (congenital factor IX deficiency) with FIX inhibitors and of age 12 years or more.
	Proposed (if applicable) In addition to the above 'Current' indications, the following 2 indications are proposed: Alhemo® is indicated for routine prophylaxis of bleeding in patients with: • severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without FVIII inhibitors and of 12 years of age or more. • moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤2%) without FIX inhibitors and of 12 years of age or more.

Dosage in the EEA	**Current (if applicable)**
	The recommended dosing regimen is
	• Day 1: a loading dose of 1 mg/kg once.
	• Day 2 and until individual maintenance dose setting (see below): once daily dosing of 0.20 mg/kg.
	• Four (4) weeks after initiation of treatment: measurement of concizumab plasma concentration prior to administration of the next scheduled dose. The measurement must be performed using a validated *in vitro* diagnostic test.
	• When the concizumab plasma concentration result is available, the individual maintenance dose is set once based on the concizumab plasma concentration as indicated below:
	  • <200 ng/mL: 0.25 mg/kg Alhemo® once daily.
	  • 200−4,000 ng/mL: 0.20 mg/kg Alhemo® once daily.
	  • >4,000 ng/mL: 0.15 mg/kg Alhemo® once daily.
	
	Individual maintenance dose setting should be performed at the earliest convenience (after the concizumab plasma concentration result is available) and recommended no later than 8 weeks after initiation of treatment.

	Proposed (if applicable) None.
Pharmaceutical form(s) and strengths	**Current (if applicable)** Alhemo® (concizumab) is a solution for injection in a pre-filled pen. The strengths are: • Alhemo® 15 mg/1.5 mL solution for injection • Alhemo® 60 mg/1.5 mL solution for injection • Alhemo® 150 mg/1.5 mL solution for injection • Alhemo® 300 mg/3 mL solution for injection
	Proposed (if applicable) None.
Is/will the product be subject to additional monitoring in the EU?	Yes

Abbreviations: CHO = Chinese Hamster Ovary; EEA = European Economic Area; FIX = coagulation factor IX; FVIII = coagulation factor VIII; K2 = Kunitz 2 domain; TF = tissue factor; TFPI = tissue factor pathway inhibitor.

2 Safety specification

2.1 Module SI: Epidemiology of the indication(s) and target population

2.1.1 Haemophilia A with and without FVIII inhibitors

Congenital haemophilia A is a rare X-linked recessive bleeding disorder characterised by insufficiency or lack of coagulation factor VIII (FVIII). This leads to an impaired ability to control bleeding through normal haemostatic processes of coagulation.

The severity of bleeding in haemophilia A is generally correlated with the endogenous FVIII plasma activity level, and the disorder is classified as 'severe' (<1% of normal FVIII activity), 'moderate' (1–5%) or 'mild' (>5% to <40%) according to these levels.[1]

Inhibitor development is a serious complication following replacement therapy with the deficient coagulation factor that mainly occurs in people with severe congenital haemophilia. Inhibitors are polyclonal high-affinity immunoglobulin G (IgG) antibodies directed against the deficient coagulation factor that partially or completely neutralise the clotting factor activity. Inhibitor levels, measured in Bethesda units (BU), are classified as high titre (≥5 BU/mL) or low titre (0.6 to <5 BU/mL). Low titre inhibitors are often of a transient nature, whereas high titre inhibitors tend to be persistent. When persistent and at a high titre, inhibitors preclude the standard replacement treatment with FVIII concentrates.

2.1.1.1 Incidence and prevalence

According to the World Federation of Hemophilia (WFH) 2021 global annual survey, 185,318 people have been diagnosed with haemophilia A globally.[2] Most of these are males (see further details in Section 2.1.1.2). The estimated birth incidence of haemophilia A is 24.6 cases per 100,000 males for haemophilia A of any severity (9.5 cases per 100,000 males for severe haemophilia A). The estimated prevalence is 17.1 cases per 100,000 males for haemophilia A of any severity (6.0 cases per 100,000 males for severe haemophilia A).[2]

According to the WFH 2021 survey, the prevalence of inhibitors among people with haemophilia A is typically around of 4−5%, whereas the incidence is on the order of 0.5 per 100 person-years. Prevalence and incidence of both HA and HAwI vary among regions worldwide (Table 2-1), due to factors including differences in reporting and clinical standards practices.

Among European countries that provided information on prevalence of HA in the WFH 2021 survey, the highest reported prevalence of HA were found in Ireland, France, Slovakia and the UK, which all had over one thousand cases per 10 million inhabitants.[2]

Table 2-1 Prevalence and incidence of haemophilia A by region

Region	HA	HAwI		
	Prevalence per 10,000,000 inhabitants	Prevalence per 10,000,000 inhabitants	Prevalence per 100 patients with haemophilia A	Incidence[a] per 100 person-years
Africa	74.0	2.09	2.82	1.24
Americas	576	21.3	3.70	0.79
Canada	*869*	*14.4*	*1.66*	*0.24*
South and Central America	*549*	*22.0*	*4.00*	*0.87*
United States	*425*	*24.6*	*5.80*	*NA*
Eastern Mediterranean	343	27.4	8.00	0.91
Europe	911	27.3	3.00	0.21
Southeast Asia	269	17.8	6.63	1.31
Western Pacific	304	14.8	4.88	0.49
Total	**350**	**16.7**	**4.76**	**0.69**

Note: Numbers are based on the reported cases in the countries with complete data included in the WFH 2021 survey.[2]

[a]New cases reported in 2021.

Abbreviations: HA= haemophilia A without inhibitors, HAwI = haemophilia A with inhibitors; NA = not available; WFH = World Federation of Haemophilia.

2.1.1.2 Demographics of the target population – Age, gender, racial and ethnic origin

The distribution by age group of patients with haemophilia A with or without inhibitors is presented in Table 2-2 for major European countries, the U.S., Canada, and Australia (data from the WFH 2021 annual report).

Table 2-2 Distribution of patients with haemophilia A by age group in major European countries, the U.S., Canada, and Australia

Country	0–4 years (%)	5–13 years (%)	14–18 years (%)	19–44 years (%)	>45 years (%)
France	5%	14%	9%	39%	33%
Italy[a]	3%	13%	11%	21%	52%
Netherlands	3%	12%	7%	35%	43%
United Kingdom	6%	13%	7%	39%	36%
United States	8%	23%	12%	38%	19%
Canada	3%	11%	7%	42%	36%
Australia	5%	14%	8%	38%	35%

Note:

- Numbers are from the WFH 2021 global survey, in which 106 countries reported age data for haemophilia A.[2]
- Demographic data (age, gender, racial and ethnic origin) on the population of patients with HAwI are not available in the WFH 2021 global annual report.

[a]Data are from the WFH 2020 version.

Abbreviations: WFH = World Federation of Haemophilia.

Haemophilia A mostly affects males, as it is due to a gene defect inherited in an X-linked recessive manner. Females are mostly carriers due to the X-linked recessive nature of the disorder. In the WFH 2021 annual global survey, 3.4% of the patients with haemophilia A were reported as females.[2]

Females with severe or moderate haemophilia are uncommon, even in specialized care centres, according to a U.S. study.[3] As the risk of inhibitor development increases with haemophilia severity (see Section 2.1.1.3), the number of female patients with HAwI globally is expected to be particularly low.

Haemophilia A affects people from all racial and ethnic groups. However, one study reported that the risk of inhibitor formation is higher in non-Hispanic black and Hispanic people with haemophilia A compared with non-Hispanic white people with haemophilia A.[4]

2.1.1.3 Risk factors for the disease

Congenital haemophilia A is caused by any of a variety of genetic anomalies distributed throughout the defective *F8* gene located on the X-chromosome. As congenital haemophilia is caused by an inherited X-linked recessive trait, being male (and thereby having only one copy of the X chromosome) and having a family history of haemophilia A are risk factors. However, both haemophilia A and B arise as de novo mutations in approximately 30–50% of all cases.[5]

The potential risk factors for inhibitor development in haemophilia A include both genetic and treatment-related risk factors:[6-10]

Potential genetic risk factors

- Type of mutation in the *F8* gene

- Severity of haemophilia (see Table 2-3)
- Family history of haemophilia with inhibitors
- Ethnicity
- Immune-regulatory cytokine gene polymorphisms
- HLA polymorphisms

Potential treatment-related risk factors

- Exposure to FVIII products
- Type of treatment (prophylaxis [PPX] or on-demand)
- Intensive FVIII treatment (including high mean FVIII dose)
- FVIII product type (recombinant versus plasma-derived products)

2.1.1.4 The main existing treatment options

The standard treatment options for patients with haemophilia A are replacement therapy with plasma-derived FVIII (pdFVIII) or recombinant FVIII (rFVIII) products, bypassing agents, and non-factor therapy with a humanized bispecific monoclonal antibody that can replace FVIII in the tenase complex. Treatment with FVIII products is only available through intravenous (i.v.) administration. Emicizumab was the only product on the market with subcutaneous (s.c.) administration. Recently, concizumab (s.c.) has been approved in some countries for HAwI (≥ 12 years of age). Marstacimab, an anti-TFPI, has been approved by EMA and FDA (U.S.) for PPX to prevent or reduce the frequency of bleeding episodes in adults and paediatric patients 12 years of age and older with HA or HB. The product is given (s.c.) once a week.

The development of FVIII inhibitors significantly limits the treatment options (see details below).

Replacement therapy can be provided as a prophylactic regimen, an on-demand regimen or procedural therapy. For patients with severe phenotype haemophilia A, the WFH recommends regular long-term PPX as the standard of care.

Prophylactic treatment

Factor replacement therapy: Patients with HA can be treated prophylactically with FVIII and patients with HAwI may be treated prophylactically with FVIII products at higher doses if the inhibitor titre is low and it is a low-responding inhibitor.

Bypassing agents: Activated prothrombin complex concentrate (aPCC) is an i.v. administered bypassing agent ('bypasses' the action of FVIII) approved for PPX in patients with HAwI. However, aPCC is less efficacious when used as PPX in the treatment of haemophilia A or B with inhibitors (annualised bleeding rate [ABR]: 7.9) than specific factor replacement therapy in patients without inhibitors (mean ABR ~4).[11, 12]

Non-factor therapies: A bispecific monoclonal antibody that can replace FVIII in the tenase complex is approved for routine PPX in patients with HA and HAwI. TFPI is available for PPX in patients with HA.

Treatment of bleeding episodes

Factor replacement therapy: Patients with HA and HAwI with low titre and 'low responding' inhibitors can often continue receiving factor replacement therapy (FVIII products), although at higher doses than those administered in the absence of inhibitors.

Bypassing agents: Recombinant factor VIIa (rFVIIa) and aPCC can be used as on-demand treatment of bleeds in patients with HAwI.

Permanent eradication of inhibitors

Immune tolerance induction (ITI) is considered the standard of care for inhibitor eradication in patients with haemophilia, predominantly in patients with severe haemophilia A. ITI refers to frequent and regular exposure to higher doses of FVIII concentrates over the course of several months to years, as a method to induce tolerance.

2.1.1.5 Natural history of the indicated condition including mortality and morbidity

The clinical manifestations of congenital haemophilia are bleeding episodes due to impaired haemostasis. The bleeds in people with severe haemophilia typically occur spontaneously or after mild trauma in joints, muscles, and soft tissues. Bleeding episodes may occur in all parts of the body, most often occurring in the muscles and joints of the elbows, knees, and ankles causing acute haemarthrosis. Bleeding episodes may also include life-threatening bleeding in the central nervous system (CNS), gastrointestinal and urinary tracts, throat, neck, or retroperitoneum.

