17 October 2024
EMA/511415/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alhemo

International non-proprietary name: concizumab

Procedure No. EMEA/H/C/005938/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

ABR	annualised bleeding rate
ADA	anti-drug antibodies
ADS	analysis data set
AE	adverse event
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AT	antithrombin
BMI	body mass index
BU	Bethesda units
CACO	confirmatory analyses cut-off
CI	confidence interval
CPoC	clinical proof of concept
CTR	clinical trial report
DIC	disseminated intravascular coagulation
DMC	data monitoring committee
EMA	European Medicinal Agency
ETD	estimated treatment difference
ETR	estimated treatment ratios
FAS	full analyses set
FDA	US Food and Drug Administration
FIX	coagulation factor IX
FVII	coagulation factor VII
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GCP	good clinical practice
GFR	glomerular filtration rate
HA	haemophilia A without inhibitors
Haem-A-QoL	haemophilia quality of life questionnaire for adults
HAwI	haemophilia A with inhibitors
HB	haemophilia B without inhibitors
HBwI	haemophilia B with inhibitors
Hemo-TEM	haemophilia treatment experience measure
H-PPQ	the haemophilia patient preference questionnaire
ICH	international council for harmonisation of technical requirements for pharmaceuticals for human use
IPAS	intra-patient analysis set
ISI	integrated summary of immunogenicity
ITexBR	on-treatment without data before restart
ITexIR	in-trial excl. data on initial regimen for patients exposed to both regimens
IU	international units
LAR	legally acceptable representative
LD	loading dose
LLoQ	lower limit of quantification
LTFU	lost to follow up
MI	multiple imputation
MMRM	mixed model for repeated measurements
MRD	minimum required dilution

MVPA	moderate or vigorous physical activity relative to awake time
NA	not applicable
NIS	non-interventional study
NN	Novo Nordisk
NOAEL	no-observed-adverse-effects-level
OT	on-treatment
OTexIR	on-treatment without data on initial regimen
OTwoAT	on-treatment without ancillary therapy
OTwoATexIR	on-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens
PACO	primary analysis cut-off
PD	pharmacodynamic
PGI-C	patient global impression of change
PGI-S	patient global impression of severity
PK	pharmacokinetic
PPX	prophylaxis
PRO	patient-reported outcome
PROMIS	patient-reported outcomes measurement information system
SAE	serious adverse event
SAP	statistical analysis plan
s.c.	subcutaneous
SD	standard deviation
SF-36v2	36-item short form health survey
TF	tissue factor
TFL	tables, figures and listings
TFPI	tissue factor pathway inhibitor
TMA	thrombotic microangiopathy
TMDD	target-mediated drug disposition
US	United States

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Novo Nordisk A/S submitted on 5 January 2023 an application for marketing authorisation to the European Medicines Agency (EMA) for Alhemo, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication:

Alhemo is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding in patients with:

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors ≥ 12 years of age.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors of any age.

1.2. Legal basis, dossier content

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application.

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

1.3. Information on paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision(s) P/0371/2021 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0371/2021 was not yet completed as some measures were deferred.

1.4. Information relating to orphan market exclusivity

1.4.1. Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

1.4.2. New active substance status

The applicant requested the active substance concizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

1.5. Scientific advice

The applicant received the following scientific advice on the development relevant for the indication subject to the present application:

Date	Reference
20/10/2011	SA/2178/1/2011/III
23/10/2014	SA/2178/2/2014/I
18/12/2014	SA/2178/1/FU/1/2014/III
23/06/2016	SA/2178/1/FU/2/2016/PA/III
28/03/2019	SA/2178/3/2019/PA/III, SA/2178/4/2019/PA/III
22/05/2019	SA/2178/3-4/2019/PA/III Clarification
10/12/2020	EMEA/H/SA/2178/1/FU/3/2020/PA/II, EMEA/H/SA/2178/1/FU/4/2020/PA/II

The scientific advice pertained to the following quality, non-clinical and clinical aspects:

SA/2178/1/2011/III – Nonclinical and Clinical development

- Adequacy of the completed non-clinical programme to initiate the proposed clinical phase 2 trial; design of the proposed toxicity study to support a future clinical phase 3 trial of 12 months exposure.
- Design of a proposed phase 2 study, including dose selection based on TFPI target saturation, and handling of break-through bleeds; whether the phase 1 first in human dose trial and the planned phase 2 trial could support inclusion of haemophilia B patients in the phase 3 program.

EMEA/H/SA/2178/2/2014/I – Quality development

- Sufficiency of the proposed analyses for characterisation of the structure, purity and biological activity of concizumab active substance batches; the approach used to establish the specification for concizumab active substance and finished product; agreement whether the current coagulation potency assay for concizumab could be replaced by a binding assay; comparability assessment related to manufacturing changes for AS and FP.

EMEA/H/SA/2178/1/FU/1/2014/III - Nonclinical and Clinical development

- The strategy to investigate the hypothesis that the polymers are related to the observed vascular and inflammatory changes in toxicology studies; potential cross-reactivity of concizumab to Kunitz-type domains of endogenous human proteins, including TFPI-2; adequacy of the rabbit efficacy model to guide the initial selection of drug exposure levels for the phase 1b trial.

- Selection of dose levels and planned exposure levels in the proposed phase 1b trial; inclusion of adolescent patients in the phase 3 part of the phase 2/3 trial; whether efficacy data collected in patients with haemophilia A without inhibitors will also be valid for haemophilia A and B patients with inhibitors and that clinical activities in inhibitor patients will essential be safety trials; design of a phase 1b multiple dose trial investigating safety, PK and PD of concizumab administered subcutaneously to adult patients with haemophilia A without inhibitors; whether the phase 1b trial will provide sufficient data to adequately predict steady state exposure and to support selection of dose regimens for subsequent trial, and to support 6 months or longer home treatment trials; acceptability of a confirmatory phase II/III trial with adaptive design.

EMEA/H/SA/2178/2/FU/1/2016/PA/I - Quality development

- Acceptance that addition of a preservative (phenol) to the liquid formulation used in the ongoing explorer™3 trial does not negatively affect the finished product quality and that animal pharmacology or human comparability studies are not required before the initiation of the planned phase 2 trials; stability testing strategy and shelf-life.

EMEA/H/SA/2178/1/FU/2/2016/PA/III - Nonclinical and Clinical development

- Adequacy of nonclinical safety data (incl. a study in Cynomolgus monkeys) before administering rFVIIa to patients on concizumab prophylaxis.
- Design of the phase 2 explorer™4 trial in haemophilia A and B patients with inhibitors; design of the phase II study "explorer 5" in severe haemophilia A patients without inhibitors; whether the results of the phase 2 trials where no haemophilia B patients are planned to be enrolled could support initiation of a phase 3 trial in haemophilia B patients; paediatric development; PRO instruments for label claim.

EMEA/H/SA/2178/3/2019/PA/III – Quality, Nonclinical and Clinical development

- Active substance and finished product specification; primary stability data.
- Sufficiency of the completed nonclinical programme for phase 3 and for the filing of MAA.
- Adequacy of the available phase 2 data to support further development of concizumab in the proposed phase 3 program in adult and adolescent HA and HB patients with and without inhibitors; design of the phase 3 trial (NN7415-4311) intended to support the indication of routine PPX in adult and adolescent HAwI and HBwI patients; design of the phase 3 trial design (NN7415-4307) to support the indication of routine PPX in adult and adolescent HA and HB patients; sufficiency of the phase 2 data generated in HA, HAwI and HBwI patients to support the extrapolation to and inclusion of HB patients in phase 3; dose selection for phase 3; treatment of breakthrough bleeds; adequacy of planned PK data for MAA filing; immunogenicity strategy; the proposed paediatric development program.

EMEA/H/SA/2178/4/2019/PA/III
Identical to EMEA/H/SA/2178/3/2019/PA/III.

EMEA/H/SA/2178/1/FU/3/2020/PA/II - Clinical development

- The proposed revised primary analysis including data inclusion and associated sensitivity analyses of the phase 3 trials 4311 and 4307; the proposed plan for submitting a CMA based on the efficacy and safety data available at the time of the primary analysis in trial 4311 for (1) the indication of routine PPX in adults and adolescents with HBwI, and (2) the indication of routine PPX in adults and adolescents with HawI.

EMEA/H/SA/2178/1/FU/4/2020/PA/II
Identical to EMEA/H/SA/2178/1/FU/3/2020/PA/II.

1.6. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Patrick Vrijlandt Co-Rapporteur: Daniela Philadelphy

The application was received by the EMA on	5 January 2023
The procedure started on	26 January 2023
The CHMP Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 April 2023
The CHMP Co-Rapporteur's first Assessment Report was circulated to all CHMP and PRAC members on	17 April 2023
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC and CHMP members on	3 May 2023
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	25 May 2023
The applicant submitted the responses to the CHMP consolidated List of Questions on	9 August 2023
The following GMP inspection was requested by the CHMP and their outcome taken into consideration as part of the Quality/Safety/Efficacy assessment of the product:	20 June 2024
A pre-pproval GMP inspection at Patheon Biologics LLC 4766 Laguardia Drive Saint Louis 63134-3116 United States intended for the manufacturing activities of manufacturer and Quality control testing of the active substance was carried out between from 17 to 20 June 2024. The outcome of the inspection was positive and the corresponding EU	20 June 2024

GMP certificate was issued.	
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	21 September 2023
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	28 September 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	6 October 2023
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	12 October 2023
The applicant submitted the responses to the CHMP List of Outstanding Issues on	13 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	30 November 2023
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Updated Assessment Report on the responses to the List of Questions to all CHMP and PRAC members on	7 December 2023
The CHMP agreed on a 2nd list of outstanding issues in writing to be sent to the applicant on	14 December 2023
The applicant submitted the responses to the 2nd CHMP List of Outstanding Issues on	19 January 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	7 February 2024
The CHMP agreed on a 3rd list of outstanding issues in writing to be sent to the applicant on	22 February 2024
The applicant submitted the responses to the 3rd CHMP List of Outstanding Issues on	12 September 2024
The CHMP Rapporteurs circulated the CHMP and PRAC Rapporteurs Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP and PRAC members on	4 October 2024
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Alhemo on	17 October 2024
The CHMP adopted a report on similarity of Alhemo with Alprolix,	17 October 2024

Idelvion, Roctavian, Hemgenix and Altuvoct on (see Appendix on similarity)	
Furthermore, the CHMP adopted a report on New Active Substance (NAS) status of the active substance contained in the medicinal product (see Appendix on NAS)	17 October 2024

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Haemophilia A and B are bleeding disorders caused by a deficiency of coagulation Factor VIII (FVIII) or coagulation Factor IX (FIX) respectively, each of which is a key component of the intrinsic pathway. Blood coagulation is achieved by a highly regulated cascade of plasma proteins, which ensures that bleeding can be rapidly stopped and that once bleeding is stopped, the cascade is shut down to prevent thrombosis. This regulation is achieved by 2 overlapping pathways, the extrinsic (initiation) and intrinsic (amplification) pathways, which converge in a final common pathway of coagulation.

The applicant proposes the following indication: Alhemo is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding in patients with

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors ≥ 12 years of age.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors of any age.

2.1.2. Epidemiology and risk factors, screening tools/prevention

Incidence

Globally, haemophilia A occurs at a rate of approximately 17.1 cases per 100,000 males[7]. The estimated average incidence rate was 1 in 5,617 male births for haemophilia A in the US in a study using the Haemophilia Treatment Centers (HTC) network, with an incidence rate at birth of 17.9 per 100,000 male births[10]. According to the US Centers for Disease Control and Prevention (CDC), approximately 400 boys are born with haemophilia A each year in the US[9]. The prevalence at birth was 24.6 cases per 100,000 male births for all severities of haemophilia A and 9.5 cases for severe haemophilia based on data from the 3 most established registries (Canada, France, and the United Kingdom)[10].

Haemophilia B occurs globally at an annual rate of approximately 1 in 30,000 (3.33 per 100,000) male live births[3] and the incidence rate in the US is 5.3 per 100,000 male births[8]. While the CDC doesn't report an estimate for how many boys are born annually with haemophilia B, haemophilia B is estimated to be about 3.4 times less common than hemophilia A[8]. The prevalence at birth was 5 cases per 100,000 male births for all severities of hemophilia B and 1.5 cases for severe hemophilia B in an international study including Australia, Canada, France, Italy, New Zealand, and the United Kingdom[10].

Prevalence

The prevalence (per 100,000 males) is 6.0 cases for severe haemophilia A, and 1.1 cases for severe haemophilia B[12]. The current worldwide population of patients with a diagnosis of haemophilia A, as determined by the World Federation of Hemophilia (WFH) 2021 survey (representing data reported from approximately 7.14 billion persons or roughly 91% of the world population), is estimated to be 185,318 individuals. An estimated 37,998 individuals have a diagnosis of haemophilia B[7].

Data from the 2021 WFH Annual Global Survey collected from 118 countries show that males represented 81% of haemophilia A cases, females represented 3% of haemophilia A cases, and gender unknown represented 5% of hemophilia A cases. For haemophilia B, males represented 79% of cases, females represented 6% of cases, with 5% with gender unknown (note that numbers do not add up to 100% as not all countries provided gender data)[7].

According to the WFH Annual Global Survey 2021, the reported number of patients with a diagnosis of haemophilia A (all severities) in various countries is as follows: United Kingdom (UK), n = 7,064; Germany, n = 3,793; France, n = 7,623; and the Netherlands, n = 1,376.[7]

For haemophilia B, the distribution of patients in Europe differs from that of haemophilia A. The WFH Annual Global Survey 2021 reported that the number of patients with a diagnosis of haemophilia B (all severities) in various European countries is as follows: UK, n = 1,607; France, n= 1,841; Poland, n = 477; and Ireland, n = 223.[9]

The prevalence at birth (per 100,000 males) is 24.6 and 24.0 cases for all severities of haemophilia A, and 10.2 and 8.6 cases for severe haemophilia A in the UK and in France, respectively.[10]

2.1.3. Biologic features, aetiology and pathogenesis

The genes encoding FVIII and FIX are on the long arm of the X chromosome. Haemophilia A and B are the only hereditary clotting diseases inherited in a sex-linked recessive pattern. The genetic mutations cause a quantitative decrease in protein expression, a qualitative decrease in protein activity, or both. Approximately 5% to 10% of patients with haemophilia A and 40% to 50% of patients with haemophilia B make a dysfunctional protein, which results in decreased protein activity without a quantitative decrease. More than 1000 mutations in either the factor VIII or factor IX genes have been identified to cause clinical haemophilia. There is a high rate of spontaneous mutation (approximately one-third of cases) such that even in the absence of a family history, haemophilia should be suspected in a newborn with bleeding and a prolongation in the PTT.[1]

2.1.4. Clinical presentation, diagnosis and stage/prognosis

Haemophilia A and B are bleeding disorders caused by a deficiency of coagulation Factor VIII (FVIII) or coagulation Factor IX (FIX) respectively, each of which is a key component of the intrinsic pathway. Blood coagulation is achieved by a highly regulated cascade of plasma proteins, which ensures that bleeding can be rapidly stopped and that once bleeding is stopped, the cascade is shut down to prevent thrombosis. This regulation is achieved by 2 overlapping pathways, the extrinsic (initiation) and intrinsic (amplification) pathways, which converge in a final common pathway of coagulation.

Individuals with haemophilia A have a FVIII activity level below the normal range [4,5], while those with haemophilia B have a FIX activity level below the normal range. Severity of haemophilia A or B is defined into

3 categories based on circulating FVIII or FIX activity levels in the plasma, each of which is characterised by different bleeding profiles as presented in Table 1.

Table 1: Relationship of bleeding to factor activity level for Haemophilia A and B

Severity	Clotting Factor Level	Bleeding Episodes
Severe	<1% of normal (<1 IU/dL)	Spontaneous bleeding into joints or muscles, predominantly in the absence of identifiable hemostatic challenge
Moderate	1% to 5% of normal (1 to 5 IU/dL)	Occasional spontaneous bleeding; prolonged bleeding with minor trauma or surgery
Mild	5% to <40% of normal (5 to 40 IU/dL)	Rare spontaneous bleeding; severe bleeding with major trauma or surgery
Source: WFH Guidelines[8]		

The most common haemophilia bleeds are prolonged spontaneous and/or traumatic bleeding within the musculoskeletal system and joints, as well as in the muscle and mucosal soft tissues. While less common, some types of bleeds, including intracranial and gastrointestinal bleeds, can be life-threatening. An individual's bleeding phenotype is the result of their genotype, joint health status and behaviour. Even among patients with severe haemophilia there can be considerable heterogeneity in bleeding phaenotypes[6].

2.1.5. Management

Treatment of haemophilia is primarily through replacement of the missing FVIII or FIX. The replacement factor products are commonly standard half-life (SHL) or extended half-life (EHL) recombinant factor products, but plasma-derived products of various purities are still in use. Treatment with the replacement coagulation factor can either be episodic, treating bleeding episodes on-demand as they occur, or prophylactic, preventing bleeding episodes by a regular schedule of FVIII or FIX infusions to maintain factor levels in a range >1%. Significant evidence exists that prophylactic treatment prevents bleeding episodes and the associated joint damage that is a major morbidity in haemophilic patients.[11,12,13,14,15]

Due to the relatively short half-lives of FVIII and FIX, effective prophylactic treatment in patients without inhibitors may require frequent intravenous (IV) administration, with the most frequent administration being every 2 days for SHL FVIII products, and up to twice weekly for SHL FIX products.[6,13,14,15] The recent development of EHL factor replacement products have helped reduce treatment burden for patients with haemophilia by lowering prophylactic infusion rates and maintaining higher trough levels.[16,17,18] However, despite the approval of newer EHL products, patients still may require regular factor replacement IV infusions at frequencies ranging from twice weekly to once every 2 weeks.[23,24]

Emicizumab (Hemlibra) is a bi-specific antibody that bridges activated coagulation Factor IXa and Factor X (to replace the function of missing activated FVIII). Hemlibra received approval by the EMA on 23 February 2018 for "routine prophylaxis of bleeding episodes in patients with haemophilia A (congenital factor VIII deficiency) with factor VIII inhibitors", "Hemlibra can be used in all age groups"[22] and on 11 March 2019 received approval for "routine prophylaxis of bleeding episodes in patients with severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without factor VIII inhibitors", and is currently approved for once weekly (QW) administration for the first 4 weeks, followed by SC administration weekly, or every 2 or 4 weeks.[23,24]

Several newer treatments for haemophilia A or B are available in some markets or have submissions currently under regulatory review. Hemgenix (etranacogene dezxaparvovec) is a gene therapy treatment conditionally approved in the EU for treatment of adults with haemophilia B.[25,26] Roctavian (valoctocogene roxparvovec) is a gene therapy treatment that has been conditionally approved in the EU for the treatment of

haemophilia A.[28] Hympavzi (marstacimab) is a human monoclonal antibody which inhibits the anticoagulation function of tissue factor pathway inhibitor (TPFI) that received a positive CHMP opinion in September 2024. Finally, Alhemo (concizumab) which is the subject of this application, is a new monoclonal humanised IgG4 antibody that targets the K2 domain of TFPI. Concizumab was approved in Canada in March 2023[29] and also in Australia in July 2023[30] for use in haemophilia B patients with inhibitors and was approved in Canada in July 2023 for use in haemophilia A patients with inhibitors.[31]

Pilot "CHMP early contact with patient organisations"

Feedback was collected from patient organization European Haemophilia Consortium (EHC) via the EMA to share patients' perspectives on behalf of its patient/carer members:

"*Welcoming this CHMP/CAT early dialogue on Alhemo (concizumab), we offer the below perspectives on prophylaxis for haemophilia A and B, noting different potential benefits, risks and quality-of-life impacts based on those with and without inhibitors. It is important to remember, that patients across Europe have varying degrees of access to prophylaxis for the prevention of bleeding episodes. This ranges from:*

- *low to high dose intravenous prophylaxis with clotting factor concentrate for those with haemophilia A and B without inhibitors*
- *subcutaneous prophylaxis with a bi-specific antibody for those with Haemophilia A with and without inhibitors*
- *By-passing agent activated prothrombin complex concentrate (aPCC) for those with Haemophilia A and B with inhibitors. rFVIIa is not licenced for use prophylactically but is used off-license on occasion based on need and access.*

Access to these therapies is increasing throughout Europe, but there may still be many situations between countries and even within a country, where access to prophylaxis is still very limited or unavailable.

Who Alhemo (concizumab) might provide significant benefit for:

(1) <u>Patients with Haemophilia B with inhibitors</u> currently have a very limited set of options for therapy. The two main therapies, known as by-passing agents, are aPCC (Activated prothrombin complex concentrate) and recombinant FVIIa (rFVIIa)[1]. Haemophilia B with inhibitors is one of the remaining orphan rare bleeding disorders and would welcome a therapy offering effective prophylaxis. Currently, rFVIIa is not licenced for prophylaxis for patients with inhibitors, but in the few situations where it is available, this requires a significant infusion and financial burden, while having varying degrees of success. The second therapy, aPCC, is licenced for prophylaxis. While this offers advantages over rFVIIa in that respect it, it has other issues that need to be considered. In comparison to adequate prophylaxis in haemophilia A with/without inhibitors, and haemophilia B patients without inhibitors seen with licenced therapies, patients on prophylaxis with aPCC have higher annual bleeding rates[2]. This results in patients having multiple bleeds per year that could be avoided if adequate prophylaxis was available. Another element with the use of aPCC, is trace amounts of FIXa contained in the product. Patients with haemophilia B with inhibitors can have a larger immune response which on some occasions may not allow aPCC to be used as a treatment option due hypersensitivity and anaphylaxis[1].

Finally, there are only 3 dose sizes available for the aPCC product. The result being the physical size of treatment can be large. This means large dosing volumes, longer infusion times, a large storage

space in the home and very bulky treatment required when travelling. Also in some cases, such as children, a Port-a-Cath/Hickman line is inserted to manage the frequency of infusions. Consequentially, these devices may get infected requiring use of antibiotics and if not controlled, surgical procedures to remove and replace these devices. With the above in mind, a product like concizumab, offers multiple benefits for these patients. In a recent presentation at EAHAD Congress 2023, prophylactic results indicate bleeding rates equivalent to other highly effective forms of prophylaxis for haemophilia[3]. The subcutaneous administration reduces the need for central venous access as well as being beneficial for patients in their day-to-day management. The daily subcutaneous application rate can be less than that required during a bleeding event or when applied prophylaxis with rFVIIa is used. The size of the dose and the delivery pen, offer significant benefit in terms of treating, home storage and travel. As a result, in terms of bleed protection and improved quality of life, concizumab may offer Haemophilia B patients with inhibitors significant benefit.

(2) *Patients with Haemophilia B without inhibitors, currently have access to two types of therapy. Standard half-life (SHL) and extended half-life (EHL) clotting factor concentrates. Currently, regimens with SHL typically require 1-2 intravenous injections/week and baseline factor IX trough levels being targeted are in the region of 1-3%. EHL, with extension's in half-life, up to 5-fold, typically require 1-2 intravenous injections every 2 weeks and depending on the EHL and the level of access, FIX trough levels are often above 5%[4]. As a result, if adequate access to SHL and EHL prophylaxis is possible, the reported bleed rates are low and quality of life has increased over time. There are still some areas of need within this group. Unlike their haemophilia A counterparts, there is no subcutaneous alternative for those with poor venous access or have difficulty with mobility, which can lead to reduce adherence and inadequate protection. Although, these Haemophilia B patients benefit from a peak (period of "normal" levels after infusion), the FIX trough level can be low relative to the risk of traumatic bleeding events[5]. A product like concizumab, could offer a higher steady state clotting potential than current therapies via a subcutaneous route[6]. Switching to a daily subcutaneous administration required for concizumab would be shared decision based on the patient need to balance their current ability to maintain intravenous infusions, requirement for when FIX peak levels occurs and bleeding tendency in order to assess individual benefit. With the availability of other therapies for Haemophilia B without inhibitors, the benefit may be slightly less compared to those with Haemophilia B with inhibitors.*

(3) *Patients with Haemophilia A with/without inhibitors currently have access to SHL and EHL prophylaxis, as well as a subcutaneous bi-specific antibody prophylaxis. SHL typically requires 2-3.5 infusions per week. The EHL extension in half-life is approximately 1.5-fold, resulting in choosing between reduced frequency of infusion to maintain a lower trough [1-3%] (in patients who bleed less or who are less active) and the same rate of infusions with a higher trough [3-8%] (those with a higher bleeding rate or more active)[7]. The subcutaneous bi-specific antibody mimics a 12-20% FVIII level, with 1-4 times per month administration[6,8,9]. Depending on the individual, all of these therapies already offer very low bleeding rates if adherence is maintained. The availability of the subcutaneous alternative has offered significant benefits for patients in terms of reduced need for venous access or less issues with infusion due to mobility issues, as well as offering significant bleed protection and increased quality of life for patients. As a result the benefit of concizumab in this population is less significant. The main cohort who could benefit are for those who may have developed anti-drug antibodies to the bi-specific antibody (1-3% of patients) and/or those for whom the burden of infusion with SHL and EHL is difficult.*

As described above, the benefits in the four main types of patients are present but vary in terms of size depending on current access to adequate therapy, treatment options within each cohort and a number of personal factors (activity level, bleeding tendency, venous access, mobility, etc.).

The side-effect associated with this therapy are also very important to highlight:

(1) Thrombosis.

a. Due to the mechanism of action the risk of thrombosis appears to be higher in clinical trials than seen in currently licensed clotting factor concentrate therapies trials. There was already a pause and restart due to thrombosis within concizumab clinical trials. The resulting modification to the trial protocol in monitoring the levels of TFPI and dose adjusting is welcomed, which potentially means no dose adjustment on other therapies (Clotting Factor Concentrates/By-passing agents) to treat a bleeding event will be required. However, caution will be needed in real world use to fully understand this modification. The careful monitoring of patients using concizumab is essential and information must be provided on what to do in the event of a bleeding event, trauma, or surgical procedures for the safety of the patient. This will need additional education for the patient also.

b. Within the real world setting understanding the difference between thrombotic risk and levels approaching normalization of clotting in FVIII and FIX deficient patients remains an area where more research is required. Head to head, or more likely post-marketing surveillance is required to greater understand and reveal the real thrombotic risk and as such should require strict reporting in order to ensure the safety of patients using these products.

(2) Dose adjustment monitoring – concizumab now requires a dose adjust to ensure the patients TFPI level is within certain range. It is vital that this should be carried out for the safety of the patients. As a result the access to this therapy should only be provided in centres who are adequately resourced to provide this testing and monitoring to ensure the safety of the patient.

Finally, the mechanism of action needs greater understanding on the short and long term consequences of rebalancing the coagulation cascade. The risk benefit balance as a result is more difficult categorise across the 4 different cohorts of patients."

References

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2.2. About the product

Concizumab is a monoclonal humanised IgG4 anti-tissue factor pathway inhibitor (anti-TFPI) antibody. It is specific for the Kunitz-2 domain of TFPI, which is specific for inhibition of activated factor Xa (FXa). The binding of concizumab to TFPI prevents that TFPI inhibits FXa. The increased FXa activity prolongs the initiation phase of coagulation and allows sufficient thrombin generation for effective haemostasis. Concizumab acts independently from FVIII and FIX and the effect of concizumab is not influenced by the presence of inhibitory antibodies to FVIII or FIX.

Concizumab is intended for routine prophylaxis of bleeding in patients with:

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and of 12 years of age or more.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors and of 12 years of age or more.

Alhemo will be available as solution for injection (for subcutaneous administration) in pre-filled pens containing 15 mg/1.5 ml, 60 mg/1.5, 150 mg/1.5 ml or 300 mg/3 ml of concizumab. Concizumab drug product is clear to slightly opalescent, colourless to slightly yellow liquid and practically free from visible particles, that may contain translucent to white particles of protein.

Treatment should be initiated in a non-bleeding state. Treatment with rFVIIa should be discontinued at least 12 hours before starting concizumab therapy and treatment with aPCC should be discontinued at least 48 hours before. Since concizumab is dosed per body weight (mg/kg), it is important to recalculate the dose (mg) when the body weight changes.

The recommended dosing regimen comprise a loading dose of 1 mg/kg followed by an initial once daily dosing of 0.20 mg/kg until individual maintenance dose setting. Based on the concizumab exposure level (plasma concentration) measured after 4 weeks of treatment, the maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg once daily. Importantly, the individual maintenance dose should be performed at the earliest convenience (after concizumab plasma concentration result is available) and recommended no later than 8 weeks after initiation of treatment.

Concizumab is clear to slightly opalescent, colourless to slightly yellow liquid and practically free from visible particles, that may contain translucent to white particles of protein.

2.3. Type of application and aspects on development

The CHMP did not agree to the applicant's request for an accelerated assessment as the product was not considered to be of major public health interest. This was based on the following argumentation:

Overall, while there is an unmet medical need especially in a subpopulation of the intended indication, available data do not allow straightforward conclusions on PK/PD, efficacy and safety. Furthermore, in a relevant subgroup of the population with highest unmet medical need (children < 12 years of age), only very limited data are available from compassionate use of which it is uncertain how this data will contribute to the B/R assessment across the full age range of the applied indication. Therefore, no straightforward conclusions are possible at this point in time if the product indeed addresses the unmet medical need in the entire range of the applied indication preventing to grant accelerated assessment.

2.4. Quality aspects

2.4.1. Introduction

Alhemo is presented as a solution for injection containing concizumab as active substance (AS). Other ingredients are: L-Histidine, L-Arginine hydrochloride, Sucrose, Sodium chloride, Polysorbate 80 and Phenol.

The finished product (FP) is a solution for injection for subcutaneous use consisting of medicinal product constituent (concizumab finished product in primary packaging: 1.5 mL or 3 mL glass cartridge) and a device constituent (PDS290 concizumab pre-filled, multi-use pen-injector). The cartridge is closed at the bottom with a rubber disc, and at the top with a laminate rubber disc sealed with an aluminium cap.

The FP is available in four different presentations assembled in a product-specific PDS290 concizumab pen-injector: 10 mg/mL of concizumab in 1.5 mL cartridge, 40 mg/mL in 1.5 mL cartridge, 100 mg/mL in 1.5 mL cartridge, and 100 mg/mL in 3 mL cartridge. The composition of the four presentations is the same except for the content of the active substance concizumab.

Alhemo is intended to be available in the different pack sizes, and the dose button and the cartridge holder on the pen-injector is colour–coded according to strength: 15 mg/1.5 mL (blue); 60 mg/1.5 mL (brown); 150 mg/1.5 mL and 300 mg/3 mL (gold).

2.4.2. Active substance

2.4.2.1. General information

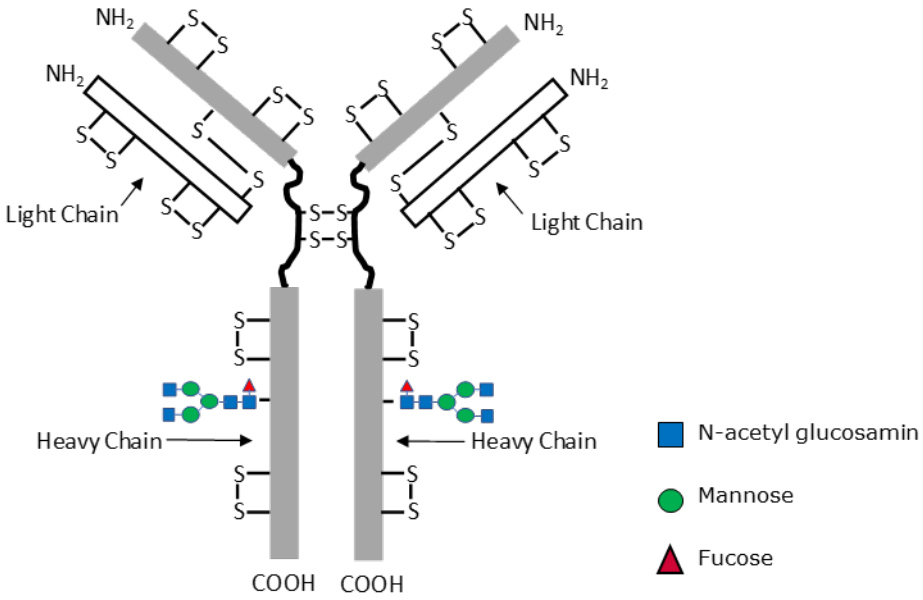
The international non-proprietary name (INN) of the molecule is concizumab.

Concizumab is a humanised intact IgG4 monoclonal antibody (mAb) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells, targeting the Kunitz 2 (K2) domain of the human tissue factor pathway inhibitor (TFPI) isoforms, TFPIα and TFPIβ.

It is a polypeptide with a molecular mass of approximately 149 kDa containing 2 heavy chains (each with 448 amino acid residues) and 2 light chains (each with 219 amino acid residues), connected by 16 disulphide bridges. It is glycosylated with a core-fucosylated bi-antennary structure at Asn298 of the heavy chain (Figure 1).

To retain the high affinity for the K2 domain in TFPI, 7 back mutations were included. In order to prevent formation of half-antibodies, the serine at position 241 (Kabat annotation) in the heavy chain was replaced with a proline (Ser241Pro).

Figure 1: Schematic structure of concizumab



2.4.2.2. Manufacture, characterisation and process controls

All sites involved in manufacture and control of the active substance operate in accordance with EU GMP.

The active substance is manufactured at Patheon Biologics LLC, 4766 LaGuardia Drive, St. Louis, MO 63134, USA. The manufacturer responsible for batch release is Novo Nordisk A/S, Novo Alle 1, 2880 Bagsvaerd, Denmark.

A major objection was raised in relation to the lack of adequate confirmation of GMP compliance for the active substance manufacturer. During the assessment, the applicant has provided a recent GMP certificate, issued by the Danish authority, which is considered acceptable and the MO was considered solved.

Description of the manufacturing process

The concizumab active substance manufacturing process has been adequately described. A flow chart and description of the manufacturing process, batch and scale definition are provided. One AS batch is produced from one vial from the working cell bank.

The process consists of a cultivation process and purification as typical for production of monoclonal antibodies. Cell cultivation is performed in a production bioreactor, which is harvested and followed by a series of chromatography and virus removal/inactivation steps. Several steps are validated for virus removal.

Flow diagrams have been provided for the upstream and the downstream process which illustrate the manufacturing route from the thaw of the working cell bank vial up to the final filling into bulk containers. Input materials, process materials, in-process tests, main purpose of the process steps are listed for each step. The qualitative and quantitative composition of culture media and buffers as used in the process is described.

Transport conditions between sites and holding times are provided and sufficiently validated.

Overall, the active substance manufacturing process is considered acceptable.

Control of materials

The cell banking system, the generation of the expression vector, the source and history of the initial cell clone (from which the cell banks used for concizumab production are derived), the manufacture and characterization of MCB (Master Cell Bank) and WCB (Working Cell Bank) are described in sufficient detail. A protocol for establishment of future WCBs is provided in the dossier.

MCB, WCB, End-of-Production Cells (EPC) and Cells at the limit (CLA) have been tested according to ICH Q5A and Q5D. Based on the results of these tests, the MCB and WCB are suitable for their use in the manufacture of concizumab, and the proposed operational ranges are sufficiently justified.

A list of raw materials is provided with specifications. None of the raw materials are of human or animal origin. In general, the raw materials are sufficiently described.

Control of critical steps and intermediates

In-process controls are defined as process parameters and in-process tests. In-process controls have been established for each manufacturing step. Process parameters are controlled within defined ranges to control the process. To provide additional control to the process, in-process tests are used for monitoring the process performance. Limits have been established for those process parameters and in-process tests for the process steps where the quality potentially could be affected or should be evaluated if limits are exceeded.

The control strategy, i.e. the approach to control of critical quality attributes (CQAs) is in general considered appropriate.

Process Validation

The AS manufacturing process is fairly straightforward and typical for a mAb and has been validated adequately. As such, the process description has been derived from Prior Knowledge and the main outline is as such justified.

In accordance with the PPQ protocol, three PPQ batches were needed for process qualification. One additional supportive PPQ batch was produced. The Process performance qualification (PPQ) exercise has successfully demonstrated that the manufacturing process is in control and consistently and reproducibly produces concizumab active substance of the specified quality. In general, the implemented in-process controls are considered adequate and ensure that the active substance manufacturing can be kept under control.

The applicant has set a maximum number of reuse cycles for the protein A column. This number was sufficiently justified in the dossier.

Based on the provided transport validation report, the transportation of the AS is considered to be sufficiently validated.

Manufacturing process development

A number of process changes were implemented during development. Between clinical phase 2 and 3, the manufacturing process was transferred to the proposed commercial facility Patheon (USA). A list of batches manufactured during development was provided, with indication of the respective manufacturing date, facility, cell bank, bioreactor, AS concentration, AS container, batch size and batch use.

In general, the results of the comparability studies support sufficient comparability regardless of the applied manufacturing process and manufacturing site. No new impurities were detected above the quantitation limit of the analytical methods applied. While changes were implemented in the analytical methods during development, in the comparability studies the results of representative batches were compared using the same method on all batches in the study.

Characterisation

In general, the characterisation work reported by the applicant provides a good indication of the structure, properties, biological activity and impurities of concizumab.

The characterisation of structure consisted of a primary sequence analysis, N- terminal and C-terminal amino acid analysis (primary structure), location of disulphide bridges and CD spectroscopy (higher order structure), N-linked glycosylation (PTM) and molecular mass.

Physico-chemical properties addressed are UV-absorbance, solubility (in relation to pH), charge heterogeneity (iCIEF), thermal stability (Differential scanning calorimetry and Dynamic light scattering), hydrodynamic radius and colloidal stability (Dynamic Light scattering).

The biological activity is studied through an in-house coagulation assay. The principle of this method, as widely applied as diagnostic tool, is described and the method itself is part of the analytical program for release testing. During development, the biological activity has been tested for AS and FP, stability testing and in forced degradation studies. While the principle of this assay is relevant for the proposed indication of concizumab, several concerns have been raised with respect to this assay, which constituted an MO and have been resolved during the assessment period with additional data provided by the applicant.

Data on TFPI binding kinetics studied by surface plasmon resonance analysis and studies on Fc receptor binding/ ADCC were included in the dossier and considered to be sufficient and not raising concerns.

The applicant has evaluated and listed product-related impurities identified for concizumab: fragments, oxidised forms, deamidated forms and isomerised forms.

In summary, the characterization is considered appropriate for this type of molecule.

2.4.2.1. Specification, analytical procedures, reference standards, batch analysis, and container closure

Specifications are in place for Appearance (Ph.Eur.), pH (Ph.Eur.), Identity (by iCIEF and Peptide mapping), Specific activity (i.e. potency per mg concizumab), content and HMWP (by SE-HPLC), Purity and total fragments (by CE-SDS), Main, Acidic and Basic Isoforms by iCIEF, Fd and Fc/2 oxidised forms (by RP-HPLC), Fucosylation and Glycosylation (HPLC Carbohydrate map), HCP (HCP ELISA), Residual protein A (ELISA), osmotic pressure, Bioburden and "undesirable organisms" (Ph.Eur.) and Bacterial Endotoxin (Ph.Eur.).

The specifications and test panel includes the test items generally recommended according to ICH Q6B. A recommendation is made of the applicant's commitment to monitor the levels of a defined HCP in additional AS batches and to re-evaluate the specification and the manufacturing process with respect to reduction of this HCP (REC).

The proposed release specifications for the AS are based on multiple batches and a statistical analysis of the data obtained from these batches with use of tolerance intervals. In relation to the FP release specifications

specific activity, HMWP, total fragments, oxidized forms and iCIEF specifications are the same. Overall, the proposed specifications have been sufficiently justified.

Analytical procedures

Descriptions and validation reports are provided for the non-compendial methods used for AS release testing. The method validations were generally performed in line with ICHQ2. The methods to be used for both AS and FP are also validated for FP in addition to the validation using AS.

Reference Material

The reference material (RM) is in general sufficiently documented and acceptable. It is not traceable to any international or compendial reference standard of concizumab, as no such material exists.
Consequently, a primary reference standard has been established from a clinical phase 3 active substance batch which is representative for the commercial material. The characterisation, storage, shelf life and stability has been appropriately described. In addition, a secondary reference material has been established for analytical use during the clinical phase 3 programme and for the marketed product.
Concizumab secondary reference material is used for quality control of concizumab active substance and finished product and was produced from clinical phase 3 trials material. As for the primary reference standard the characterisation, storage, shelf life and stability has been appropriately described. Furthermore, for both, primary and secondary reference standard, protocol describing how future reference standards will be established have been included.
In summary, a two-tiered reference standard system is in place which has been sufficiently described.

Batch analysis

Release data have been provided for Novo Nordisk batches and Patheon (Commercial facility) batches. Use and genealogy of these batches is listed. The data provided do not give raise to specific concerns. The results are within the specifications and confirm consistency of the manufacturing process.

Container closure

The AS is stored in a container with a screw cap. The containers including screw cap are sterilized according to ISO 11137 guidelines and the materials used are Ph. Eur. Compliant. Based on the information provided, the containers are suitable for long term storage of concizumab AS at the proposed storage conditions of -80°C ± 10°C.

2.4.2.2. Stability

The applicant proposes a shelf life of 60 months for concizumab AS stored in containers at -80°C.

The proposed shelf life is based on batches with 48 months of primary stability data, supportive batches with 60 months of stability data and 36 months of PPQ stability, all performed at long-term storage conditions (-80°C) and showing only little variation and no trends.

Additionally, stability testing at accelerated conditions at elevated temperatures (5°C and 25°C) has been performed to investigate the stability profile at accelerated storage conditions.

Comparable stability of active substance batches manufactured for phase 1 and 2 clinical trials at Novo Nordisk A/S and active substance batches manufactured at the commercial manufacturing facility at Patheon for phase 3 clinical trials and during phase 3 and PPQ has been demonstrated.

The forced degradation study examined concizumab AS and FP degradation under extreme conditions such as acidic and alkaline conditions, elevated temperature, light, oxidation, and mechanical stress. The study confirmed the major pathways of degradation for concizumab and a number of analytical methods were confirmed to be stability indicating.

In general, the stability studies were performed in line with ICH stability guidelines. The containers used in the stability studies are considered sufficiently representative of the proposed commercial containers.

Based on the summarised stability data from Supportive, Primary and PPQ stability studies, the proposed shelf life of 60 months is supported for concizumab active substance when stored at long-term storage conditions at -80°C.

2.4.3. Finished Medicinal Product

2.4.3.1. Description of the product and pharmaceutical development

The finished product is a solution for injection in a pre-filled pen. The proposed FP is developed in three strengths: concizumab 10 mg/mL (15 mg/1.5 mL), concizumab 40 mg/mL (60 mg/1.5 mL) and concizumab 100 mg/mL (150 mg/1.5 mL and 300 mg/3 mL).

The solution appears as a clear to slightly opalescent and colourless to slightly yellow liquid, that is practically free from visible particles but may contain translucent to white proteinaceous particles. The different FP strengths can be distinguished by the colour of the pen-injector.

The FP solution is composed of concizumab, L-Histidine, L-arginine hydrochloride, sodium chloride, sucrose, polysorbate 80, phenol and water for injections. Furthermore, hydrochloric acid and sodium hydroxide are used for pH adjustment. The concentration of excipients is below target in the FP due to protein displacement occurring during manufacture of the active substance. Detailed information regarding the quantitative composition and the effect of this displacement on the AS and FP was lacking and was requested during the assessment (major objection). The applicant had provided additional data, including a robustness of formulation study, demonstrating that the FP quality is maintained upon variation of the excipients, and that protein displacement is without impact for the FP quality. Besides the target composition, the actual compositions based on measured values for the three different strengths were provided as well. When more data becomes available, the actual composition tables should be updated (**REC**).

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur standards. There are no novel excipients used in the finished product formulation.

Development work was performed to obtain a multiple use liquid formulation of FP, stable at 2-8°C. A fundamental understanding of the finished product has been achieved based on prior knowledge of multiple use products in Novo Nordisk A/S, formulation development studies, and risk assessment of the manufacturing process.

The information provided regarding the changes in the manufacturing process during development is very brief but considered sufficient. The composition and manufacturing process of FP used in phase 3 trials is identical to the one intended for market.

The comparability study carried out to document comparability between concizumab finished product 10 mg/mL, 40 mg/mL and 100 mg/mL, between cartridge sizes 1.5 mL and 3 mL and between manufacturing facilities showed comparable impurity profiles and the results were all within specification limits.

The FP solution in a cartridge is packed in a portable multi-dose disposable pre-filled pen, which consists of a 1.5 mL or 3 mL glass cartridge sealed in a pen-injector, made of plastic components and metal springs. The closure at one end of the cartridge is a cap that consists of a laminate rubber disc (Ph. Eur. And USP) and a seal of aluminium. The closure at the other end of the cartridge is a plunger made of rubber (Ph. Eur. and USP). The rubber discs and rubber plunger are not made with natural latex.

The pen-injector is not in contact with the FP solution. Whereas the FP solution is sensitive to light when stored in the cartridge, the pen-injector provides sufficient protection against light exposure. Furthermore, the integrity of the container closure system has been demonstrated using different tests. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

A notified body opinion was provided, concluding that the medical device part fulfils the applicable General Safety and Performance Requirements of the MDR.

2.4.3.2. Manufacture of the product and process controls

The FP is manufactured at Novo Nordisk A/S. All sites involved in manufacture and quality control (QC) testing of the finished product operate in accordance with EU GMP.

A flow diagram for the Manufacturing Process of Finished Product is provided. A flow-chart demonstrating the manufacturing of the drug device combination (AS filled cartridge assembled into the PDS290 pen injector) is also included in the dossier.

The FP is formulated by preparing an excipient solution. The AS is thawed and added to the excipient solution followed by addition of the remaining excipient. Water for injections is added to the final batch volume and the solution is sterile filtered. The filtrated solution is filled aseptically into sterilised and depyrogenated cartridges with plungers inserted. The cartridges are sealed with aluminium caps.

The manufacturing process is a non-standard process. Process characterization was performed

Process performance qualification was performed for consecutive batches at production scale at the proposed manufacturing site. A bracketing approach was applied for the different strengths, fill volumes and batch sizes. The results demonstrate that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

2.4.3.3. Product specification, analytical procedures, batch analysis

Specifications for the FP are set in accordance with ICH Q6B. All relevant characteristics of the FP (appearance, identity, phenol identification, polysorbate 80, sterility, dose accuracy and extractable volume, HMWP, purity, total fragments, main-; acidic- and basic isoforms, Fd oxidized form and Fc/2 oxidized forms, pH, specific activity, content, phenol content, osmotic pressure, particulate matter and endotoxins, appearance and functionality of the pen-injector are adequately covered.

The release and shelf-life specifications are acceptable and the analytical procedures are sufficiently described and validated.

Batch analysis

Batch analysis data are provided for batches used for among others PPQ, stability, clinical and non-clinical studies, specification setting and process justification. The PPQ batches are produced at the proposed manufacturing site at commercial scale; data are provided for batches of the 10 mg/ml strength, 40 mg/ml strength and 100 mg/ml strength (filled in 1.5 ml and 3 ml cartridge). The batches are compliant with the proposed specification. No major differences are seen in the batch analysis data for all commercial scale batches.

The potential presence of elemental impurities in the finished product has been assessed on a risk-based approach in line with the ICH Q3D Guideline for Elemental Impurities. Batch analysis data was provided, demonstrating that each relevant elemental impurity was not detected above 30% of the respective PDE. Based on the risk assessment and the presented batch data it can be concluded that it is not necessary to include any elemental impurity controls in the finished product specification.

A major objection was raised regarding the evaluation of nitrosamines. Upon request, the applicant has performed a complete risk evaluation concerning the presence of nitrosamine impurities in the finished product, considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/applicants on the CHMP opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report- Procedure under Article 5(3) of Regulation EC (No) 726/2004- Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or the related finished product. Therefore, no additional control measures are deemed necessary and the provided information regarding impurities is considered sufficient.

Reference materials

The reference standard used for finished product testing is the same as for the active substance.

Container closure system

The finished product solution is contained in a glass cartridge (type I), which is sealed with a rubber plunger and rubber disc. The cartridge is assembled into the PDS290 concizumab pen-injector. This pen-injector is not in contact with the finished product solution. The cartridge components are in compliance with the Ph. Eur. A notified body opinion is provided for the pen-injector, concluding that the pen-injector fulfils the applicable General Safety and Performance Requirements of the MDR.

2.4.3.4. Stability of the product

The proposed shelf-life and storage conditions for the finished product is 36 months at 2-8°C including an in-use period of 4 weeks below 30°C. The pen-injector should be stored with the cap on to protect the FP solution against light. The finished product should not be frozen.

Long-term (5°C ± 3°C) and accelerated (30°C ± 2°C) stability studies were performed with primary stability batches, PPQ batches and supportive batches.

Primary batches from each presentation of concizumab FP and each FP presentation assembled in PDS290 pen-injector are tested in stability for 36 months at long-term storage conditions and for 6 months at accelerated storage conditions.

Supportive stability studies were performed, with batches manufactured at the proposed manufacturing site tested for 36 months at long-term storage conditions and for 6 months at accelerated storage conditions.

Data from PPQ batches produced at the proposed manufacturing site are provided for batches of the 10 mg/ml strength, of the 40 mg/ml strength and of the 100 mg/ml strength (filled in 1.5 ml and 3 ml cartridge). The batches are compliant with the proposed specification.

Furthermore, in-use stability (both 5°C ± 3°C and 30°C ± 2°C), the effect of assembly, packaging and transport, the effect of temperature cycling and photostability was tested. Performance of the pen-injector was tested for long-term, accelerated and in-use stability. The formulation, batch size, manufacturing process and cartridge of the batches included in the stability studies are representative of the ones intended for market. For some stability studies, the cartridge is assembled into the PDS290 pen-injector; this is either the commercial pen-injector, or a related pen-injector used in clinical trials.

All results from the long-term stability studies are within the proposed FP specification limits. Photostability was tested in line with ICH Q1B. The FP solution is sensitive to light. However, the PDS290 concizumab pen-injector provides adequate protection from light for the FP solution.

During 4 weeks of in-use simulation when stored at 30°C ± 2°C, all results are within the proposed FP specification limits. During 4 weeks of in-use simulation when stored at 5°C ± 3°C, all the test parameters remain constant or almost constant throughout the study, and all results are within the proposed FP specification limits.

The results currently available support the sustained performance of the PDS290 concizumab pen-injector after long-term storage for 36 months, followed by an in-use period of 4 weeks.

Overall, the proposed shelf-life and storage conditions for concizumab FP of 36 months at 2-8°C including an in-use period of 4 weeks below 30°C are acceptable.

2.4.3.5. Adventitious agents

Virus clearance data for each model virus is presented obtained from a validated scaled-down laboratory model of the commercial scale manufacture process, according to recommendations given in ICH Q5A.

The applicant has confirmed that no human or animal derived raw materials have been used during the establishment of the MCB, propagation and production of the WCB and further onwards to the manufacture of concizumab active substance. Likewise, no excipients of human or animal origin are used during the manufacturing process of the final FP. Based on this, transmissible spongiform encephalopathy (TSE) safety is sufficiently assured.

MCB, WCB and CLA as used in the commercial production of concizumab have been tested for viruses according to ICH Q5A, and for mycoplasma according to ICH Q5D and Ph.Eur.

The down scaled study parameters are either worst case or similar to the full-scale parameters applied in the virus reduction steps, as appropriate.

Reports of all virus clearance evaluation studies are provided and support in general acceptable execution of these studies in line with ICH Q5A.

2.4.4. Discussion on chemical, pharmaceutical and biological aspects

Concizumab is a humanised intact IgG4 monoclonal antibody (mAb) produced by recombinant DNA technology in Chinese Hamster Ovary (CHO) cells, targeting the Kunitz 2 (K2) domain of the human tissue factor pathway inhibitor (TFPI) isoforms.

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The AS and FP manufacturing process are adequately described and validated. Stability studies have been provided and support the proposed shelf-life.

The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

During the assessment, major objections raised on the GMP status of the active substance manufacturing site, the potency assay, the effect of protein displacement on the finished product and on the evaluation of risk for nitrosamine impurities were adequately addressed by the applicant during the assessment.

Several recommendations are proposed and these have been agreed with the applicant. These relate to the ongoing leachables study for the AS container, evaluation of the levels of a defined HCP in AS batches, and reporting of the average values for the concentration of excipients in the FP.

2.4.5. Conclusions on the chemical, pharmaceutical and biological aspects

As conclusion, the quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on viral/TSE safety.

2.4.6. Recommendation(s) for future quality development

In the context of the obligation of the APPLICANTs to take due account of technical and scientific progress, the CHMP recommends points for investigation.

2.5. Non-clinical aspects

2.5.1. Introduction

Concizumab is a humanised recombinant Immunoglobulin G (IgG) 4 monoclonal antibody (mAb) indicated for routine prophylaxis of bleeding in patients with haemophilia A (HA) (congenital factor VIII deficiency) and haemophilia B (HB) (congenital factor IX deficiency) with inhibitors to FVIII and FIX, respectively.

Concizumab is administered as a subcutaneous (s.c.) injection and intended for long-term prophylactic treatment.

The nonclinical safety programme was designed according to the International Committee for Harmonisation (ICH) M3(R2), ICH S6(R1), and ICH S7A guidelines. The pivotal repeat-dose toxicity and safety pharmacology studies in *Cynomolgus* monkeys were conducted in an Organisation for Economic Co-operation and Development (OECD) member country in accordance with either OECD or US FDA Good Laboratory Practice (GLP).

The nonclinical data for concizumab include primary and secondary pharmacodynamics, safety pharmacology, pharmacokinetics/toxicokinetics, and toxicology, including fertility assessment. Dedicated studies on reproductive toxicity, juvenile toxicity, genotoxicity and carcinogenicity were not conducted. A weight of evidence assessment was undertaken to evaluate the potential risk of carcinogenicity. The *Cynomolgus* monkey and rabbit have been identified as relevant nonclinical species. The rabbit was selected as efficacy species, the *Cynomolgus* monkey was selected as the nonrodent safety species and both species were used in pharmacokinetic/pharmacodynamic (PK/PD) assessment. Toxicity studies of up to 52-week duration have been conducted in *Cynomolgus* monkeys with a normal coagulation system (non-haemophilic). In repeat-dose toxicity studies, concizumab was dosed i.v. once weekly or s.c. once daily. Daily administration of concizumab was used in toxicology studies to overcome the exposure related effects of target-mediated drug disposition (TMDD), particularly at lower doses. Both i.v. and s.c. dosing was evaluated to support the clinical development programme.

To evaluate the potential for interaction of co-administration of recombinant activated factor VII (rFVIIa; NovoSeven), activated prothrombin complex concentrate (aPCC; FEIBA), recombinant FVIII or recombinant FIX for treatment of bleeds in haemophilia patients on prophylactic treatment with concizumab, *in vitro*, e*x vivo* and *in vivo* drug-drug interaction studies were performed.

2.5.2. Pharmacology

2.5.2.1. Primary pharmacodynamic studies

Concizumab is directed against TFPI, which is involved in down-regulation of the initiation of the coagulation cascade. Concizumab binds specifically to the Kunitz domain 2 (K2) of TFPI and prevents TFPI from binding to the active site of FXa. When the TFPI inhibitory activity is reduced, the FXa produced by the activated factor VII (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 of FVIII or FIX and concizumab was therefore proposed for the treatment of both HA and HB, regardless of inhibitor status. *Cynomolgus* monkey and rabbit were identified as pharmacologically relevant species due to very high sequence similarity of the Kunitz 2 (K2) domains site of TFPI. Data base searches revealed no other species with similar Kunitz

domains, except for K2 from rabbit and monkey species. Non Human Primates (NHP) share a similar coagulation system to human providing further physiological justification for its use as a species in toxicology studies.

Characterisation of concizumab binding to TFPI showed high affinity, sub-nanomolar binding to rabbit, NHP and human TFPI with similar binding constants (KD of 0.22 nM, 0.06 nM and 0.04 nM for rabbit, *Cynomolgus* monkey and human, respectively). Association and dissociation constants were also similar between these species. Functional binding studies revealed an absence of prothrombin time modulation in a modified PT clot assay when using plasma of mouse, rat, dog and guinea pig. In contrast, concizumab effectively enhanced clot time in *Cynomolgus* and rabbit plasma (EC_{50} of 0.41 nM and 0.49 nM, respectively, which are in the same range as in human FVIII-deficient plasma (EC_{50} of 0.62 nM)), further demonstrating that the rabbit and NHP are pharmacologically relevant species.

Effective neutralisation of TFPI binding was demonstrated using purified FX (EC_{50} of 0.8 nM) and FX and FVIIIa/TF/FXa (EC_{50} of 1.1 nM). Concizumab was able to dose dependently neutralize TFPI function on human endothelial cells (HUVEC cells, EC50 below 0.5 nM) and on human endothelial-like cells (ECV304 cells, EC50 below 0.5 nM). In human plasma, concizumab resulted in dose dependent TFPI neutralisation and FX activation (EC_{50} 6 nM). Incubation of concizumab with antibody induced haemophilia A (using anti-FVIII antibody) or haemophilia B (using anti-FIX antibody) human blood dose dependently enhanced FXa mediated thrombin generation resulting in improved clot time (EC_{50} of 0.43 nM and 0.44 nM, respectively) and clot development (EC_{50} of 2.2 nM and 2.6 nM, respectively compared to untreated controls. Inter-donor variability was apparent in this experiment but adequately demonstrated the proof of concept. Using blood from *Cynomolgus* monkeys resulted in comparable, dose-dependent enhancement of clot time and clot development (EC_{50} of 0.38 and 0.54 nM, respectively).

Concizumab (or, its murine variant Mu4F36) enhanced thrombin generation in absence of FVIII. In presence of FVIII, concizumab still contributed to thrombin generation at increasing concentrations of FVIII. Clot time and clot formation was also enhanced in presence of concizumab, although at moderately higher FVIII concentrations (0.05 IU/ml and above) this effect was diminished. At normal levels of FVIII there was no clinically significant effect of concizumab co-incubation.

In vitro safety data was presented to suggest that concizumab has limited capability to release TFPI from endothelial cells, which could result in an anticoagulant effect. Concizumab increased TFPI concentrations at concentrations of 1 µM and above. In contrast, the positive control heparin resulted in TFPI release from 5 U/ml onwards and at 1µM anti TFPI antibody against the K3 domain induced higher TFPI release than 1µM concizumab, which is in line with the role of K3 in cellular anchoring of TFPI. Therefore, concizumab is a potent and high affinity binding antibody directed against the K2 domain of TFPI. Functional effects of TFPI inhibition by concizumab were shown to lead to enhanced coagulation in assays comprising human plasma and whole blood, demonstrating the mode of action.

Concizumab shortened clotting time in plasma from rabbit and *Cynomolgus* and enhanced whole blood clot formation in *Cynomolgus* blood with EC_{50} values similar to the values obtained in human plasma or blood, providing in vitro evidence for a proof of concept.

Concizumab is unlikely to result in TFPI release in therapeutic ranges. Concizumab has been shown to be most effective as a prophylactic treatment. Pre-treatment with concizumab dose dependently reduced blood loss in antibody-induced haemophilia A rabbits after cuticle bleeding induction (ED_{50} of 0.23 mg/kg), but concizumab was less effective when administered after induction of bleeding. Increasing the time between treatment further reduced the effectiveness of concizumab in this animal model. Administration of a single 20

mg/kg concizumab i.v. dose in antibody-induced haemophilia A rabbits resulted in a sustained effect on reduced blood loss after cuticle bleeding compared to controls over a 7-day period. After 7 days, concizumab was no longer effective in reducing blood loss. Subcutaneous administration of 10 mg/kg concizumab also significantly reduced blood loss compared to controls in this model, but there was no assessment of duration of effect in this study.

In a venous stasis model using naïve rabbits, 2 mg/kg concizumab did not affect the number nor the size of clots, and did not alter platelet counts, prothrombin time (PT), thrombin–antithrombin complex (TAT) nor fibrinogen. Clot formation was significantly increased compared to controls in this model after inducing crush injury to ligated facial veins and could be prevented by administration of LMW heparin before inducing the injury, without altering other coagulation parameters.

2.5.2.2. Secondary pharmacodynamic studies

To study if concizumab affected activation of protein C and the action of anti-thrombin (AT), *in vitro* studies were performed using Human Umbilical Vein Endothelial Cells (HUVECs) as the source of TFPI and thrombomodulin (TM). The conclusion of the study was that concizumab had no effect on protein C activation and no effect on AT inhibition of thrombin.

Concizumab does not interfere with protein C activation nor with antithrombin across a broad dose range as confirmed in the repeat dose toxicity studies in monkeys. Concizumab is an IgG4 monoclonal antibody. Therefore, no Fc-effector functions such as antibody-dependent cell-mediated cytotoxicity (ADCC) and complement activation are anticipated. This was confirmed *in vitro*, where concizumab bound to FcγRI with a KD of 2 nM, and FcRn, FcγRIIa (131R and 131H variants). FcγRIIb, and FcγRIIIa (158V variant) had KD values of 0.4 – 1.7 µM, while only weak binding of FcγRIIIa (158F variant) was observed. Similar affinities were obtained for the human IgG4 control antibody. Concizumab did not activate complement via the C4 component, nor did concizumab induce ADCC similar to the human IgG4 control antibody. Concizumab did not bind to any peripheral blood cell nor induced cytokine release *in vivo*. In repeat dose toxicity study, no untoward effects were observed on central nervous system (CNS), respiratory or cardiovascular function.

2.5.2.3. Safety pharmacology programme

The *in vitro* safety pharmacology programme performed with concizumab consisted of the assessment of Fc receptor (FcR) binding, ADCC complement fixation and binding to peripheral blood mononuclear cells (PBMCs). In these assays, the results with concizumab were not different compared to an isotype IgG4 control antibody. *In vivo* safety pharmacology endpoints (blood pressure measurement, electrocardiogram (ECG), respiration rate, urinalysis and applicable Central Nervous System (CNS) endpoints) as well as evaluation of a potential cytokine release (Interleukin (IL)-2, IL-4, IL-5, IL-6, Tumour Necrosis Factor (TNF)-α, Interferon (IFN)-γ) were included in the dose range finding (DRF) toxicity study and in the pivotal 13-week repeat-dose toxicity study in *Cynomolgus* monkeys, in accordance with the ICH S6(R1) and the ICH S7A guidelines for nonclinical safety testing. Additionally, ECG and urinalysis were included in the 52-week toxicity study. No effects of concizumab on safety pharmacology endpoints were observed in any of these studies at repeat doses up to 200 mg/kg/once weekly (i.v.) and 50 mg/kg/day (s.c.). These doses result in an exposure far exceeding (>1000-fold) the clinically relevant exposures.

2.5.2.4. Pharmacodynamic drug interactions

Pharmacodynamic drug interactions between rhFVIIa (Novoseven) and activated prothrombin complex concentrates (aPCC, FEIBA) with concizumab were evaluated *in vitro*, *ex vivo* and *in vivo*. In human plasma with or without inhibitors from HA patients, addition of rhFVIIa or aPCC increased thrombin in absence or presence of concizumab. Coadministration with concizumab led to an additive and synergistic affect that accounted for up to 40% of the total observed effect. Interaction studies with rhFVIII and rFIX similarly showed increased thrombin generation with additive effects and a synergistic effect of concizumab up to 22% of the total observed effect. The observed synergistic effects are in accordance with the mechanism of action of concizumab and other procoagulant compounds, which enhance thrombin generation via enhanced FX activation.

2.5.3. Pharmacokinetics

Concizumab pharmacokinetic profile was characterised following intravenous (IV) and subcutaneous (SC) administration to rabbits (2-20 mg/kg) and *Cynomolgus* monkeys (0.1-20 mg/kg). Toxicokinetic profiles were characterised in monkey following once weekly IV or daily SC dosing for a total duration of up to 52 weeks, with doses of 0.5-200 mg/kg.

Methods of analysis

The assay for the analysis of concizumab plasma concentrations was an enzyme-linked immunosorbent assay (ELISA) and the assay was validated for the GLP studies (Table 9). Further, five functional/PD assays were established based on the pharmacological activity of concizumab. For anti-drug antibody (ADA) analysis, a bridging ELISA was used for detection of anti-concizumab antibodies in the nonclinical GLP studies. Furthermore, two assays detecting immune complexes (ICs) in plasma were included: one specifically detecting ADA/concizumab complexes and one detecting the presence of circulating immune complexes (CICs) irrespective of their composition, i.e. not specific to concizumab.

Table 9: Assays used in nonclinical samples

Assay	Used for pharmacology studies (rabbit)		Used for safety studies (cynomolgus monkey)	
	Yes / No	Assay-status	Yes / No	Assay-status
Pharmacokinetic assays				
Concizumab ELISA	Yes	Non-GLP	Yes	GLP
rFVIIa (clot)	No	N/A	Yes	GLP
Pharmacodynamic assays				
Free TFPI ELISA	Yes	Non-GLP	Yes	Non-GLP/GLP
Total TFPI ELISA	Yes	Non-GLP	Yes	Non-GLP
Actichrome®/TFPI functionality	Yes	Non-GLP	Yes	Non-GLP/GLP
S2222/TFPI functionality	No	N/A	Yes	GLP
Dilute prothrombin time (dPT)	Yes	Non-GLP	Yes	Non-GLP
Antibody assays				
Binding antibodies	No	N/A	Yes	GLP
Detection of ADA/concizumab specific immune complexes by size exclusion chromatography and immune complex ELISA	N/A	N/A	Yes	Non-GLP
Circulating immune complexes	N/A	N/A	Yes	Non-GLP

Abbreviations: ADA = anti-drug antibody; CRO = contract research organisation; dPT = dilute prothrombin time; ELISA = enzyme-linked immunosorbent assay; GLP = Good Laboratory Practice; N/A = not applicable; rFVIIa = recombinant activated coagulation factor VII; TFPI = tissue factor pathway inhibitor.

Absorption

Single dose pharmacokinetic studies were performed in rabbits and *Cynomolgus* monkeys, with IV doses of 2-20 mg/kg in rabbit and 0.1-20 mg/kg in monkey and SC doses of 2-20 mg/kg in rabbit and 0.5-20 mg/kg in monkey. At all dose levels, except from most monkeys dosed with 0.5 mg/kg sc, exposure in plasma was confirmed. In both rabbits and monkeys, clearance and distribution volume decreased with increasing dose, whereas T1/2 increased. In addition, dose normalised Cmax and -AUC increased with increasing dose, suggesting that target mediated drug disposition occurs. In monkeys, the target-mediated drug disposition becomes saturated at concentrations of concizumab above 10,000-20,000 ng/mL. At high dose levels, when target is saturated, plasma clearance is low (0.50-0.63 ml/h/kg in rabbits, 0.31-0.40 ml/h/kg in monkeys) and T1/2 was long in rabbits (32-162h in rabbits, 210h in monkeys), as expected for a monoclonal antibody. Volume of distribution at high doses was also low (52.4-120 ml/kg in rabbits, 130 ml/kg in monkeys), consistent with other monoclonal antibodies. Reported values for both volume of distribution and terminal elimination T1/2 varies largely between studies, especially in the rabbit studies (at similar dose levels), due to large inter-animal variability due to TMDD.

The SC bioavailability of concizumab was approximately 80% in rabbits and monkeys. There were no relevant (>2) gender differences in exposure in monkeys (in rabbits either males or females were exposed in the provided studies, so no conclusion on gender effects can be made).

PK modelling was used to describe the TMDD. At concentrations resulting in saturated TMDD, clearance was estimated to be 0.14 ml/h/kg. Estimated values for the non-linear clearance were described by the Michaelis-Menten expression (11,000 ng/h/kg for Vmax and 514 ng/mL for Km).

Multiple dose pharmaco- and toxicokinetic studies were performed in *Cynomolgus* monkeys 4, 13, 26 (SC and IV) and 56 weeks (SC only) at dose levels of 30-200 (mg/kg IV weekly) and 0.5-50 mg/kg (SC daily). SC concizumab was administered daily so that plasma concentrations maintaining target saturation could be achieved. In humans, target saturation is reached by administration of a loading dose, followed by daily SC doses. At steady state, Tmax varied between 3 and 24h and systemic exposure of concizumab increased in a dose proportional manner in the 13 and 26 weeks studies (3-9 mg/kg/d sc), but in a greater than dose-proportional manner in the 52 week study which used lower dose levels (0.5-9 mg/kg/d). The mean terminal elimination half-life of concizumab administered SC ranged from 59.9-389h in the 26 weeks study (at steady state, no dose-relationship).

As expected with daily SC dosing of an antibody with slow absorption and a long half-life, accumulation was high, particularly at low dose levels (up to 278-fold). After once weekly intravenous dosing, accumulation was only low (2.6-4.9x at week 22 in the 26 weeks study). In some studies, exposure tended to be lower in females, however, no relevant gender differences were observed (all differences were < a factor 2).

At the lower dose levels (0.1-9 mg/kg SC), anti-drug antibodies were observed in some to all of the animals (2/9 in the low dose of the 13 weeks study, 1/10 and 1/9 in the low and high dose of the 26 weeks study and 15/17 and 5/18 in the low and mid dose of the 52 weeks study). In most animals positive for ADA's, exposure to concizumab was reduced. At higher dose levels, plasma concentration of concizumab was above the drug interference level of the ADA assay (in presence of up to 100 µg/mL concizumab, sensitivity was 1000 ng/mL) and no ADAs could be detected. However, no abnormal plasma levels of concizumab were observed in the higher dose animals. In the 13 weeks study, antibodies to concizumab were detected in 9/10 monkeys in the control group at end of dosing period and 4/4 at end of recovery, whereas concizumab levels in the control animals were below LLOQ. No explanation could be provided for the presence of anti-drug antibodies in the control animals. The high number of animals positive for ADA's suggest that very low levels

of concizumab may be present in the control animals (below LLOQ). No ADA's were detected in the control group of the longer, more pivotal studies (26 and 52 weeks).

Free TFPI levels and TFPI function was decreased when concizumab exposure was high, whereas the total levels of TFPI (free and concizumab-bound) were increased during concizumab exposure. In the recovery period, or in most animals with an ADA response, the levels of free and total TFPI returned to baseline, as did TFPI functionality.