Up to 80% of people with haemophilia experience haemarthrosis, 10-20% experience muscle bleeding, and less than 5% experience bleeding in the CNS.[1] Recurrent joint bleeding causes synovial proliferation and inflammation (haemophilic synovitis) that contribute to end-stage degeneration (haemophilic arthropathy). This can lead to chronic pain and limitation of motion due to chronic synovitis, joint destruction and muscle contractures.[13] Depending on the location, some muscle haematomas can be hazardous causing for example acute severe anaemia and compartment syndrome (neurovascular compression).[14]

Intracranial haemorrhage (ICH) is a potentially life-threatening condition that is more common among people with haemophilia than in the general population. A systematic literature review and meta-analysis reported a pooled estimate for ICH incidence among people with haemophilia of 2.3 (95% CI 1.2-4.8) per 1,000 person-years and a pooled cumulative ICH incidence of 2.1% (95% CI, 1.5-2.8) per 100 live births among neonates with haemophilia.[15] The ICH risk is bi-modal, with high risk at birth and at higher ages, when risk factors such as hypertension are more commonly observed.[16] Among children with haemophilia, ICH is relatively rare when on full PPX (0.33 cases of ICH per 1,000 person-years) compared with children on no PPX (17 cases of ICH per 1,000 person-years; rate ratio 50.06) or children on partial PPX (5.0 cases of ICH per 1,000 person-years, rate ratio 14.92) compared to full PPX.[17]

A study of young adults with haemophilia in the U.S. found that approximately 20% only experienced joint pain and limited range of motion (ROM) when they were bleeding, 15% experienced pain all or most of the time, and 25% had limited ROM that affected their daily activities.[18] Another study in people with haemophilia reported that 20% experienced acute pain,

34% chronic pain, and 32% both acute and chronic pain, and those experiencing pain were more likely to be depressed, obese, and have lower health-related quality of life and lower functionality.[19]

Incidence and prevalence of HA and HAwI have been included in the Section 2.1.1.1. A challenging complication of the standard replacement therapy in haemophilia A is the development of FVIII inhibitors (neutralising antibodies directed against FVIII). The incidence rate of inhibitors depends on the severity of the disease (Table 2-3). Approximately 30% of patients with severe haemophilia A and 5% of patients with mild and moderate haemophilia A develop inhibitors.[2] Reports to the United Kingdom National Haemophilia Database (NHD) suggest that FVIII inhibitors arise in people with haemophilia A throughout life with a bimodal risk, being greatest in early childhood and in old age.[20]

The consequences of inhibitor development in haemophilia include reduced efficacy of factor replacement therapy and increased morbidity and mortality.[21, 22] Among European patients with severe haemophilia, patients with high-responding inhibitors more often reported problems with mobility, self-care, daily activities, pain/discomfort and anxiety/depression compared with patients who never had inhibitors or had inhibitors <5 BU in the past (but no current inhibitors).[23]

Table 2-3 Incidence rate of inhibitors in haemophilia A by severity

General population	Severe haemophilia A	Mild/moderate haemophilia A
3.2 per 1,000	6.4 per 1,000	0.1–0.3 per 1,000

Note: Incidence rates are in person-years.[24, 25]

The clinical spectrum of severe haemophilia has evolved from being a condition with high mortality and morbidity in the 20th century to being a chronic and manageable disorder in recent decades.[26] The most common specific causes of death in the post-2000 era were haemorrhage (32%), liver disease (14%), HIV (14%), cancer (13%) and cardiovascular disease (CVD, 13%) as reported in a review and meta-analysis in 2021.[27] This study found an all-cause standardized mortality ratio (SMR) of 1.93 for people with haemophilia compared with the general population.

Haemophilia-related causes of death have been reported to be more frequent among people with haemophilia with an inhibitor (42%) than among those without (12%) an inhibitor.[24, 28]

2.1.1.6 Important co-morbidities found in the target population

Improvement of treatment has increased the life expectancy of people with congenital haemophilia in developed countries. With this increased longevity and improved quality of life due to advances in medical care comes a generation of middle-aged and elderly people with haemophilia, who are experiencing age-related health conditions.

Co-morbidities in the target population can be divided into haemophilia-related conditions (haemophilic arthropathy, osteoporosis and viral infections), age-related conditions (CVD, renal disease, and cancer, e.g., lung cancer, prostate cancer, and colon cancer) and psychiatric issues. Co-morbidities in the target population that are considered important are summarised in Table 2-4.

Table 2-4 Important co-morbidities in the target population

Important co-morbidities	Supporting details
Viral infections and potential complications	Blood-borne viral infections like HCV, HIV and HBV, transmitted via plasma-derived factor products, were considered the most important co-morbidities in people with haemophilia (PWH) prior to the introduction of viral inactivation procedures for haemoderivates in the 1980s. HIV infection is currently effectively controlled by highly active antiretroviral treatment (HAART) but chronic HCV infection has potentially life-threatening effects in co-infected patients, in particular the progression to cirrhosis and end-stage liver failure and the development of hepatocellular carcinoma. In the WFH global survey 2021, 9.9% were identified as currently infected with HCV and 2.1% had HIV among the PWH for which data on both HCV and HIV were available (132,571 patients).[2]
Cardiovascular disease	The existing literature presents conflicting evidence regarding the possibility of a protective effect of haemophilia against CVD.[29] In a 5-year cross-sectional study of PWH in the U.S. (above the age of 35 years), the predicted 10-year risk of fatal myocardial infarction (MI) or stroke was found to be significantly higher (8.9%) than in the general population (6.7%), based on typical factors determining cardiovascular risk (age, blood pressure, total/high-density lipoprotein cholesterol, BMI, and smoking, and history of diabetes mellitus).[30] PWH had twice the lifetime prevalence of coronary artery disease, stroke and MI compared to non-Hispanic white males overall. Nearly 40% of PWH in this study had 2 or more traditional risk factors for CVD.[30]
Renal disease	During a 6-year period, 2.9% of 3,000 PWH presented alterations in renal function requiring hospitalization. The average rate of acute renal disease was 3.4 per 1,000 person years (as compared with an estimated rate of 1.9 per 1,000 person years in the general male population), while chronic renal disease was diagnosed with a rate of 4.7 per 1000 person years (as compared with an estimated rate of 2.9 in the general male population). Risk factors for the development of renal disease in PWH are hypertension, diabetes mellitus, older age, HIV or HCV infection, drug nephrotoxicity (antivirals, antibiotics, etc.), nephrolithiasis and kidney bleeding.[31]
Cancer	HIV-associated non-Hodgkin's lymphomas and HCV-associated hepatocellular carcinomas (HCC) are important causes of death among the virus-infected ageing population of PWH.[32] The risk of HCC is increased in people with chronic HCV infection and this is reflected in the fact that HCC is a frequent cause of death in PWH.[33] A Swedish longitudinal registry study, conducted between the years 1972 and 2008, showed that PWH had a significantly higher incidence of malignant diseases than controls.[34]
Musculoskeletal diseases	Many adults with severe haemophilia advancing into older age were not treated with prophylaxis as children and therefore have established joint disease with the associated burden of joint deformity, muscle weakness and impaired proprioception. Such conditions may cause difficulty with mobility, pain, increased risk of falls and social isolation.[33]

Abbreviations: CVD = cardiovascular disease; HBV = hepatitis B virus; HCC = hepatocellular carcinoma; HCV = hepatitis C virus; HIV = human immunodeficiency virus; MI = myocardial infarction; PWH = people with haemophilia.

2.1.2 Haemophilia B with and without FIX inhibitors

Congenital haemophilia B is a rare X-linked recessive bleeding disorder characterised by insufficiency or lack of FIX. This leads to an impaired ability to control bleeding through normal haemostatic processes of coagulation. Although congenital haemophilia B is a hereditary disorder, it also occurs by de novo mutations in the *F9* gene.

The severity of bleeding in haemophilia B is generally correlated with the endogenous FIX plasma activity level and the disorder is classified as 'severe' (<1% of normal FIX activity), 'moderate' (1-5%) or 'mild' (>5% to <40%) according to these levels.

Inhibitor development is a serious complication occurring mainly in people with severe haemophilia. For further details, see Section 2.1.1.

2.1.2.1 Incidence and prevalence

According to the WFH 2021 annual global survey, the number of people diagnosed with haemophilia B globally is 37,998.[2] Most of these are males, while females are mostly carriers due to the X-linked recessive nature of the disorder (see further details in Section 2.1.2.2). The estimated birth incidence globally is 5.0 per 100,000 males for haemophilia B of any severity (1.5 per 100,000 males for severe haemophilia B). The estimated prevalence of haemophilia B of any severity is 3.8 cases per 100,000 males (1.1 cases per 100,000 males for severe haemophilia B). Notably, the prevalence and incidence of haemophilia B vary across regions and economic classes.[2]

According to the WFH 2021 global survey, the prevalence of inhibitors among patients with haemophilia B is typically around of 1-2%, whereas the incidence is on the order of 0.2 per 100 person-years, but the numbers vary among regions worldwide (Table 2-5). Among the European countries that provided information on prevalence of HB in the WFH 2021 survey, the highest prevalence per 10,000,000 inhabitants was reported in Ireland (443), followed by France (272) and Hungary (250).[2]

Table 2-5 Prevalence and incidence of haemophilia B by region

Region	HB	HBwI		
	Prevalence per 10,000,000 inhabitants	Prevalence per 10,000,000 inhabitants	Prevalence per 100 patients with haemophilia B	Incidence[a] per 100 person-years
Africa	16.0	0.16	1.03	0.57
Americas	116	1.32	1.14	0.33
Canada	*190*	*0.26*	*0.14*	*0*
South and Central America	*108*	*1.43*	*1.32*	*0.38*
United States	*130*	*2.38*	*1.84*	*NA*
Eastern Mediterranean	74.1	0.99	1.34	0.11
Europe	203	2.03	1.00	0.11
Southeast Asia	32.3	0.14	0.44	0
Western Pacific	62.5	0.45	0.72	0.06
Total	77.5	0.85	1.10	0.19

Note:

- Numbers are based on the reported cases in the countries included in the WFH 2021 survey.[2]
- Data on the incidence of inhibitors in the U.S. were not available in the WFH 2021 Annual Global Survey report.

[a]New cases reported in 2021.

Abbreviations: HB = haemophilia B without inhibitors; HBwI = haemophilia A with inhibitors; NA = not available; WFH = World Federation of Hemophilia.

2.1.2.2 Demographics of the target population – Age, gender, racial and ethnic origin

The distribution by age group of patients with haemophilia B with or without inhibitors is presented in Table 2-6 for major European countries, the U.S., Canada, and Australia (data from the WFH 2021 global survey).

Table 2-6 Distribution of patients with haemophilia B by age group in major European countries, the U.S., Canada, and Australia

Country	0–4 years	5–13 years	14–18 years	19–44 years	>45 years
France	5%	15%	10%	35%	34%
Italy[a]	3%	12%	13%	36%	37%
Netherlands	4%	12%	9%	37%	39%
United Kingdom	5%	15%	6%	37%	37%
United States	10%	21%	12%	33%	24%
Canada	3%	10%	7%	40%	40%
Australia	4%	10%	10%	37%	40%

Note:

- Numbers are from the WFH 2021 global survey, in which 106 countries reported age data for haemophilia B.[2]
- Demographic data (age, gender, racial and ethnic origin) on the population of patients with HBwI are not available in the report on the WFH 2021 annual global survey.

[a]Data are from the WFH 2020 version.

Abbreviations: WFH = World Federation of Haemophilia.

Haemophilia B is a congenital disease that mostly affects men, as it is due to a gene defect inherited in an X-linked recessive manner. In the WFH 2021 global survey, 6% of the patients with haemophilia B were reported as females.[2]

Females with severe or moderate haemophilia are uncommon.[3] As the risk of inhibitor development increases with haemophilia severity (Table 2-7), the number of female patients with HBwI globally is expected to be low.

Haemophilia B affects people from all racial and ethnic groups, but the risk of inhibitor development has been reported to be higher in certain ethnic/racial groups (see Section 2.1.1.2).

2.1.2.3 Risk factors for the disease

Congenital haemophilia B is caused by any of a variety of genetic anomalies distributed throughout the *F9* gene located on the X chromosome. Like haemophilia A, it is inherited in X-linked recessive manner and thereby being male and having a family history of haemophilia B are risk factors (see also Section 2.1.1.3).

As for haemophilia A, the potential risk factors for inhibitor development in people with haemophilia B include genetic (i.e., type of mutation in the *F9* gene) and treatment-related risk factors (see Section 2.1.1.3).

2.1.2.4 The main existing treatment options

The standard treatment for patients with haemophilia B is replacement therapy with plasma-derived FIX (pdFIX) or recombinant FIX (rFIX) products as well as bypassing agents, all i.v. administered. Recently, concizumab (s.c.) has been approved in some countries for HBwI (≥ 12 years of age). Marstacimab has been approved by EMA and FDA (U.S.) for PPX to prevent or reduce the

frequency of bleeding episodes in adults and paediatric patients 12 years of age and older with HB. The product is given (s.c.) once a week.

Development of FIX inhibitors significantly limits the treatment options.

For patients with severe phenotype haemophilia B, the WFH recommends regular long-term PPX as the standard of care.

Prophylactic treatment

Factor replacement therapy: Patients with HB can be treated prophylactically with FIX and patients with HBwI with low titre and low responding inhibitors may be treated prophylactically with replacement therapy (FIX products), although at higher doses than those administered in the absence of inhibitors. This is only an option if the patient has not developed complications associated with inhibitors, e.g., anaphylactic reactions or nephrotic syndrome.

Bypassing agents: The i.v. administered bypassing agent aPCC is approved for PPX in patients with HBwI. However, aPCC used as PPX to overcome the haemostatic interference of an inhibitor in haemophilia B is less efficacious than factor treatment in patients without inhibitors (see Section 2.1.1.4). Also, aPCC is contraindicated for the majority of HBwI patients due to the risk of anaphylactic reactions or severe hypersensitivity reactions.

Non-factor therapies: TFPI is available for PPX in patients with HB.

Treatment of bleeding episodes

Factor replacement therapy: Patients with haemophilia B who have low titre and low responding inhibitors can continue receiving factor replacement therapy for on-demand treatment of bleeds, although at higher doses, if they have not developed inhibitor-associated complications.

Bypassing agents: Recombinant factor VIIa (rFVIIa) and aPCC can be used as on-demand treatment of bleeds. However, most patients with HBwI are not treated with aPCC due to the risk of anaphylactic or severe hypersensitivity reactions. Thus, rFVIIa is the main treatment option.