Distribution

Formal tissue distribution and protein binding studies were not conducted with concizumab, which is agreed. Consistent with the known biodistribution of monoclonal antibodies, concizumab has a low volume of distribution at high doses 52.4-120 ml in rabbits, 130 ml/kg in monkeys), suggesting a distribution to plasma and extravascular fluid. At low doses (<9 mg/kg), distribution volume appears to be increased, due to target mediated drug disposition. Immunohistology in rabbits with a non-humanised, murine antibody showed localisation of the antibody on the endothelium of the microvasculature in several organs. In addition, co-localisation with endogenous rabbit TFPI was observed.

No reproduction and development studies have been performed and therefore there is no information on foetal exposure and/or excretion to milk.

Metabolism

No metabolism studies with concizumab were conducted in animals in accordance with ICH S6(R1).

Excretion

As concizumab is a monoclonal antibody, it is expected to be proteolytic digested into peptides and amino acid. No specific studies to measure excretion of concizumab were conducted in accordance with ICH S6(R1).

Pharmacokinetic drug interactions

The potential drug-drug interaction between concizumab and rFVIIa was investigated in a 4-week drug-interaction study in *Cynomolgus* monkeys. Concizumab was administered by daily s.c. administration (9 mg/kg/day for the first four days and 1 mg/kg/day for the rest of the study). At day 28, rFVIIa was administered i.v. at dose levels of 0.25, 0.5 or 1 mg/kg/dose (three i.v. injections at two-hour intervals). A control group receiving 1 mg/kg rFVIIa but no concizumab was included. Concizumab did not affect rFVIIa exposure, but it has not been investigated whether rFVIIa affects concizumab exposure. Nevertheless, since free TFPI concentrations remain below the LLOQ (except for 1 animal that developed ADA), this suggests that concizumab exposure or efficacy are at least not affected to a clinical relevant extent.

PK modelling

PK modelling was used to describe the TMDD. Two models were developed, the second was based on the lower dose levels as used in the 52-week toxicity study. At concentrations resulting in saturated TMDD, clearance was estimated to be 0.14 ml/h/kg. Estimated values for the non-linear clearance were described by the Michaelis-Menten expression (9,020 ng/h/kg for Vmax and 816 ng/mL for Km). Estimates for clearance were comparable in the two models.

2.5.4. Toxicology

The toxicological profile of concizumab was evaluated in single- and repeat-dose toxicity studies in *Cynomolgus* monkey with a normal coagulation system (non-haemophilic).

Table 10: Overview of toxicology studies in *Cynomolgus* monkeys

Discipline	Route of administration (dose interval)	Dose levels (NOAEL) (mg/kg)	Adverse findings
Single-dose toxicology			
Single-dose PK (with toxicity endpoints; non-GLP)[a]	i.v.	2 and 20	None
Repeat single-dose PK/PD study (with toxicity endpoints; GLP)[a]	i.v. (2-weeks)	0, 0.1, 0.5, 1.0	None
Repeat single-dose (escalating doses; Dose Range Finding; non-GLP)[a]	s.c. (2 weeks)	2, 20 and 80 20, 80 and 160 80, 160 and 200	None
Repeat-dose toxicology (GLP)			
4 weeks[a]	i.v. (weekly) s.c. (daily)	0, 30 3, 9	None
13 weeks[a,c]	i.v. (weekly) s.c. (daily)	200 0, 1, 10, 50	Thrombi and focal vascular changes due to immune complexes secondary to ADAs
26 weeks[b,d]	i.v. (weekly) s.c. (daily)	30 0, 3, 9	Thrombi and focal vascular changes due to immune complexes secondary to ADAs
52 weeks[b,e]	s.c.	0, 0.5, 1, 9	Thrombi and focal vascular changes due to immune complexes secondary to ADAs
Genotoxicity	No studies performed		
Carcinogenicity	No studies performed – Weight of evidence assessment		
Reproductive toxicity	No studies performed – Fertility assessed in 26-week toxicity study		
Local tolerance	Assessed in repeat-dose toxicity studies		

Discipline	Route of administration (dose interval)	Dose levels (NOAEL) (mg/kg)	Adverse findings
Other toxicology			
Tissue cross-reactivity	N/A	N/A	None
Potential functional differences between monomeric and polymeric forms of HMWP	N/A	N/A	N/A
Mechanistic studies to investigate immune complex-mediated pathology	N/A	N/A	N/A
Drug-drug interaction study with rFVIIa - 4-week study in cynomolgus monkeys	Concizumab s.c. (daily) rFVIIa, i.v. (3 doses with 2 h interval on Day 28)	0 (Day 1-28), or 9 (Day 1-4) + 1 (Day 5-28) 0.25, 0.5, 1 mg/kg (Day 28)	None
Biomarker evaluations in toxicity studies	N/A	N/A	N/A

Note: No NOAEL identified in 26-week study.

[a]Juvenile monkeys: 2.0-3.3 years of age at study start, [b]Sexually mature monkeys: 3.5-6 years of age at study start [c]The study included an 11-week recovery group [d]The impurity profile of the batch used is not representative for clinical trial material. The study included a 13-week recovery group [e]The study included 13- and 26-week interim groups.

Abbreviations: GLP = Good Laboratory Practice; N/A = not applicable; NOAEL = no observed adverse effect level; rFVIIa = recombinant activated coagulation factor VII.

2.5.4.1. Single dose toxicity

A single dose of 2 or 20 mg/kg concizumab was well tolerated in *Cynomolgus* monkeys. There were no adverse effects noted in this non-GLP PK study.

2.5.4.2. Repeat dose toxicity

Cynomolgus monkeys were selected as a pharmacologically relevant test species for repeat dose toxicity studies. Monkeys in these studies were juvenile to adult at the start of each study. Concizumab had no effect on body weight, food consumption, ophthalmoscopy, haematology, clinical chemistry, urinalysis and organ weights. There was also no effect of concizumab on any of the measured reproductive endpoints, suggesting that it is unlikely that concizumab influences male or female fertility.

Administration of concizumab resulted in anticipated pharmacological effects and included a sustained and dose dependent increase in TFPI, decreased fibrinogen, increased TAT and increased D-dimers.

Findings were limited to exaggerated pharmacology and anti-drug antibody mediated toxicity. No off-target toxicity was noted.

Overall, thrombus formation, primarily in lung but also in several other organs, was the finding that determined the NOAEL. The NOAEL was always sufficiently more than the intended clinical exposure.

ADA were measured in every study and were accompanied by loss of exposure in ADA positive animals. Overall, there were sufficient exposed animals in each study so that the quality of the study nor the interpretation of the findings were affected. Mechanistic studies showed that the subendothelial thickening in lungs, endothelial hyperplasia and hypertrophy in lungs and choroid plexus as well as the inflammatory changes in the choroid plexus were considered related to deposition of immune complexes in these tissues, secondary to development of ADAs. Immune complexes were found in plasma of all animals with these lesions, and immunohistochemical examinations revealed presence of immune complexes in the vascular lesions in choroid plexus and/or lungs.

Individual studies are briefly discussed below:

In a 4-week repeat dose toxicity study in juvenile *Cynomolgus* monkeys, animals received daily s.c. doses of 0, 3 or 9 mg/kg concizumab or a weekly dose of 30 mg/kg concizumab. There were no notable changes of clinical signs, body weight, food consumption, clinical chemistry, haematology or macro- and microscopic pathology. Pharmacological findings included a dose dependent decrease in fibrinogen and dose independent increases in TAT and D-dimers with high inter animal variability. There was a slight increase in injection site findings in the SC treated animals but incidence was largely comparable with control animals. The NOAEL in this study was 9 mg/kg after s.c. administration and 30 mg/kg after i.v. administration.

In a 13-week repeat dose toxicity with an 11-week recovery period in juvenile *Cynomolgus* monkeys, animals received 0, 1, 10 or 50 mg/kg concizumab s.c. per day or 200 mg/kg concizumab i.v. per week. There were no remarkable adverse changes in clinical signs, body weight, food consumption, ophthalmoscopy, safety pharmacology endpoints, clinical chemistry, urinary composition, haematology, cytokines or organ weights. Similar to the 4-week study, anticipated pharmacological effects were noted which included an inhibited plasma TFPI functionality, decreased fibrinogen in all treatment groups and increases in TAT and D-dimer with high inter-animal variability. At exposures above the low dose there was no recovery of these findings due to sustained presence of concizumab at the end of the recovery period. In male monkeys only, there was a transient but dose dependent increase in activated partial thromboplastin time (APPT) on day 16, which

coincided with higher APPT in control males. Without any other corollary findings, it is unlikely that this increase is toxicologically meaningful. Furthermore, it was not observed in the other *Cynomolgus* studies with concizumab. Thrombi were noted in the heart of one animal in the 50 mg/kg/day dose group and in the lungs of one animal in 50 mg/kg/day and one animal in the 200 mg/kg/week dose groups. Vascular changes were also observed in lungs of animals in the 50mg/kg/day and 200mg/kg/week dose groups and were typified by intimal proliferation, which were recoverable. A single early thrombus in liver was observed in a euthanised male receiving 10 mg concizumab/kg/day although the cause of death was not considered to be treatment related. Thrombi were observed in heart and lungs of one female recovery animal that was previously dosed with 50mg/kg/day. The NOAEL was established at 1 mg/kg/day for s.c. dosing and was not determined for i.v. dosing based on thrombus formation in lung. Anti-drug antibody (ADA) resulted in loss of exposure, which restored changes in coagulation parameters to baseline values. Nevertheless, sufficient animals were exposed during the study to allow a meaningful interpretation of the safety profile of concizumab.

In a 26-week repeat dose toxicology study in sexually mature *Cynomolgus* monkeys, animals were given 0, 3 or 9 mg concizumab/kg/day s.c. or 30 mg/kg/week i.v. with a 13-week recovery period. Of note, in this study animals received a formulation with high molecular weight proteins, which included multimers of concizumab. This differs from the clinical formulation and the formulations used for the 4-, 13-, and 52-week studies. There was no effect of treatment on clinical signs, body weight, food consumption, menstrual cycle duration, length, width and volume of testes, total sperm count, sperm motility and sperm morphology, ophthalmoscopy, clinical chemistry, urinary composition, haematology or organ weights. Pharmacological effects of concizumab on coagulation were in line with previous findings of the 4- and 13-week repeat dose toxicity studies. One female in the 9 mg/kg/day group was euthanised in week 18 due to adverse clinical signs. The cause of death was anaemia and lung thrombi leading to necrosis of lung parenchyma.

Thrombi were also observed in lungs of animals across all dose groups (1, 3, 2 and 3 animals in groups receiving 0, 3 or 9 mg/kg/day s.c. or 30 mg/kg/week i.v., respectively), which could be accompanied by a single thrombus in epididymis, thymus, liver, heart or injection sites from single animals that also had lung thrombi. At all dose levels, vascular or perivascular changes in or immediately adjacent to the choroid plexus in the brain (inflammation, endothelial hypertrophy/hyperplasia and smooth muscle hypertrophy and medial thickening) were observed. Similarly, at all dose levels (including in the decedent animal 34F), treatment-related vascular changes (subendothelial or intimal thickening, endothelial hypertrophy and hyperplasia) were observed in the lungs. Vascular changes were attributed to ADA mediated toxicity and related to immune complex depositions and resolved after the recovery period. Immune complexes were also detected in all animals with these lesions and immunohistochemical examinations revealed presence of IC in the vascular lesions in choroid plexus and/or lungs. Due to thrombus formation, a NOAEL was not determined for this study.

In a 52-week repeat dose toxicity study in sexually mature *Cynomolgus* monkeys, animals received 0.5, 1 or 9 mg concizumab/kg/day for 52 weeks. The choice of the high dose at 9 mg/kg/day is not fully understood since this was already determined to be an adverse dose. No remarkable effects of treatment on clinical signs, body weight, food consumption, electrocardiography, ophthalmoscopy, clinical chemistry, urinary composition or organ weights were observed in this study. There were no changes in haematology parameters except for decreased platelet counts in the high dose group and in some animals in lower dose groups, predominantly in males. Pharmacological effects on coagulation were observed and were in line with previous studies including decreases in fibrinogen, increases in D-dimer and inhibition of plasma TFPI activation. Slightly prolonged PT was observed in the high dose group up to week 26, and from thereon only in a few cases. Slight prolongation of APPT was also observed at this dose in a few cases, which are likely attributed to hypofibrinogenaemia in naïve animals. Formation of thrombi in lung, choroid plexus, axillary and

mesenteric lymph nodes, epididymis and/or spleen liver, heart and injection sites was observed in animals from 1 mg/kg/day onwards. There were no thrombi in the 1 mg/kg/day dose group before week 26. There were no instances of thrombi in animals receiving 0.5 mg concizumab/kg/day. Subendothelial intimal thickening in small to medium-sized blood vessels in the lung or liver was observed at 9 mg/kg/day as well as in one female receiving 1 mg/kg/day. In addition, inflammatory cell infiltration was observed in the choroid plexus in all dose groups. Cellular infiltrate and vascular changes were related to immune complex deposition secondary to ADA formation. The NOAEL for this study was 0.5 mg/kg/day based on thrombus formation. The exposure at the NOAEL was approximately 70-times that of the intended clinical exposure. Before 26-weeks the NOAEL was 1 mg/kg/day based on the absence of thrombi.

2.5.4.3. Genotoxicity

According to ICH S6(R1), genotoxicity studies were not performed.

2.5.4.4. Carcinogenicity

Standard carcinogenicity studies are not required for biotechnology-derived medicinal products as laid down in the Guideline ICH S6 (R1) EMA/CHMP/ICH/731268/1998. Considering that concizumab is a monoclonal antibody, a direct pro-oncogenic effect is not anticipated. A thorough weight of evidence evaluation, in combination with data from the repeat dose toxicity studies, which included exposure to concizumab up to 52 weeks, does not suggest that concizumab has carcinogenic potential.

2.5.4.5. Reproductive and developmental toxicity

An assessment of reproductive organs in a 26-week repeat dose toxicity study did not reveal any adverse findings on menstrual cycle duration, length, width and volume of each testis, total sperm count, sperm motility or sperm morphology. There were no histopathological changes in reproductive organs in juvenile or adult monkeys exposed for up to 52-weeks.

Based on literature data, inactivation of the TFPI-gene in mice resulted in embryofetal lethality suggesting a role for development in these species. Placental transfer of IgG is limited in the first and second trimester in humans. However, recurrent pregnancy loss in women who had TFPI deficiency in combination with an Activated Protein C (APC) resistance phenotype or in women with anti-TFPI antibodies in combination antiphospholipid antibodies has been described, indicating that TFPI may be important for a normal pregnancy. The absence of dedicated EPPND studies with concizumab is acknowledged given that the patient population is almost exclusively male. With respect to juvenile animal studies, the haemostatic system is the only target organ for toxicity. This is fully mature in the early months of life in humans. There were also no notable differences in juvenile and mature animals exposed to concizumab in the repeat dose toxicity studies.

2.5.4.6. Toxicokinetic data

Plasma concentrations increased in a dose-proportional (higher dose levels) to greater than dose-proportional manner (lower dose levels) in the repeated dose toxicity studies with concizumab, due to target mediated drug disposition.

The applicant used the mean clinical exposure (after titrating) in trial NN7415-4311 to calculate the exposure margins since exposure (both Cmax and AUC) were higher after adjustment of the dose (measured at week

24) than at baseline (measured in week 4). Exposure margins at the NOAEL are 71 when based on Cmax and 85 when based on AUC.

Anti-concizumab antibodies were measured in all monkey studies and seemed to reduce the exposure level of concizumab. However, sufficient animals without ADA formation and/or reduction in concizumab remained to conduct an adequate assessment of the safety of concizumab in this species.

2.5.4.7. Local Tolerance

Local tolerance was assessed as part of the repeat-dose toxicity studies in *Cynomolgus* monkeys and the drug-drug interaction toxicity study with rFVIIa. No dedicated local toxicity studies were performed. Injection site reactions were not apparent after i.v. administration except for a thrombus in a single animal in the 26-week repeat dose toxicity study. Injection site reactions, typical for mAb therapeutics, were observed after s.c. administration of concizumab and were characterised by histopathological observations. These predominantly included inflammatory cell foci/perivascular accumulation of leukocytes in all dose groups. All injection site reactions were reversible.

2.5.4.8. Other toxicity studies

In a tissue cross reactivity study, concizumab showed anticipated binding to tissue in which TFPI is expressed. Off target binding was observed for cytoplasm but it is very unlikely that concizumab will be able to reach the cytoplasm *in vivo*.

Concizumab induced ADA in all repeat dose toxicity studies. ADA led to loss in exposure although this did not affect the overall interpretation of the studies. In the repeat dose toxicity studies and toxicokinetics, the toxic vascular changes were attributed to immune complex deposition leading to inflammation based on a series of mechanistic *in vitro* studies. This is further corroborated by the fact that vascular findings were increased in the 26-week study which used a high molecular weight protein formulation and was likely more immunogenic for this reason. Of note, an increased incidence in animal ADA status was not immediately apparent in this study compared to the 52-week study. Impurities for concizumab in the finished product are considered to have been qualified in the nonclinical studies and the proposed end-of-shelf-life and in-use acceptance criteria are considered justified. Leachables from the primary packing material have been evaluated and are considered not to pose any safety concerns to the patients.

2.5.5. Ecotoxicity/environmental risk assessment

In accordance with the CHMP guideline for Environmental risk assessment of medicinal products for human use" [EMEA/CHMP/SWP/4447/00 corr 2], as the proposed product falls within the classification of a products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an environmental risk assessment (ERA) is not required.

2.5.6. Discussion on non-clinical aspects

Pharmacology

Histopathological examination showed thrombus formations in the lungs of three out of 6 rabbits (50%) treated with the anti-TFPI antibody, in study pjoh090201 (Acute effects of a humanised anti-TFPI antibody on clot formation and coagulation markers in a venous stasis model in rabbits). Furthermore, the analysis showed thrombus formations in the heart of 1 out of 4 rabbits treated with the isotype control antibody (25%). Clots were found in 33% and 12.5% of the ligated veins in the rabbits receiving the anti-TFPI antibody and the isotype control antibody, respectively ($p< 0.62$).

It is acknowledged that there is no relationship to the clot formation in the ligated veins and there is no evident concomitant activation of the coagulation system. However, the safety investigations of the anti-TFPI antibody in a validated *Cynomolgus* monkey toxicity model identified thrombosis, which was considered an exaggerated pharmacological effect. Thrombi were indeed considered to be a sign of exaggerated pharmacology when administering a procoagulant compound like concizumab to animals with a normal coagulation system (non-haemophilic). Animals (without transiently induced haemophilia-A) treated with anti-TFPI displayed a higher frequency of thrombi compared to control animals. This could be explained by the effect of the anti-TFPI treatment of animals with hypercoagulable blood or by an effect of the anti-TFPI treatment itself.

The finding in the isotype control antibody B72.3 treated animal, to be expected without a significant pharmacological effect was attributed to naïve rabbits, which undergoing catheterisation, surgery and prolonged anaesthetic procedures may develop thrombi.

Considering the above the following was added in section 5.3 of the SmPC: Pharmacology mediated formation of thrombi was observed in a 52-week toxicology study in *Cynomolgus* monkeys at subcutaneous doses of ≥ 1 mg/kg/day (corresponding to 300-fold the human exposure based on AUC0-24h). In addition, a warning has been added in section 4.4 of the SmPC with regards to thromboembolic events.

Data from a previous study (Lauritzen 2009; BLz090103), raised concern that HzTFPI4F36 might have a U-formed dose-response curve. However, the finally generated data show that this was not the case. The measurement of HzTFPI4F36 levels in plasma by LOCI antigen down-immunoassay was comprehensibly presented in this study (209135 Plasma ELISA of HzTFPI4F36).

Secondary pharmacodynamics

Concizumab does not interfere with protein C activation nor with antithrombin across a broad dose range as confirmed in the repeat dose toxicity studies in monkeys.

Safety pharmacology

No effects of concizumab on safety pharmacology endpoints were observed in any of the submitted studies at repeat doses up to 200 mg/kg/once weekly (i.v.) and 50 mg/kg/day (s.c.). These doses result in an exposure far exceeding (>1000-fold) the clinically relevant exposures.

Pharmacodynamic drug interaction studies

In vitro and *ex vivo* drug-drug interaction studies were performed with rFVIIa, aPCC, rFVIII or rFIX in blood from haemophilia patients who are on prophylactic treatment with concizumab. These studies did not suggest clinically relevant drug-drug interactions. However, based on the provided non-clinical assays, there is a possibility of hypercoagulability with rFVIIa, aPCC, FVIII or FIX in combination with concizumab due to the additive effects, observed in plasma pools tested. In general, the *in vitro* preclinical data presented on the potential risk of additive and/or synergistic effects of the combination of concizumab and a bypassing product

are rather uncertain and partly controversial. Against this background, the specific informative value of the preclinical data for the clinical situation must be considered limited.

The following statement has been added in section 5.3 of the SmPC with regards to drug-drug interaction: In a 28-day drug-drug interaction toxicity study in cynomolgus monkeys with daily dosing of 1 mg/kg concizumab to achieve steady state, three consecutive intravenous doses of up to 1 mg/kg rFVIIa were administered with 2-hour intervals to the concizumab dosed animals. No adverse findings were observed at a concizumab exposure corresponding to 200-fold the human exposure, based on AUC0-24h.

Pharmacokinetics

The reported values for both volume of distribution and terminal elimination T1/2 varies largely between the PK studies, especially in the rabbit studies (at similar dose levels). According to the applicant, this large variation between studies (even at similar doses) in PK parameters is caused by TMDD, which may be affected by study set-up and results in large inter-animal variability.

Toxicology

Overall, thrombus formation, primarily in lung but also in several other organs, was the finding that determined the NOAEL. The NOAEL was always sufficiently more than the intended clinical exposure and approximately 70 times the intended clinical exposure at the NOAEL in the 52-week study. Furthermore, in the 52-week repeat dose toxicity study, slightly prolonged PT was observed in the high dose group up to week 26, and from thereon only in a few cases. Slight prolongation of APPT was also observed at this dose in a few cases, which could be attributed to hypofibrinogenaemia in naïve animals.

Male and female juvenile (2-3 years) and sexually mature (3.5-6 years) *Cynomolgus* monkeys with a normal coagulation system were used in the conducted repeat-dose toxicity studies. It is accepted that the human coagulation cascade reaches maturity at a very young age, however regarding the initially targeted indication of haemophilia B patients at all ages, the use of concizumab in the youngest human age group (below ~8 years of age) is not covered by the provided nonclinical data. This is however in accordance with the protocol assistance received in 2019 from the CHMP [EMEA/H/SA/2178/3/2019/PA/III]). No significant differences were observed in the PK profile between juvenile and adult animals in the conducted studies.

Vascular changes were observed in *Cynomolgus* monkeys in the 26-weeks and 52-week RDT study. While thrombi were an exaggerated pharmacological effect, focal vascular changes observed primarily in choroid plexus, lungs and at the injection sites were considered related to immune complex formation secondary to ADA development rather than to 'other factors' as listed in the previous discussion. Further, the applicant provided literature references on drug-induced vascular injuries (DIVI) which confirm that DIVI for biopharmaceuticals like concizumab could be related to immunological responses to the compound with subsequent immune complex formation and deposition in many cases. No treatment related changes in inflammatory markers were observed in the conducted studies by the applicant. Half of the evaluated animals showed immune complex related granular deposits located nearby the vascular changes using IHC and immune complexes were found in the plasma of all animals identified with adverse vascular changes. ADAs were detected in some but not all animals, which was thought to be due to drug interference of high concizumab plasma levels in the ADA assay. Justification was provided why immune complex formation could not be associated with vascular lesions in all animals treated using IHC. Taking all these arguments together, immune complex deposition appears to be the most plausible cause for reported adverse findings in the vasculature of lungs and choroid plexus.

Genotoxicity

In line with ICH S6(R1), genotoxicity studies were not performed as concizumab is a mAb, consisting of naturally endogenous amino acids and is not expected to be genotoxic or to interact directly with DNA or other chromosomal material. There are no mechanistic data to suggest a mutagenic or proliferative potential of concizumab.

Carcinogenicity

Standard carcinogenicity studies are not required for biotechnology-derived medicinal products as laid down in the Guideline ICH S6 (R1) EMA/CHMP/ICH/731268/1998. Considering that concizumab is a monoclonal antibody, a direct pro-oncogenic effect is not anticipated. A thorough weight of evidence evaluation, in combination with data from the repeat dose toxicity studies, which included exposure to concizumab up to 52 weeks, does not suggest that concizumab has carcinogenic potential.

Reproductive and developmental toxicity

An assessment of reproductive organs in a 26-week repeat dose toxicity study did not reveal any adverse findings on menstrual cycle duration, length, width and volume of each testis, total sperm count, sperm motility or sperm morphology.

Placental transfer of IgG is limited in the first and second trimester in humans. However, recurrent pregnancy loss in women who had TFPI deficiency in combination with an Activated Protein C (APC) resistance phenotype or in women with anti-TFPI antibodies in combination antiphospholipid antibodies has been described, indicating that TFPI may be important for a normal pregnancy.

Considering the above, the following statements have been added in the SmPC:

Section 5.3 of the SmPC provides information with regards to fertility and teratogenicity as follows:

Fertility: In a 26-week toxicity study in sexually mature male and female cynomolgus monkeys with subcutaneous doses up to 9 mg/kg/day (corresponding to 3 400-fold the human exposure, based on AUC0-24h), concizumab did not affect fertility (testicular size, sperm functionality or menstrual cycle duration) and did not cause any changes in the male or female reproductive organs.

Teratogenicity: No data are available with respect to potential side effects of concizumab on embryofoetal development.

Section 4.6 of the SmPC: Women of childbearing potential/contraception in males and females: Women of childbearing potential receiving concizumab should use highly effective contraception during treatment with concizumab and until 7 weeks after end of treatment. The benefits and thromboembolic risks of the type of contraceptives used should be evaluated by the treating physician.

Local tolerance

Local tolerance was assessed as part of the repeat-dose toxicity studies in *Cynomolgus* monkeys and the drug-drug interaction toxicity study with rFVIIa. All injection site reactions were reversible.

Environmental Risk Assessment

The active substance is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, concizumab is not expected to pose a risk to the environment.

2.5.7. Conclusion on the non-clinical aspects

Concizumab is a potent and high affinity binding antibody directed against the K2 domain of TFPI. Functional effects of TFPI inhibition by concizumab were shown to lead to enhanced coagulation in assays comprising human plasma and whole blood, demonstrating the mode of action. Concizumab shortened clotting time in plasma from rabbit and *Cynomolgus* and enhanced whole blood clot formation in *Cynomolgus* blood with EC50 values similar to the values obtained in human plasma or blood, providing *in vitro* evidence for a proof of concept. Concizumab is unlikely to result in TFPI release in therapeutic ranges. Studies with rabbit models of haemophilia A provide a proof of concept for the clinical treatment of haemophilia A and B. Concizumab does not interfere with protein C activation nor with antithrombin across a broad dose range. Concizumab did not bind to any peripheral blood cell, nor did it induce cytokine release *in vivo*. In repeat dose toxicity study, no untoward effects were observed on CNS-, respiratory- or cardiovascular function.

From the pharmacokinetic point of view, the rabbit and monkey were the most relevant species for non-clinical efficacy and safety studies. Target mediated drug disposition was clearly demonstrated at lower dose levels. The use of short dosing intervals (daily subcutaneous dosing) results in target saturation. ADA formation against concizumab after treatment of *Cynomolgus* monkeys occurred at expectable levels and non-surprisingly affected the functional effects on the coagulation system.

From a toxicological perspective, administration of concizumab resulted in anticipated pharmacological effects and included: a sustained and dose dependent increase in TFPI; decreased fibrinogen; increased TAT and increased D-dimers. In the repeat dose studies, findings were limited to exaggerated pharmacology and anti-drug antibody mediated toxicity. No off-target toxicity was noted. Overall, thrombus formation, primarily in lung but also in several other organs, was the finding that determined the NOAEL. The NOAEL was always sufficiently more than the intended clinical exposure.

All relevant information has been reflected in sections 4.6 and 5.3 of the SmPC.

2.6. Clinical aspects

2.6.1. Introduction

GCP aspects

The Clinical trials were performed in accordance with GCP as claimed by the applicant

The applicant has provided a statement to the effect that clinical trials conducted outside the Community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

The concizumab global clinical trial programme forming the basis for this application (use of concizumab for routine PPX of bleeding in HAwI and HBwI patients) comprises:

- Four clinical pharmacology trials (2 single dose and 2 multiple dose) (trials 3813, 3981, 3986 and 4159).
- Two phase 2 trials (1 in HwI and 1 in HA) (trials 4255 and 4310).
- One phase 3 therapeutic confirmatory trial in HAwI and HBwI (primary analysis cut-off [PACO] and 56-week cut-off reached, extension ongoing) (trial 4311).
- One phase 3 therapeutic confirmatory trial in HA and HB (confirmatory analysis cut-off [CACO] reached, extension ongoing) (trial 4307).
- One non-interventional study (NIS 4322) providing baseline information on details of haemophilia and physical activity tracker from patients who would subsequently be offered screening for the phase 3a trials; this was primarily to allow for a within-patient comparison of the ABR for patients previously receiving PPX in trial 4307. Participants were not treated with concizumab.
- One ongoing paediatric phase 3 trial, mainly in patients ≤12 years with HAwI, HBwI, HA or HB. Only narratives on serious adverse events (SAEs) and adverse events of special interest (AESIs) (thromboembolic events) from this trial were included in the current application (trial 4616).

In addition, the application includes results for concizumab distributed for compassionate use to support extrapolation of efficacy and safety results to patients below 12 years of age. The cut-off date for inclusion of data from completed and ongoing trials as well as compassionate use in the application was 30 August 2022.

- **Tabular overview of clinical studies**

Table 11: Summary of trials contributing data to the population PK and exposure-response analyses of concizumab

Trial	3813	3981	3986	4159	4255	4310	4311	4307
Clinical stage	Phase 1	Phase 1	Phase 1	Phase 1	Phase 2	Phase 2	Phase 3	Phase 3
Report location	Trial 3813 (M5.3.3.1)	Trial 3981 (M5.3.3.1)	Trial 3986 (M5.3.3.1)	Trial 4159 (M5.3.4.2)	Trial 4255 main part (M5.3.5.2) and Trial 4255 extension part (M5.3.5.2)	Trial 4310 main part (M5.3.5.1) and Trial 4310 extension part (M5.3.5.1)	Trial 4311 PACO (M5.3.5.1) and Trial 4311 56wk (M5.3.5.1)	Trial 4307 (M5.3.5.1)
N	38	6	4	18	36	25	127[a]	151[b]
Population	Healthy, HA, HB	Healthy Japanese	Healthy	HA	HA	HAwI, HBwI	HAwI, HBwI	HA, HB
Age group	Adults	Adults	Adults	Adults	Adults	Adults	Adults, adolescent	Adults, adolescent
Dose frequency	SD	SD	Q2D	Q4D	QD	QD	QD	QD
Comparator arm	Placebo	Placebo	-	Placebo	-	On-demand	On- demand	On-demand
Concizumab doses (mg/kg)	iv: 0.0005, 0.005, 0.05, 0.25, 1, 3, 9 sc : 0.05, 0.25, 1, 3	0.25, 1	0.25	0.25, 0.5, 0.8	0.15, escalation options 0.20, 0.25	LD 0.5 then 0.15, escalation options: 0.20, 0.25	LD 1 then 0.20, options for 0.15, 0.25	LD 1 then 0.20, options for 0.15, 0.25
Treatment duration	1 dose	1 dose	8 doses	12 doses	Main 24w Extension up to 126w	Main 24w Extension up to 118w	Main 32w (24w for on-demand arm) Extension up to total of 160w	Main 32w (24w for on-demand arm) Extension up to total of 160w
Samples in rich PK profile	iv: 22 sc: 20	20	-	-	7	8	5	5
Sparse PK sampling timepoints	-	-	Day 0[c], 2[c], 4[c], 6[c], 8[c], 10[c], 12[c], 14[c], 21, 34	Day 0, 1, 5, 9, 13, 17[c], 21, 25, 29, 33, 37, 41[c], 43, 48, 55, 69, 76	Week 0, 1, every 4w for w4-24, every 8w for w32-126	Week 0, 1, every 4w for w4-48, every 8w for w56-118	Week 0, 1, every 4w for w4-48, every 8w for w56-160	Week 0, 1, every 4w for w4-48, every 8w for w56-160

N: number of subjects receiving concizumab treatment, HA: haemophilia A, HB: haemophilia B, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, SD: single dose, LD: loading dose; w: week.
a. after the restart in trial 4311, 112 patients had concizumab dosing and 111 had PK measurements; **b.** after the restart in trial 4307, 144 patients had concizumab dosing and PK measurements; **c.** 2 PK samples, one before dose and one after dose.

2.6.2. Clinical pharmacology

2.6.2.1. Pharmacokinetics

The pharmacokinetic (PK) but also pharmacodynamics properties of concizumab in humans are evaluated in:

- four phase 1 trials (3813, 3981, 3986 and 4159)
- two phase 2 trials (4255 and 4310)
- two phase 3 trials (data obtained up until the 56-week cut-off in trial 4311 and data obtained up until the confirmatory analyses cut-off in trial 4307)

Furthermore, PK (and PD) results for concizumab in the compassionate use setting through the compassionate use programme (CUP) (4807) were also included some patients younger than 12 year of age.

Additionally, a population PK model was developed based on all available data in concizumab-treated patients. This included data from healthy volunteers and patients with haemophilia across clinical pharmacology, phase 2 and phase 3 trials, and included trials with detailed PK assessments and sparse PK sampling.

Absorption

Single dose

Following a s.c. SD administration of 0.05 – 3 mg/kg concizumab in healthy subjects and haemophilia patients (trial 3813), the C_{max} and AUC increased with increasing dose in a greater-than-dose-proportional manner following s.c. administration. The geometric mean C_{max} ranged from 8.93 to 15437 ng/mL (at doses 0.05−3 mg/kg) and the geometric mean $AUC_{0-\infty}$ ranged from 8197 to 2.16×10^6 ng×h/mL (at doses 0.25−3 mg/kg). The median t_{max} ranged from 12 to 70.4 hours (0.5 to 2.9 days).

In SD trial 3981, the systemic exposure of concizumab in healthy Japanese subjects increased at the higher dose level (1 mg/kg) compared to the lower dose level (0.25 mg/kg). The geometric mean C_{max} was 55.1 ng/mL and 252.4 ng/mL, while the geometric mean $AUC_{0-\infty}$ was 7067.8 and 24988 ng×h/mL, following dosing at 0.25 and 1 mg/kg, respectively. The median t_{max} was 12.1 and 11.8 hours, respectively.