Permanent eradication of inhibitors

ITI is considered the standard of care for inhibitor eradication in patients with haemophilia (see also Section 2.1.1.4). The administration of high doses of FIX concentrate with or without simultaneous immunosuppression may be used to reduce or eliminate inhibitors in patients with HBwI. Nephrotic syndrome is a recognized complication of ITI particularly in patients with haemophilia B who have experienced anaphylactic reactions to FIX concentrate.[35]

2.1.2.5 Natural history of the indicated condition including mortality and morbidity

The clinical manifestations of haemophilia B are very similar to those with haemophilia A, i.e., bleeding episodes due to impaired haemostasis (see details in Section 2.1.1.5). As with haemophilia A, the most challenging complication in the treatment of haemophilia B is the development of inhibitors.[21] Although the incidence of inhibitors in patients with haemophilia B is low (Table 2-5 and Table 2-7), most are ‘high titre’ and can be associated with related complications.

Table 2-7 Incidence rate of inhibitors in haemophilia B by severity

General population	Severe haemophilia B	Mild/moderate haemophilia B
0.3 per 1,000	1.0 per 1,000	0.2–0.6 per 1,000

Note: Incidence rates are in person-years.[24, 25]

The development of acute anaphylactic reactions to factor concentrates is a well-known phenomenon in patients with HBwI.[7] Anaphylaxis was reported in 56 out of 94 cases of complications associated with inhibitors in people with haemophilia B in a study with data from a FIX inhibitor registry covering haemophilia centres in North America, Europe, Japan, and Australia. The other 38 cases concerned severe allergic reactions.[35] In some of these patients, anaphylaxis or severe allergic reactions occurred concurrently with inhibitor detection, whereas in others, these events occurred weeks or months apart.

After developing inhibitors, patients with HBwI have a higher risk of developing nephrotic syndrome if the FIX exposure continues, e.g., during ITI therapy.[36] Even if the inhibitor titre is low or the inhibitor test negative after interruption of FIX exposure, these patients are still treated as inhibitor patients due to the risk of recurrence of the inhibitor, anaphylaxis and nephrotic syndrome, i.e., the treatment options are limited to bypassing agents.

Overall, morbidity and mortality in patients with haemophilia B are similar to those described for haemophilia A. In both subtypes of congenital haemophilia, inhibitor development has significant impact on morbidity and mortality (see Section 2.1.1.5).

2.1.2.6 Important co-morbidities found in the target population

The co-morbidities in people with congenital haemophilia are overall the same for people with haemophilia A and B. Important co-morbidities for congenital haemophilia A are presented in Section 2.1.1.6.

2.2 Module SII: Nonclinical safety findings

2.2.1 Important nonclinical safety findings and their relevance to human use

In the nonclinical studies, concizumab was generally s.c. administered. In Table 2-8, the important nonclinical safety findings have been summarised along with assessments of the human relevance.

Table 2-8 Important nonclinical safety findings and their relevance to human use

Key nonclinical safety findings	Relevance to human usage
Repeat-dose toxicity, including important safety pharmacology findings	
Thrombi Thrombi were observed in the lungs, heart, and several other organs in repeat-dose toxicology studies of 13 weeks and up to 52 weeks duration, conducted in male and female juvenile (2-3 years) and sexually mature (3.5-6 years) cynomolgus monkeys.	The occurrence of thrombi in repeat dose toxicity studies was considered a result of exaggerated pharmacology of a procoagulant compound (concizumab) administered to animals with a normal coagulation system. Thromboembolic events have been classified as an important identified risk in the RMP (see details on the risk in Section 2.7.3.1).

Key nonclinical safety findings	Relevance to human usage
Focal vascular changes Focal vascular changes, which included endothelial hypertrophy, subendothelial thickening and inflammatory cell infiltration, in the choroid plexus and lungs were observed in repeat dose toxicity studies of 13 weeks and up to 52 weeks duration (cynomolgus monkeys). These focal vascular changes are considered to be caused by an immunogenic reaction related to development of anti-drug antibodies (ADA), as described for other biologics. ADA-related immune complexes were formed to an extent exceeding the animals' physiological clearance capacity for immune complexes, leading to deposition of immune complexes in the tissues, with secondary tissue damage.	The risk of immune complex formation exceeding the clearance capacity is considered lower in humans, as patients are expected to have a lower immunogenic response towards a humanised monoclonal antibody like concizumab and will be exposed to lower concentrations of concizumab than the cynomolgus monkeys in the repeat dose studies. It is generally recognised that animal studies have limited ability to predict human immune responses to therapeutic proteins. Based on an overall evaluation, the risk of focal vascular changes is not carried forward as an important potential risk in the RMP.
Juvenile toxicity	
The toxicity of concizumab is considered adequately characterised through the general toxicology programme in juvenile (2-3 years) and sexually mature (3.5-6 years) cynomolgus moneys, and dedicated studies in juvenile animals have therefore not been performed. Thrombi and focal vascular changes were observed in the general toxicology programme in juvenile as well as adult animals.	The relevance to human use of the thrombi and focal vascular changes observed in the general toxicology programme is described above.
Reproductive and developmental toxicity	
No reproductive and developmental toxicity studies have been performed with concizumab as the target population is people with haemophilia A or B, which mostly affect males. The concizumab interventional clinical trials only included male patients. Fertility: Fertility endpoints were included in the 26-week toxicity study in cynomolgus monkeys. No treatment-related effects on menstrual cycle duration, testicular size, sperm count, sperm motility and sperm morphology were seen. Histopathological investigation of the reproductive organs from the conducted toxicity studies up to 52 weeks duration in juvenile and sexually mature cynomolgus monkeys did not indicate any adverse effect on the reproductive organs.	No dedicated nonclinical reproductive and developmental toxicity studies were performed. The implications of TFPI inhibition in pregnant women are not known, and pregnant female patients were not included in the development programme.
Local tolerance	
Local effects at the s.c. injection sites were observed in the toxicity studies in monkeys. The inflammatory cell foci/perivascular accumulation of leukocytes observed were similar to findings in animals after s.c. injection of other human proteins. The effects were reversible and are considered to be related to an immunogenic response to concizumab.	The observed changes at the injection sites in repeat dose toxicity studies in monkeys are considered acceptable for clinical administration of human proteins. Local reaction has been assessed as part of the clinical development programme. Injection site reactions are not considered an important risk for inclusion in the list of safety concerns in the RMP (Table 2-17).

Abbreviations: ADA = anti-drug antibodies; RMP = risk management plan; s.c. = subcutaneous; TFPI = tissue factor pathway inhibitor.

2.2.2 Conclusions on nonclinical data

In conclusion, the comprehensive nonclinical programme did not identify any safety concerns that prohibit chronic s.c. administration of concizumab to humans. Based on the evaluations of

nonclinical data, the risk related to thromboembolic events (TEs) is brought forward as a safety concern (Table 2-9).

Table 2-9 Nonclinical summary of safety concerns

Safety concerns
Important identified risks (confirmed by clinical data) • Thromboembolic events
Important potential risks (not refuted by clinical data or of unknown significance) • None
Missing information • None

2.3 Module SIII: Clinical study exposure

2.3.1 Clinical exposure to concizumab - introduction

The clinical development programme was initiated in 2010. Clinical studies conducted with concizumab as investigational product are identified with the project number NN7415, followed by a unique four-digit number, e.g., NN7415-1234.

The global clinical study programme for concizumab comprises:

- Four (4) completed phase 1 studies (2 single dose and 2 multiple-dose studies)
- Two (2) completed phase 2 studies (in participants with HA, HAwI or HBwI)
- Three (3) ongoing phase 3 therapeutic confirmatory studies:
  - One (1) study (NN7415-4311) in participants ≥12 years of age with HAwI or HBwI (primary analysis cut-off [PACO] and 56-week data cut-off reached)
  - One (1) study (NN7415-4307) in participants ≥12 years of age with HA or HB (confirmatory analysis cut-off [CACO] and 56-week data cut-off reached after initial submission)
  - One (1) study (NN7415-4616) in participants with HA, HB, HAwI or HBwI

An overview of all interventional clinical studies included in the concizumab clinical development programme as of the data lock point (DLP) of the RMP is provided in Table 2-10.

Table 2-10 Overview of clinical studies with concizumab as primary investigational product

Concizumab clinical development programme – interventional studies					
Study name	**Study ID**	**Phase**	**Population/indication (age)**	**Dosing**	**Status**
EXPLORER 1	NN7415-3813	1	HA, HB, healthy participants (18–65 years)	Single dose	Completed
-	NN7415-3981	1	Healthy Japanese participants (20–64 years)	Single dose	Completed
EXPLORER 2	NN7415-3986	1	Healthy participants, HA[a] (18–64 years)	Multiple dose	Completed
EXPLORER 3	NN7415-4159	1b	HA (18–64 years)	Multiple dose	Completed
EXPLORER 4	NN7415-4310	2	HAwI, HBwI (≥18 years)	Once-daily dosing	Completed
EXPLORER 5	NN7415-4255	2	HA (≥18 years)	Once-daily dosing	Completed
EXPLORER 7	NN7415-4311	3	HAwI, HBwI (≥12 years)	Once-daily dosing	PACO and 56-week data cut-off reached[b] Extension part ongoing
EXPLORER 8	NN7415-4307	3	HA, HB (≥12 years)	Once-daily dosing	CACO and 56-week data cut-off reached[b] Extension part ongoing
EXPLORER 10	NN7415-4616	3	HA, HB, HAwI, HBwI **Arm 1:** Concizumab-naive male patients <12 years of age. **Arm 2:** Male patients (regardless of age) previously treated with concizumab via compassionate use.	Once-daily dosing	Ongoing

[a]Study NN7415-3986 was terminated before any participants with haemophilia A had been included.

[b]The PACO and 56-week data cut-off for study NN7415-4311, and CACO and 56-week cut-off for study -4307 are defined in the clinical study reports.

Abbreviations: CACO = confirmatory analysis cut-off; HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; HAwI = haemophilia A with inhibitors; HBwI = haemophilia B with inhibitors; PACO = primary analysis cut-off.

Clinical study exposure is presented in Section 2.3.2.

Results from compassionate use with concizumab in patients with HBwI who have received concizumab via the compassionate use programme (CUP) and/or individual patient basis (IPB) are

also included in the safety evaluation of concizumab. Compassionate use exposure is presented in Section 2.3.3.

2.3.2 Clinical study exposure

Pooling strategy for the safety evaluation

Pooled results from five multiple-dose studies in male participants with haemophilia was the main basis for the evaluation of the safety profile of concizumab. The *pooled safety evaluation* of concizumab included data from the multiple-dose studies NN7415-4159, -4310, -4255, -4311 and −4307 (see Annex 7A for details). The five studies were overall similar with respect to study population (inclusion/exclusion criteria) for the respective haemophilia subtypes (HA, HB, HAwI and HBwI), whereas differences in design features, including dosing regimen and treatment duration are apparent across studies.

As of the DLP of the RMP, 61 participants had been exposed at least once to concizumab in the clinical study NN7415-4616. The exposure data from this study were not included in the pooled exposure tables (see below), since no interim database lock (DBL) had been reached. Overall, no TEs or adverse event of special interest (AESI) or deaths had been reported from clinical study NN7415-4646 from first participant first visit until the DLP of the RMP.

Three (3) completed phase 1 studies did not contribute to the pooled safety evaluation performed with the causality assessment included: NN7415-3813, -3981, and -3986 (see Table 2-10). Safety data from these studies are generally of limited value when establishing the safety profile of an investigational product.

Concizumab treatment pause in phase 3 studies

Novo Nordisk paused concizumab treatment in the phase 3 clinical studies (NN7415-4311 and -4307) in March 2020, and the studies were subsequently put on clinical hold, due to the occurrence of serious TEs (all non-fatal) in 3 participants. Findings in the investigations of the TEs led Novo Nordisk to implement changes to study protocols as risk mitigating activities (see Section 2.7.3.1). The clinical hold was lifted in August 2020 and treatment with concizumab in the two phase 3 studies was restarted.

Clinical exposure in the phase 3 studies NN7415-4311 and -4307 reflects exposure prior to and after the treatment pause, i.e., the period of the treatment pause is not included as concizumab exposure time. Exposure time is calculated as duration from first exposure to study product until the last exposure to study product, excluding the duration of the treatment pause.

Exposure to concizumab in clinical studies

Clinical study exposure in this section is presented by duration, age range and racial group for the five multiple-dose studies in haemophilia. For the two pivotal phase 3 studies NN7415-4311 and -4307, exposure is included up until the 56-week cut-off (13 Jun 2022 and 27 Dec 2022, respectively).

Table 2-11 shows the total number of study participants exposed to concizumab in the five multiple-dose studies that contributed to the *pooled safety evaluation* and in the three completed phase 1 studies that did not contribute to this evaluation.

Table 2-11 Overview of clinical study exposure to concizumab

Clinical studies	Number of participants	Total exposure (PYE)
Multiple-dose studies (HA, HB, HAwI, HBwI)[a]	320	455.6
Phase 1 studies (single dose or multiple dose in healthy participants)[b]	49	N/A

Note:

- Details on the clinical studies are presented in Table 2-10.
- Exposure (PYE) is calculated as duration from first exposure to study product until the last exposure to study product. For the ongoing phase 3 studies NN7415-4311 and -4307, the duration of the concizumab treatment pause is excluded.

[a]Multiple-dose studies in the pooled safety evaluation, NN7415-4159, -4310, -4255, -4311 and -4307.

[b]Studies NN7415-3813, 3981, and 3986.

Abbreviations: N/A = not applicable; PYE = participant-years of exposure.

A total of 320 unique participants with haemophilia have been exposed to concizumab across the five multiple-dose studies with a total of 455.6 PYE (see Table 2-11).

Exposure to concizumab by haemophilia subpopulation across the five multiple-dose studies:

- 125 participants with HA (187.2 PYE)
- 64 participants with HB (72.5 PYE)
- 78 participants with HAwI (116.5 PYE)
- 53 participants with HBwI (79.4 PYE)

Thus, a total of 189 were participants without inhibitors (HA and HB, PYE: 259.7) and 131 were participants with inhibitors (HAwI and HBwI, PYE: 195.9).

Exposure to concizumab in the five multiple-dose studies is presented below by duration (Figure 2-1 and Table 2-12), age range (Table 2-13) and racial group (Table 2-14).

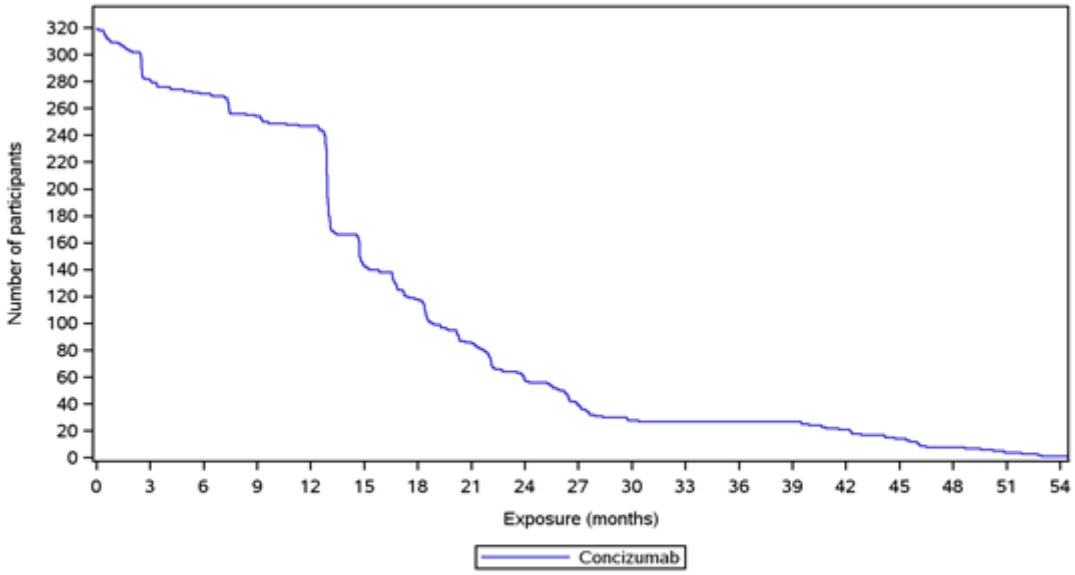
Exposure by dose

Due to differences in concizumab PPX dosing regimens and dose setting criteria, it is not meaningful to directly compare total exposure time by dose across the five multiple-dose studies in participants with haemophilia. Therefore, no across study exposure by dose level is presented in this section.

Comparator exposure

In the pooled safety evaluation, the comparator arms across the five multiple-dose studies have not been combined due to the inherent difference between the 'no PPX, on-demand treatment only' comparator arms (in studies NN7415-4310, -4311 and -4307) and the placebo comparator (in study NN7415-4159) as well as to avoid a mixture of within- and between-participant comparisons. Therefore, no across study exposure to comparators is presented in this section.

Figure 2-1 Duration of exposure to concizumab in clinical studies by monthly intervals (all populations/indications)



Studies included: NN7415-4159, NN7415-4255, NN7415-4310, NN7415-4311 (56 weeks cut-off) and NN7415-4307 (56 weeks cut-off).
Exposure is calculated as duration from first exposure to the study product until the last exposure to the study product. For studies NN7415-4311 and NN7415-4307, the duration for which concizumab was paused is excluded for arm 2, 3, and 4.

nn7415/nn7415-safety-update/rmp_cutoff_20240930_er
01OCT2024:10:19:27 - fexpoconz/fexpoconz.png

Table 2-12 Duration of exposure to concizumab in clinical studies by monthly intervals and population/indication

Indication	Duration	Number of participants
HA	>0 months	125
	>3 months	98
	>6 months	95
	>9 months	91
	>12 months	88
	>15 months	60
	>18 months	58
	>21 months	49
	>24 months	38
	>27 months	24
	>30 months	14
	>33 months	13
	>36 months	13
	>39 months	13
	>42 months	9
	>45 months	8
	>48 months	7
	>51 months	5
	>54 months	2
	>57 months	0
HB	>0 months	64
	>3 months	61
	>6 months	58
	>9 months	50
	>12 months	49
	>15 months	18
	>18 months	16
	>21 months	10
	>24 months	1
	>27 months	0
HAwI	>0 months	78
	>3 months	75
	>6 months	74
	>9 months	72
	>12 months	72
	>15 months	37
	>18 months	26
	>21 months	15
	>24 months	11
	>27 months	9
	>30 months	8
	>33 months	8
	>36 months	8
	>39 months	8
	>42 months	6
	>45 months	3
	>48 months	1
	>51 months	0
HBwI	>0 months	53
	>3 months	48
	>6 months	45
	>9 months	42
	>12 months	39
	>15 months	29

Indication	Duration	Number of participants
HBwI	>18 months	19
	>21 months	13
	>24 months	9
	>27 months	8
	>30 months	7
	>33 months	7
	>36 months	7
	>39 months	7
	>42 months	7
	>45 months	4
	>48 months	1
	>51 months	0
HAwI+HBwI	>0 months	131
	>3 months	123
	>6 months	119
	>9 months	114
	>12 months	111
	>15 months	66
	>18 months	45
	>21 months	28
	>24 months	20
	>27 months	17
	>30 months	15
	>33 months	15
	>36 months	15
	>39 months	15
	>42 months	13
	>45 months	7
	>48 months	2
	>51 months	0
All participants	>0 months	320
	>3 months	282
	>6 months	272
	>9 months	255
	>12 months	248
	>15 months	144
	>18 months	119
	>21 months	87
	>24 months	59
	>27 months	41
	>30 months	29
	>33 months	28
	>36 months	28
	>39 months	28
	>42 months	22
	>45 months	15
	>48 months	9
	>51 months	5
	>54 months	2
	>57 months	0

Note:

- Studies included: NN7415-4159, -4255, -4310, -4311 (56-week data) and -4307 (56-week data).
- Exposure is calculated as duration from first exposure to the study product until the last exposure to the study product. For studies NN7415-4311 and -4307, the duration for which concizumab was paused is excluded for arm 2, 3, and 4.

Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors.

Table 2-13 Cumulative exposure to concizumab by population and age range

Population/ Indication	Age range	Concizumab N (PYE)
Clinical pharmacology clinical studies (4159)		
HA	Adults (18-64 years)	18 (3.8)
	Total	18 (3.8)
All participants	Adults (18-64 years)	18 (3.8)
	Total	18 (3.8)
Exploratory/confirmatory studies		
HA	Adolescents (12-17 years)	21 (26.4)
	Adults (18-64 years)	83 (148.6)
	Elderly (65-74 years)	3 (8.5)
	Total	107 (183.4)
HB	Adolescents (12-17 years)	15 (16.8)
	Adults (18-64 years)	49 (55.7)
	Total	64 (72.5)
HAwI	Adolescents (12-17 years)	22 (28.2)
	Adults (18-64 years)	56 (88.3)
	Total	78 (116.5)
HBwI	Adolescents (12-17 years)	20 (23.2)
	Adults (18-64 years)	32 (56.1)
	Elderly (75-84 years)*	1 (0.1)
	Total	53 (79.4)
HAwI+HBwI	Adolescents (12-17 years)	42 (51.4)
	Adults (18-64 years)	88 (144.4)
	Elderly (75-84 years)*	1 (0.1)
	Total	131 (195.9)
All participants	Adolescents (12-17 years)	78 (94.6)
	Adults (18-64 years)	220 (348.7)
	Elderly (65-74 years)	3 (8.5)
	Elderly (75-84 years)*	1 (0.1)
	Total	302 (451.8)
All participants		
HA	Adolescents (12-17 years)	21 (26.4)
	Adults (18-64 years)	101 (152.4)
	Elderly (65-74 years)	3 (8.5)
	Total	125 (187.2)
HB	Adolescents (12-17 years)	15 (16.8)
	Adults (18-64 years)	49 (55.7)
	Total	64 (72.5)
HAwI	Adolescents (12-17 years)	22 (28.2)
	Adults (18-64 years)	56 (88.3)
	Total	78 (116.5)
HBwI	Adolescents (12-17 years)	20 (23.2)
	Adults (18-64 years)	32 (56.1)

Population/ Indication	Age range	Concizumab N (PYE)
HBwI	Elderly (75-84 years)*	1 (0.1)
	Total	53 (79.4)
HAwI+HBwI	Adolescents (12-17 years)	42 (51.4)
	Adults (18-64 years)	88 (144.4)
	Elderly (75-84 years)*	1 (0.1)
	Total	131 (195.9)
All participants	Adolescents (12-17 years)	78 (94.6)
	Adults (18-64 years)	238 (352.5)
	Elderly (65-74 years)	3 (8.5)
	Elderly (75-84 years)*	1 (0.1)
	Total	320 (455.6)

Note:

- Studies included: NN7415-4159, -4310, -4255, -4311 (56-week data) and -4307 (56-week data). All participants are males.
- Exposure is calculated as duration from first exposure to the study product until the last exposure to the study product. For studies NN7415-4311 and -4307, the duration for which concizumab was paused is excluded for arm 2, 3, and 4.

*The elderly participant in study NN7415-4311 did not re-start after the concizumab treatment pause.

Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; PYE = participant-years of exposure.

Table 2-14 Cumulative exposure to concizumab by population and racial group

Population/ Indication	Racial group	Concizumab N (PYE)
All participants		
HA	American Indian or Alaska Native	2 (2.1)
	Asian	31 (56.4)
	Black or African American	3 (1.7)
	White	84 (116.9)
	Other	2 (2.0)
	Not reported	3 (8.1)
	Total	125 (187.2)
HB	American Indian or Alaska Native	1 (0.3)
	Asian	16 (16.6)
	Black or African American	2 (2.8)
	White	44 (51.2)
	Other	1 (1.7)
	Total	64 (72.5)
HAwI	American Indian or Alaska Native	1 (1.1)
	Asian	21 (33.5)
	Black or African American	7 (8.2)
	White	49 (73.7)
	Total	78 (116.5)
HBwI	American Indian or Alaska Native	2 (1.5)
	Asian	15 (19.0)
	Black or African American	2 (2.4)
	White	29 (51.7)
	Not reported	5 (4.8)
	Total	53 (79.4)
HAwI+HBwI	American Indian or Alaska Native	3 (2.6)
	Asian	36 (52.5)
	Black or African American	9 (10.6)
	White	78 (125.5)
	Not reported	5 (4.8)
	Total	131 (195.9)
All participants	American Indian or Alaska Native	6 (5.0)
	Asian	83 (125.5)
	Black or African American	14 (15.0)
	White	206 (293.6)
	Other	3 (3.7)
	Not reported	8 (12.9)
	Total	320 (455.6)

Note:

- Studies included: NN7415-4159, -4310, -4255, -4311 (56-week data) and -4307 (56-week data). All participants are males.
- Exposure is calculated as duration from first exposure to the study product until the last exposure to the study product. For studies NN7415-4311 and -4307, the duration for which concizumab was paused is excluded for arm 2, 3, and 4.

Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; PYE = participant-years of exposure.

In summary, most study participants exposed to concizumab in the five multiple-dose studies were adults (aged 18-64 years; 238 out of 320; 74%) or adolescents (aged 12-17 years; 78 out of 320; 24%) and White (206 out of 320; 64%) or Asian (83 out of 320; 26%).

2.3.3 Compassionate use exposure

Results on exposure from compassionate use are based on the cleaned data available as per 28 Feb 2024 for patients receiving concizumab on IPB and up until the interim cut-off date (07 Nov 2023) for patients in the CUP (NN7415-4807, Annex 7B).

Concizumab was provided to a total of 27 patients with HBwI:

- 19 patients had received concizumab on an IPB, whereby patients can obtain health authority agreement to receive unapproved medicinal products outside a clinical study.
- 11 patients had been included in the CUP, which was covered by a specific protocol (NN7415-4807) and ClinicalTrials.gov Identifier (NCT04921956), and where patients can apply globally. Three of the 11 patients had also previously received concizumab on an IPB.

Patients were aged between 11 months and 31 years when they first received concizumab and treatment exposure ranged from 1 month to 4 years and 5 months. Eighteen (18) of the 27 patients were below the age of 12 years when they first received concizumab.

In addition, between the above cut-offs and the DLP of the RMP, a total of 28 patients (14 on IPB and 14 in CUP) were received treatment with concizumab.

2.4 Module SIV: Populations not studied in clinical studies

2.4.1 Exclusion criteria in pivotal clinical studies within the development programme

This section summarises the important exclusion criteria in the pivotal phase 3 studies and presents the reason for the exclusion as well as the rationale for why the excluded population has not been classified as missing information for concizumab (Table 2-15).