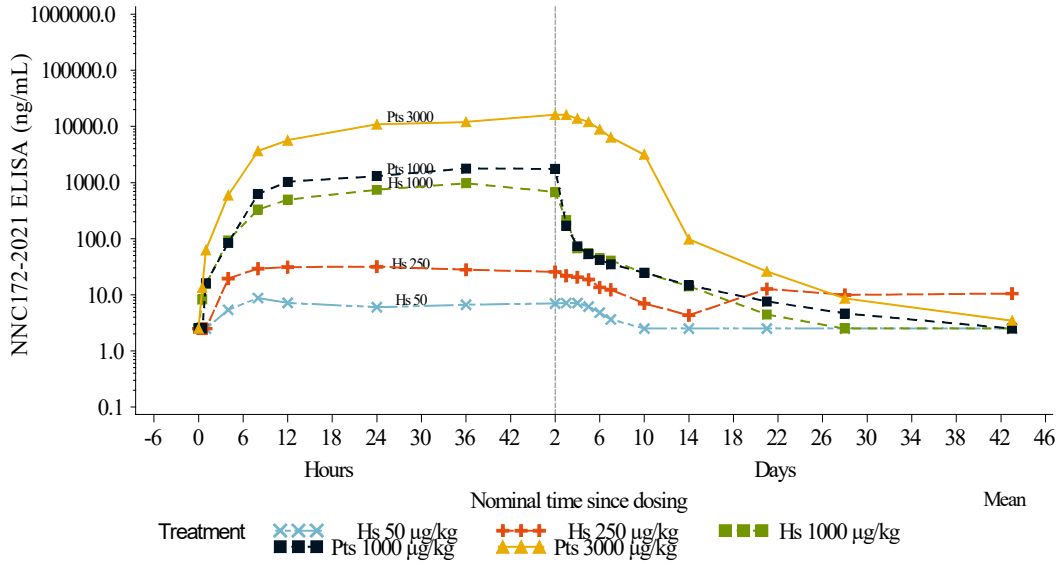
In study 3813, all of the haemophilia B subjects (n=3; of 24 haemophilia patients in total) were randomised to the i.v. treatment arm. It was confirmed that all of the haemophilia subjects were FVIII inhibitor negative (<0.6 BU) at baseline.

A total of 3 haemophilia B subjects were negative for FIX inhibitors.

An unexpected increase in concizumab plasma concentration in one healthy subject dosed at 250 µg/kg s.c. (single dose) occurred after an initial decline of concizumab concentration, as observed for all other study participants. This unexpected increase remains unexplained, but reassuringly appears not to impact free TFPI levels. It is agreed that the exceptionally high measured concizumab concentrations at later time points may be regarded as outliers and that stating a tmax of 99 hours in Section 5.2 of the SmPC is sufficient to highlight the possibility of a rather long tmax, considering a daily dosing frequency.

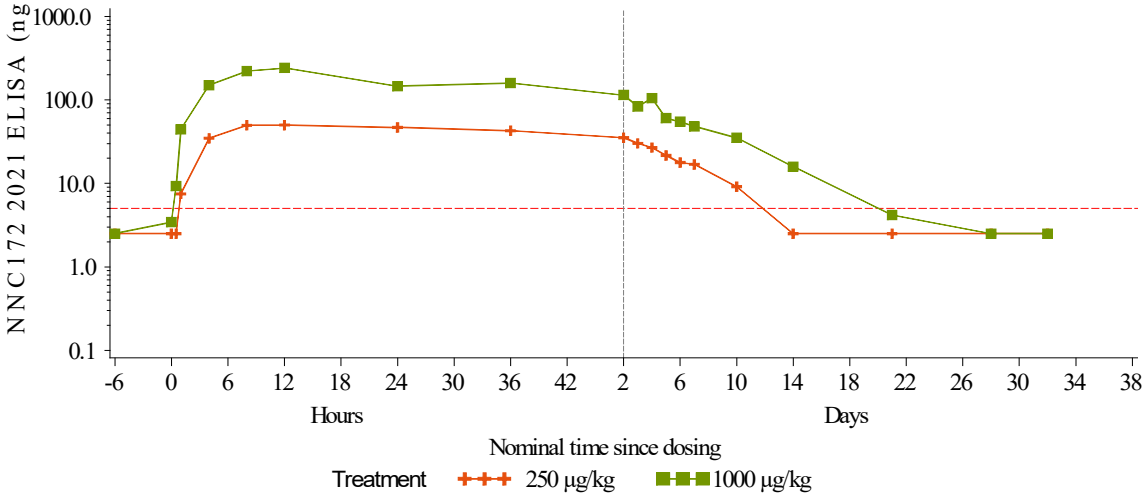
Mean s.c. SD PK profiles for trials 3813 and 3981 are presented in Figure 3 and Figure 4, respectively. The PK parameters for trials 3813 and 3981 are presented in the table below.

Figure 3: Mean plasma concentration–time profiles of concizumab following single-dose subcutaneous administration in healthy subjects and haemophilia patients - trial 3813



The vertical dashed line presents a shift in scale from hours to days at 2 days.

Figure 4: Mean plasma concentration–time profiles of concizumab following single-dose subcutaneous administration in healthy Japanese subjects - trial 3981



Notes: N=3 in each dose cohort.

Table 12: Pharmacokinetic parameters in healthy subjects and haemophilia patients following subcutaneous administration of concizumab - trials 3813 and 3981

PK parameter	Healthy subjects – s.c. – trial 3813		
	0.05 mg/kg[a]	0.25 mg/kg	1 mg/kg
N	3	3	3
C_{max} (ng/mL) (geometric mean (CV[%]))	8.93 (27.3)	35.5 (18.8)	934 (42.7)
$AUC_{0-\infty}$ (ng*h/mL) (geometric mean (CV[%]))	-	8197 (93.4)	52375 (36.8)
CL/F (ml/h/kg) (geometric mean (CV[%]))	-	30.6 (60.7)	19.1 (33.6)
$t_{½}$ (h) (geometric mean (CV[%]))	-	89.4 (20.1)	114 (4.8)
t_{max} (h) (median)	12	24	36
PK parameter	**Haemophilia patients – s.c. – trial 3813**		
	1 mg/kg	**3 mg/kg**	
N	3	3	
C_{max} (ng/mL) (geometric mean (CV[%]))	838 (88.6)	15437 (42.4)	
$AUC_{0-\infty}$ (ng*h/mL) (geometric mean (CV[%]))	83244 (70.8)	2163346 (52.0)	
CL/F (ml/h/kg) (geometric mean (CV[%]))	12 (103.0)	1.39 (71.9)	
$t_{½}$ (h) (geometric mean (CV[%]))	104 (59.5)	69.4 (42.0)	
t_{max} (h) (median)	46.4	70.4	
PK parameter	**Healthy Japanese subjects – s.c. – trial 3981**		
	0.25 mg/kg	**1 mg/kg**	
N	3	3	
C_{max} (ng/mL) (geometric mean (CV[%])	55.1 (7.0)	252.4 (55.2)	
$AUC_{0-\infty}$ (ng*h/mL) (geometric mean (CV[%])	7067.8 (9.7)	24988.0 (23.3)	

CL/F (ml/h/kg) (geometric mean (CV[%])	35.5 (8.6)	40.0 (20.9)
$t_{½}$ (h) (geometric mean (CV[%])	96.1 (10.5)	109.0 (15.1)
t_{max} (h) (median)	12.1	11.8

Notes: [a] For the 0.05 mg/kg dose cohort, $AUC_{0-\infty}$, CL/F and $t_{½}$ were not calculated, as no subjects had continuous profiles above the lower limit of quantification (LLoQ = 5 ng/mL).

The exposure of concizumab has been shown to increase with dose in a non-linear manner and with high between-subject variability. This was shown for i.v. as well as for s.c. route of administration. Absolute bioavailability of concizumab could not be established due to the highly non-linear PK. However, in general absolute bioavailability of antibodies following the SC route is high (~70%, Sánchez-Félix *et al.,* Advanced Drug Delivery Reviews 2020). High absolute bioavailability was also indicated in monkeys and rabbits (around 80%; see non-clinical AR). Overall, pharmacokinetics of concizumab could be sufficiently characterised without the need for a precise estimation on the absolute bioavailability.

Distribution

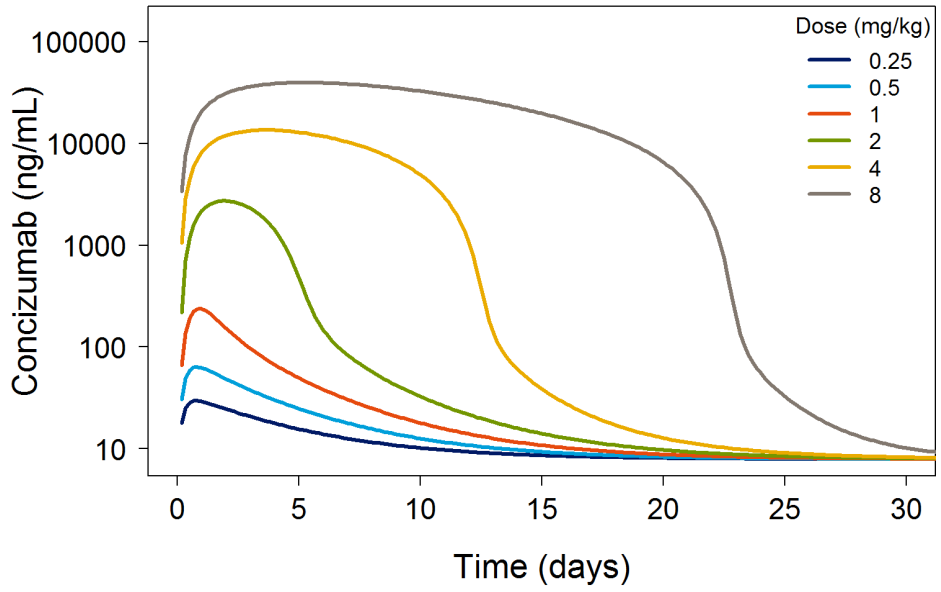
Because concizumab is a monoclonal antibody, traditional protein binding studies were not conducted. According to the final population pharmacokinetic model a volume of distribution of 2.96 L was estimated.

Elimination

Following a s.c. SD administration of 0.05 – 3 mg/kg concizumab in healthy subjects and haemophilia patients (trial 3813 and 3981), the geometric mean CL/F of concizumab decreased in a dose-related manner and ranged from 30.6 mL/h/kg (at 0.25 mg/kg) to 1.39 mL/h/kg (at 3 mg/kg). The geometric mean $t_{½}$ ranged from 69.4 to 114 hours (2.9 to 4.8 days), but with no clear dose relationship and with notable variation between subjects. In trial 3981, following dosing at 0.25 and 1 mg/kg, respectively, the mean CL/F was 35.5 and 40 mL/h/kg, the mean $t_{½}$ of concizumab was 96.1 and 109 hours (4 and 4.5 days).

The applicant performed simulations for concizumab concentration-time profiles following subcutaneous dosing for a typical subject with a body weight of 75 kg based on the final population PK model as showed in Figure 5 below.

Figure 5: Simulated PK profiles of single s.c. doses of concizumab



Simulations of concizumab concentration-time profiles following subcutaneous dosing for a typical subject with a body weight of 75 kg based on the final population PK model. Cross-reference: Modified from Modelling report, Figure 6-5

At high concentrations, linear elimination of concizumab is dominant and the estimated half-life is approximately 22 days for a 75 kg patient based on population PK modelling analysis. At these concentrations the elimination t1/2 of concizumab is consistent with other IgG4 monoclonal antibodies (20-22 days).

At low concentrations, the non-linear elimination is dominant. In healthy subjects and haemophilia patients dosed with a single s.c. dose of concizumab at 0.25 – 3 mg/kg, t½ ranged from 39 hours (1.6 days) to 195 hours (8.1 days). The shorter observed half-life compared to the predicted half-life of the linear elimination was due to the contribution of the non-linear drug-target complex elimination pathway. Monoclonal antibodies such as concizumab are mainly metabolized and eliminated through proteolytic degradation into small peptide fragments or amino acids that are ready for renal excretion or recycling into protein synthesis.

Dose proportionality and time dependencies

Dose proportionality was evaluated using the intensive PK data from SD study 3813 and 3981 in healthy subjects and haemophilia patients. Pharmacokinetic parameters in healthy subjects and haemophilia patients following subcutaneous administration of concizumab (trials 3813 and 3981) are presented in the table above. Additionally, based on the final population PK model, simulations of concizumab concentration-time profiles following subcutaneous dosing (dosages between 0.25 and 8 mg/kg) for a typical subject with a body weight of 75 kg were performed and presented in the figure above. The PK of concizumab at low concentrations seems nearly linear due to the drug-target complex being eliminated rapidly and the target not being saturated. At increasing (intermediate) concentrations of concizumab, the pharmacokinetics are non-linear as the target becomes increasingly saturated. At high concentrations of concizumab, the contribution from the non-linear drug-target complex elimination pathway is negligible, while the linear

pathway becomes dominant. The PK of concizumab becomes nearly linear with a half-life of approximately 3 weeks similar to that of other monoclonal antibodies.

The target size – i.e., the pool of TFPI at the endothelium – determines when non-linear PK occurs during concizumab dosing. The variability in exposure of concizumab may be due to differences in the pool of endothelial-bound TFPI between subjects. Smaller pools of TFPI at the endothelium become saturated more quickly. No information on time dependencies was provided.

Pharmacokinetics in target population

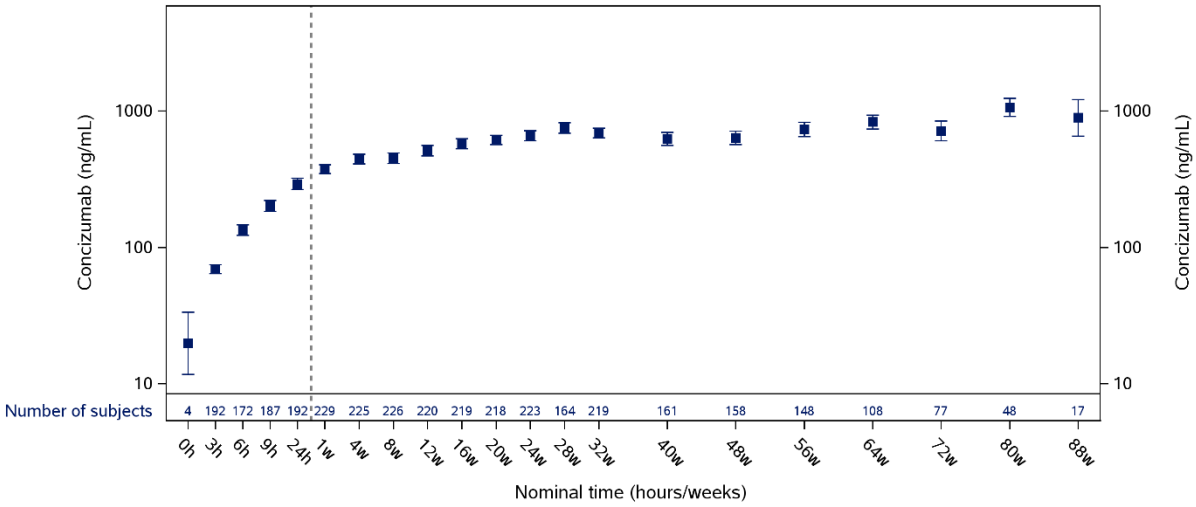
The PK of concizumab during long-term PPX in HAwI, HBwI, HA and HB patients was assessed based on combined results from phase 3 trials 4311 (HAwI and HBwI) and 4307 (HA and HB). Both trials employed the same dosing regimen, allowing for direct assessments of the effect of subtype on the PK of concizumab in patients of all four included haemophilia subtypes.

A total of 67 HAwI and 45 HBwI patients (in arms 1–4) from trial 4311 and 73 HA and 54 HB patients (in arms 2–4) from trial 4307 after the treatment pause restart each received a single s.c. loading dose of concizumab at 1 mg/kg and initial daily doses of 0.20 mg/kg. Following measurement of concizumab plasma concentration after at least 4 weeks, the individual maintenance dose was to be set to either 0.15, 0.20 or 0.25 mg/kg for the rest of the trial. Data obtained up until the 56-week cut-off in trial 4311 and up until the confirmatory analyses cut-off in trial 4307 is included.

Concizumab exposure rapidly increased to steady-state levels within 24 hours following administration of the concizumab loading dose and remained at this level over time for HAwI, HBwI, HA and HB patients (arms 1–4 in trial 4311; arms 2–4 in trial 4307) in the figure below. Geometric mean C_{trough} levels were comparable for HAwI, HBwI, HA and HB patients (arms 1–4 in trial 4311; arms 2–4 in trial 4307) at week 24 and over time during concizumab PPX (Figure 7**:**). This is supported by PK modelling, where no statistically significant differences were observed between the haemophilia subtypes (Final POP-PK model).

Mean pre-dose Ctrough levels of concizumab were higher in HBwI compared to HAwI at Week 24 (HBwI: 740.3 ng/ml vs HAwI: 625.4 ng/ml) and even more so at Week 56 (HBwI: 999.8 ng/ml vs HAwI: 527.5 ng/ml). Due to low sample size, in particular at Week 56 in the HBwI group (n=35), this observation needs to be interpreted with caution.

Figure 6: Concizumab plasma concentration (ng/mL) - geometric mean plot - HAwI+HBwI+HA+HB - OTexIR+OTexBR - safety analysis set - trial 4311 (56week cut-off+ trial 4307 (CACO)



CACO: confirmatory analyses cut-off, HA: haemophilia A, HB: haemophilia B,HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: on-treatment without data on initial regimen, OTexBR: On-treatment without data before restart.

Error bars represent +/- standard error of the geometric mean. Plasma concentrations below lower limit of quantification (LLOQ) are set to half of LLOQ. Lower limit of quantification (LLOQ) for concizumab concentration is 5 ng/mL. Values below lower limit of quantification (LLOQ) at time zero are set to zero and are thus not displayed since concentrations on the y-axis are on log scale. Numbers shown in the bottom of the figure reflect the number of patients contributing with non-zero values. The following arms are included: concizumab PPX (arms 1-4) from trial 4311 and concizumab PPX (arms 2-4) from trial 4307. Data from 24-hour profiles at baseline (only arms 2-4 included, visit 2/2a) as well as pre-dose trough values during the trial are included, and the dotted vertical line separates these two different kinds of data.

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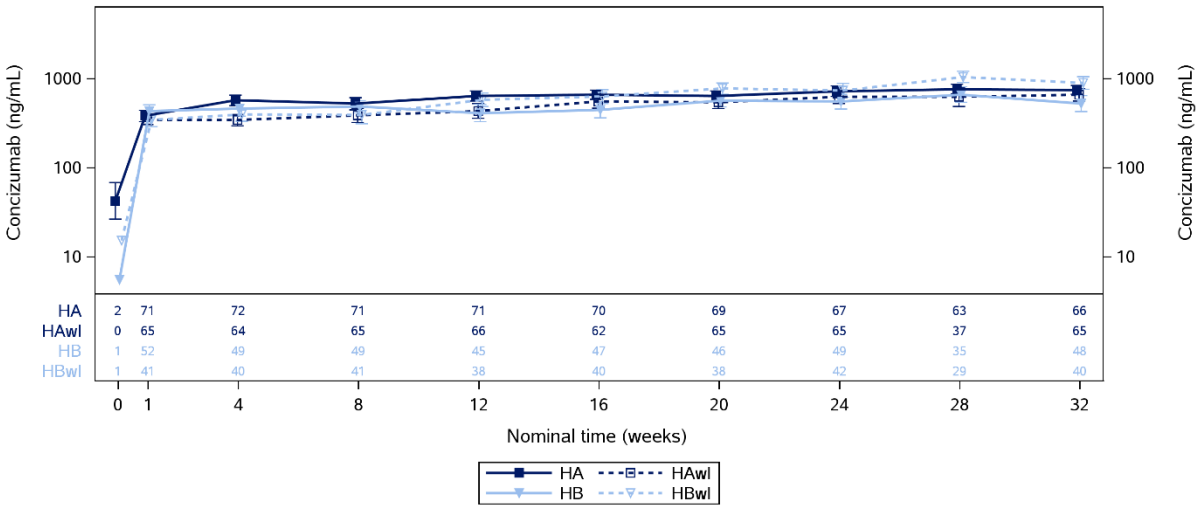
Table 13: Pre-dose trough concizumab plasma concentration (ng/mL) - by haemophilia type - week 24 - descriptive statistics - HAwI+HBwI+HA+HB - OTexIR+OTexBR - safety analysis set - trial 4311 (56-week cut-off) + trial 4307 (CACO)

N (haemophilia type)	67 (HawI)	49 (HbwI)	65 (HA)	42 (HB)	Total number: 223
Geometric mean (CV[%])	724.4 (153.5)	554.9 (215.6)	625.4 (250.5)	740.3 (165.5)	657.2 (194.2)
Min ; Max	31.6 ; 6850.0	23.8 ; 6320.0	2.5 ; 5300.0	26.2 ; 4520.0	2.5 ; 6850.0
Median	817.0	554.9 (3.7)	651.0	801.5	771.0
P25 ; P75	323.0 ; 1710.0	237.0 ; 1340.0	300.0 ; 1770.0	464.0 ; 1640.0	323.0 ; 1710.0

Figure 7: Concizumab pre-dose through plasma concentration (ng/mL) - by haemophilia subtype - - OTexIR+OTexBR - safety analysis set – trial 4311 (56-week cut-off) + trial 4307 (CACO)



CACO: confirmatory analyses cut-off, HA: haemophilia A, HB: haemophilia B,HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: on-treatment without data on initial regimen, OTexBR: On-treatment without data before restart.

The following arms are included: concizumab PPX (arms 1-4) from trial 4311 and concizumab PPX (arms 2-4) from trial 4307. Week numbers are relative to visit 9a for concizumab PPX arm1 and visit 2a for concizumab PPX (arms 2, 3 and 4). Error bars represent +/- standard error of the geometric mean. Plasma concentrations below lower limit of quantification (LLOQ) are set to half of LLOQ. Lower limit of quantification (LLOQ) for concizumab concentration is 5 ng/mL. Values below lower limit of quantification (LLOQ) at time zero are set to zero and are thus not displayed since concentrations on the y-axis are on log scale. Numbers shown in the bottom of the figure reflect the number of patients contributing with non-zero values.

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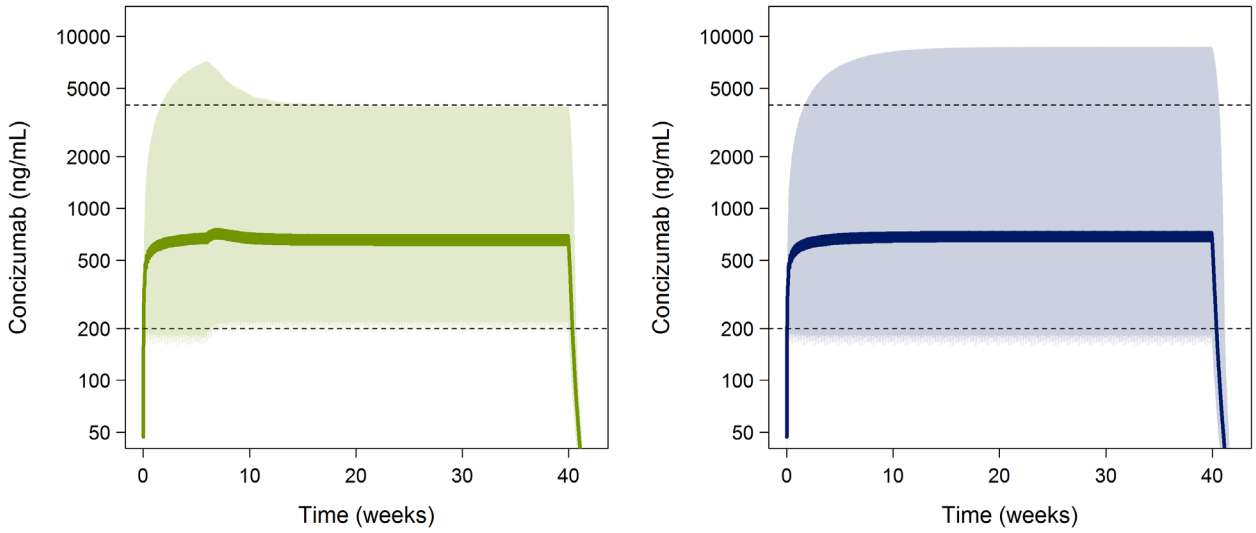
Descriptive statistics for Cmax, AUC0-τ and Cmax/Ctrough ratio at baseline and week 24 are provided for patients with different haemophilia subtype in trial 4311 are presented in Table 14.

Table 1: Pharmacokinetic parameters determined during a 24-hour dosing interval for patients on concizumab PPX (arms 2–4) - by haemophilia subtype - baseline and week 24 - HAwI+HBwI - OTexIR - safety analysis set - trial 4311 (56-week cut-off)

	HAwI Concizumab PPX (arms 2–4)		HBwI Concizumab PPX (arms 2–4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	53	42	31	27
C_{max} (ng/mL) (geometric mean (CV[%])	313.3 (278.0)	1165.9 (147.3)	351.7 (207.9)	1168.9 (102.9)
$AUC_{0-\tau}$ (ng*hr/mL) (geometric mean (CV[%])	4923.6 (233.9)	22327.7 (142.4)	5274.2 (186.7)	22511.7 (109.1)
C_{max}/C_{trough} ratio (mean [SD])	-	2.6 (6.6)	-	1.5 (0.5)

PK simulations of the impact of maintenance dose setting on concizumab exposure are presented in Figure 8. The simulations suggest that maintenance dose setting reduces the population-level variability in concizumab exposure, supporting that the dose should be adjusted for patients with low or high concizumab exposure according to the maintenance dose setting, resulting in more similar exposure across patients.

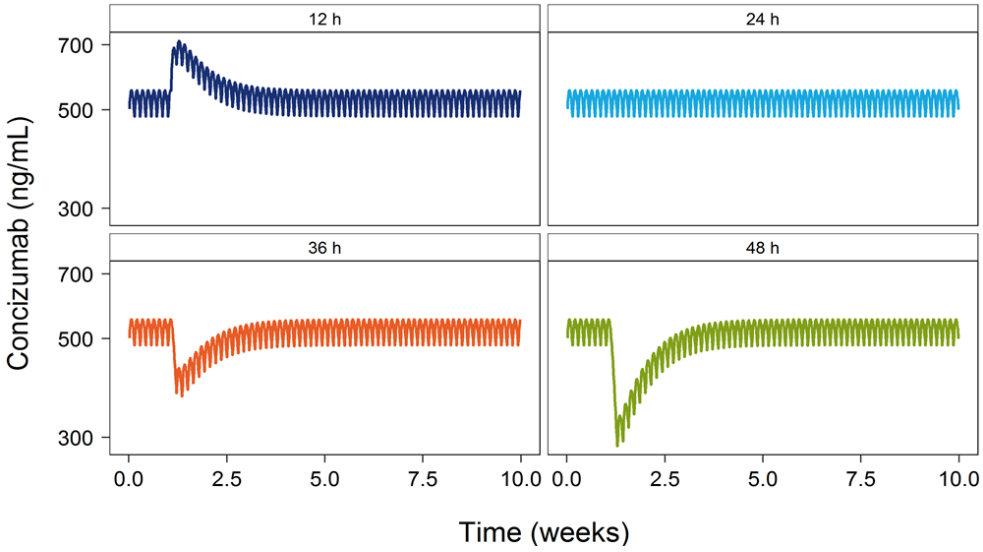
Figure 8: Simulated exposure with (left) and without (right) maintenance dose setting



Individual concentration-time profiles (without residual unexplained variability) were simulated based on the final model assuming a body weight distribution similar to trial 4311 and 4307 (>10,000 subjects simulated). Shaded area represents the 90% prediction interval, and dark line represents the geometric mean exposure levels. Maintenance dose setting was implemented as a dose increase or decrease at week 6, based on C_{trough} values (including residual unexplained variability) occurring at week 4. Dotted lines indicate the 200 and 4000 ng/mL levels for maintenance dose setting.

PK simulations of the effect of altering the time interval between doses are presented in the figure below. The changes in dosing intervals, i.e., reduced or prolonged time interval between dosing, result only in minor changes in concizumab exposure, after which the concizumab plasma concentrations quickly return to their previous levels.

Figure 9: Pharmacokinetic simulation of changes in dosing interval for a typical subject at steady state



Simulations of concizumab plasma concentration-time profiles at steady state following subcutaneous dosing of 0.20 mg/kg concizumab for a typical subject with a body weight of 75 kg based on the final population PK model. Each subplot shows the impact of changing the interval between two doses to 12 (dark blue), 24

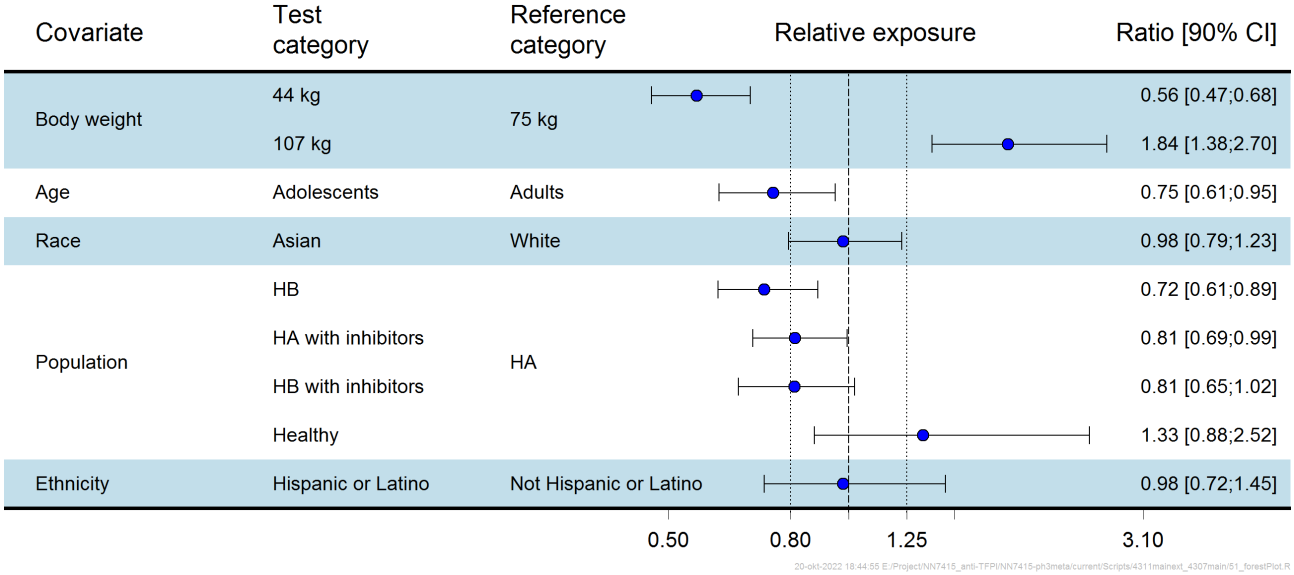
(light blue; default interval), 36 (red) and 48 (green) hours, respectively. For all other doses the dosing interval is 24 h. Note that time 0 is at steady state and not at initiation of concizumab PPX.

Special populations

The PK of concizumab in phase 3 was described by a 2-compartment model with combined linear clearance and TMDD based on data from all phases 1 and 2, data obtained up until the 56-week cut-off in trial 4311 in HAwI and HBwI patients and data obtained up until the confirmatory analyses cut-off in trial 4307 in HA and HB patients. The concizumab PK model was used to evaluate covariate effects on concizumab exposure, the impact of maintenance dose setting on concizumab exposure and the effect of changing timing intervals between doses based on predicted steady-state average concizumab plasma concentration.

The effect of different covariates was investigated relative to a reference subject (non-Hispanic or Latino, White, adult male ≥ 18 years, body weight 75 kg; reference group defined as relative exposure 1.0) as presented in the table below based on simulated steady-state exposure for 0.20 mg/kg concizumab in all subjects. The influence of a single covariate was investigated while adjusting for remaining covariates, based on the full model, including all pre-specified covariates.

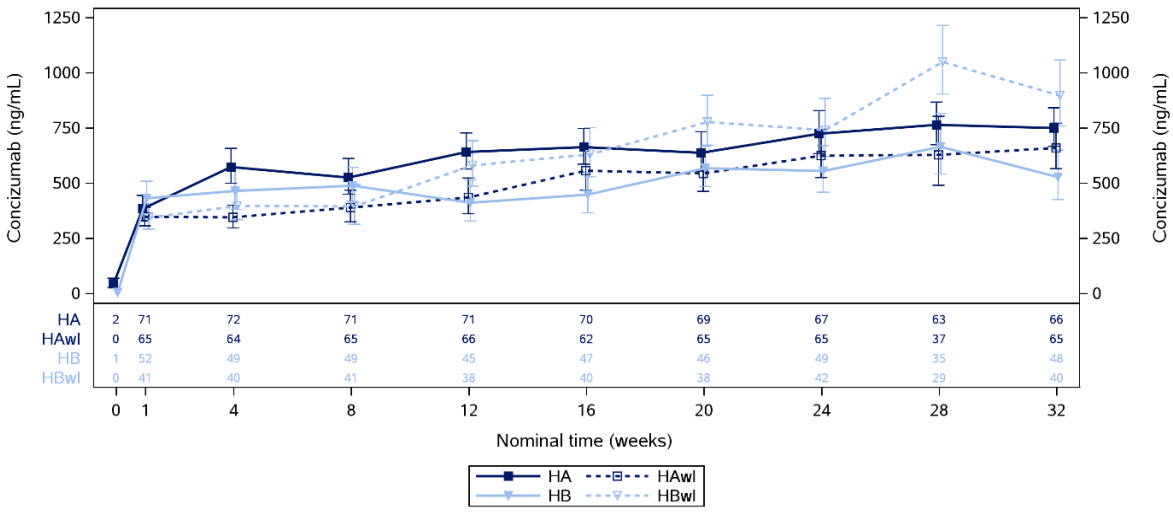
Figure 10: Forest plot of covariate effects on concizumab exposure (0.20 mg/kg)



Notes: *Data is expressed as steady-state average concizumab concentrations (C_{avg}) following administration of 0.20 mg/kg relative to the reference subject profile, based on the full population PK model. The reference subject profile was non-Hispanic or Latino, White, adult male (≥18 years), with a body weight of 75 kg not enrolled in phase 3. The points and bars (the column on the right) show point estimates (based on the maximum likelihood estimates) and 90% confidence intervals based on SIR relative to the reference subject. The reference body weight of 75 kg corresponds to the approximate median in the population. Body weight test categories (44 and 107 kg) represent the 5% and 95% percentiles, respectively in the data set. Vertical dotted lines indicate the [0.80;1.25]-limits.*

A significantly lower exposure in HB patients compared to HA patients (without inhibitors) was observed, but similar exposure was observed in patients with inhibitors. The presence of inhibitors per se appears to have an impact, as exposure was significantly lower in HAwI compared to HA and lower in HBwI – albeit not reaching statistical significance – compared to HA (but exposure in HBwI was higher compared to HB).