Table 2-15 Discussion of important exclusion criteria in pivotal clinical studies within the development programme (HA, HB, HAwI and HBwI)

Exclusion criterion	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Known or suspected hypersensitivity to any constituent of the study product or related products.	Allergic reactions may be potentially severe, life-threatening, or fatal. This patient population is excluded to minimise the risk of allergic reactions and other hypersensitivity reactions to the study product in the study.	No The product is not anticipated to be used in patients with known or suspected hypersensitivity to any constituent of the study product or related products. Due to the potential health impact in these patients, use of concizumab in this population is contraindicated.
Platelets ≤ $100x10^{9/}$L at screening	Patients with significant thrombocytopenia (defined as platelets ≤ $100x10^{9/}$L) may have an increased bleeding tendency that is not related to insufficiency or lack of FVIII or FIX. Low platelet counts could therefore potentially confound the study results. They were also excluded to avoid jeopardizing their safety.	No A low platelet count (thrombocytopenia) may add to the bleeding tendency in patients with haemophilia A or B, but a different safety profile of concizumab is not expected in this population.
Fibrinogen below laboratory lower normal limit at screening	Patients with low fibrinogen levels may have an increased bleeding tendency due to impaired clot formation. Low fibrinogen levels could therefore have a potential confounding effect on study results.	No Low fibrinogen levels will add to the bleeding tendency in patients with haemophilia A or B, but a different safety profile of concizumab is not expected in this population.
Hepatic dysfunction defined as AST and/or ALT > 3 times the upper limit combined with total bilirubin > 1,5 times the upper limit at screening	Participants with biochemical signs of clinically significant hepatic impairment at screening were excluded to avoid participants with a serious condition that could potentially interfere with study schedule, study procedures and study results. They were also excluded to avoid jeopardizing their safety.	No There is no medical or scientific reason to expect a different safety profile of concizumab in this population, considering the mechanism of action and elimination of concizumab (see Section 2.4.3.1). No impact on concizumab exposure has been observed in participants with hepatic impairment defined as AST and/or ALT ≥ 1.5 times ULN.

Exclusion criterion	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) ≤ 30 ml/min/1.73 m^2 for serum creatinine measured at screening	Participants with biochemical signs of clinically significant renal impairment were excluded to avoid participants with a serious condition that could potentially interfere with study schedule, study procedures and study results. They were also excluded to avoid jeopardizing their safety.	No There is no medical or scientific reason to expect a different safety profile of concizumab in this population, considering the mechanism of action and elimination of concizumab (see Section 2.4.3.2). No impact on concizumab exposure has been observed in participants with reduced renal function defined as eGFR < 90 ml/min/1.73 m^2.
Known inherited or acquired coagulation disorder other than congenital haemophilia	Patients with congenital or acquired abnormalities in the coagulation system other than congenital haemophilia were excluded to avoid potential confounding effects on study results by concomitant illness affecting the haemostatic system.	No Concizumab is not indicated for use in patients with other coagulation disorders than congenital haemophilia. No studies have been conducted with concizumab in patients with other rare coagulation disorders. However, the safety profile of concizumab is not expected to be different in patients with other inherited or acquired bleeding disorders based on its mechanism of action.
History of thromboembolic disease[a]. Current clinical signs of or treatment for thromboembolic disease. Patients who in the judgement of the investigator are considered at high risk of thromboembolic events[b]	Patients at high risk of thrombotic manifestations were excluded to avoid jeopardizing their safety, as concizumab is a procoagulant drug and therefore might further increase the risk of thromboembolic events.	No 'Thromboembolic events' is included as an important identified risk in the RMP. The safety of concizumab in these patient populations will be monitored via activities planned to further characterise the risk of thromboembolic events (see Section 2.7.3.1).
A known systemic inflammatory condition requiring systemic treatment at screening	Patients with a known systemic inflammatory condition that required systemic treatment at screening were excluded due to a theoretical concern that TFPI inhibition might enhance inflammation. TFPI is a natural inhibitor of tissue factor (TF), which is involved in a variety of coagulation-independent processes, including inflammation. Based on results from animal models as well as *in vivo* and *in vitro* nonclinical toxicology studies, the primary risk related to an increased TF expression is considered to be thrombosis.	No The population was excluded due to a theoretical concern that TFPI inhibition might enhance inflammation and thereby lead to an increased risk of thromboembolic events. This safety concern will be monitored via the important identified risk of thromboembolic events (see Section 2.7.3.1).

Exclusion criterion	Reason for being an exclusion criterion	Missing information (Yes/No) Rationale if not a missing information
Treatment with emicizumab within 180 days before screening	Patients treated with emicizumab within 180 days before screening were excluded to avoid concomitant exposure to the two procoagulant drugs, emicizumab and concizumab. Excretion of emicizumab may last up to 180 days. The safety of concomitant exposure has not been established.	No Concizumab is not indicated for use in patients receiving emicizumab. Therefore, the population is not included as missing information.
Ongoing or planned immune tolerance induction treatment	Patients receiving immune tolerance induction (ITI) treatment were not eligible for inclusion in the pivotal clinical studies because ITI typically requires long term and frequent administration of high doses of FVIII or FIX, and the safety of concomitant use of concizumab under these conditions has not been established.	No The population has not been carried forward as missing information in the RMP because it is not expected that patients on concizumab are also receiving ITI. No further characterisation of this risk is currently needed.

[a]Includes arterial and venous thrombosis including myocardial infarction, pulmonary embolism, cerebral infarction/thrombosis, deep vein thrombosis, other clinically significant thromboembolic events and peripheral artery occlusion.

[b]Thromboembolic risk factors could include, but are not limited to, hypercholesterolemia, diabetes mellitus, hypertension, obesity, smoking, family history of thromboembolic events, arteriosclerosis, other conditions associated with increased risk of thromboembolic events.

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; eGFR = estimated glomerular filtration rate: FIX = coagulation factor IX; FVIII = coagulation factor VIII; HA = haemophilia A without inhibitors; HAwI = haemophilia with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; ITI = immune tolerance induction; RMP = risk management plan; TF = tissue factor; TFPI = tissue factor pathway inhibitor; ULN = upper limit of normal.

2.4.2 Limitations of ADR detection common to clinical study development programmes

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged (long-term) exposure or cumulative exposure.

2.4.3 Limitations with respect to populations typically under-represented in clinical study development programmes

An overview of special populations typically under-represented in clinical development programmes is presented in Table 2-16.

Table 2-16 Exposure of special populations included or not in clinical study development programme

Type of special population	Exposure
Female patients, including pregnant and lactating women	Female patients, including pregnant and breastfeeding women, were not included in the randomised clinical studies investigating concizumab safety and efficacy. Therefore, there is no experience with use of concizumab in pregnant and breastfeeding women from clinical studies. One female patient with HBwI (aged 3 years) has been treated with concizumab via compassionate use.
Patients with hepatic impairment	No dedicated studies on the effect of hepatic impairment on the pharmacokinetics of concizumab have been conducted. Hepatic dysfunction was an exclusion criterion in the pivotal studies (Table 2-15). Thus, the clinical study experience in patients with hepatic impairment is limited (see further details in Section 2.4.3.1) Nine (9) participants exposed to concizumab had elevated liver enzymes (alanine transaminase [ALT] or aspartate transaminase [AST] ≥ 1.5 ULN) at baseline in the multiple-dose studies NN7415-4311 (56-weeks data cut-off), -4307 (56-weeks data cut-off), -4255, -4310, and -4159 for whom ALT and AST baseline data were available. Use in patients with hepatic impairment has not been included as missing information in the RMP as there is no medical or scientific reason to expect a different safety profile of concizumab in this population, considering the mechanism of action and elimination of concizumab.

Type of special population	Exposure
Patients with renal impairment	No dedicated studies on the effect of renal impairment on the pharmacokinetics of concizumab have been conducted. Patients with biochemical signs of clinically significant renal impairment (estimated Glomerular Filtration Rate [eGFR] ≤30 ml/min/1.73 m^2 for serum creatinine) were excluded from the pivotal studies (Table 2-15). Thus, the clinical study experience in patients with severe renal impairment is limited (see further details in Section 2.4.3.1). Nineteen (19) participants exposed to concizumab had reduced renal function, defined as eGFR < 90 mL/min /1.73m^2, at baseline in the multiple-dose studies NN7415-4311 (56-weeks data cut-off), -4307 (56-weeks data cut-off), -4255, and -4310 for whom data were available. Use in patients with renal impairment has not been included as missing information in the RMP as there is no medical or scientific reason to expect a different safety profile of concizumab in this population, considering the mechanism of action and elimination of concizumab.
Patients with cardiac impairment	No baseline measurements on cardiac function were performed in patients or healthy participants in the clinical studies. A different safety profile of concizumab is not expected in this population based on the mechanism of action of concizumab as well as the pathophysiology of the diseases that cause cardiac impairment. Therefore, this population has not been included as 'missing information' in the RMP.
Immunocompromised patients	Not included in the clinical development programme. HIV-positive patients were included in the clinical studies but with the current treatment options, most of these patients are not considered to be immunocompromised. Use in immunocompromised patients has not been included as 'missing information' in the RMP because the safety profile of concizumab is not expected to be different in this population based on the mechanism of action of concizumab.
Patients with a disease severity different from inclusion criteria in clinical trials	Not included in the clinical development programme. Studies NN7415-4159 and -4255 included participants with severe HA. Study NN7415-4307 included participants with severe HA and severe/moderate HB. Studies NN7415-4310 and -4311 included participants with HAwI and HBwI of any severity. The severity classification is less relevant for patients with HAwI or HBwI since inhibitor development is considered a serious complication. Concizumab is indicated for use in patients with HAwI and HBwI; thus, this special population is not considered missing information.

Type of special population	Exposure
Population with relevant different ethnic origin	Concizumab has been investigated in patients from various racial/ethnic groups in clinical studies but primarily in White and Asian patients (see Table 2-14). No difference in the therapeutic response to concizumab is expected based on racial or ethnic origin; hence, this population is not considered missing information.
Subpopulations carrying relevant genetic polymorphisms	Concizumab is not metabolised by any of the genetically polymorphic drug-metabolizing enzymes for which genetic variants are known to differ in enzymatic activity, e.g., CYP2D6, CYP2C9, CYP2C19, thiopurine-S-methyltransferase, or dihydropyrimidine dehydrogenase. No difference in the therapeutic response to concizumab is expected based on genetic polymorphisms; hence, this population is not considered missing information.

Abbreviations: ALT = alanine transaminase; AST = aspartate transaminase; CYP = cytochrome P450; eGFR = estimated glomerular filtration rate; FVIII = coagulation factor VIII; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; HIV = human immunodeficiency virus; RMP = risk management plan; ULN = upper limit of normal.

2.4.3.1 Patients with hepatic impairment

The clinical study experience with concizumab exposure in patients with severe hepatic impairment is limited. 'Hepatic dysfunction defined as 'AST and/or ALT >3 times the upper limit with total bilirubin > 1.5 times the upper limit' was an exclusion criterion in the pivotal phase 3 studies (see Table 2-15). Similar criteria were used in the 3 other multiple-dose studies in haemophilia (NN7415-4159, -4310 and -4255). HCV and HBV are common co-morbidities in patients with haemophilia that may lead to hepatic dysfunction (see Section 2.1.1.6).

Few participants were identified as having elevated liver enzymes (ALT or AST ≥ 1.5 x ULN) at baseline for whom ALT and AST baseline data were available across five multiple-dose studies (see Table 2-16). There was no indication of a different safety profile of concizumab in these patients as compared with patients with normal liver function. No impact on concizumab exposure was observed in participants with hepatic impairment (defined as AST and/or ALT ≥1.5 x ULN) in the pivotal phase 3 studies as of the DLP of the RMP. The impact of hepatic impairment on the concizumab plasma exposure level was not assessed in other studies.

The safety profile of concizumab in patients with hepatic impairment is not expected to be different from that in patients with normal liver function based on the mechanism of action and elimination of concizumab. Thus, use of concizumab in this population has not been carried forward as 'missing information'. Hepatic function will be monitored through routine pharmacovigilance activities in clinical studies and in the post-marketing setting.

2.4.3.2 Patients with renal impairment

The clinical study experience with concizumab in patients with severe renal impairment is limited. 'Renal impairment defined as eGFR ≤ 30 ml/min/1.73 m^2 for serum creatinine measured at screening' was an exclusion criterion in the pivotal phase 3 studies (see Table 2-15). In study NN7415-4159, participants with 'renal dysfunction (i.e., dialysis and/or creatinine level ≥1.25 times above upper normal limit according to central laboratory ranges at screening)' were excluded.

Few participants were identified as having 'reduced renal function' at baseline, defined as eGFR <90 mL/min/1.73 m^2, for whom data were available across four multiple-dose studies (see Table 2-16). There was no indication of a different safety profile of concizumab in these patients as compared with patients with normal renal function. A different assessment of baseline renal function was used in the phase 1 study NN7415-4159 (creatinine levels were evaluated, but eGFR values were not determined). No impact on concizumab exposure was observed in participants with reduced renal function in the pivotal phase 3 studies as of the DLP of the RMP. The impact of reduced renal function on concizumab plasma exposure was not assessed in other studies.