Figure 11: Concizumab pre-dose through plasma concentration (ng/mL) – by haemophilia subtype – HAwI + HBwI + HA + HB – OTexIR + OTexBR – safety analysis set – trial 4311 (56-week cut-off) and 4307 (CACO)



CACO: confirmatory analyses cut-off, HA: haemophilia A, HB: haemophilia B, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen, OTexBR: On-treatment without data before restart.
The following arms are included: concizumab PPX (arms 1-4) from trial 4311 and concizumab PPX (arms 2-4) from trial 4307. Week numbers are relative to visit 9a for concizumab PPX arm1 and visit 2a for concizumab PPX (arms 2, 3 and 4). Error bars represent +/- standard error of the geometric mean. Plasma concentrations below lower limit of quantification (LLOQ) are set to half of LLOQ. Lower limit of quantification (LLOQ) for concizumab concentration is 5 ng/mL. Numbers shown in the bottom of the figure reflect the number of patients contributing with non-zero values.

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The comparison of exposure over time for all subgroups on a linear scale shows differences in exposure between subgroups and an increase of exposure over time, suggesting an increase of concizumab – albeit slow – in all subgroups within the first 32 weeks of treatment, as suspected from the popPK model.

The presence of inhibitors appears to affect thrombin peak levels based on the exposure-response model (Summary 2.7.2, Fig 3-41), i.e. predicted pre-dose peak thrombin levels are higher in patients with inhibitors (study 4311) at comparable concizumab exposures, which is also confirmed by observed data at Week 24 (median 116.5 nmol/L and 96.0 nmol/L in patients with and without inhibitors, respectively). It is nevertheless agreed that pre-dose thrombin peak increased to be within the range of normal plasma for both patients with and without inhibitors.

It is acknowledged that the currently available data do not support the modification of the dosing regimen for specific subgroups. Also, no further associations regarding PD, efficacy and safety were apparent.

Based on PK data evaluated in phase 2 dose-response studies (4255 and 4310, suggested a possible risk of accumulation of concizumab over time at the highest maintenance dose of 0.25 mg/kg,). Further information, however, indicated that model-predicted concizumab exposure over time in the phase 2 trials show concizumab concentrations by final dose level without indication of time of dose escalation(s). Hence, the concentration-time profiles for the patients in the 0.25 mg/kg group also include periods on doses of 0.15 and 0.20 mg/kg. Plots of individual concizumab plasma concentrations over time indicated the profiles reflect gradual increases in concizumab exposure resulting from dose escalations rather than accumulation at the same dose level.

In Phase 3 trials (4311 and 4307), patients on a maintenance dose of 0.25 mg/kg concizumab are expected to have continuously lower concizumab exposure, if they were kept on a lower maintenance dose. At the

individual level, patients who had their maintenance dose increased to 0.25 mg/kg, concizumab plasma concentrations generally increased until they reached a new steady-state level within a stable range. Thus, although mean concizumab levels appear to increase over time, accumulation at an individual patient level on a stable maintenance dose is deemed unlikely.

Finally, the biological rationale provided, i.e. that endothelial TFPI becomes fully saturated with concizumab at the higher dose, and excess concizumab will be eliminated via the linear elimination pathway with a longer half-life, can be followed.

Therefore, the current criteria for additional concizumab concentration measurements included in 4.2 of the SmPC are considered sufficient to mitigate an individual's thromboembolic risk.

No dedicated renal impairment study was performed. The individual concizumab plasma concentrations over time for the 5 patients with reduced eGFR were within the exposure range of the total trial population. However, due to low number of patients with renal impairment no definite conclusions can be made about the impact of renal impairment on the PK of emicizumab. Since concizumab is a large protein, it is not expected to be renally excreted intactly. It is agreed that no dose modification is needed for patients with mild or moderate renal impairment. Concizumab has not been studied in subjects with severe renal impairment to end-stage renal disease (CrCl <30 mL/min). No dedicated trials on the effect of hepatic impairment on the pharmacokinetics of concizumab have been conducted. Only patients with mild hepatic abnormalities were included in the clinical studies. The individual concizumab plasma concentrations over time for the 4 patients with elevated ALT or AST were within the exposure range of the total trial population. No data is available on differences of pharmacokinetics of Concizumab in gender. PK data is not available for elderly patients (>64 years) on concizumab PPX after restart in trial 4311, as the 2 elderly patients in the trial did not restart treatment after the pause. The effect of age group (adolescents and adults) on the PK of concizumab following daily s.c. administration in adult and adolescent HAwI and HBwI patients was assessed in trial 4311. Descriptive statistics for C_{trough} at weeks 24 and 56 are provided in the table below. Descriptive statistics for C_{max}, AUC0-τ and $Cmax/C_{trough}$ ratio at baseline and week 24 are provided in table below. Available data on elderly haemophilia patients with inhibitors (study 4311) are limited, as one of two included patients never received concizumab and the other one did not restart treatment after the treatment pause. Data before the treatment pause indicate no apparent differences in PK/PD of this patient compared to the overall population.

The individual concizumab plasma concentrations for 2 elderly patients in trial 4307 (haemophilia without inhibitors) did not differ from the exposure range of the total trial population.

In the literature, no difference in TFPI levels for age groups was reported in male subjects. An age-related increase of TFPI levels in females is considered negligible for concizumab treatment since the between-subject variability is generally high, and since the TFPI levels in elderly females are similar to overall male TFPI levels. If anything, the PK of concizumab in younger females (<30y) may be altered due to lower TFPI levels. However, the overall differences between genders are minor compared to the overall variability between subjects.

Table 2 Mean concentrations of plasma total TFPI and plasma TFPIα in male and female elderly and younger subjects

Parameter	Young - male (<30 years of age)	Elderly - male (>70 years of age)	Increase per year (%)[a]	P-value[a]
Plasma total TFPI (ng/mL)	66.6 (60.3–73.0; N=57)	66.8 (57.8–75.8; N=15)	No change	-[b]
Plasma TFPIα (ng/mL)	14.5 (13.5–15.4; N=57)	17.3 (14.9–19.8; N=15)	No change	-[b]
Parameter	**Young - female (<30 years of age)**	**Elderly - female (>70 years of age)**	**Increase per year (%)[a]**	**P-value[a]**
Plasma total TFPI (ng/mL)	48.8 (40.7–57.0; N=41)	67.3 (55.4–79.1; N=16)	0.55%	P = 0.0006
Plasma TFPIα (ng/mL)	8.6 (7.5–9.6; N=41)	18.8 (15.3–22.3; N=16)	0.85%	$P = 4*10^{-7}$

Notes: As reported in 3.
The numbers in parentheses represent the 95% confidence interval and the number of donors in that group.
a Increase per year as examined for the entire age range reported in the cited literature.
b Exact value not reported in the cited literature.
Abbreviations: TFPI: tissue factor pathway inhibitor.

Table 3: Pre-dose trough concizumab plasma concentration (ng/mL) - by age group - descriptive statistics - HAwI+HBwI - OTexIR - safety analysis set - trial 4311 (56-week cut-off)

	Adolescents Concizumab PPX (arms 1–4)		**Adults Concizumab PPX (arms 1–4)**	
Parameter	Week 24	Week 56	Week 24	Week 56
N	37	35	70	61
Geometric mean (CV[%])	560.9 (168.3)	557.9 (289.5)	733.0 (239.6)	737.2 (325.6)
Min ; Max	10.4 ; 3030.0	2.5 ; 3820.0	2.5 ; 5300.0	2.5 ; 6880.0
Median	640.0	692.0	835.5	952.0
P25 ; P75	444.0 ; 1150.0	278.0 ; 1270.0	301.0 ; 2260.0	369.0 ; 2260.0

Notes: Baseline is defined as visit 9a for concizumab PPX in arm 1 and visit 2a if available (otherwise visit 2) for concizumab PPX in arms 2–4. Week numbers are relative to visit 9a for concizumab PPX in arm 1 and visit 2a for concizumab PPX in arms 2–4. Values below the lower limit of quantification (LLoQ = 5 ng/mL) are set to ½ LLoQ = 2.5 ng/mL.

Table 4: Pharmacokinetic parameters determined during a 24-hour dosing interval for patients on concizumab PPX (arms 2–4) - by age group - baseline and week 24 - HAwI+HBwI - OTexIR - safety analysis set - trial 4311 (56-week cut-off)

	Adolescents Concizumab PPX (arms 2–4)		**Adults Concizumab PPX (arms 2–4)**	
Parameter	Baseline	Week 24	Baseline	Week 24
N	31	23	53	46
C_{max} (ng/mL) (geometric mean (CV[%])	319.7 (225.5)	878.9 (100.9)	331.2 (266.7)	1344.8 (137.7)
AUC_{0-T} (ng*hr/mL) (geometric mean (CV[%])	4856.9 (188.0)	17416.2 (102.8)	5166.8 (233.1)	25402.8 (137.5)
C_{max}/C_{trough} ratio (mean (SD))	-	1.8 (1.2)	-	2.3 (6.3)

Notes: Baseline profiles were collected at visit 2 for patients starting before the trial restart and at visit 2a for patients starting after the trial restart. Week 24 is relative to the baseline after restart. Profiles for 2 patients at baseline and 8 patients at week 24 are not included in calculations due to issues related to the date/time of the concizumab dose recorded at the visit.

CUP program in children

For the 7 patients in the **CUP program 4807**, available concizumab plasma concentrations and free TFPI plasma concentrations at visits 1–4 (prior to dosing and at weeks 4, 13 and 26) are provided in the table below. Measurements were not available for all patients at all visits.

Table 5 Concizumab and free TFPI plasma concentrations in the compassionate use programme

Visit number	**Week number**	**Patient number, age, exposure duration and concizumab dose**						
		1 day 0.25 mg/kg	**196 days 0.25 mg/kg**	**175 days 0.25 mg/kg**	**184 days NK**	**182 days NK**	**86 days NK**	**195 days 0.25 mg/kg[d]**
		Concizumab plasma concentration (ng/mL)						
1	0	1520	NA	943	<5	<5	NA	<5
2	4	–	634	NA	1430	371	208	37.2
3	13	–	654	858	3110	349	–	230
4	26	–	NA	1220	6810	811	–	799
		Free TFPI plasma concentration (ng/mL)						
1	0	<9.6	NA	14.0	57.0	92.2	NA	NA
2	4	–	NA	15.2	15.8	26.5	NA	46.1
3	13	–	NA	16.9	16.3	21.8	NA	26.4
4	26	–	NA	14.2	12.9	24.4	–	NA

Notes: [a]Patient previously received concizumab on an individual patient basis (patient ID).
[b]Patient previously received concizumab on an individual patient basis (patient ID).
[c]Patient previously received concizumab on an individual patient basis (patient ID).
[d]First dose given in the compassionate use programme was a loading dose of 1.0 mg/kg and the patient had his dose increased to 0.25 mg/kg during the programme. Units in statistical output for concizumab and TFPI plasma concentrations are included as µg/L.

In the POP-PK model, exposure of concizumab does not appear to be dependent on age, however, exposure in children may potentially be lower compared to adults due to the lower body weight in these patients. The certainty and relevance of this finding of lower exposure in children was unclear, as predictions of exposure below the investigated body weight range (<27 kg) are associated with greater uncertainty, and since the

use of maintenance dose setting is expected to lead to the use of a higher dose in patients with low exposure.

Descriptive statistics indicated slightly lower geometric mean C_{trough} and geometric mean C_{max} and $AUC_{0-\tau}$ for adolescents compared to adults on concizumab PPX (HAwI and HBwI patients). In the PK modelling, no statistically significant differences were observed between the age groups, indicating that the slightly lower concizumab exposure in the adolescents may be due to lower body weight, as body weight was the most important covariate for predicting concizumab exposure. The concizumab dosing regimen allows for the dose to be increased in the case of low exposure.

Additionally, some information on the pharmacokinetics of Concizumab was available in the compassionate use program 4807. For the 6 patients with measurements after initiation of concizumab PPX, the concizumab plasma concentrations were roughly within the same range as for adult and adolescent HAwI, HBwI, HA and HB patients in trial 4311 and 4307. However, due to the limited number of data no definite conclusions can be made.

Pharmacokinetic interaction studies

Drug-drug interaction studies were not conducted as PK drug-drug interactions are not expected given that the metabolic pathways (monoclonal antibodies are neither metabolized via the cytochrome P450 system nor is there conjugation with glucuronic acid, esterases, etc.) and elimination pathways of small molecules do not overlap with metabolism or elimination of antibodies. Moreover, antibodies are not bound to drug transporters such as p-glycoprotein, breast cancer resistance protein, organic cation transporters, or organic anion transporter.

The potential pharmacokinetic interaction of concizumab and rFVIIa was included in a 4-week drug-interaction toxicity study in Cynomolgus monkeys (Study 215431). This study is further discussed in the pre-clinical part of the assessment report. In this study concizumab did not affect rFVIIa exposure.

The applicant did not discuss the potential for an indirect interaction between concizumab and CYP450s via changes in cytokine levels, especially given the known interaction between cytokines and the coagulation system.

2.6.2.2. Pharmacodynamics

As stated above, the pharmacodynamic (PD) and PK properties of concizumab in humans were evaluated in:

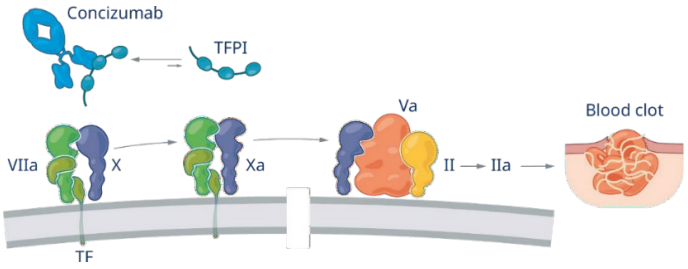
- four phase 1 trials (3813, 3981, 3986 and 4159)
- two phase 2 trials (4255 and 4310)
- two phase 3 trials (data obtained up until the 56-week cut-off in trial 4311 and data obtained up until the confirmatory analyses cut-off in trial 4307).

Furthermore, PD (and PK) results for concizumab in the compassionate use setting through the CUP (4807) are also included where results are available for some patients <12 year of age.

Mechanism of action

Concizumab is a monoclonal humanized IgG4 anti-tissue factor pathway inhibitor (anti-TFPI) antibody. It is specific for the Kunitz-2 domain of TFPI, which domain is specific for inhibition of activated factor Xa (FXa). The binding of concizumab to TFPI prevents that TFPI inhibits FXa. The increased FXa activity prolongs the initiation phase of coagulation and allows sufficient thrombin generation for effective haemostasis. Concizumab acts independently from FVIII and FIX and the effect of concizumab is not influenced by the presence of inhibitory antibodies to FVIII or FIX.

Figure 2: Mechanism of action



Abbreviations: a = activated; TF = tissue factor; TFPI = tissue factor pathway inhibitor.

Primary and Secondary pharmacology

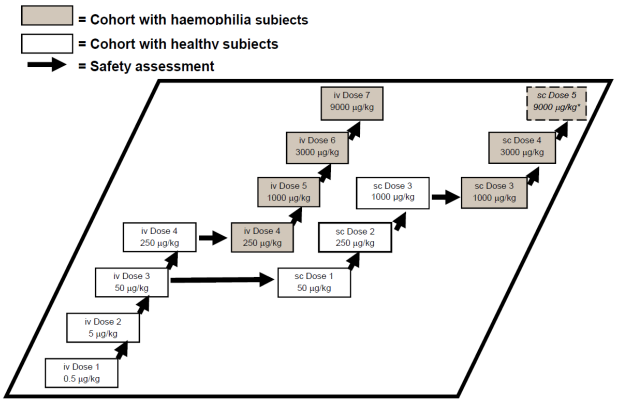
PD in phase 1 studies

Phase 1 single-dose study 3813 (Explorer 1) – first-in-human study

Study design

Study 3813 was a first-in-human, multi-centre, randomised, double-blind, placebo-controlled, single-dose, dose-escalation trial investigating safety, PK, and PD of concizumab administered intravenously (i.v.) and subcutaneously (s.c.) to healthy male subjects and severe haemophilia male subjects.

Figure 3: Study design



Study dosing

Concizumab was administered i.v. at doses of 0.5, 5, 50 and 250 µg/kg (12 healthy subjects) and 250, 1000, 3000 and 9000 µg/kg (9 haemophilia subjects), and s.c. at doses of 50, 250 and 1000 µg/kg (9 healthy subjects) and 1000 and 3000 µg/kg (6 haemophilia subjects). Each trial subject received a single dose of concizumab or placebo administered i.v. or s.c. The subjects were randomised in a 3:1 manner to receive either concizumab or placebo.

- Rationale for starting dose and dose escalation: In accordance with first human dose recommendations outlined in EMA guidance the starting doses of 0.5 µg/kg i.v. and 50 µg/kg s.c. were selected based on results from non-clinical studies and PK/PD modelling. The selection of subsequent dose levels was also supported by modelling.
- Rationale maximum dose: If safety allowed, i.v. dose escalation could be continued in haemophilia subjects until an i.v. dose was reached, which was expected to result in approximately 2 weeks of full target saturation as defined by PK, based on non-clinical modelling data and the available preliminary clinical PK data. The rationale for escalating to this dose level was to establish safety of this magnitude of exposure, as it may be necessary if the i.v. route is developed for prophylactic treatment. For the s.c. part the maximum dose to be administered was determined by the highest dose that was supported by safety evaluation of the preceding s.c. and i.v. doses. The planned maximum s.c. dose was 9000 µg/kg, but the actual maximum s.c. dose administered in this trial was 3000 µg/kg. After safety assessment of the 3000 µg/kg s.c. cohort in haemophilia subjects the trial safety group decided that it was safe to dose-escalate to the last planned s.c. cohort of 9000 µg/kg. However, it was decided not to proceed to this dose level as the applicant did no longer see a justification to dose escalate to a higher s.c. cohort than 3000 µg/kg since relevant drug development information for future trials had been obtained with the completed cohorts.
- Rationale for switching from healthy subjects to haemophilia subjects at a defined dose: Based on PK/PD modelling of nonclinical data, an i.v. dose of 250 µg/kg and an s.c. dose of 1000 µg/kg were considered the maximum dose to be administered to healthy subjects in order to avoid or limit target saturation.

Study participants

A total of 52 subjects were distributed between the 4 treatment arms. Within each dose cohort 4 subjects were randomised to receive either a single dose of concizumab (n=3) or placebo (n=1).

Main inclusion criteria were male healthy subjects and haemophilia subjects between 18 and 65 years, with a body weight between 50 and 100 kg and a body mass index (BMI) between 18 and 25 kg/m^2 (first i.v. cohort) or 18 and 30 kg/m^2 (all remaining cohorts). The haemophilia subjects were to be diagnosed with severe haemophilia A or B.

PD study endpoints

- diluted PT (dPT) clot time
- residual TFPI functionality in plasma.
- total free TFPI (exploratory) (i.e., TFPI not bound to concizumab)

They were analysed using descriptive statistics.

Safety coagulation-related parameters:

- D-dimers,
- prothrombin fragment 1 and 2 (F1+2),
- activated partial thromboplastin time (aPTT),
- fibrinogen

Rationale for measuring the coagulation-related parameters:

The prevention of TFPI-mediated FXa-inhibition by concizumab is expected to result in enhanced FXa generation followed by thrombin generation. FXa generates thrombin from prothrombin by cleaving off prothrombin fragments 1 and 2 (F1+2). Thus, F1+2 may serve as a marker of thrombin generation. Thrombin catalyses the conversion of fibrinogen into non-cross-linked fibrin as well as soluble fibrin. D-dimers are formed as a result of plasmin degradation of the cross-linked fibrin. In the process of fibrinolysis (break down of coagulation), plasmin is the central molecule in the process of fibrinolysis, where the tissue plasminogen activator (tPA) converts plasminogen into plasmin. Plasmin then degrades fibrin or fibrinogen into fibrin- or fibrinogen degradation products (FDPs).

PD results

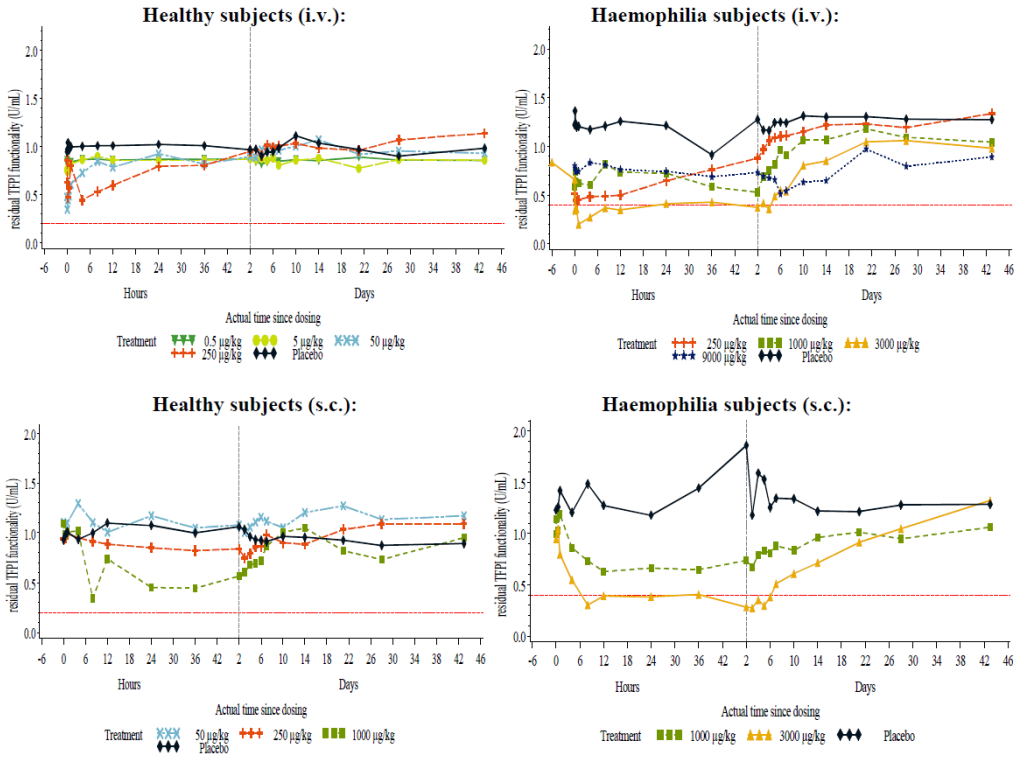
- *Diluted PT (dPT) clot time*

The results of the dPT assay were only available for the lowest i.v. cohort. During the analyses for the first i.v. cohort the results of dPT clot time were noninterpretable. Varying scattered responses over the entire trial period was observed in all 4 subjects in this cohort, i.e. also for the subject receiving placebo. Therefore, sampling and analysis for dPT clot time was discontinued after the first i.v. cohort.

- *Residual TFPI functionality (FXa activity)*

Mean plasma profiles for residual TFPI functionality following i.v. administration of trial product to healthy subjects and haemophilia subjects are presented in the figure below.

Figure 4 Mean residual TFPI functionality in plasma (U/mL) after i.v and s.c. administration of trial product (healthy subjects and haemophilia subjects) - FAS



The vertical dashed line indicates a shift in scale from hours to days at Day 2. The horizontal dashed line indicates LLOQ . Original values below LLOQ are set to ½*LLOQ; Original values below ULOQ (2.400 U/mL) are set equal to ULOQ.

Healthy subjects

With i.v. dosing, the mean residual TFPI functionality levels decreased after i.v. dosing at the highest dose (250 µg/kg) and were back to baseline levels after 24 hours. At 50 µg/kg the levels increased after dosing. However, the increase in residual TFPI functionality levels at this dose was not considered a PD effect of concizumab, but rather reflected low pre-dose levels in this dose cohort.

With s.c. dosing, residual TFPI functionality levels decreased at the highest dose (1000 µg/kg). The decrease was generally seen after 8 hours and levels increased gradually again after 48 hours.

Haemophilia patients (severe HA or HB)

With i.v. dosing, mean residual TFPI functionality decreased. The time varied until the levels returned to baseline values.

With s.c. dosing, residual TFPI functionality decreased in a concizumab dose-dependent manner at both doses administered (1000 and 3000 µg/kg). The decrease was generally seen after 4 hours and the levels gradually increased again after 6-7 days.

- *Total free TFPI (exploratory)*

Healthy subjects

Following i.v. administration of concizumab, total free TFPI plasma concentrations in healthy subjects decreased in a dose-dependent manner and was most pronounced at i.v. doses ⩾ 50 µg/kg; see Figure

below. The suppression of TFPI levels lasted for a mean period of 1−24 hours, and thereafter the TFPI levels increased back to baseline values. The duration of the suppression was dose-related.

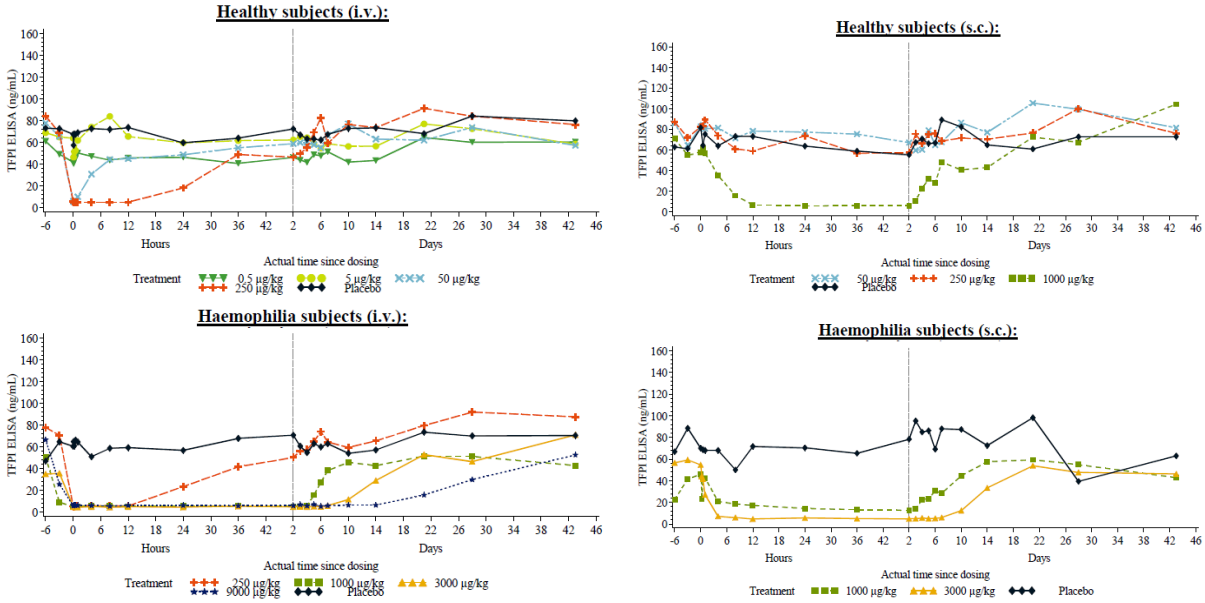
Following s.c. administration of concizumab, total free TFPI plasma concentrations decreased in a dose-dependent manner. The decrease was most pronounced at the highest dose (1000 µg/kg). The suppression of TFPI levels varied from a mean period of 4 days at 1000 µg/kg.

Haemophilia subjects

Following i.v. administration of concizumab, total free TFPI plasma concentrations in haemophilia subjects decreased in a dose-dependent manner. TFPI levels were decreased at all i.v. dose levels (⩾250 µg/kg) in a clear dose-related manner; see Figure 15. The suppression of TFPI levels lasted up to 14 days at the highest dose of 9000 µg/kg, where after the levels gradually increased during the rest of the trial period.

Following s.c. administration of concizumab, total free TFPI plasma concentrations were substantially decreased at both dose levels (1000 and 3000 µg/kg) in a dose-related manner; see Figure 15. The suppression of TFPI levels varied from a mean period of 4 days at 1000 µg/kg up to 10 days at the highest s.c. dose of 3000 µg/kg, and thereafter the TFPI levels increased gradually back to baseline values.

Figure 5 TFPI (ng/mL) – mean profiles after i.v. and s.c. administration of trial product (healthy subjects and haemophilia subjects) – safety analysis set.



Safety parameters

- *Coagulation-related parameter - D-dimers*

Healthy subjects

Increased levels of D-dimers were seen in healthy subjects following i.v. and s.c. administration of concizumab.

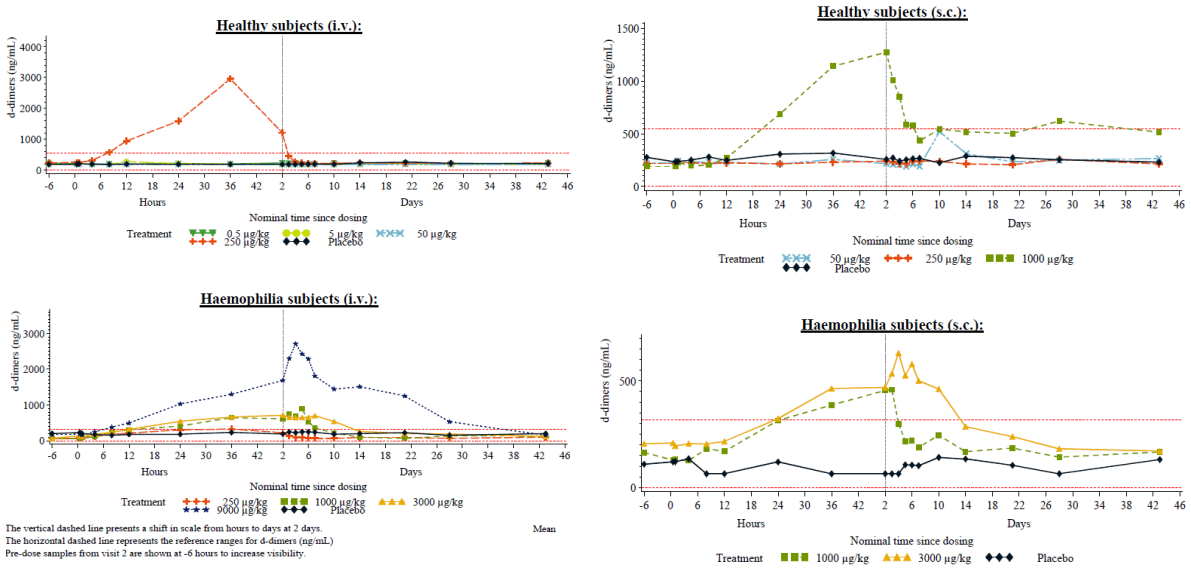
In healthy subjects, the increase in D-dimers was seen at the highest dose s.c. (1000 µg/kg). The D-dimer levels peaked at 48 hours post-dosing and returned to levels within normal reference range at Day 4−5 post-dosing, except for 1 subject, who had elevated levels throughout the whole trial period.

Haemophilia subjects

Increased levels of D-dimers were seen following i.v. and s.c. administration of concizumab in haemophilia subjects.

In haemophilia subjects, the D-dimer levels were slightly increased at both s.c. dose levels (1000 and 3000 µg/kg) in a dose-related manner; see Figure below. The mean D-dimer levels peaked at Day 3−4 post-dosing.

Figure 6 D-dimers (ng/mL) – mean profiles after i.v. and s.c. administration of trial product (healthy subjects and haemophilia subjects) – safety analysis set.



- *Coagulation-related parameter - Prothrombin fragment 1 and 2 (F1+2)*

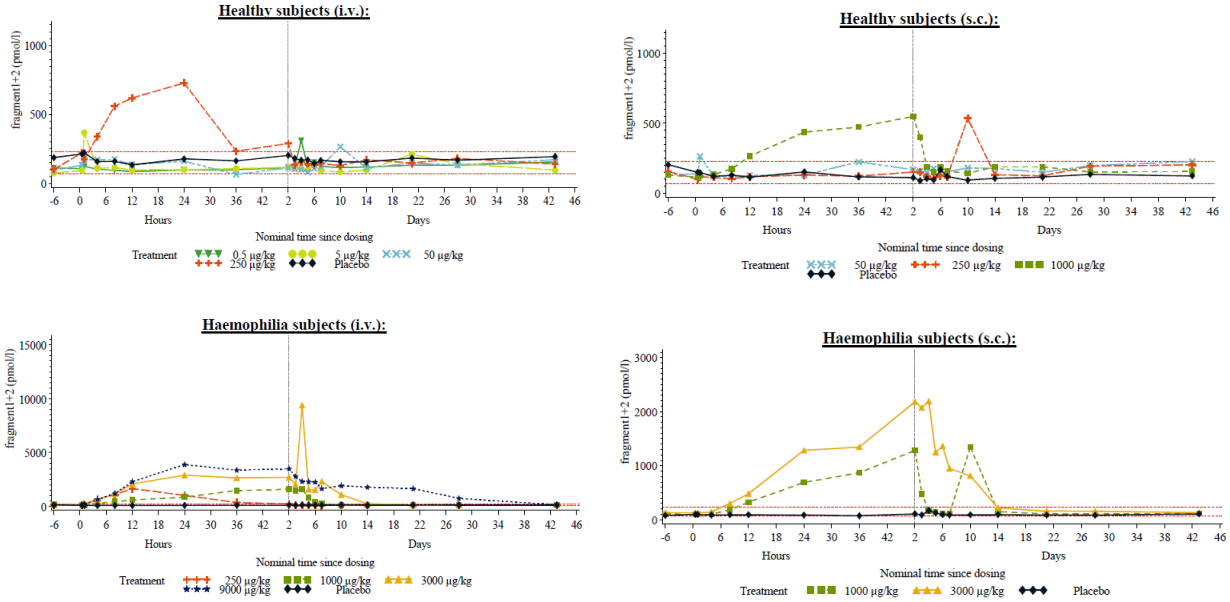
Healthy subjects

In healthy subjects, the increase in prothrombin F1+2 levels was seen at the highest dose i.v. (250 µg/kg), the increase in prothrombin F1+2 levels was seen at the highest dose s.c. (1000 µg/kg). The mean prothrombin F1+2 levels peaked at 48 hours postdosing and returned to levels within normal reference range at Day 4 post-dosing. At the lower doses a few measurements were seen outside the reference range, but with no clear pattern.

Haemophilia subjects

In haemophilia subjects, the prothrombin F1+2 levels were increased at all i.v. dose levels (⩾ 250 µg/kg) in a dose-related manner. In haemophilia subjects, the prothrombin F1+2 levels were increased at both s.c. dose levels (1000 and 3000 µg/kg) in a dose-related manner. The mean prothrombin F1+2 levels peaked at 48 hours postdosing and returned to levels within normal reference range at Day 14 post-dosing.

Figure 7: Prothrombin F1+2 (pmol/L) – mean profiles after i.v. and s.c. administration of trial product (healthy subjects and haemophilia subjects) – safety analysis set.



- *Coagulation-related parameter - Prothrombin time (PT) and international normalised ratio (INR)*

No noteworthy change over the trial period was apparent for PT or INR after administration of the trial product. The majority of values were within the reference range of 10−12 or 10−13 seconds for PT and 0.9−1.2 or 0.5−1.5 for INR (ranges from the central laboratories analysing samples from healthy subjects and haemophilia subjects, respectively).

- *Coagulation-related parameter - Activated partial thromboplastin time (aPTT)*

No noteworthy change over the trial period was apparent for aPTT after administration of the trial product. In *healthy subjects* the vast majority of values were within the reference range of 22−41 seconds. In *haemophilia subjects* most values were above the reference range of 21−40 seconds throughout the trial, both following i.v. and s.c. administration of concizumab as well as placebo.