The safety profile of concizumab in patients with renal impairment is not expected to be different from that in patients with normal renal function based on the mechanism of action and elimination of concizumab. Thus, use of concizumab in this population has not been carried forward as 'missing information'. Renal function will be monitored through routine pharmacovigilance activities in clinical studies and in the post-marketing setting.

2.5 Module SV: Post-authorisation experience

Concizumab has been marketed as Alhemo® since December 2023. Total post-marketing exposure to Alhemo® at the DLP of the RMP, estimated from the sales volume of 54,750 mg, was 10 patient-years of exposure (PYE).

No TEs have been reported from post-marketing sources for patients treated with Alhemo®.

2.6 Module SVI: Additional EU requirements for the safety specification

2.6.1 Potential for misuse for illegal purposes

No potential for misuse of concizumab has been identified from any sources. Concizumab is highly unlikely to be misused for illegal purposes based on its mechanism of action. This area is therefore not considered a safety concern.

2.7 Module SVII: Identified and potential risks

2.7.1 Identification of safety concerns in the initial RMP submission

2.7.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Risks that are not considered important for the purpose of risk management planning are grouped based on the rationale for non-inclusion (Table 2-17). Overall, the impact of these risks on the benefit–risk balance of concizumab is evaluated to be low.

Table 2-17 Risks not considered important for inclusion in the list of safety concerns

Risk	Benefit−risk impact
Risks with minimal clinical impact on patients in relation to the severity of the indication treated	
Injection site reactions[a]	Injection site reactions are listed as a very common ADR in the SmPC, as these reactions were reported in 24% of patients with haemophilia treated with at least one dose of concizumab across five multiple-dose clinical studies.[b] Among the reported injection site reactions, the most frequently reported events were injection site erythema (reported in 5.9% of the patients), injection site bruising (4.4%) and injection site haematoma (4.1%). All injection site reactions were reported as non-serious and as mild (95%) or moderate (5%) in severity. Most events (98%) were reported with the outcome recovered or recovering; the remaining events were reported as not recovered at the time of the clinical data cut-off. The impact of the injection site reactions on the benefit-risk balance of concizumab is considered minimal based on the severity of the events (most were mild). Injection site reactions are considered expected for any drug administered by subcutaneous injection such as concizumab.
Risks with potentially serious clinical consequences that occur at low frequencies and therefore are considered to be acceptable in relation to the severity of the indication treated	
Medication errors[c]	In total, 12 medication errors were captured by the pre-defined MedDRA search in 10 patients (3.1%) on concizumab treatment across five multiple-dose studies in patients with haemophilia. Seven (7) of the medication errors (in 5 patients) concerned overdose and the remaining events were: 2 events of incorrect dose administration; 2 events of underdose and 1 event of accidental overdose. All medication errors were of mild (11 out of 12 events) or moderate (1 event) severity and reported as resolved. One AE of tachycardia was co-reported with a medication error (PT Accidental overdose); the AE was reported as mild in severity and resolved on the same day and (medical history included anxiety). No other AEs were co-reported with the medication errors. Medication errors of under- or overdosing could have potentially serious clinical consequences. Repetitive underdosing might reduce the protective effect against bleeds and a consistently higher dose than studied in clinical studies may have undesired, yet unknown, clinical consequences. Based on the available evidence, including the low frequency of medication errors in the clinical studies, the impact on the benefit-risk balance of this risk is evaluated to be very low.
Hypersensitivity	'Hypersensitivity' is listed as a common ADR in the SmPC. AEs of PT Hypersensitivity were reported in 1.3% of the patients with haemophilia on treatment with concizumab across five multiple-dose clinical studies. Hypersensitivity is included as an ADR based on a few cases reported from the phase 3 study in patients with HAwI and HBwI (NN7415-4311) for which a causal relationship between the event and concizumab treatment could not be ruled out. Most (75%, 6 events) of the AEs of hypersensitivity (8 events in 4 patients) were reported as non-serious and mild in severity (1 as moderate and 1 as severe). All events were reported as recovered. Five (5) of the events (in 3 patients) were reported as possibly related to concizumab by the investigator. One SAE of hypersensitivity has led to hospitalisation and permanent discontinuation of therapy in a patient. Section 4.4 of the SmPC includes a warning regarding hypersensitivity with the use of concizumab. Additionally, the SmPC also includes clinical consequences and further course of action to be taken in case of hypersensitivity. Hypersensitivity reactions, including anaphylaxis, anaphylactoid and systemic hypersensitivity reactions are potential class effects for all protein-based medicinal products, and these can be severe life-threatening reactions. Hence, the use of concizumab in patients with known hypersensitivity towards concizumab (or excipients) is a contraindication in the SmPC. No cases of anaphylaxis were reported across the five multiple-dose studies in participants on concizumab treatment.

Risk	Benefit−risk impact
	The impact of the risk of hypersensitivity reactions on the benefit-risk balance of concizumab is considered minimal based on the seriousness and severity of the reported events.

[a]Injection site reactions include the PTs Injection site rash, Injection site erythema, Injection site urticaria, Injection site reaction, Injection site bruising, Injection site haematoma, Injection site swelling, Injection site pruritus, Injection site haemorrhage, Injection site hypoesthesia, Injection site induration, Injection site pain, injection site nodule and injection site mass.

[b]Studies NN7415-4159, -4255, -4310, -4311 (56-week data cut off) and -4307 (CACO).

[c]The events were captured by the SMQ Medication errors (broad and narrow scope).

Abbreviations: ADR = adverse drug reaction; AE = adverse events; CACO = confirmatory analysis cut-off; ELISA = enzyme-linked immunosorbent assay; MedDRA = medicinal dictionary for regulatory activities; PT = preferred term; SAE = serious adverse event; SmPC = Summary of Product Characteristics; SMQ = standardised MedDRA query.

The overall safety profile of concizumab in the initial RMP submission was based on safety results from all completed and ongoing studies as well as compassionate use with concizumab, as of the application cut-off date 30 August 2022. This included pooled safety data from five multiple-dose clinical studies in haemophilia, NN7415-4159, -4255, -4310, -4311 (56-week data) and -4307 (CACO).

Overall, no difference in the safety profile was identified across the haemophilia populations (HA, HB, HAwI, and HBwI) based on data from clinical studies and compassionate use up until 30 Aug 2022.

2.7.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Risks considered important for inclusion in the list of safety concerns for further evaluation as part of the pharmacovigilance plan or risk minimisation activities and their benefit−risk impact are briefly discussed in Table 2-18. Further details on the safety concerns are presented in Section 2.7.3.

Table 2-18 Brief presentation of important safety concerns

Safety concerns	Benefit−risk impact
Important identified risks	
Thromboembolic events	This is a risk for all procoagulant compounds. Thromboembolic events can be serious and life-threatening, which is why the risk has been included as an important risk in the RMP. The potential benefits of treatment with concizumab should be weighed against the risk of thromboembolic complications. Cases of serious non-fatal thromboembolic events have been reported in phase 3 studies. An overall medical assessment of the cases revealed multiple risk factors that may have contributed to the development of each of these events. These were a combination of different thromboembolic risk factors and the use of high or frequent doses of breakthrough bleed treatment (see further details in Section 2.7.3.1). Considering the severity of the indicated disease haemophilia, which can lead to life-threatening bleeding episodes, the benefit of treatment is expected to outweigh the risk of thromboembolic events when taking into account the few cases with risk factors observed in the clinical studies, the overall low incidence rate of thromboembolic events in haemophilia[37, 38] and the risk minimisation measures implemented.
Important potential risks	

Safety concerns	Benefit−risk impact
None	
Missing information	
None	

Abbreviations: RMP = risk management plan.

2.7.2 New safety concerns and reclassification with a submission of an updated RMP

No new safety concerns have been identified, and no reclassification of the existing important identified risk (TEs) has been made with submission of current RMP.

2.7.3 Details of important identified risks, important potential risks, and missing information

2.7.3.1 Important identified risk: Thromboembolic events

Potential mechanisms

As observed for other procoagulant compounds, there is a potential risk of thrombosis due to exaggerated pharmacology. Concizumab is an anti-TFPI antibody that acts independently from FVIII and FIX by enhancing the initiation phase of coagulation through increased FXa production. TF is the high-affinity receptor and cofactor for FVII/VIIa. The TF-FVIIa complex is the primary initiator of blood coagulation and plays an essential role in haemostasis.

Evidence source and strength of evidence

This is a risk for all procoagulant compounds. Thrombosis formation consistent with an exaggerated pharmacological effect was observed in repeat-dose toxicology studies conducted in normo-coagulant cynomolgus monkeys at high concizumab exposures. Cases of non-fatal arterial and venous TEs had been reported in the concizumab clinical studies. An overall medical assessment of the events revealed multiple risk factors that may have contributed to the development of these events. These were a combination of different thromboembolic risk factors and the use of high or frequent doses of breakthrough bleed treatment. Novo Nordisk has evaluated the available evidence supporting the risk as limited.

Characterisation of the risk

Pooled clinical data from multiple-dose studies in participants with haemophilia

The predefined MedDRA search for TEs (SMQ Embolic and thrombotic events) had captured a total of 11 events in 6 of 320 participants on concizumab across five multiple-dose studies in participants with haemophilia (NN7415-4159, -4310, -4255, -4311 [56-week data] and -4307 [including 56-week data]).

Five (5) of the 11 events were serious TEs reported as AESI and judged as possibly/probably related to concizumab by the investigators. These 5 SAEs were reported in 3 participants in the studies NN7415-4311 and -4307 (Table 2-19) and led to a treatment pause (see Section 2.3.2).

Table 2-19 Serious thromboembolic events reported as AESI – phase 3 studies NN7415-4311 (56-week cut-off) and -4307(56-week cut-off)

Study ID/ Haemophilia subtype	Age-range	PT/ Onset (study day)	Severity/ Outcome/ Causality/	Thromboembolic risk factors
NN7415-4307/ HA	>40 – <50	Acute myocardial infarction/ (59)	Severe/ Recovered/ Possible	• Smoking for [redacted] years • Increased blood pressure noted at screening visit • Chest pain on few occasions the month before event, not reported to investigator • Chronic tooth inflammation with tooth extraction and removal of stitches (both under 60IU/kg FVIII) few weeks prior to event onset • Use of ACE-inhibitor a few times over last [redacted] years • Nitroglycerin ready at home with no report on angina • Treated [redacted] joint bleed FVIII 70IU/kg on day of event
NN7415-4307/ HA	>40 – <50	1. Deep vein thrombosis/ (86) 2. Pulmonary embolism/ (92) 3. Superficial vein thrombosis/ (92)	1. Moderate/ Recovering/ Probable 2. Moderate/ Recovering/ Probable 3. Mild/ Recovering/ Probable	• Obesity • [redacted] oedema since [redacted] • Daily treatment with 35 IU/kg FVIII since start of concizumab (except for 3 days) • Increasing blood pressure for each visit considered by investigator due to obesity and salty food intake (Visit 3: 140/90; Visit 4: 131/97; Visit 5: 151/101)
NN7415-4311/ HBwI	>20 – <30	Renal infarct/ (21)	Severe/ Recovered with sequelae/ Possible	• Possible/potential renal infarct prior to study entry was assessed (not confirmed)[a] • Obesity (Prader Willi Syndrome) with fatty liver • NovoSeven for [redacted] bleed during 3 days up to event (90-130µg/kg/8hrs) • Multiple CVAD removal/replacements due to "history of infection or malfunctioning port a cath" • Hypercholesterolaemia

Note:

- For the completed part of study NN7415-4307, the 56-week cut-off was on 27 Dec 2022.
- Study day is calculated based on the treatment start date. Causality is the investigator's assessment.

[a]The investigations were finalised as inconclusive.

Abbreviations: ACE = angiotensin-converting enzyme; AESI = adverse event of special interest; CVAD = central venous access device; FVIII = coagulation factor VIII; HA = haemophilia A without inhibitors; HBwI = haemophilia B with inhibitors; PPX = prophylaxis; PT = preferred term.

The other 6 events (of the 11 events captured with the MedDRA search) were:

- 1 serious event (PT Hemiparesis) in a participant with HA (study NN7415-4307)
- 2 non-serious events (PT Shunt thrombosis) in 1 participant with HAwI (study NN7415-4311)
- 3 non-serious events (PT Haemorrhoids thrombosed) in 1 participant with HA (study NN7415-4255)

The serious and severe event of Hemiparesis was judged as unlikely related to concizumab by the investigator and Novo Nordisk. Hemiparesis was co-reported with an SAE of Craniocerebral injury after the participant had fallen on the stairs, developing an intracranial subdural haematoma and skull fracture. No TEs were reported for the participant. The outcome for the event of hemiparesis was ‘not recovered’; as per investigator the participant's condition was chronic.

Of the 5 non-serious events (see above), 2 were reported as mild, 2 as moderate and 1 as severe. The outcome was reported as ‘recovered’ for the 3 events of Haemorrhoids thrombosed and ‘not recovered’ for the 2 events of Shunt thrombosis. All 5 events were judged as unlikely related to concizumab by the investigator.