- *Coagulation-related parameter - Fibrinogen*

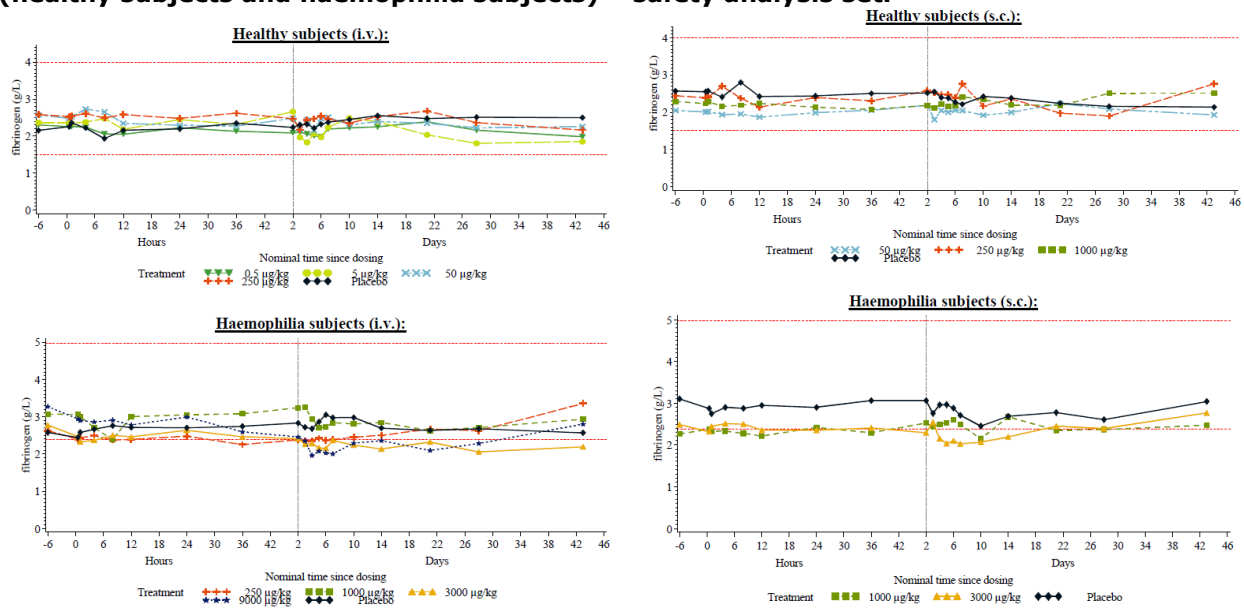
Healthy subjects

The reference range at the laboratory analysing samples from healthy subjects was 1.5−4 g/L. There was a tendency to transiently decreased levels in some healthy subjects at the highest dose levels.

Haemophilia subjects

After i.v. administration, many of the fibrinogen values in haemophilia subjects were below normal reference range, also at baseline. However, the central laboratory, which tested fibrinogen samples from haemophilia subjects had an unusually high normal reference range (2.38−4.98 g/L). There was a tendency to transiently decreased levels in haemophilia subjects at the highest dose levels. The possible decrease was to a large extent confounded by high intra- and inter-subject variation and firm conclusions could therefore not be made. The reason for this potential decrease was unknown. Also for s.c. administration a possible, although weaker tendency to transiently reduced fibrinogen levels in some haemophilia subjects at the highest dose levels.

Figure 8 Fibrinogen (g/L) – mean profiles after i.v. and s.c. administration of trial product (healthy subjects and haemophilia subjects) – safety analysis set.



- *Coagulation-related parameter - Antithrombin*

No noteworthy change over the trial period was apparent for antithrombin after administration the trial product. Most values were within the reference range. The values outside the reference range were only marginally out of range and did not show any treatment- or dose-related pattern. As antithrombin was analysed at local laboratories the reference ranges varied between laboratories (70 to 150% [IU/dL].

Immunogenicity

No anti-concizumab antibodies were detected during the trial.

Other safety results

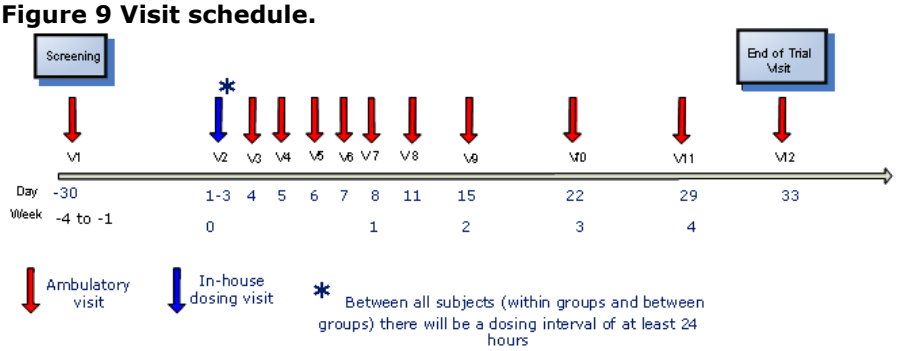
There were no deaths or other serious adverse events (AEs) reported. A total of 76 AEs in 34 out of 52 subjects were recorded of which the vast majority were of mild or moderate severity. Across all dose cohorts, a total of 5 AEs were evaluated by the investigator to be possibly or probably related to trial product. No treatment- or dose-relationship was seen. Two were recorded as medical event of special interest (MESIs), both of moderate severity. One case of superficial thrombophlebitis (1000 µg/kg s.c., healthy subject) was reported, of which symptoms appeared 5 days post-dosing and resolved spontaneously 7 days post-dosing; the event was considered clinically insignificant by the investigator and applicant. No other thromboembolic events were recorded in the trial. The second case was hypersensitivity (placebo i.v., haemophilia subject): allergic skin reaction the reaction was treated and disappeared 2 days later.

Phase 1 study 3981 (Explorer 2) – single-dose study in healthy volunteers

Study design

Study 3981 was a randomised, double-blind, placebo-controlled, single-centre, single-dose trial, assessing the PK and PD of concizumab, administered subcutaneously at two different dose levels (250 µg/kg or 1000 µg/kg), in healthy Japanese subjects (Figure 19**:**).

Figure 9 Visit schedule.



Study dosing

A total of 8 subjects received a single s.c. dose of concizumab (250 µg/kg or 1000 µg/kg) or placebo. The subjects were randomised in a 3:1 manner to receive either concizumab or placebo. The 2 doses investigated in this trial, 250 and 1000 µg/kg s.c., are the same as the 2 highest doses that have been tested in healthy subjects in the first human-dose trial (study 3813).

Study participants

Main inclusion criteria were healthy male Japanese subjects defined as: a) subjects born in Japan, b) time residing outside of Japan did not exceed 5 years and c) both parents and all 4 grandparents of Japanese descent. The subjects should be between 20 and 64 years, with a body weight between 50 and 100 kg and a body mass index (BMI) between 18 and 30 kg/m^2.

PD study endpoints

- Residual TFPI functionality in plasma up to 33 days post-dosing
- Total free TFPI concentration in plasma up to 33 days post-dosing
- Coagulation-related parameters

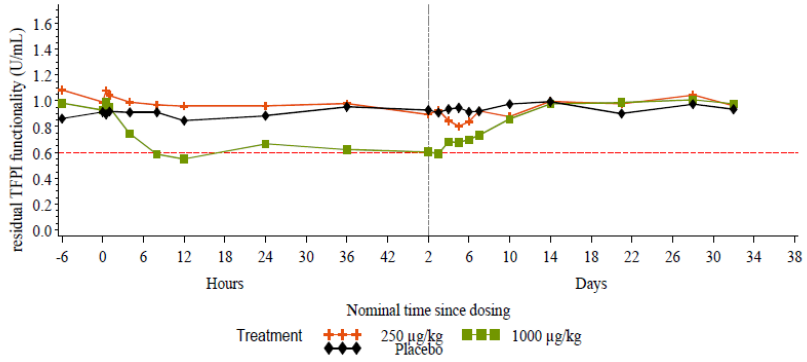
They were analysed using descriptive statistics.

PD results

- *Residual TFPI functionality*

A decrease in residual TFPI functionality levels was seen at the highest s.c. dose level (1000 µg/kg), whereas there were no marked changes at 250 µg/kg when compared to placebo. Individual profiles showed that the decrease in mean profiles at 1000 µg/kg was mainly ascribed a decrease in 2 of the 3 subjects at this dose level. The mean levels had returned to baseline values at 10−14 days post-dosing (figure below).

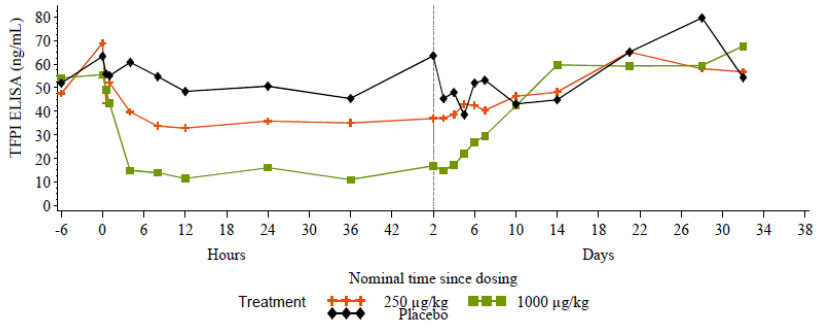
Figure 20: Mean residual TFPI functionality in plasma (U/mL) – full analysis set.



- *Total free TFPI concentration*

Mean total free TFPI plasma profiles are presented in the Figure below. A decrease in TFPI levels was seen at both dose levels of concizumab as compared to placebo. The levels decreased in a dose-dependent manner. The mean levels had returned to baseline values at 14 days post-dosing.

Figure 21: Mean profiles of total free TFPI in plasma (ng/mL) – full analysis set.

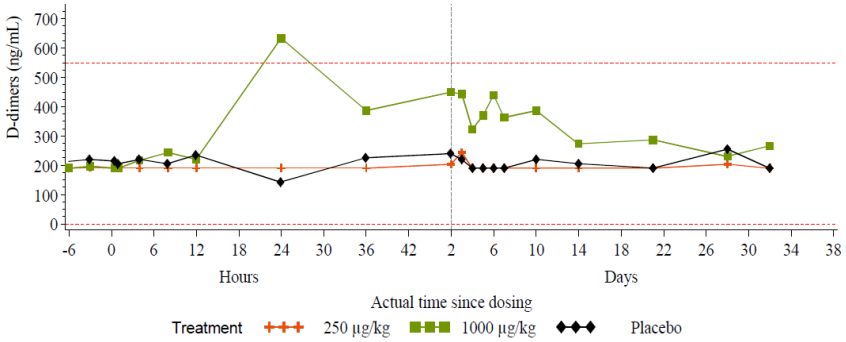


- *Coagulation-related parameters*

D-dimers

Increased levels of D-dimers were observed at 1000 µg/kg; see the Figure 22 below. The increase in D-dimers was seen in 2 out of 3 subjects dosed at this dose level. The mean levels peaked slightly above the upper limit of the normal reference range at 24 hours post-dosing. The time to reach baseline values varied; one subject had levels of D-dimers above normal reference range up to 14 days post-dosing whereas the levels in this patient had returned to baseline at 4 days post-dosing.

Figure 10 Mean profiles of D-dimers (ng/mL) – safety analysis set.



The two subjects with increased levels of D-dimers also had a slight increase in the levels of prothrombin F1+2 levels 24 hours post-dosing. The mean profiles were within normal reference range. Increased levels of D-dimers and to a lesser extent prothrombin F1+2 levels were observed at 1000 µg/kg.

aPTT, fibrinogen, antithrombin and PT/INR

The results of all other coagulation-related parameters (aPTT, fibrinogen, antithrombin and PT/INR), showed no noteworthy change over the trial period. Most values were within reference range. The values outside the reference range were not considered clinically relevant as they were only marginally out of range or occurred sporadically with no clear relationship with treatment.

Antibodies

No anti-concizumab antibodies were detected during the trial.

Other safety results

There were no deaths or other serious adverse events observed in this trial. A total of 5 AEs were reported in 4 subjects; 4 events were recorded in subjects receiving concizumab and 1 event was recorded in a subject receiving placebo (n=3 nasopharyngitis (in placebo, 0.25 mg/kg and 1 mg/kg), n=1 presyncope and light-headedness due to venepuncture (1 mg/kg)). All events were judged by the investigator to be unlikely related to trial product.

Phase 1 study 3986 (Explorer 2) – multiple dose study

Study design

The multi-centre, open-labelled, multiple-dosing trial investigating safety, PK and PD concizumab administered subcutaneously to healthy male subjects and haemophilia subjects at a dose of 250, 500 or 1000 µg/kg: 250 µg/kg (healthy subjects), 500 µg/kg (haemophilia subjects) or 1000 µg/kg (haemophilia subjects) every other day.

The trial was terminated prematurely. During the conduct of the trial, non-clinical safety findings were seen in the nonclinical programme for concizumab, which had to be investigated before exposing further human subjects to the trial product. Therefore, the trial was set on hold and a decision to prematurely end the trial was subsequently made. This was due to findings in a then ongoing 26-week toxicity study leading to an unscheduled sacrifice of one monkey.

There were no changes to the benefit-risk profile which had impact on the planned follow-up of the subjects who had participated in the trial.

All subjects were asked to attend a screening visit (Visit 1), 8 dosing visits (Visits 2−9, Days 1−15) followed by a follow-up visit (Visit 10, Day 22), as well as a final end-of-trial visit (Visit 11, Day 35). Blood sampling for PK, PD and laboratory safety parameters was done at all visits. At the dosing visits, samples for PK and PD assessment were collected at pre-dose and 1-hour post-dose.

Study dosing

The trial was planned to include 3 ascending dose tiers. Each subject was planned to receive concizumab s.c. at a dose level of either 250, 500 or 1000 µg/kg: 250 µg/kg (healthy subjects), 500 µg/kg (haemophilia subjects) or 1000 µg/kg (haemophilia subjects) every other day (EOD) 8 times. At each dose tier 4 subjects were planned to be included.

Study participants

Key inclusion criteria for all trial subjects (healthy subjects and haemophilia subjects) were male subjects and aged between 18 and 64, both inclusive. Additional key criteria for haemophilia subjects only were subjects diagnosed with haemophilia A with a baseline level of Factor VIII < 2 % without inhibitors.

Key exclusion criteria were thrombocyte count below the lower limit of normal range at screening, any clinical signs or known history of thromboembolic events, high risk of thromboembolic events or increased risk of cardiovascular disease.

PD study endpoints

- Residual TFPI functionality in plasma up to 35 days post-dosing
- Total free TFPI concentration in plasma up to 35 days post-dosing
- Thrombin generation (TG) in plasma up to 35 days post-dosing

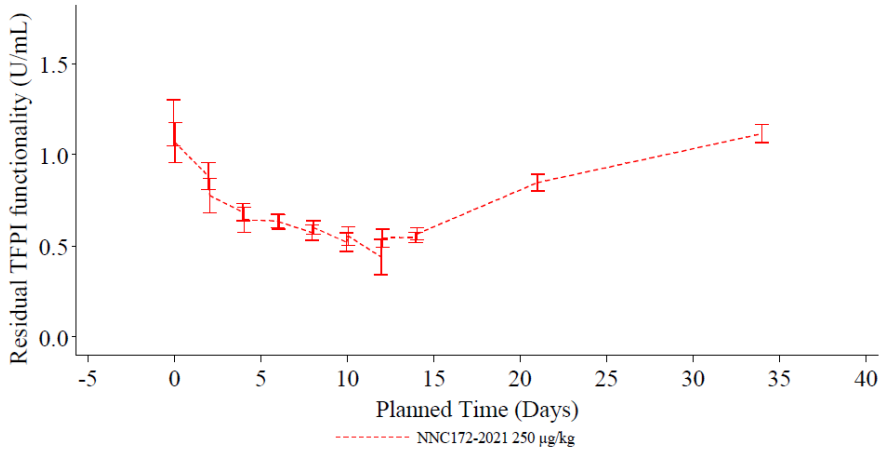
They were analysed using descriptive statistics.

PD results (dose of 250 µg/kg s.c. every other day in healthy male subjects)

- *Residual TFPI functionality (FXa activity)*

A decrease in residual TFPI functionality levels from baseline was seen (Figure 23**:**). The mean levels had returned to baseline values at the end-of-trial visit. The reduction in mean residual TFPI functionality levels from baseline (1.174 U/mL) to Day 15 (0.565 U/mL) was 51.9%.

Figure 11 Mean residual TFPI functionality in plasma (U/mL) – full analysis set.

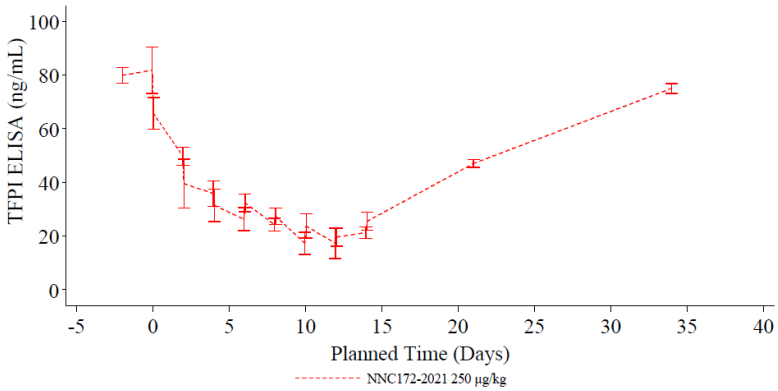


- *Total free TFPI*

Total free TFPI (ng/mL) in plasma was measured by ELISA.

Mean total free TFPI plasma profiles are presented in Figure 24**:** (linear scale). A decrease in TFPI levels from baseline was seen. The mean levels had returned to baseline values at the end-of-trial visit. The reduction in mean TFPI levels from baseline (79.9 ng/mL) to Day 15 (25.5 ng/mL) was 68.1%.

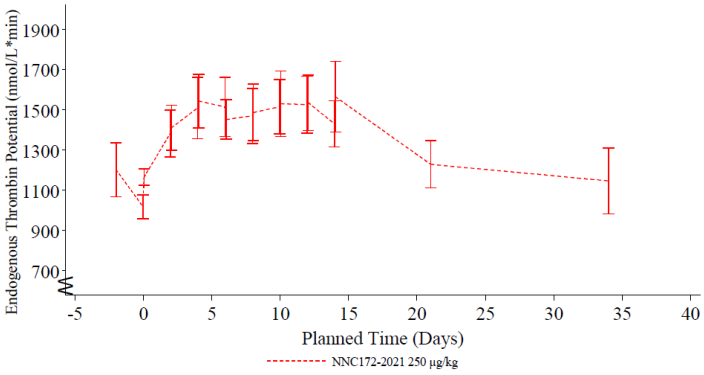
Figure 12 Mean profiles of total free TFPI in plasma (ng/mL) – full analysis set.



- *Thrombin generation (TG)*

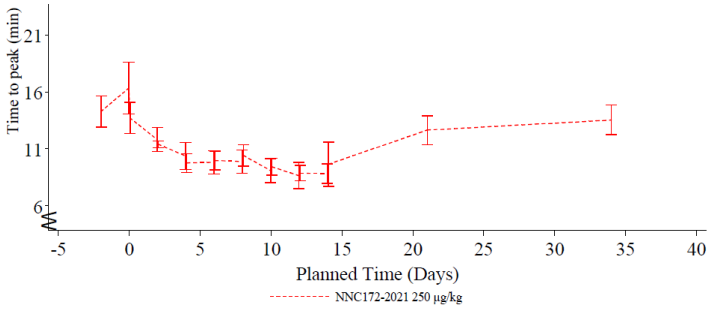
Mean profiles of endogenous thrombin potential (ETP) (= area under the thrombin generation curve) is presented in Figure 25**:**. An increase from baseline in ETP was seen following administration of concizumab.

Figure 13 Mean profiles of ETP (nmol/L*min) - full analysis set.



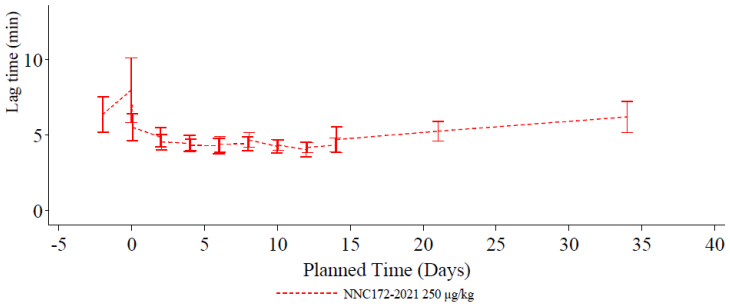
A decrease from baseline in TG time to peak was seen following administration of concizumab; see Figure 26**:** (mean profiles).

Figure 14 Mean profiles of TG time to peak (min) - full analysis set.



A decrease from baseline in TG lag time was seen following administration of concizumab; see Figure 27**:** (mean profiles).

Figure 15 Mean profiles of TG lag time (min) - full analysis set.



Apart from the above pre-planned TG endpoints 2 other parameters (velocity index and peak thrombin value) were automatically calculated and provided by the CAT analysis instrument. Concizumab increased both the TG velocity index and the TG peak thrombin value. Both parameters showed high between-subject variability.

Phase 1 study 4159 (Explorer 3) – multiple dose study in HA patients

Study design

Study 4159 (explorer 3) was multi-centre, randomised, placebo-controlled, double-blinded, multiple-dose, dose-escalation trial investigating safety, PK, PD of concizumab administered subcutaneously to haemophilia A subjects. The trial duration was approximately 11 weeks.

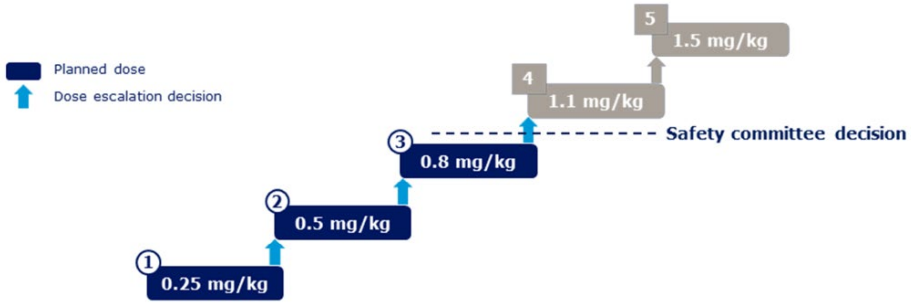
Study dosing

Five dose levels of concizumab (0.25, 0.50, 0.80, 1.1 and 1.5 mg/kg), corresponding to a predicted approximate 3–4 fold increase in exposure between each group, administered s.c. every fourth day were planned to be investigated. Eight haemophilia A subjects were included at each dose level and treated with concizumab or placebo in a 3:1 randomisation. In total, 12 administrations over a 42 day period were given to each subject (Figure 28**:**).

- Rationale for dosing levels: Concizumab dose levels were based on data from a cuticle bleeding model in rabbits, and selected to reach predefined plasma concentration levels comparable to, below and above the exposure observed to be effective in the rabbit efficacy model. The doses needed to reach these predefined target plasma levels were predicted using a population PK model.

- Rationale for dosing interval: The number of doses and the dosing interval was chosen to achieve steady state exposure for a sufficient period of time to accumulate safety data and the relation between concizumab exposure and PD.

Figure 16 Trial design



Study participants

24 subjects (6 in each of the three concizumab dose groups and 6 in the placebo group) were randomised and completed the trial.

Main key inclusion criteria were male subjects diagnosed with haemophilia A without inhibitors present at screening and currently treated on-demand with baseline level of factor VIII ⩽2 % based on medical records, aged between 18-64 years, both inclusive, and body weight between 50-100 kg, both inclusive.

Main key exclusion criteria were platelet count below 50x10^9/L at screening, clinical signs or known history of thromboembolic events, or high risk of thromboembolic events or increased risk of cardiovascular disease.

PD study endpoints

- Residual TFPI functionality: max change from baseline, time of max change from baseline, value prior to the last dose administration (day 42)
- Free TFPI concentration: max change from baseline, time of max change from baseline, value prior to the last dose administration (day 42)
- Immunogenicity: Frequency of (binding or neutralizing) anti-concizumab antibodies

For safety coagulation-related parameters, i.e. D-dimers, prothrombin fragment 1 and 2 (F1+2), activated partial thromboplastin time (aPTT) and fibrinogen, were tested.

Furthermore, although this was not an efficacy trial, the treatment duration of 42 days allowed for a preliminary assessment of the ability of concizumab to prevent bleeding episodes.

All were analysed using descriptive statistics.

Trial finalization following the completion of the 0.80 mg/kg group

This trial was finalised following the completion of the 0.80 mg/kg group. Blinded preliminary safety and PK/PD data from the 0.80 mg/kg group was reviewed by the safety committee. Marked changes in coagulation parameters were observed, including a decrease from baseline in fibrinogen, and a pronounced increase in D-dimer and F1+2 outside of normal range. In addition, a substantial between-subject variation in pro-coagulant response to concizumab was observed. Based on this, the safety committee decided not to

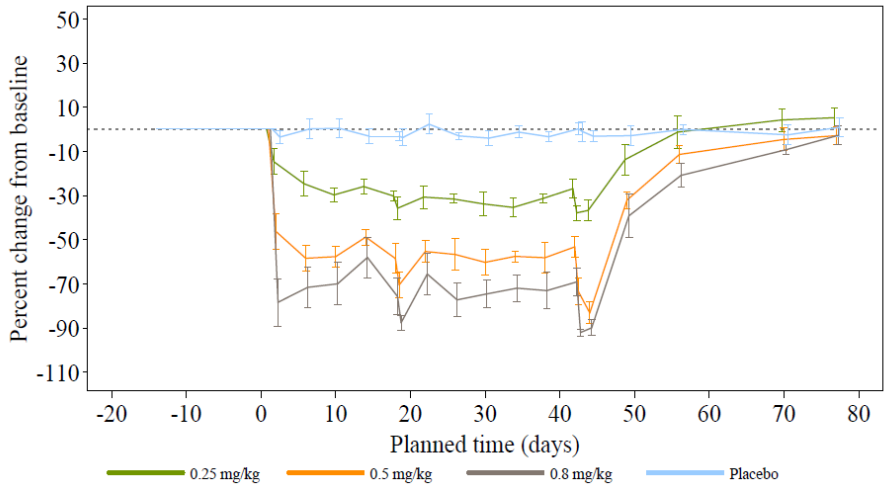
proceed to the 1.1 mg/kg concizumab dose level. No clinical consequences or serious adverse were seen in the completed dose groups. No changes were made to the benefit-risk profile with impact on the planned follow-up of trial subjects. Therefore, a total of 24 subjects were randomised and completed the trial. Overall, the demographics and body measurements in the 4 groups were comparable.

PD results with 0.25, 0.50, 0.80 mg/kg

- *Free TFPI*

During the dosing period, free TFPI compared to baseline was reduced approximately 27%, 55%, and 75% during the dosing period when concizumab was administered at 0.25 mg/kg, 0.50 mg/kg, and at the highest dose regimen of 0.80 mg/kg, respectively (Figure 29**:**9).

Figure 17 Mean profiles of free TFPI (ng/mL) - safety analysis set.



Free TFPI was reduced with increasing concizumab dose, and the time to reach the highest level of reduction was also decreased, see Table 19**:**. Furthermore, mean free TFPI prior to last dose represented the last measured mean trough value in the dosing period when steady-state exposure was achieved. The values were, as expected, inversely correlated with total concizumab exposure (AUC), see Table 19**:**.

Table 6 Summary of free TFPI (ng/mL) – safety analysis set.

	0.25 mg/kg	0.50 mg/kg	0.80 mg/kg	Placebo
Number of subjects	6	6	6	6
Max change from baseline[a]				
Geometric Mean	34.08	69.63	80.71	12.83
Min ; Max	23.80 ; 42.80	58.40 ; 80.80	68.50 ; 101.6	9.00 ; 22.80
Time (days)to max change[a]				
Geometric Mean	23.61	11.08	4.22	21.31
Min ; Max	10.00 ; 34.00	5.00 ; 29.00	2.00 ; 22.00	10.00 ; 43.00
Value prior to last dose[b]				
Geometric Mean	61.75	43.29	22.31	102.3
Min ; Max	51.20 ; 75.00	22.70 ; 58.90	4.80 ; 48.30	82.90 ; 128.2

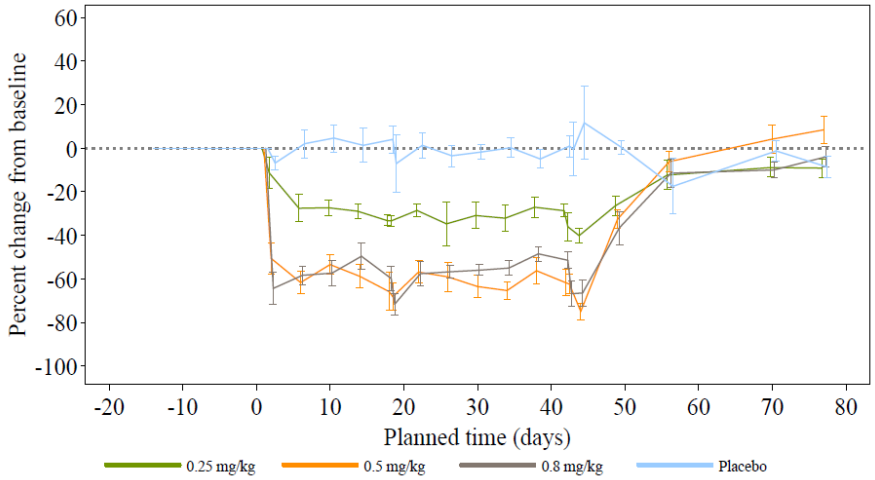
[a] Pre-dose (trough) assessments only.
[b] Value of free TFPI (ng/mL)

- *Residual TFPI functionality (FXa activity)*

Residual TFPI functionality was measured as inhibition of FXa activity (U/mL), which is a prerequisite for thrombin generation. Residual TFPI functionality was reduced in all concizumab-treated haemophilia A subjects, see Figure 30 below. An approximate 30% reduction was observed in the 0.25 mg/kg group, and a

60-70% reduction was observed in the 0.5 and 0.80 mg/kg groups. Thus, the reduction of TFPI functionality between the 0.5 and 0.80 mg/kg groups was similar.

Figure 30: Residual TFPI functionality (U/mL) - safety analysis set.



Data points show the mean and error bars represent ±SEM. Blood samples were taken at pre-dose (trough). In addition, two 4h post-dose blood samples were taken: one on planned day 18 and one on planned day 42 (last dosing visit). Treatment period: planned day 1-42. Follow-up period: planned day 43-77.

- *Total TFPI*

Total TFPI was assessed by an exploratory ELISA method that identified TFPI in circulation, both bound to concizumab or in free form. Total TFPI concentrations for individual haemophilia A subjects were reduced in the concizumab-treatment period for the 0.25 mg/kg and the 0.50 mg/kg group. However, in the highest dose group of 0.80 mg/kg, total TFPI concentrations increased slightly during dosing, mainly due to this patient. This subject had an up to 4-fold increase in total TFPI concentration during the concizumab treatment period, but with no associated AEs.

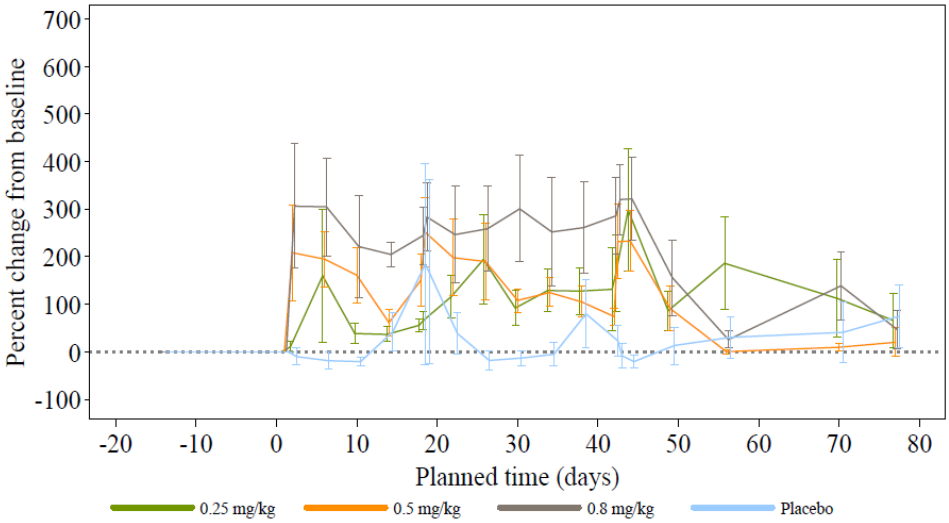
Due to data variation, especially in the 0.80 mg/kg group, the following supportive exploratory endpoints for total TFPI: maximum change from baseline, time to max change from baseline, and value prior to last s.c. dose administration (planned day 42) did not provide for any meaningful interpretation.

- *Thrombin generation test*

Despite large between-subject variability and a possible influence by treatment of breakthrough bleeding episodes with FVIII in these haemophilia A subjects, a concizumab dose-dependent increase in the amount of thrombin generated was observed. The ETP for the 0.80 mg/kg group increased by approximately 3-fold in the concizumab-treatment period compared to baseline levels.

The additional amount of endogenous thrombin generated in the concizumab-treated groups was also characterised by a steeper incline (velocity index) towards a higher thrombin peak, but a similar onset (lag-time) compared to placebo.

Figure 31: Mean profiles of endogenous thrombin potential - safety analysis set.