An overview of all 11 events is presented in Table 2-20. Notably, for studies NN7415-4307 and -4311 the events included are from the on-treatment (OT) analysis dataset.

Table 2-20 Overview of all treatment-emergent thromboembolic events by haemophilia type – HA, HB, HAwI, HBwI

	HA			HB			HAwI			HBwI			HAwI + HBwI			Total		
	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]
All participants	125			64			78			53			131			320		
Total exposure (years)	195.8			73.5			121.3			84.0			205.3			474.7		
Any thrombosis event	4	(3.2)	8 [0.0]	0			1	(1.3)	2 [0.0]	1	(1.9)	1 [0.0]	2	(1.5)	3 [0.0]	6	(1.9)	11 [0.0]
Serious																		
Yes	3	(2.4)	5 [0.0]	0			0			1	(1.9)	1 [0.0]	1	(0.8)	1 [0.0]	4	(1.3)	6 [0.0]
No	1	(0.8)	3 [0.0]	0			1	(1.3)	2 [0.0]	0			1	(0.8)	2 [0.0]	2	(0.6)	5 [0.0]
Severity																		
Severe	2	(1.6)	2 [0.0]	0			1	(1.3)	1 [0.0]	1	(1.9)	1 [0.0]	2	(1.5)	2 [0.0]	4	(1.3)	4 [0.0]
Moderate	2	(1.6)	4 [0.0]	0			0			0			0			2	(0.6)	4 [0.0]
Mild	2	(1.6)	2 [0.0]	0			1	(1.3)	1 [0.0]	0			1	(0.8)	1 [0.0]	3	(0.9)	3 [0.0]
Relationship to study product																		
Probable	1	(0.8)	3 [0.0]	0			0			0			0			1	(0.3)	3 [0.0]
Possible	1	(0.8)	1 [0.0]	0			0			1	(1.9)	1 [0.0]	1	(0.8)	1 [0.0]	2	(0.6)	2 [0.0]
Unlikely	2	(1.6)	4 [0.0]	0			1	(1.3)	2 [0.0]	0			1	(0.8)	2 [0.0]	3	(0.9)	6 [0.0]
Outcome																		
Fatal	0			0			0			0			0			0		
Not Recovered	1	(0.8)	1 [0.0]	0			1	(1.3)	2 [0.0]	0			1	(0.8)	2 [0.0]	2	(0.6)	3 [0.0]
Recovered with sequelae	0			0			0			1	(1.9)	1 [0.0]	1	(0.8)	1 [0.0]	1	(0.3)	1 [0.0]
Recovering	1	(0.8)	3 [0.0]	0			0			0			0			1	(0.3)	3 [0.0]
Recovered	2	(1.6)	4 [0.0]	0			0			0			0			2	(0.6)	4 [0.0]
Unknown	0			0			0			0			0			0		
AE leading to discontinuation of study product																		
Yes	2	(1.6)	2 [0.0]	0			0			1	(1.9)	1 [0.0]	1	(0.8)	1 [0.0]	3	(0.9)	3 [0.0]

Cumulative reporting period: start of first study – 30 Sep 2024.
Studies included: NN7415-4159, -4255, -4310, -4311 (56-week cut-off) and -4307 (56-week cut-off).
Search criteria: Embolic and thrombotic events (SMQ).
Relationship to study product is based on investigator(s)'s assessment.
For studies NN7415-4311 and -4307, follow-up period (7 weeks) after start of pause is taken into account.
Abbreviations: E: Number of events; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; MedDRA = Medical dictionary for regulatory activities; N = Number of participants; % = Percentage of participants; R = Events/Exposure Years; SMQ = standardised MedDRA query.

Findings of the serious TEs judged as possibly/probably related to concizumab and all available data led Novo Nordisk to implement changes to the phase 3 study protocols to reduce the risk. The changes included:

- a new guidance for treatment of mild and moderate breakthrough bleeding episodes with specific guidance for use of the lowest approved dose of factor product or bypassing agent while on concizumab PPX.
- the information that participants must contact the study site prior to treating a suspected bleed.
- a new concizumab dosing regimen including an initial daily dose of 0.20 mg/kg concizumab (decreased from 0.25 mg/kg). Criteria for an increase or decrease in the daily maintenance dose to 0.25 mg/kg or 0.15 mg/kg, respectively (based on concizumab exposure levels at the week 4 visit) were provided. The loading dose remained 1.0 mg/kg.

No TEs had been reported from study NN7415-4311 after the treatment pause up until the DLP of the RMP.

Three (3) events (2 serious and 1 non-serious) had been reported from study NN7415-4307 after the 56-week cut-off date and until the DLP of the RMP. Two (2) of the 3 events were assessed as causally related to concizumab (1 serious and 1 non-serious) and 1 SAE assessed as unlikely related (see Table 2-21).

Table 2-21 Thromboembolic events reported after 56-week cut-off (NN7415-4307)

Study ID/ Haemophilia subtype	Age-range (years)	PT/ Onset (study day)	Seriousness/ Severity/ Outcome/ Causality	Thromboembolic risk factors
7415-4307/ HA	>30 − <40	Ischemic stroke (901)	Serious/ Severe/ Recovered Possible	• Hypertension • History: CNS bleeding • Treatment medication: enoxaparin
	>50 − <60	Mesenteric artery thrombosis (1,627)	Non-serious/ Mild/ Not recovered/ Probable	• Diabetes • Medical history of non-occlusive thrombus located at the superior mesenteric artery (CT scan October 2023)
	>60 − <70	Cerebral infarction (1,263)	Serious/ Severe/ Recovered with sequelae/ Unlikely	• Hypertension • Advanced age

Abbreviations: HA = haemophilia A without inhibitors; CNS = central nervous system; CT = computed tomography; PT = preferred term.

Overall, TE is categorised as an important identified risk for concizumab. The 2 case reports on TEs and assessed as possibly/probably related, where the serious case was reported with confounding factors (e.g., hypertension) and the non-serious case was reported for an asymptomatic participant after it was found by incidence during a CT scan, do not change the safety profile of concizumab.

Results from compassionate use of concizumab

No TEs have been reported in patients with haemophilia participating in the CUP (NN7415-4807) or on IPB as of the DLP of the RMP.

Data from literature sources

Incidence and prevalence

In a systematic review of prospective studies (1990-2011) that included 5,528 patients (4,420 with HA, 748 with HB, and 361 with von Willebrand's disease [VWD]) from 71 studies, the incidence of TEs was 3.6 per 1,000 patients, and 1.1 per 100,000 infusions. Of the 20 TEs reported (HA: 2; HB: 11; VWD: 7), two were major venous thromboembolic episodes (both in patients with VWD on prolonged replacement for surgery) and the remaining 18 TEs were superficial thrombophlebitis.[38]

A recent analysis of real-world data found a similar incidence of MI and pulmonary embolism (PE) in people with HA (N ≈ 3,490) compared to a non-HA population (N=16,380) matched by age and sex, whereas the incidence rates of ischemic stroke and deep vein thrombosis (DVT) were slightly higher in patients with HA.[37] The adjusted incidence rate ratios for MI, PE, ischemic stroke and DVT were 1.23 [95% CI: 0.82–1.86]; 0.89 [95% CI: 0.45–1.77]; 1.48 [95% CI: 1.01–2.16]) and 1.53 [95% CI: 1.00–2.32], respectively. Overall, these findings suggest that patients with haemophilia and thromboembolic risk factors are not protected from TEs such as MI and PE, despite their hypo-coagulable conditions. As an alternative explanation, the authors propose that the individuals in whom the TEs occur have other risk factors for ischemic stroke and DVT but do not receive appropriate prophylaxis or interventions against TEs due to their underlying disease (HA).

Risk factors and risk groups

Possible risk factors include a history of TE, thromboembolism in the family, obesity, arrhythmias, hypertension, diabetes, hypercholesterolaemia, smoking, post-surgical status (total hip arthroplasty, total knee arthroplasty, major surgery and general surgery within 3 months), immobilisation, infection, liver disease and old age. The use of high or frequent doses of breakthrough bleed treatment with factor products could be a risk factor for the development of TEs.

In general, patients with a pathological condition in which TF is expressed more extensively than considered physiological, e.g. advanced atherosclerosis, cancer, crush injury, or septicaemia, may be at a higher risk of developing TEs and disseminated intravascular coagulation (DIC).[39, 40.]

Preventability

In patients at high risk of TEs, caution should be exercised when administering concizumab. The potential benefit of treatment with concizumab should be weighed against the risk of thrombotic complications.

Impact on the benefit-risk balance of the product

TEs can be serious and life-threatening. However, considering the severity of the indicated disease haemophilia, which can lead to life-threatening bleeding episodes, the benefit of treatment is expected to outweigh the risk of TEs when taking into account the few cases with risk factors observed in the clinical studies, the overall low incidence rate of TEs in haemophilia[37] and the risk minimisation measures implemented.

Public health impact

Considering that the target population of patients with haemophilia is relatively small and the incidence rate of TEs is predicted to be low, the absolute risk is expected to be very low, and the potential impact on public health is evaluated as negligible.

2.8 Module SVIII: Summary of safety concerns

Summary of safety concerns for concizumab is presented in Table 2-22.

Table 2-22 Summary of safety concerns for concizumab

Summary of safety concerns	
Important identified risks	• Thromboembolic events
Important potential risks	• None
Missing information	• None

3 Pharmacovigilance plan

3.1 Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection

3.1.1 Specific adverse reaction follow-up questionnaires

No specific follow-up forms or questionnaires are used for the important risk included in the RMP for concizumab. Routine case follow-up, including a number of targeted questions relating to the diagnosis and description of the event, is considered sufficient. Based on medical evaluation, the relevant questions are returned to the reporter in an attempt to get further information to be used in the evaluation of the events.

3.1.2 Other forms of routine pharmacovigilance activities

No other forms of routine pharmacovigilance activities are applied for concizumab.

3.2 Additional pharmacovigilance activities

3.2.1 Registry-based cohort study summary (NN7415-7533)

Study title:

A registry-based observational cohort study to characterise the safety profile of concizumab in PWH in the real-world setting.

Rationale and study objectives:

Cases of non-fatal arterial and venous TEs have been reported in the concizumab clinical studies. These cases occurred in patients with multiple risk factors including high or frequent dosing for breakthrough bleeds. Based on these cases, ‘thromboembolic events’ has been classified as an important identified risk. The primary objective is to estimate the TE rate in people with haemophilia on concizumab in the real-world setting. The secondary objectives are 1) to describe

individual cases of TEs including any risk factors, 2) to estimate the rate of hypersensitivity reactions in people with haemophilia on concizumab in the real-world setting and to describe individual cases of hypersensitivity and 3) to estimate the rate of other AEs in people with haemophilia on concizumab in the real-world setting.

Study design:

This registry-based observational cohort study will collect data from the American Thrombosis and Haemostasis Network (ATHN) and from the European Haemophilia Safety Surveillance System (EUHASS) registries.[41] ATHN is an ongoing HIPAA-compliant de-identified patient health dataset containing data from individuals with bleeding and clotting disorders receiving care through ATHN's US haemophilia treatment centres (HTCs) network. Individuals consent or opt-in to contribute their data in order to help establish a better understanding of bleeding and clotting disorders. The ATHN dataset contains data recorded in the electronic medical records at individual HTCs and entered into the ATHN dataset, primarily reflecting health care interactions at the HTC. Due to great detail in its data, ATHN is the primary data source for the registry-based cohort study.

EUHASS is a pharmacovigilance program dedicated to monitoring the safety of treatments in people with inherited bleeding disorders across Europe. The haemophilia centres participating in the EUHASS registry provide information on patients who experience certain AEs, including but not limited to TEs and allergic reactions. The participating centres provide information on AEs by completing a web-based AE reporting form and also have the option of reporting an event at the time of its occurrence. Annually, centres provide information on the number of patients treated with each type of coagulation product. EUHASS is the auxiliary data source for the registry-based study (NN7415-7533).

The registry-based study will utilise data obtained from ATHN and EUHASS; EUHASS data will be received in the form of product-specific annual reports, which take EUHASS approximately one year to produce from raw data. Raw data will be received from ATHN. Based on the data obtained from ATHN and the product-specific annual reports received from EUHASS, Novo Nordisk will generate PASS reports for study NN7415-7533.

In addition, Novo Nordisk is investigating the possibility of including data from European registries that provide detailed data, including FranceCoag and the United Kingdom Haemophilia Centre Doctors' Organisation (UKHCDO).

Study populations:

The study population will consist of all PWH treated with concizumab according to the approved label and reported on by the ATHN and EUHASS registries. The decision to initiate treatment with commercially available concizumab has been made by the patient/Legally Acceptable Representative (LAR) and the treating physician before and independently from the decision to include the patient in the registries in scope.

All eligible PWH on concizumab that report to ATHN and EUHASS will be included in the study. The sample size will depend on the approval and uptake of concizumab and on the number of PWH participating in ATHN and EUHASS.

Milestones for the study NN7415-7533 will be included in the study protocol.

3.3 Summary table of additional pharmacovigilance activities

An overview of the registry-based cohort study NN7415-7533 is presented in Table 3-1 and Annex 2.