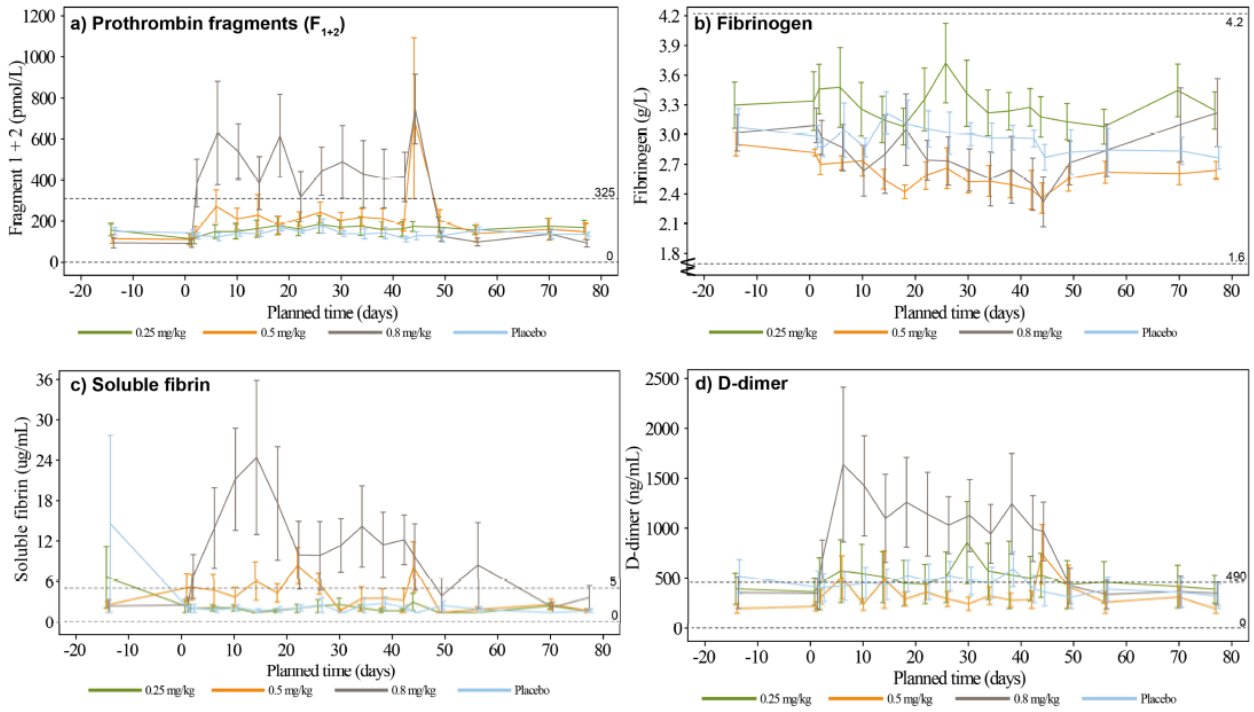
Data points show mean endogenous thrombin potential (ETP; nM□min), error bars represent ±SEM. Blood samples were taken at pre-dose (trough). In addition, two 4h post-dose blood samples were taken: one on planned day 18 and one on planned day 42 (last dosing visit). Treatment period: planned day 1-42. Follow-up period: planned day 43-77.

- *Coagulation-related parameters - F1+2, fibrinogen, soluble fibrin, and D-dimers*

Overall, substantial changes in coagulation parameters were observed mainly for the 0.80 mg/kg group, indicating activation of the coagulation and fibrinolytic pathways.

In the 0.80 mg/kg group, marked changes in mean levels of F1+2 and fibrinogen were also followed by marked increases above the normal reference range for mean levels of soluble fibrin and D-dimers.

Figure 18 Mean profiles F1+2, fibrinogen, soluble fibrin, and D-dimers - safety analysis set.



Bleeding episodes and annualised bleeding rates (over a period of 42 days)

A total of 91 bleeding episodes were recorded during the trial, with the majority (67 [73.6%]) being spontaneous bleeding episodes. The bleeding episodes were generally classified as mild/moderate with the exception of 2 severe bleeding episodes: 1 haemarthrosis in the 0.50 mg/kg dose group, and 1 muscular bleeding in the placebo group. A dose-response in the frequency of bleeding episodes was not observed throughout the three concizumab dose levels.

Post hoc analysis: Annualised bleeding rates during treatment period. The ABRs were analysed using a negative binomial regression model including all available data. 'Treatment' and 'days since dosing' were used as factors and ABR in the follow-up period as covariate. The results in Table 20 show a numerical concizumab dose-response in ABR estimates when applying 'treatment' and 'days since dosing' as factors in the statistical model.

Table 20: Annualised bleeding rates during treatment period.

Effect	ABR estimate*	ABR Lower 95% CL	ABR Upper 95% CL
<= 2d	9.62	5.93	15.63
> 2d	15.44	9.81	24.30
0.25 mg/kg	17.77	10.13	31.19
0.50 mg/kg	12.72	7.21	22.43
0.80 mg/kg	6.90	2.93	16.23
Placebo	14.16	5.99	33.44

Immunogenicity endpoints

During this trial, no ADAs (neutralising or non-neutralising) were detected.

Other safety results

No deaths or other SAEs were reported during this trial. Across all dose groups, 56 AEs were reported in 19 subjects, which were all mild or moderate in severity. A total of 13 AEs in 8 subjects were judged by the investigator to be possibly or probably related to trial product. No apparent relationship to treatment or dose was observed. No AEs led to subject withdrawal. Two MESIs were reported; both were medication errors. No thromboembolic events occurred during the trial.

PD in phase 2 studies

Phase 2 study 4310 (Explorer 4) – clinical proof-of-concept study

Study 4310 results are further discussed in this AR. The PD part is discussed in the current section.

Study design

This study was an interventional multi-national, multicentre, randomised (2:1), open-label, active-controlled, efficacy and safety trial evaluating concizumab 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) administered daily s.c. versus on-demand treatment with eptacog alfa ((rFVIIa) in male haemophilia A and B patients with inhibitors. The trial consisted of a 2-week screening period, a main comparative part of 24 weeks, an extension part of 52-94 weeks treatment period and an 8-week follow up period.

Study dosing

A loading dose of 0.5 mg/kg concizumab was given as the first dose, followed by daily s.c. injections at doses of 0.15 mg/kg (with the possibility to escalate the dose to 0.20 mg/kg and 0.25 mg/kg). Dose escalation criteria were if a patient experienced ⩾3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab, the patient could be escalated to the next dose level.

Study participants

Key inclusion criteria were male haemophilia A or B patients with inhibitors aged ⩾ 18 years currently treated on-demand with a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening, documented history of high-titer inhibitors towards FVIII or FIX.

PD study endpoints

- Plasma free TFPI concentration (Value prior to the last dose administration at 24 weeks)
- Thrombin generation with peak thrombin generation (nM) prior to the last dose administration at 24 weeks, endogenous thrombin potential (nM*min) prior to the last dose administration at 24 weeks and velocity index (nM/min) prior to the last dose administration at 24 weeks.

PD results

- *Free TFPI prior to the last dose administration at 24 weeks*

Concizumab lowered free TFPI from a mean (SD) of 100.7 ng/mL (12.8) at baseline to 26.9 ng/mL (12.2) prior to or at the last dose administration at 24 weeks (see Table 21). As expected, free TFPI level was unchanged after 24 weeks of treatment with eptacog alfa (rFVIIa) on-demand.

Table 21: Free TFPI concentration (ng/mL) prior to last treatment at 24 weeks – summary – full analysis set.

	last dose level Concizumab			Total	
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Concizumab	Eptacog alfa
Number of subjects	15	2	0	17	9
Free TFPI (ng/mL) at baseline					
N	15	2		17	9
Mean (SD)	99.7 (13.2)	108.6 (2.8)		100.7 (12.8)	92.5 (9.1)
Min ; Max	67.9 ; 129.6	106.6 ; 110.6		67.9 ; 129.6	78.9 ; 107.6
Median	97.3	108.6		100.1	94.0
P25 ; P75	95.4 ; 106.0	106.6 ; 110.6		95.8 ; 106.6	86.1 ; 97.8
Free TFPI (ng/mL)at 24 weeks					
N	15	2		17	8
Mean (SD)	29.9 (9.6)	4.8 (0.0)		26.9 (12.2)	94.3 (13.8)
Min ; Max	4.8 ; 42.8	4.8 ; 4.8		4.8 ; 42.8	78.1 ; 122.5
Median	29.7	4.8		28.5	93.4
P25 ; P75	24.0 ; 39.8	4.8 ; 4.8		23.2 ; 33.9	84.2 ; 99.4

- *Thrombin generation potential*

The thrombin generation parameters at baseline and prior to the last dose administration at 24 weeks are shown in Table 22**:**. The mean thrombin generation potential parameters were within the normal reference range for both dose levels after 24 weeks of concizumab treatment.

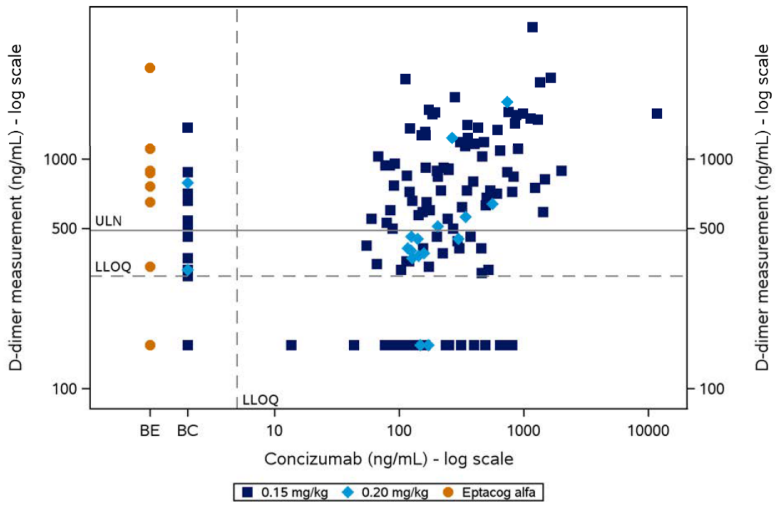
Table 22: Thrombin generation prior to last treatment at 24 weeks – summary – full analysis set.

	last dose level Concizumab			Total	
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Concizumab	Eptacog alfa
Number of subjects	15	2	0	17	9
Peak thrombin generation (nmol/L)					
N	15	2		17	1
Mean (SD)	57.8 (28.9)	119.0 (12.7)		65.0 (34.0)	12.0
Min ; Max	18.0 ; 127.0	110.0 ; 128.0		18.0 ; 128.0	12.0 ; 12.0
Median	46.0	119.0		55.0	12.0
P25 ; P75	38.0 ; 79.0	110.0 ; 128.0		40.0 ; 83.0	12.0 ; 12.0
Endogenous thrombin potential (nM*min)					
N	15	2		17	1
Mean (SD)	901.5 (347.6)	1589.5 (133.6)		982.5 (398.8)	228.0
Min ; Max	273.0 ; 1516.0	1495.0 ; 1684.0		273.0 ; 1684.0	228.0 ; 228.0
Median	827.0	1589.5		843.0	228.0
P25 ; P75	695.0 ; 1236.0	1495.0 ; 1684.0		716.0 ; 1285.0	228.0 ; 228.0
Velocity index (nM/min)					
N	15	2		17	1
Mean (SD)	5.3 (3.3)	14.5 (3.5)		6.4 (4.5)	1.0
Min ; Max	2.0 ; 15.0	12.0 ; 17.0		2.0 ; 17.0	1.0 ; 1.0
Median	4.0	14.5		5.0	1.0
P25 ; P75	3.0 ; 6.0	12.0 ; 17.0		3.0 ; 8.0	1.0 ; 1.0

Coagulation related parameters

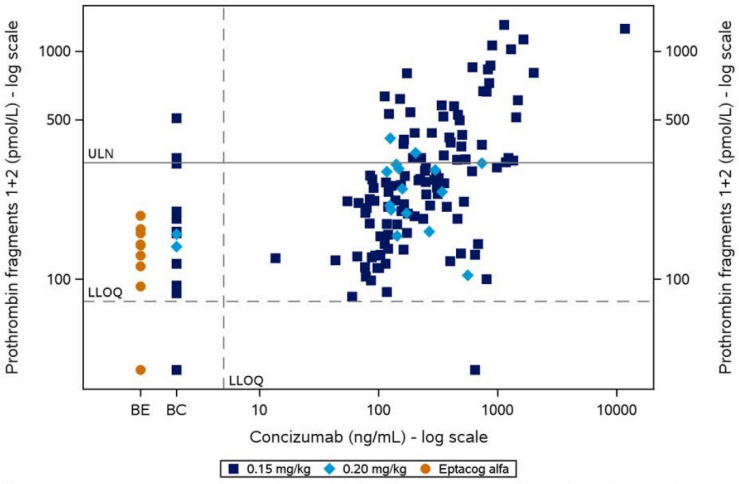
D-dimers seemed to increase with increasing concizumab concentrations (see Figure below). The mean change from baseline to week 24 (visit 9) was 265 ng/ml in the concizumab arm.

Figure 19 D-dimer (ng/mL) vs. concizumab (ng/mL) by last dose level - scatter plot – safety analysis set.



Prothrombin fragments F1+2 was shown to increase with increasing concizumab plasma concentration (see Figure 34**:**). The mean change from baseline to week 24 (visit 9) was 155 pmol/L in the concizumab arm.

Figure 20 Prothrombin fragments 1+2 (pmol/L) vs. concizumab (ng/mL) by last dose level - scatter plot - safety analysis set.



For remaining coagulation parameters (*fibrinogen, PT, INR, APTT and AT*) no clinically significant changes were seen among the different concizumab dose groups and their level remained the same during trial.

Immunogenicity

A total of 3/17 patients had positive anti-concizumab antibody (ADA) results during the main part of the trial. The titres ranged from 1 to 128 (minimum required dilution of 1:100 not factored), which are considered low titers, as the sensitivity of the assay is <1 ng/ml.

The ADAs developed from week 12. Two (2) of the 3 patients had antibodies that were neutralising in vitro. These were detected at one visit with the subsequent visit being negative for neutralising antibodies. No apparent significant changes in bleeding pattern, PK, PD, hypersensitivity reactions and other AEs or laboratory coagulation parameters were observed as a consequence of antibody development.

Phase 2 study 4255 (Explorer 5) – clinical proof-of-concept study (main part 24 weeks)

A summary of the study design, and the PD results are discussed here. An extensive discussion on the methods and further results of the current study 4255 are discussed in detail under section 3.2 'dose-response studies' of this AR.

Study design

This was a multi-national, multicentre, single-arm, uncontrolled, efficacy and safety trial of concizumab 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) administered daily s.c. in patients with severe haemophilia A without inhibitors.

Study dosing

The selected dose regimen was 0.15 mg/kg concizumab once daily with two potential dose-escalation steps, 0.20 mg/kg and 0.25 mg/kg given s.c. once daily, if >3 treatment requiring spontaneous bleeding episodes have occurred within the preceding 12 weeks of treatment with current dose level.

Study participants

The key inclusion criteria were male patients aged 18 years or older with severe haemophilia A (FVIII activity below 1%). For patients being treated on-demand with FVIII replacement therapy, minimum six documented and treated bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening.

PD study endpoints over 24 weeks (21 patients) analysed using descriptive statistics.

- *Plasma free TFPI concentration*
    1. Value prior to the last dose administration at 24 weeks
- *Thrombin generation*
    1. Peak thrombin generation (nM) prior to the last dose administration at 24 weeks
    2. Endogenous thrombin potential (nM*min) prior to the last dose administration at 24 weeks
    3. Velocity index (nM/min) prior to the last dose administration at 24 weeks

PD results

- *Plasma free TFPI prior to the last dose administration at 24 weeks*

The concentration of free TFPI was expected to decrease with increasing dose of concizumab. The baseline mean (SD) free TFPI was 96.3 (11.1) ng/mL which decreased to 30.1 (15.6) ng/mL, 64.4 (35.3) ng/mL and 12.4 (2.2) ng/mL in patients treated with 0.15 mg/kg, 0.20 mg/kg and 0.25 mg/kg concizumab dose, respectively (Table 23).

The relatively high concentration of free TFPI in the 0.20 mg/kg group could be explained by the 2 patients who had very low concizumab exposures; these patients did not show a decrease in free TFPI.

Table 23: Free TFPI concentration (ng/mL) prior to last treatment at 24 weeks - summary - FAS

	Last dose level		
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg
Number of subjects	21	7	8
Free TFPI (ng/mL)			
N	18	4	6
Mean (SD)	30.1 (15.6)	64.4 (35.3)	12.4 (2.2)
Min ; Max	4.8 ; 66.7	29.7 ; 104.0	9.7 ; 14.7
Median	29.4	61.9	12.8
P25 ; P75	18.5 ; 38.5	34.9 ; 93.9	9.8 ; 14.6

- *Thrombin generation potential at 24 weeks*

Thrombin generation potential was assessed by 3 different parameters; endogenous thrombin potential (area under the curve), peak thrombin generation and velocity index. The mean thrombin generation potential parameters were within the normal reference range, for all three dose levels after 24 weeks of concizumab treatment (see Table 24**:**, also for normal ranges).

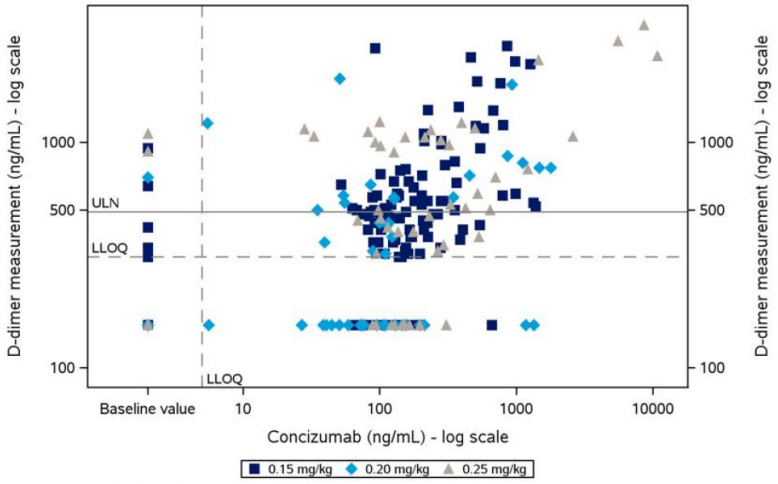
Table 7 Thrombin generation prior to last treatment at 24 weeks - summary -FAS.

	Last dose level			
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Total
Number of subjects	21	7	8	36
Endogenous thrombin potential (nM*min) (Normal range 408-1394 nM*min)				
N	18	4	5	27
Mean (SD)	1229.1 (340.6)	965.3 (362.0)	1176.0 (278.8)	1180.1 (334.2)
Min ; Max	702.0 ; 1932.0	688.0 ; 1488.0	882.0 ; 1564.0	688.0 ; 1932.0
Median	1232.5	842.5	1207.0	1225.0
P25 ; P75	942.0 ; 1380.0	725.0 ; 1205.5	933.0 ; 1294.0	910.0 ; 1380.0
Peak thrombin generation (nmol/L) (Normal range 26-147 nmol/L)				
N	18	4	5	27
Mean (SD)	88.6 (34.5)	67.5 (35.0)	83.4 (10.6)	84.5 (31.5)
Min ; Max	38.0 ; 155.0	39.0 ; 116.0	70.0 ; 95.0	38.0 ; 155.0
Median	86.5	57.5	86.0	80.0
P25 ; P75	56.0 ; 105.0	42.0 ; 93.0	75.0 ; 91.0	56.0 ; 102.0
Velocity index (nM/min) (Normal range 2-36 nM/min)				
N	18	4	5	27
Mean (SD)	9.3 (4.8)	7.0 (5.0)	8.2 (1.6)	8.7 (4.3)
Min ; Max	3.0 ; 18.0	3.0 ; 14.0	7.0 ; 11.0	3.0 ; 18.0
Median	8.0	5.5	8.0	8.0
P25 ; P75	5.0 ; 13.0	3.5 ; 10.5	7.0 ; 8.0	5.0 ; 13.0

- *Coagulation related parameters*

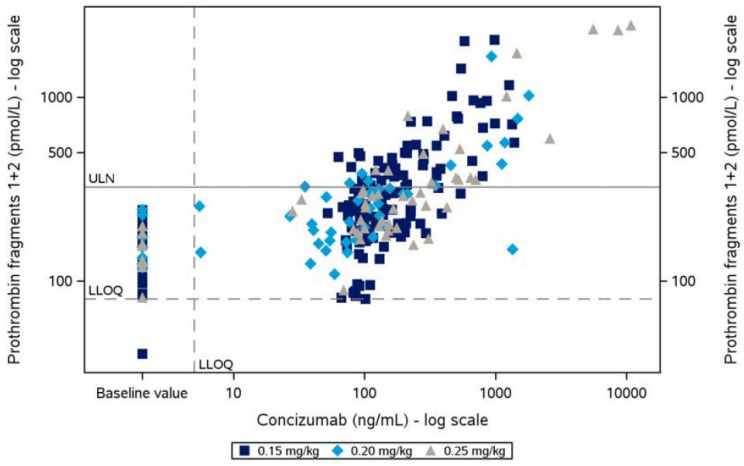
D-dimers seemed to increase with increasing concizumab concentrations (Figure 35**:**). The mean change from baseline to week 24 (visit 9) was 348.1 ng/mL with a standard deviation of 577.7.

Figure 21 D-dimer (ng/mL) vs. concizumab (ng/mL) by last dose level - scatter plot – FAS



F1+2 was shown to increase with increasing concizumab plasma concentration (Figure 36**:**). The mean change from baseline to week 24 (visit 9) was 271 pmol/L with a standard deviation of 475.

Figure 22 Prothrombin fragments 1+2 (pmol/L) vs. concizumab (ng/mL) by last dose level - scatter plot - safety analysis set.



For remaining coagulation parameters (fibrinogen, PT, INR, APTT and AT) no clinically significant changes were seen among the different concizumab dose groups and their level remained the same during trial.

Immunogenicity

A total of 3/36 patients had positive anti-concizumab antibody tests during the main part of the trial. The titres ranged from 1 to 16 (minimum required dilution of 1:100 not factored), which are considered very low titers, as the sensitivity of the assay is <1 ng/ml. The ADAs developed from week 16. One patient had antibodies that were neutralizing in vitro. This was detected at one visit with the subsequent visit being negative for neutralising antibodies. There were no significant changes in bleeding pattern, PK, PD, AEs or in laboratory coagulation parameters observed as a consequence of antibody development.

PD in phase 3 studies

Phase 3 study 4311 – pivotal study in patients with HA and HB with inhibitors

Study design

This was a 4-armed,multicentre, open label trial in patients with haemophilia A or B with inhibitors.

Study dosing

The original dosing regimen was a loading dose of 1.0 mg/kg concizumab s.c. on the first day of treatment, followed by a maintenance dose of 0.25 mg/kg concizumab given as a daily s.c. injection from the second day and onwards. In case of a bleed at a 0.25 mg/kg/day concizumab dose, a single dose escalation to 0.35 mg/kg/day concizumab was permitted during the extension phase of the trial.

The treatment was paused while 5 thromboembolic events reported in 3 patients (2 patients in trial 4307, and 1 patient in trial 4311) were investigated. Risk mitigation measures were implemented, and trial protocols were updated before resuming treatment with concizumab treatment in the trial.

Upon restart of the trial, the new dosing regimen was a loading dose of 1.0 mg/kg concizumab s.c. on the first day of treatment, followed by an initial daily dose of 0.20 mg/kg concizumab. Within the initial 5−8 week maintenance dose setting period on 0.20 mg/kg concizumab, the dose was either increased to 0.25 mg/kg if the concizumab exposure was below 200 ng/mL, decreased to 0.15 mg/kg if the exposure was above 4000

ng/mL or maintained at 0.20 mg/kg if exposure was between 200-4000 ng/mL. The dose setting was based on the concizumab exposure level after 4 weeks of concizumab exposure.

PD study endpoints collected with the new concizumab dosing regimen

- Pre-dose free TFPI at week 24 after restart,
- 24-hour free TFPI profile
- Thrombin generation.

PD endpoints and assessments are analysed and/or presented using the SAS and the OTexIR data set (on-treatment without data on initial regimen).

PD results with the new concizumab dosing regimen (main part – 104 patients 24 weeks)

- *Pre-dose free TFPI concentration at week 24 (and week 56)*

Pre-dose free TFPI plasma levels were decreased from a geometric mean value of ***88.3 ng/mL*** at baseline to ***10.7 ng/mL*** at week 24 for patients on concizumab PPX (arms 2−4), while the geometric mean levels were 76.0 ng/mL at week 24 for patients on no PPX (arm 1). Baseline geometric mean pre-dose free TFPI levels were similar for all arms. After the initial decrease, pre-dose free TFPI levels remained stable over time at all visits after baseline for patients on concizumab PPX (arms 2−4). Pre-dose free TFPI levels remained stable over time at levels similar to baseline for patients on no PPX (arm 1).

Pre-dose free TFPI in plasma was maintained at low levels at week 56 with a geometric mean value of ***12.3 ng/mL*** for patients on concizumab PPX (arms 1–4). Pre-dose free TFPI remained stable over time at levels similar to baseline for patients on no PPX (arm 1).

Figure 23 Pre-dose free tissue factor pathway inhibitor (TFPI) concentration (ng/mL) - geometric mean plot - HAwI+HBwI - OTexIR - safety analysis set.

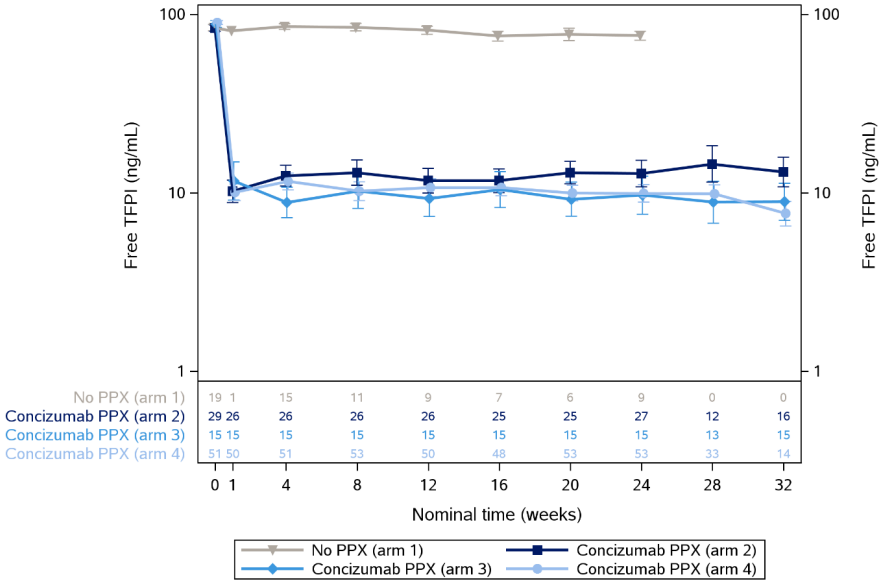


Table 8 Pre-dose free tissue factor pathway inhibitor (TFPI) concentration (ng/mL) - baseline and week 24 - descriptive statistics - HAwI+HBwI - OTexIR – safety analysis set.

	No PPX (arm 1)		Concizumab PPX (arms 2–4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	19	9	97	95
Median	85.2	85.7	89.2	11.0
P25 ; P75	74.8 ; 90.1	69.2 ; 86.2	80.9 ; 99.0	4.8 ; 15.6
Geometric mean (CV)	84.2 (0.2)	76.0 (0.2)	88.3 (0.2)	10.7 (1.0)
Min ; Max	58.1 ; 121.4	55.1 ; 92.4	42.4 ; 150.8	4.8 ; 106.6

CV: geometric coefficient of variation, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, Max: maximum, Min: minimum, OTexIR: On-treatment without data on initial regimen, P25/P75: 25th/75th percentile, PPX: prophylaxis. Baseline is defined as visit 2a for concizumab PPX (arms 2, 3 and 4) and visit 2/2a for no PPX (arm 1). Week numbers are relative to the relevant baseline.

- *24-hour free TFPI profile*

At baseline, the geometric mean free TFPI plasma level was ***87.8 ng/mL*** prior to concizumab administration for patients with a 24-hour profile assessed at the given visit. Free TFPI plasma levels decreased after concizumab administration and were reduced to a geometric mean value of ***10.0 ng/mL after 24 hours***. At week 24, free TFPI remained at similar, low levels with geometric mean values ranging from ***7.7 to 10.7 ng/mL*** throughout the 24 hours for patients with a 24-hour profile assessed at the given visit.

Figure 24 Free tissue factor pathway inhibitor (TFPI) concentration (ng/mL) - 24-hour profile - baseline - geometric mean plot - HAwI+HBwI - OTexIR – safety analysis set.

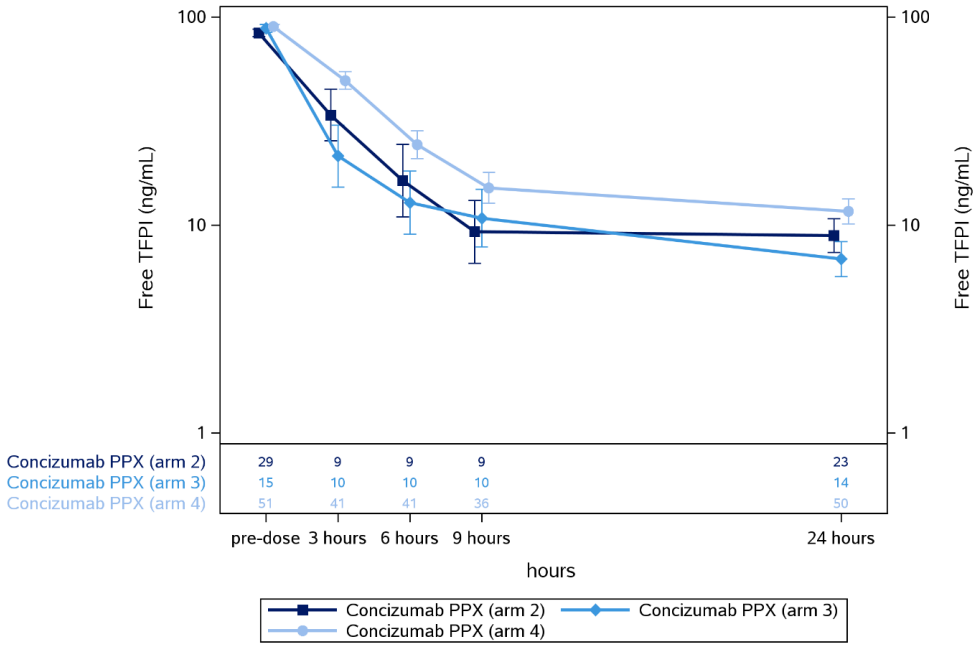
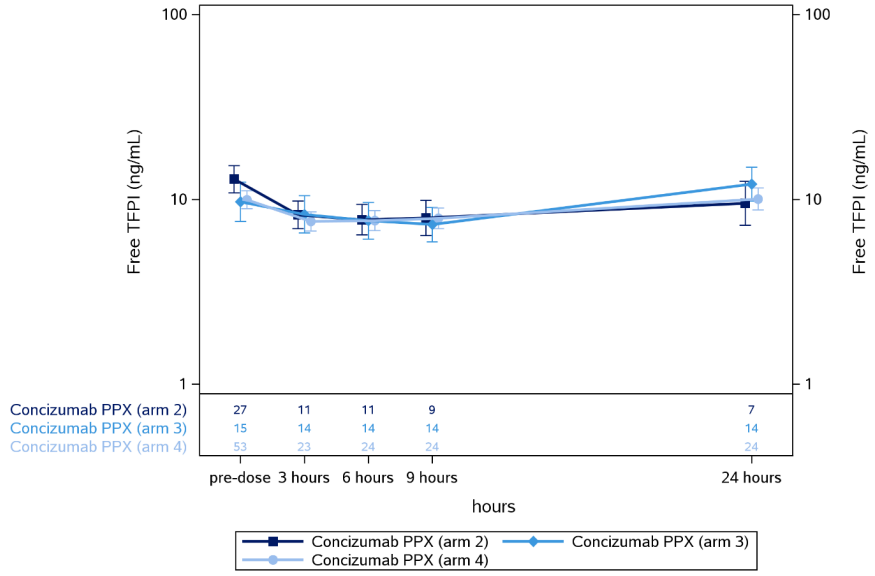


Figure 25 Free tissue factor pathway inhibitor (TFPI) concentration (ng/mL) - 24-hour profile - week 24 - geometric mean plot - HAwI+HBwI - OTexIR – safety analysis set.



- *Thrombin generation - Pre-dose thrombin peak*

Pre-dose thrombin peak levels were increased from a geometric mean value of ***13.5 nmol/L at baseline*** to ***105.4 nmol/L at week 24*** for patients on concizumab PPX (arms 2−4), while the geometric mean levels were 10.1 nmol/L at week 24 for patients on no concizumab PPX (arm 1). Baseline geometric mean pre-dose thrombin peak levels were similar for all arms. After the initial increase, pre-dose thrombin peak levels remained stable over time with low variation and within the range of normal plasma at all visits after baseline for patients on concizumab PPX (arms 2−4). Pre- dose thrombin peak levels remained stable over time at levels similar to baseline for patients on no PPX (arm 1) after week 1.

Figure 40: Pre-dose thrombin peak (nmol/L) - geometric mean plot - HAwI+HBwI - OTexIR - safety analysis set.

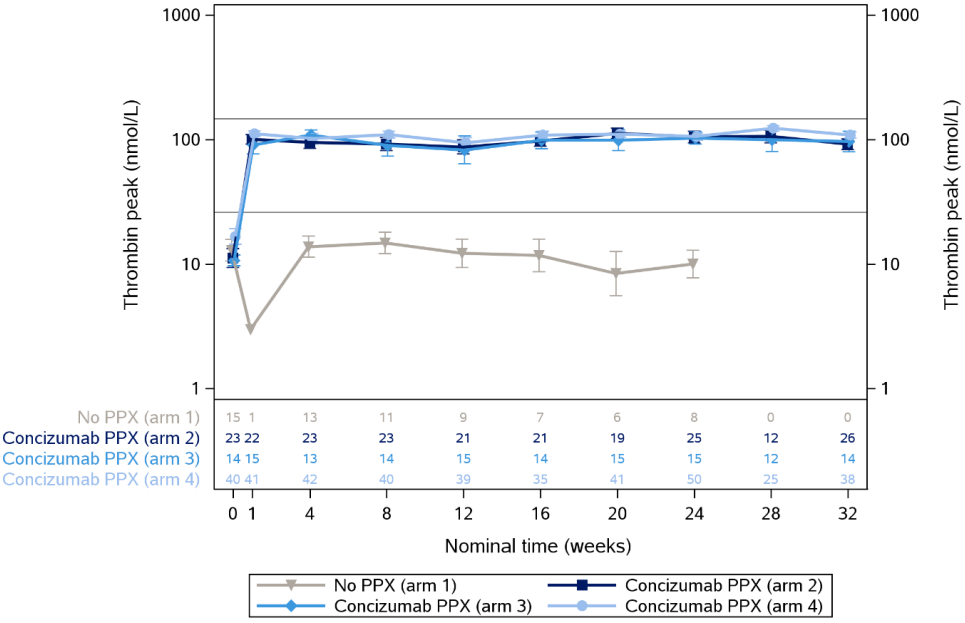


Table 26: Pre-dose thrombin peak (nmol/L) at - baseline and week 24 – descriptive statistics - HAwI+HBwI - OTexIR - safety analysis set.

	No PPX (arm 1)		Concizumab PPX (arms 2–4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	15	8	87	90
Median	14.0	10.0	14.0	117.0
P25 ; P75	8.0 ; 23.0	5.5 ; 18.5	8.0 ; 23.0	95.0 ; 139.0
Geometric mean (CV)	13.0 (0.9)	10.1 (0.8)	13.5 (1.1)	105.4 (0.5)
Min ; Max	2.0 ; 38.0	4.0 ; 29.0	1.0 ; 94.0	14.0 ; 198.0

CV: geometric coefficient of variation, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, Max: maximum, Min: minimum, OTexIR: On-treatment without data on initial regimen, P25/P75: 25th/75th percentile, PPX: prophylaxis. Baseline is defined as visit 2a for concizumab PPX (arms 2, 3 and 4) and visit 2/2a for no PPX (arm 1). Week numbers are relative to the relevant baseline.