Table 3-1 Ongoing and planned additional pharmacovigilance activities

Study **Status**	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities (by the CHMP/PRAC or NCA)				
NN7415-7533 Registry-based cohort study A registry-based observational cohort study to characterise the safety profile of concizumab in people with haemophilia in the real-world setting. Planned	The primary objective is to estimate the thromboembolic event rate in people with haemophilia on concizumab in the real-world setting. Secondary objectives: • To describe individual cases of thromboembolic events including any risk factors • To estimate the rate of hypersensitivity reactions in people with haemophilia on concizumab in the real-world setting and to describe individual cases of hypersensitivity. • To estimate the rate of other adverse events in people with haemophilia on concizumab in the real-world setting.	Thromboembolic events	Protocol submission	*Pending*
			Final report	*Q3 2030 (planned)*

Abbreviations: CHMP = Committee for Medicinal Products for Human Use; NCA = National Competent Authorities; PRAC = Pharmacovigilance Risk Assessment Committee.

4 Plans for post-authorisation efficacy studies

There are no imposed post-authorisation efficacy studies ongoing or planned for concizumab.

5 Risk minimisation measures

5.1 Routine risk minimisation measures

Summary of routine risk minimisation measure is presented in Table 5-1.

Table 5-1 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation measures
Important identified risks	
Thromboembolic events	*Routine risk communication:* Information is provided in the SmPC (Special warnings and precautions for use) that cases of non-fatal arterial and venous thromboembolic events have been reported in the concizumab clinical studies. These cases occurred in patients with multiple risk factors including high or frequent doses of breakthrough bleed treatment. The SmPC also includes a statement highlighting that caution should be exercised when the patient is at high risk of developing thromboembolic events. The PL contains a warning that blood clots (thromboembolic events) may occur and that the patient should stop using concizumab in case of signs of blood clots, and the section provides information on symptoms of thromboembolic events. *Routine risk minimisation activities recommending specific clinical measures to address the risk:* In the SmPC it is recommended that patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events, and in case of suspicion of thromboembolic events, concizumab should be discontinued and further investigations and appropriate medical treatment should be initiated. *Other risk minimisation measures beyond the Product Information:* None
Important potential risks	
None	
Missing information	
None	

Abbreviations: SmPC = Summary of Product Characteristics; PL = package leaflet.

5.2 Additional risk minimisation measures

5.2.1 Educational material to HCPs

Objectives:

Educational materials for healthcare professionals (HCPs) are distributed to increase awareness about the important identified risk of TEs with a focus on early recognition and management. Key messages of the educational material are provided in Annex 6.

Rationale for the additional risk minimisation activity:

The risk of TEs is a risk for all procoagulant compounds due to exaggerated pharmacology. Although the physicians may be aware of the risk, this might not be the case for the patients. Therefore, educational material is considered needed for HCPs to provide guidance on the management of TEs and the importance of instructing the patients about appropriate management of TEs.

Target audience and planned distribution path:

Novo Nordisk provides educational material to HCPs in the EU at the time of commercial launch. The educational material will be redistributed every year and following any significant updates to the information included in the material.

All Novo Nordisk staff responsible for contact with HTCs will have documented training in the key points of the educational material and their distribution and use. A central log of the distribution of educational material will be maintained.

Novo Nordisk staff will distribute the educational material as well as collect a signed acknowledgment form at the site visit or via email. The form will include guidance to the HCP on the importance of familiarizing themselves with the content of the educational material as well as collection and reporting of information on safety outcomes. It will also include a reminder of distribution of patient educational material to the patients.

Plans for evaluating the effectiveness of the interventions and criteria for success:

The effectiveness of the educational material will be evaluated by assessing the safety profile (incl. risk factors, management of TEs and type of TEs) in relation to the spontaneous TE cases reported to Novo Nordisk after the educational materials have been implemented.

Results from the effectiveness evaluation will be provided with the periodic safety update reports (PSURs) and the educational material will be adjusted if the effectiveness evaluation indicates that changes are needed.

5.2.2 Educational material to patients

Objectives:

Educational materials for patients and carers are distributed to raise awareness about the important identified risk of TEs and to educate patients/carers to recognize signs and symptoms of TEs. Key messages of the educational material are provided in Annex 6.

Rationale for the additional risk minimisation activity:

The risk of TEs is a risk for all procoagulant compounds due to exaggerated pharmacology. Although the physicians may be aware of the risk, this might not be the case for the patients. Therefore, educational material is considered needed to ensure appropriate management of TEs.

Target audience and planned distribution path:

Patients/carers will receive a copy of the patient/carer guide and patient alert card when the patient receives the initial treatment with concizumab and the associated training on self-administration from an HCP.

Plans for evaluating the effectiveness of the interventions and criteria for success:

The effectiveness of the educational material will be evaluated by assessing the safety profile (incl. risk factors, management of TEs and type of TEs) in relation to the spontaneous thromboembolic cases reported to Novo Nordisk after the educational materials have been implemented.

Results from the effectiveness evaluation will be provided with the PSURs and the educational material will be adjusted if the effectiveness evaluation indicates that changes are needed.

5.3 Summary table of pharmacovigilance and risk minimisation activities by safety concern

Summary of pharmacovigilance and risk minimisation activities by safety concern are presented in Table 5-2.

Table 5-2 Pharmacovigilance and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risks		
Thromboembolic events	*Routine risk minimisation measures:* Information is provided in the SmPC that cases of non-fatal arterial and venous thromboembolic events have been reported in the concizumab clinical studies. These cases occurred in patients with multiple risk factors including high or frequent doses of breakthrough bleed treatment. The SmPC also includes a statement highlighting that caution should be exercised when the patient is at high risk of developing thromboembolic events. PL contains a warning that blood clots (thromboembolic events) may occur and that the patient should stop using concizumab in case of signs of blood clots, and the section provides information on symptoms of thromboembolic events. In the SmPC, it is recommended that patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events, and in case of suspicion of thromboembolic events, concizumab should be discontinued and further investigations and appropriate medical treatment should be initiated. *Additional risk minimisation measures (see Annex 6)* • Guide for Healthcare Professionals • Guide for Patient/Carer • Patient alert card	*Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection:* None *Additional pharmacovigilance activities:* Registry-based cohort study (NN7415-7533, see Annex 2).

Abbreviations: SmPC = Summary of Product Characteristics; PL = package leaflet.

6 Summary of the risk management plan for concizumab

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

Alhemo's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how Alhemo should be used.

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

6.1 The medicine and what it is used for

Alhemo has been authorised for routine prophylaxis to prevent or reduce the frequency of bleeding in patients with haemophilia A or B with inhibitors (≥12 years) in certain countries. Alhemo will be authorised for routine prophylaxis in patients with severe haemophilia A (factor VIII [FVIII] <1%) without FVIII inhibitors and of 12 years of age or more, and moderate/severe haemophilia B (factor IX [FIX] ≤2%) without FIX inhibitors and of 12 years of age or more (see SmPC for the full indications). It contains concizumab as the active substance and it is given by the subcutaneous route of administration.

Further information about the evaluation of Alhemo's benefits can be found in Alhemo's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage: *link to the EPAR summary landing page*.

6.2 Risks associated with the medicine and activities to minimise or further characterise the risks

Important risks of Alhemo, together with measures to minimise such risks and the proposed studies for learning more about Alhemo's risks, are outlined below.

Measures to minimise 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 authorised 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 minimises its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse events is collected continuously and regularly analysed, 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 Alhemo is not yet available, it is listed under 'missing information' below.

6.2.1 List of important risks and missing information

Important risks of Alhemo are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely administered. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of Alhemo. 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 on 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). A list of important risks and missing information for Alhemo is provided in Table 6-1.

Table 6-1 List of important risks and missing information

List of important risks and missing information	
Important identified risks	• Thromboembolic events
Important potential risks	• None
Missing information	• None

6.2.2 Summary of important risks

An overview of important identified risk(s) for Alhemo is provided in Table 6-2. No important potential risks or missing information have been recognised for Alhemo.

Table 6-2 Important identified risks

Thromboembolic events	
Evidence for linking the risk to the medicine	Thrombosis formation consistent with an exaggerated pharmacological effect was observed in repeat-dose toxicology studies conducted in normo-coagulant cynomolgus monkeys at high concizumab exposures. A few patients on treatment with concizumab reported serious non-fatal thromboembolic events in the phase 3 clinical studies. An overall medical assessment of the events revealed multiple risk factors that may have contributed to the development of these events. These were a combination of different thromboembolic risk factors and the use of high or frequent doses of breakthrough bleed treatment.
Risk factors and risk groups	Possible risk factors include a history of thromboembolic events, thromboembolism in the family, obesity, arrhythmias, hypertension, diabetes, hypercholesterolaemia, smoking, post-surgical status, immobilisation, infection, liver disease and old age. The use of high or frequent doses of breakthrough bleed treatment with factor products could be a risk factor for the development of thromboembolic events. In general, patients with a pathological condition in which Tissue Factor is expressed more extensively than considered physiological, e.g., advanced atherosclerosis, cancer, crush injury, or septicaemia, may be at a higher risk of developing thromboembolic events.

Risk minimisation measures	*Routine risk minimisation measures:* Information is provided in the SmPC (Special warnings and precautions for use) that cases of non-fatal arterial and venous thromboembolic events have been reported in the concizumab clinical studies. These cases occurred in patients with multiple risk factors including high or frequent doses of breakthrough bleed treatment. The SmPC also includes a statement highlighting that caution should be exercised when the patient is at high risk of developing thromboembolic events. PL contains a warning that blood clots (thromboembolic events) may occur, and that the patient should stop using concizumab in case of signs of blood clots, and the PL provides information on symptoms of thromboembolic events. In the SmPC, it is recommended that patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events, and in case of suspicion of thromboembolic events, concizumab should be discontinued and further investigations and appropriate medical treatment should be initiated. *Additional risk minimisation measures:* • Guide for Healthcare Professionals • Guide for Patient/Carer • Patient alert card
Additional pharmacovigilance activities	*Additional pharmacovigilance activities:* Registry-based cohort study

Abbreviations: SmPC = Summary of Product Characteristics; PL = package leaflet; RMP = risk management plan.

6.2.3 Post-authorisation development plan

6.2.3.1 Studies which are conditions of the marketing authorisation

There are no studies which are conditions of the marketing authorisation or specific obligation of Alhemo.

6.2.3.2 Other studies in post-authorisation development plan

Registry-based cohort study summary (NN7415-7533)

A registry-based observational cohort study is planned to characterise the safety profile of concizumab in people with haemophilia in the real-world setting.

The primary objective is to estimate the thromboembolic event rate in people with haemophilia on concizumab in the real-world setting. The secondary objectives are 1) to describe individual cases of thromboembolic events including any risk factors, 2) to estimate the rate of hypersensitivity reactions in people with haemophilia on concizumab in the real-world setting and to describe individual cases of hypersensitivity and 3) to estimate the rate of other adverse events in people with haemophilia on concizumab in the real-world setting.

7 Annexes

Table 7-1 Annexes

Annex	Title	Included (Yes/No)
1	EudraVigilance interface	No
2	Tabulated summary of planned, ongoing, and completed pharmacovigilance study programme	Yes
3	Protocols for proposed and ongoing studies in Categories 1–3 of the section “Summary table of additional pharmacovigilance activities” in RMP Part 3	No
4	Specific adverse event follow-up forms	No
5	Protocols for proposed and ongoing studies in RMP part IV	No
6	Details of proposed additional risk minimisation measures	Yes
7	Other supporting data (including referenced material) 7A: Description of pooled clinical study data and ongoing safety data in initial safety evaluation 7B: Compassionate use safety data report	Yes
8	Summary of changes to the risk management plan over time	Yes

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Annex 6: Details of proposed additional risk minimisation measures

The educational material for healthcare professionals shall include:

- The Summary of Product Characteristics.
- Guide for healthcare professionals (HCPs) with the following key elements:
  - Brief introduction to concizumab and the risk of thromboembolic events (TEs).
  - Guidance on the use of concizumab incl. the following information:
    - Physicians should discuss with the patient and/or the caregiver about the dose and schedule of bypassing agents, if required while receiving concizumab prophylaxis.
    - Caution should be exercised when the patient is at high risk of developing TEs.
    - Patients should be informed of and monitored for the occurrence of signs and symptoms of TEs.
    - in case of suspicion of TEs, concizumab should be discontinued, and further investigations and appropriate medical treatment should be initiated.
  - Reminder to distribute the educational material to all patients and ensure they read and understand these materials.
  - Reminder that all patients receiving treatment with concizumab should be given a Patient alert card and reminded to carry it at all times and show it to healthcare professionals who may treat them.
  - Reminder to report any adverse events (AEs) associated with the use of concizumab.

The educational material for patients/carers shall include:

- The package leaflet.
- Guide for patients/carers with the following key messages:
  - Brief introduction to concizumab and the risk of TEs.
  - Description of signs and symptoms of TEs.
  - Reminder to stop using concizumab if symptoms occur and contact the physician immediately.
  - Reminder to always carry their patient card and show it to healthcare professionals who may treat them.
  - Reminder to report any AEs to their treating doctor.
- Patient alert card with the following key elements:
  - Reminder to carry the card at any time and to show it to HCPs to inform on concizumab treatment and the risk of TEs.
  - Contact details of the patient’s concizumab prescriber.