- *Thrombin generation - 24-hour thrombin peak profile*

At baseline, the geometric mean thrombin peak level was ***13.7 nmol/L*** prior to concizumab administration for patients with a 24-hour profile assessed at the given visit. Thrombin peak levels increased with small fluctuations after concizumab administration and were increased to a geometric mean value of ***111.2 nmol/L after 24 hours***. At week 24, thrombin peak remained at similar, high levels with geometric mean values ranging from ***105.4 to 115.9 nmol/L*** at the 3 measured timepoints for patients with a 24-hour profile assessed at the given visit.

Figure 41: Thrombin peak (nmol/L) - 24-hour profile - baseline - geometric mean plot - HAwI+HBwI - OTexIR - safety analysis set.

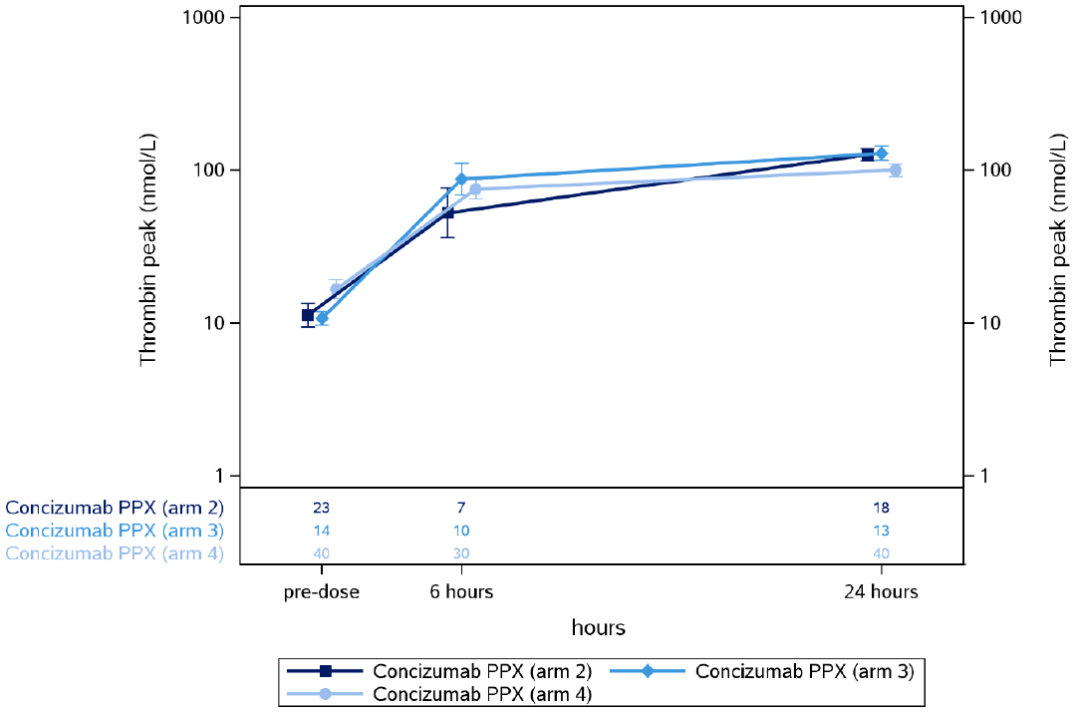
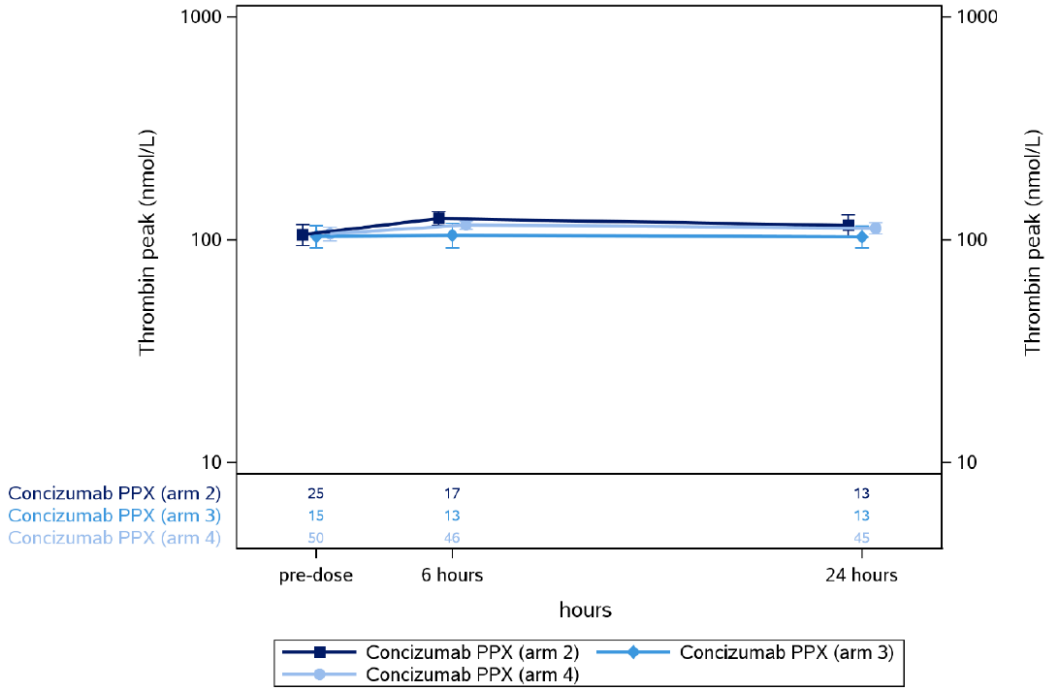


Figure 26 Thrombin peak (nmol/L) - 24-hour profile - week 24 - geometric mean plot - HAwI+HBwI - OTexIR - safety analysis set.



- *Thrombin lag time, velocity index, endogenous thrombin potential, endogenous thrombin potential ratio, time to thrombin peak*

The thrombin generation parameters lag time, velocity index, endogenous thrombin potential (ETP), ETP ratio and time to thrombin peak were measured pre-dose at all visits except for weeks 6 (visit 4a.1) and 30 (visit 9a.3) in patients on concizumab PPX (arms 2−4).

At week 24, the parameters were brought within the range of normal plasma.

Immunogenicity

Of the 127 patients exposed to concizumab in concizumab PPX arms 1−4 before, during and/or after the treatment pause, 33 patients (26%) were ADA-positive at one or more visits after first exposure to concizumab. Seroconversion took place at different timepoints after treatment start/restart. Four (4) patients (3%) were ADA-positive during the treatment pause with low ADA titres of 100−200 (with the MRD factored). Two (2) of these patients had a single positive ADA sample of titre. Eight (8) of the ADA-positive patients (6.3%) were positive for in vitro neutralising ADAs at 1 or more visits during the trial.

Apart from 1 patient transiently reaching titre 25,600 (with the MRD factored, considered a medium level titre), ADA titres ranged from 100−6400 (with the MRD factored). These are considered low titres, since the binding ADA assay sensitivity is < 1 ng/ml.

No apparent impact on bleeding pattern, AEs, PK or PD data was observed for the ADAs.

Table 9: Anti-concizumab-antibodies - overview of ADA-positive patients - summary - HAwI+HBwI safety analysis set.

	Concizumab PPX
	Total
N in SAS	133
N in SAS exposed to concizumab N (%)	127 (100)
Number of ADA-negative patients in total N (%)[1]	94 (74.0)
Number of binding ADA-positive patients N (%)[2]	33 (26.0)
Number of *in vitro* neutralising ADA-positive patients N (%)[3]	8 (6.3)

Abbreviations: HAwI = haemophilia A with inhibitors; HBwI = haemophilia B with inhibitors; N = number of subjects; PPX = prophylaxis; SAS = safety analysis set. 1: Baseline (pre-treatment) samples were either ADA-negative or -positive but all samples after first concizumab dose in trial were negative. 2: Baseline (pre-treatment) samples were either ADA-negative or -positive and at least one sample after first concizumab dose in trial was positive. 3: Subjects positive for in vitro neutralising antibodies at one or more timepoints during the trial. Total includes arm 1 patients on concizumab PPX.

Phase 3 study 4307 – pivotal study in patients with HA and HB without inhibitors

Study design

This was a 4-armed prospective, multicentre, open-label phase 3 clinical trial to compare the efficacy and safety of concizumab PPX administered s.c. vs. no PPX (on demand treatment) in adult and adolescent patients with haemophilia A or B without inhibitors) in reducing the number of bleeding episodes. Also, this trial was paused due to the reported non-fatal thromboembolic events.

Study dosing

Study dosing was similar to study 4311.

Study participants

Key inclusion criteria were male aged ⩾12 years at the time of signing informed consent, congenital severe HA (coagulation factor VIII <1%) or moderate/severe HB (coagulation factor IX ⩽2%)

PD study endpoints

The PD study endpoints were pre-dose thrombin peak, pre-dose free TFPI concentration.

PD results over 24 weeks

- *Free TFPI plasma concentration*

Free TFPI plasma concentration was measured pre-dose at all visits except weeks 6 and 30 after restart. Geometric mean plots for pre-dose free TFPI over time are provided in Figure 43.

Pre-dose free TFPI plasma levels decreased from a geometric mean value of ***84.8 ng/mL at baseline*** to 11.4 ng/mL at week 24 for patients on concizumab PPX (arms 2−4), while the geometric mean levels were ***80.6 ng/mL at week 24*** for patients on no PPX (arm 1). Baseline geometric mean pre-dose free TFPI levels were similar for all arms. After the initial decrease, pre-dose free TFPI plasma levels remained stable over time at all visits after baseline for patients on concizumab PPX (arms 2−4). Pre-dose free TFPI in plasma remained stable over time at levels similar to baseline for patients on no PPX (arm 1).

Figure 27: Pre-dose free TFPI concentration (ng/mL) - geometric mean plot - HA+HB - OTexBR - safety analysis set.

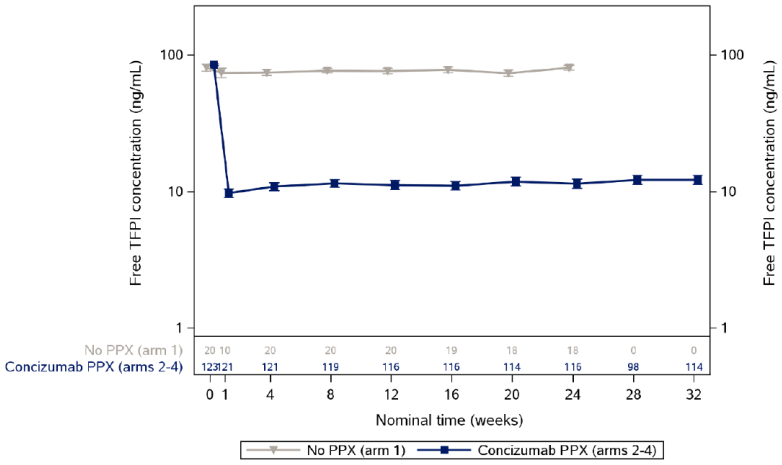


Table 10: Pre-dose free TFPI concentration (ng/mL) - descriptive statistics - HA+HB - OTexBR - safety analysis set.

	No PPX (arm 1)		Concizumab PPX (arms 2−4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	20	18	126	116
Geometric mean (CV[%])	80.6 (26.3)	80.6 (17.7)	84.8 (18.8)	11.4 (100.5)
Min ; Max	39.1 ; 133.0	55.9 ; 103.5	42.5 ; 141.4	4.8 ; 85.5
Median	83.3	79.5	85.4	11.4
P25 ; P75	70.0 ; 94.1	74.2 ; 92.2	74.8 ; 96.6	4.8 ; 19.4

Notes: Baseline is defined as visit 2a. Week numbers are relative to the relevant baseline. Values below the lower limit of quantification (LLoQ = 9.6 ng/mL) are set to ½ LLoQ = 4.8 ng/mL. Abbreviations: CV: geometric coefficient of variation (in percentage); HA: haemophilia A; HB: haemophilia B; LLoQ: lower limit of quantification; Max: maximum; Min: minimum; N: number of patients; OTexBR: on-treatment without data before restart; P25/P75: 25th/75th percentile; PPX: prophylaxis, TFPI: tissue-factor pathway inhibitor.

- *24-hour free TFPI profile*

Blood samples for 24-hour free TPFI profiles were collected pre-dosing and at 3, 6, 9 and 24 hours post-dosing at baseline (visit 2/2a) and at week 24 (visit 9a) for patients on concizumab PPX (arms 2−4). Geometric mean plots for the 24-hour profiles are provided in Figure 44**:**.

At baseline, the geometric mean pre-dose free TFPI plasma level was ***86.2 ng/mL*** for patients with a 24-hour profile assessed at the given visit (arms 2−4). Free TFPI plasma levels decreased after concizumab administration and were reduced to a geometric mean value of ***11.4 ng/mL after 24 hours*** (arms 2−4). At week 24, free TFPI in plasma remained at similar, low levels with geometric mean values ranging from ***8.3 to 12.1 ng/mL*** throughout the 24 hours for patients with a 24-hour profile assessed at the given visit (arms 2−4).

Figure 28 Free TFPI concentration (ng/mL) - 24-hour profile - baseline - geometric mean plot - HA+HB - OTexBR - safety analysis set.

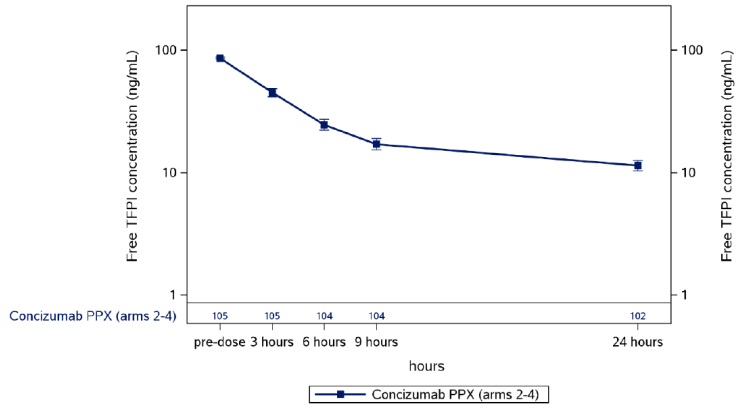
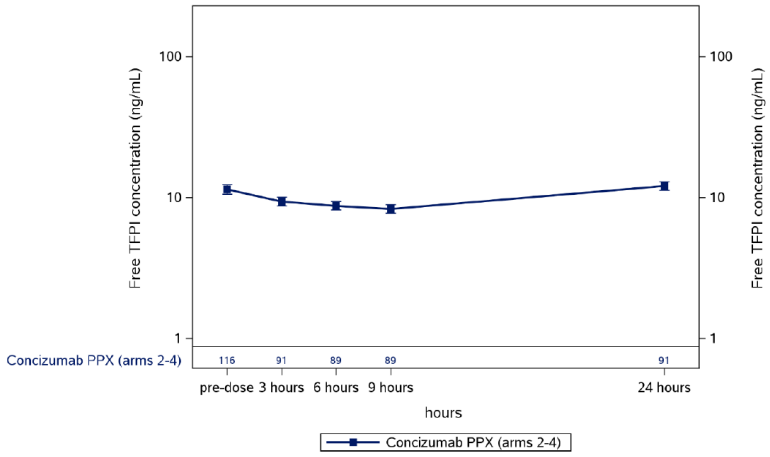


Figure 29 Free TFPI concentration (ng/mL) - 24-hour profile - week 24 - geometric mean plot - HA+HB - OTexBR - safety analysis set.



- *Thrombin generation - Pre-dose thrombin peak*

Geometric mean plots for pre-dose thrombin peak over time are provided in Figure 46**:**. Pre-dose thrombin peak at week 24 after restart was a supportive secondary endpoint. Pre-dose thrombin peak levels increased from a geometric mean value of ***23.2 nmol/L at baseline*** to ***81.1 nmol/L at week 24*** for patients on concizumab PPX (arms 2−4), while the geometric mean levels were 13.2 nmol/L at week 24 for patients on no PPX (arm 1). Baseline geometric mean pre-dose thrombin peak levels were similar for all arms. After the initial increase, pre-dose thrombin peak levels remained stable over time with low variation and within the range of normal plasma at all visits after baseline for patients on concizumab PPX (arms 2−4). Pre-dose thrombin peak remained stable over time at levels similar to baseline for patients on no PPX (arm 1).

Figure 30 Pre-dose thrombin peak (nmol/L) - geometric mean plot - HA+HB - OTexBR - safety analysis set.

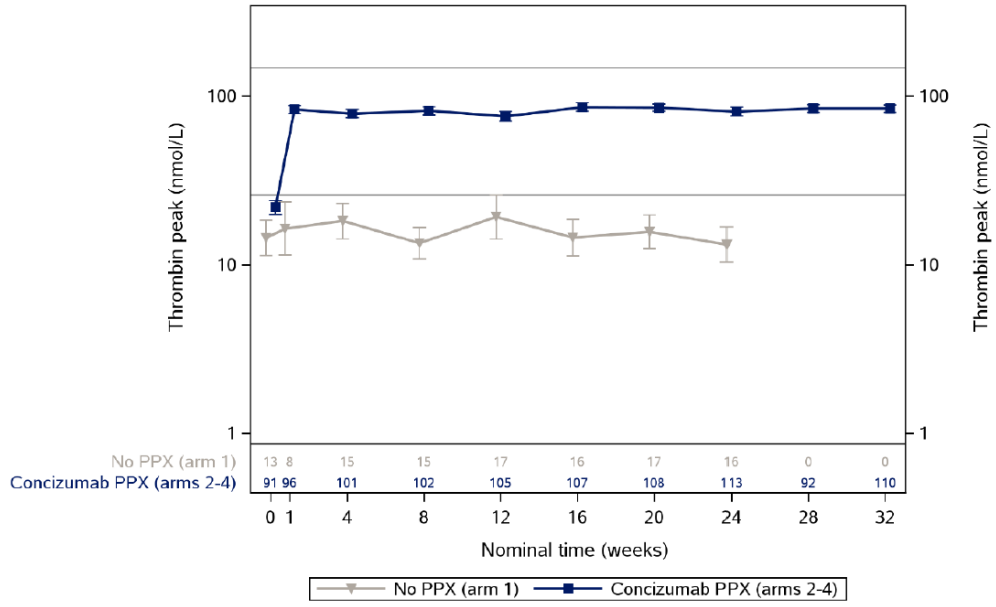


Table 11 Pre-dose thrombin peak (nmol/L) - descriptive statistics - HA+HB - OTexBR - safety analysis set.

	No PPX (arm 1)		Concizumab PPX (arms 2−4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	13	16	100	113
Geometric mean (CV[%])	14.5 (107.3)	13.2 (122.3)	23.2 (110.7)	81.1 (72.1)
Min ; Max	6.0 ; 131.0	2.0 ; 103.0	2.0 ; 173.0	5.0 ; 219.0
Median	11.0	17.0	23.0	96.0
P25 ; P75	9.0 ; 25.0	7.5 ; 21.5	13.0 ; 44.5	71.0 ; 121.0

Notes: Baseline is defined as visit 2a. Week numbers are relative to the relevant baseline. Abbreviations: CV: geometric coefficient of variation (in percentage); HA: haemophilia A; HB: haemophilia B; Max: maximum; Min: minimum; N: number of patients; OTexBR: on-treatment without data before restart; P25/P75: 25th/75th percentile; PPX: prophylaxis.

- *Thrombin generation - 24-hour thrombin peak profile*

Geometric mean plots for the 24-hour profiles are provided in Figure 47**:** and Figure 48**:**.

The geometric mean pre-dose thrombin peak level at baseline was ***21.3 nmol/L*** for patients with a 24-hour profile assessed at the given visit (arms 2−4). Thrombin peak levels increased with small fluctuations after concizumab administration and were increased to a geometric mean value of ***93.3 nmol/L after 24 hours*** (arms 2−4). At week 24, thrombin peak remained at similar levels within the range of normal plasma with geometric mean values ranging from ***81.1 to 93.8 nmol/L*** at the 3 measured timepoints for patients with a 24-hour profile assessed at the given visit (arms 2−4)

Figure 31 Thrombin peak (nmol/L) - 24-hour profile - baseline - geometric mean plot - HA+HB - OTexBR - safety analysis set.

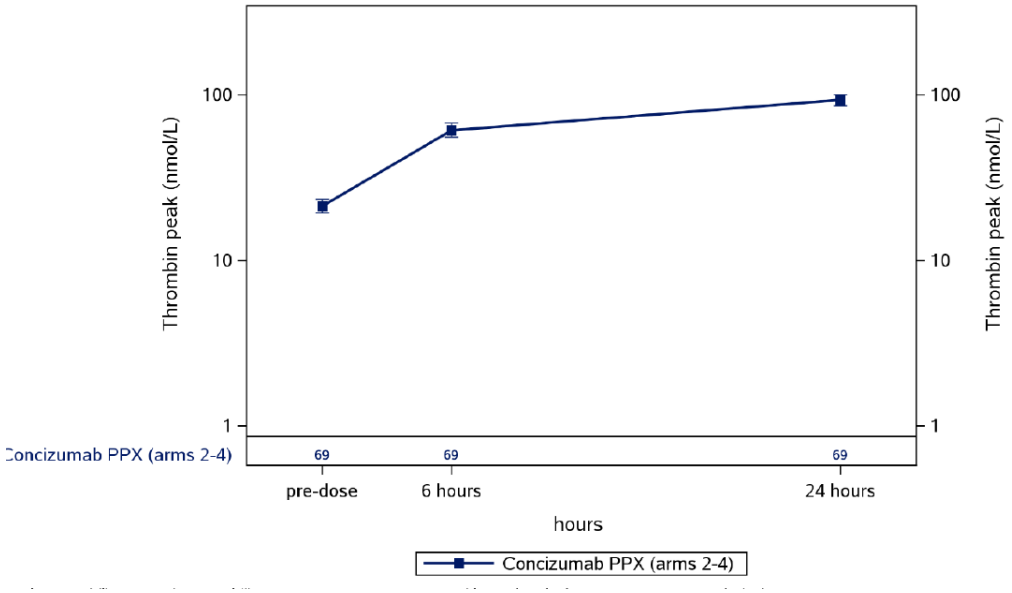
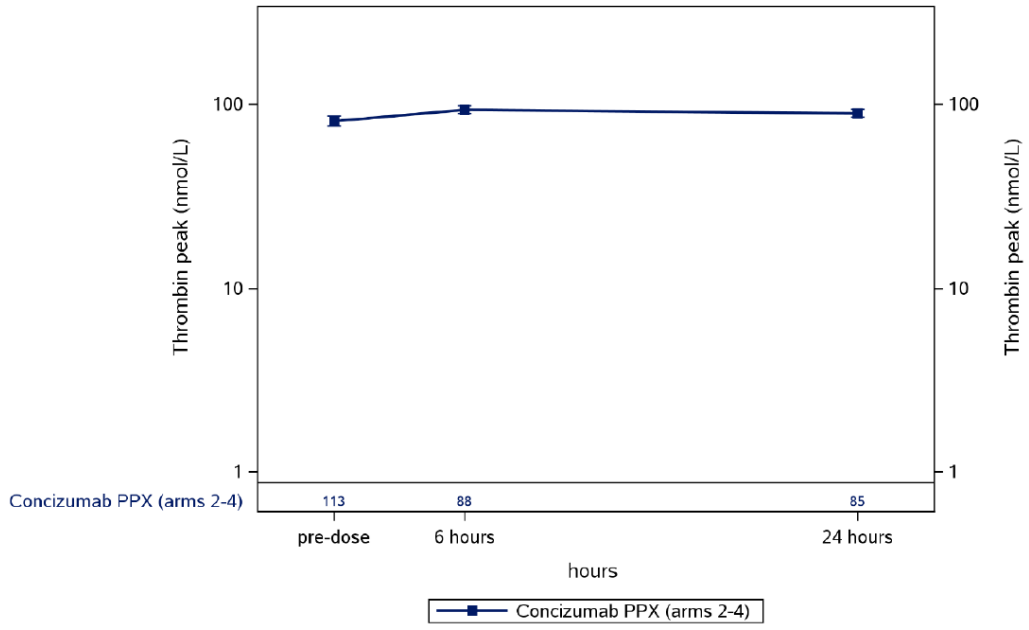
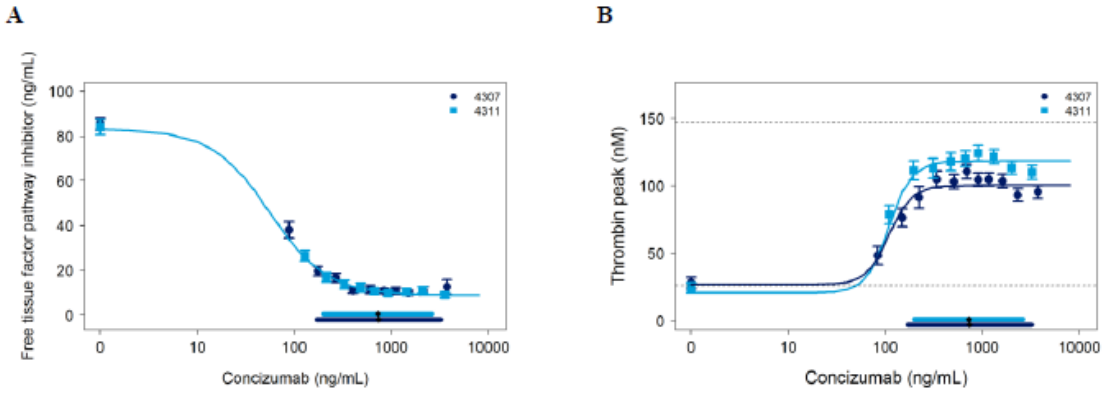


Figure 32 Thrombin peak (nmol/L) - 24-hour profile - week 24 - geometric mean plot - HA+HB - OTexBR - safety analysis set.



The thrombin generation parameters thrombin lag time, velocity index, ETP, ETP ratio and time to thrombin peak were measured pre-dose at all visits except weeks 6 (visit 4a.1) and 30 (visit 9a.3) after restart. At week 24, the thrombin generation parameters were brought within the ranges of normal plasma for patients on concizumab PPX (arms 2−4).

Figure 49: Exposure-response relationships for the free TFPI and thrombin peak as determined by exposure-response models – trials 4311 and 4307



Notes: Points with bars are mean and 95% CI of observed free TFPI (A) or observed thrombin peak levels (B) versus quantiles of observed concizumab concentration. The blue lines are mean model predictions based on population predictions (no significant covariates were found for the exposure-response model of free TFPI). The horizontal light and dark blue line at the bottom represent the median (black diamond) and the 5–95% range of the individual average exposure predicted across the trial duration for trials 4311 and 4307, respectively (only including data after restart), using $C_{avg,trial}$ estimated from the BOV PK model. Free TFPI values (A) below the lower limit of quantification (LLoQ = 9.6 ng/mL) are set to ½ LLoQ = 4.8 ng/mL. The horizontal dashed lines for thrombin peak (B) represent the normal reference range (26–147 nM).

Abbreviations: BOV: between-occasion (within-subject) variability, CI: confidence interval, PK: pharmacokinetics, TFPI: tissue-factor pathway inhibitor.

Antibodies

A summary of ADA-negative and -positive patients is provided in Table 30 below. Of the 151 patients exposed to concizumab PPX (arms 1–4), 18 (11.9%) patients were ADA-positive at 1 or more visits after first exposure to concizumab, with seroconversion occurring at different timepoints after treatment start/restart:

- All ADA titres were considered low titres (range 50−6400), given the binding ADA assay sensitivity (<1 ng/mL)
- 3 (2.0%) patients were only ADA-positive during the treatment pause with very low ADA titres of 100−200 (minimum required dilution factored)
- One (1) of these patients only had a single positive ADA sample of titre 100
- 5 (3.3%) patients were positive for in vitro neutralising ADAs at 1 or more visits during the trial, with no apparent clinical impact

Table 30: Anti-concizumab-antibodies - overview of ADA-positive patients - summary -HA or HB - safety analysis set.

Concizumab PPX	Patients with HA	Patients with HB	Total
N in SAS exposed to concizumab N (%)	87 (100)	64 (100)	151 (100)
Number of binding ADA-positive patients N (%)[a]	12 (13.8)	6 (9.4)	18 (11.9)
Number of *in vitro* neutralising ADA-positive patients N (%)[b]	3 (3.4)	2 (3.1)	5 (3.3)

Notes: aBaseline (pre-treatment) samples were either ADA-negative or -positive and at least one sample after first concizumab dose in trial was positive. bPatients positive for in vitro neutralising antibodies at one or more timepoints during the trial. Total includes arm 1 patients on concizumab PPX. Abbreviations: HA: haemophilia A; HB: haemophilia B; N: number of patients; PPX: prophylaxis; SAS: safety analysis set.

PD in children in compassionate use programme of concizumab

Concizumab has been provided on a compassionate use basis in 14 children and adolescents with HBwI at the time of the cut-off date for the compassionate use report (02 August 2022). Ten (10) patients had received concizumab on an individual patient basis, whereby health authority agreement was obtained to allow patients to receive unapproved medicinal products outside a clinical trial. Three (3) of the 10 patients went on to enrol in the compassionate use programme, in which an additional 4 patients also enrolled. No PK or PD data are available for the 7 patients who only received concizumab on an individual patient basis.

For the 7 patients in the compassionate use programme (CUP), data collected were to include exposure information in terms of concizumab plasma concentrations at each visit, where available. In addition, free TFPI was to be measured at each visit, where possible. No thrombin generation measurements were done. Further, D-dimer and prothrombin fragment 1+2 concentrations were measured.

The 7 patients were all male and were aged between 1 and 17 years when they entered the CUP. They were exposed to concizumab for between 1 and 196 days (~6.5 months) in the CUP at the time of the cut-off date. The total concizumab exposure for the 3 patients who received concizumab on an individual patient basis prior to enrolling in the CUP was approximately 7 years and 4 months (including ~5 months of pause for one of the patients).

- *Free TFPI plasma concentrations*

Available concizumab plasma concentrations and free TFPI plasma concentrations for the 7 patients in the CUP at visits 1–4 (prior to dosing and at weeks 4, 13 and 26) are provided in table below, though measurements were not available for all patients at all visits.

Free TFPI plasma levels were reduced following concizumab PPX in patients with pre- and post-dose free TFPI values, as expected due to the mode of action of concizumab (Table 31).

Table 31: Concizumab and free TFPI plasma concentrations in the compassionate use programme.

Visit number	Week number	Patient number, age, exposure duration and concizumab dose						
		1 day 0.25 mg/kg[a]	196 days 0.25 mg/kg[b]	175 days 0.25 mg/kg[c]	184 days NK	182 days NK	86 days NK	195 days 0.25 mg/kg[d]
		Concizumab plasma concentration (ng/mL)						
1	0	1520	NA	943	<5	<5	NA	<5
2	4	–	634	NA	1430	371	208	37.2
3	13	–	654	858	3110	349	–	230
4	26	–	NA	1220	6810	811	–	799
		Free TFPI plasma concentration (ng/mL)						
1	0	<9.6	NA	14.0	57.0	92.2	NA	NA
2	4	–	NA	15.2	15.8	26.5	NA	46.1
3	13	–	NA	16.9	16.3	21.8	NA	26.4
4	26	–	NA	14.2	12.9	24.4	–	NA

Notes: aPatient previously received concizumab on an individual patient basis. bPatient previously received concizumab on an individual patient basis . cPatient previously received concizumab on an individual patient basis . dFirst dose given in the compassionate use programme was a loading dose of 1.0 mg/kg and the patient had his dose increased to 0.25 mg/kg during the programme. Units in statistical output for concizumab and TFPI plasma concentrations are included as µg/L. Abbreviations: –: patient had not attended visit by the cut-off date; NA: not available; NK: not known (patients received a loading dose of 1.0 mg/kg and the subsequent maintenance dose is unknown); TFPI: tissue-factor pathway inhibitor.

- *D-dimer and prothrombin fragment 1+2 concentrations*

Plasma concentrations of D-dimer and prothrombin fragment 1+2 are included in Table 32 below and were generally above 0.49 µg/mL and 325 pmol/L, respectively, during treatment with concizumab.

Table 32: Plasma concentrations of D-dimer and prothrombin fragment 1+2.

Visit number	Week number	Patient number, age and exposure duration						
		[a]'s 1 day	[b]'s 196 days	[c]'s 175 days	184 days	182 days	86 days	195 days
		D-dimer (mg/L)						
1	0	0.80	0.45	0.85	<0.31	0.41	0.32	<0.31
2	4	–	NA	0.77	1.09	2.19	0.62	0.47
3	13	–	<0.31	0.88	1.16	NA	0.35	0.79
4	26	–	<0.31	0.63	1.39	1.15	–	2.13
		Prothrombin fragment 1+2 (pmol/L)						
1	0	NA	288	1029	110	186	211	228
2	4	–	NA	1191	1138	312	NA	205
3	13	–	721	1485	1159	236	NA	366
4	26	–	197	510	1213	196	–	NA

Notes: aPatient previously received concizumab on an individual patient basis . bPatient previously received concizumab on an individual patient basis . cPatient previously received concizumab on an individual patient basis . Normal range for D-dimer: ⩽0.49 µg/mL. Normal range for prothrombin fragment 1+2: ⩽325 pmol/L. Abbreviations: –: patient had not attended visit by the cut-off date; NA: not available.

2.6.3. Discussion on clinical pharmacology

Pharmacokinetics

The pharmacokinetics of concizumab was described in healthy subjects and male patients with haemophilia A and B with and without inhibitors. The most important covariate for predicting concizumab exposure was body weight, with exposure increasing with increasing body weight, therefore concizumab is dosed per body weight and section 4.2 of the SmPC refers to the need to recalculate the dose (mg) when the body weight changes. Continuous therapeutic monitoring of concizumab exposure is not considered necessary. However there is a possible need to further reassure physicians and patients after the maintenance dose setting and, optional concizumab measurement(s) after 8 weeks is included, which reflects situations in which an additional control of concizumab exposure might be of value in clinical practice.

Section 4.2 of the SmPC on posology also mentions that treatment with rFVIIa should be discontinued at least 12 hours before starting concizumab therapy and treatment with aPCC should be discontinued at least 48 hours before.

The recommended dosing regimen is at 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. Individual maintenance dose setting should be performed at the earliest convenience (after concizumab plasma concentration result is available) and recommended no later than 8 weeks after initiation of treatment. Additional concizumab plasma concentration measurement(s) can be taken after 8 weeks on the same maintenance dose according to the patient's medical condition. For example, this should be considered if a patient experiences an increased bleeding frequency, a large change in body weight, has missed doses before maintenance dose setting, or acquires a comorbidity, which can lead to an increase in the overall thromboembolic risk.

Since concizumab is dosed per body weight (mg/kg), it is important to recalculate the dose (mg) when the body weight changes.

Primary and secondary pharmacology

PD in phase 1 studies

Single dose studies

The first-in-human, **single-dose**, dose-escalation **phase 1 study 3813 (Explorer 1)** tested doses of concizumab 0.5−250 µg/kg i.v. and 50-1000 µg/kg s.c. in **healthy subjects** and 250-9000 µg/kg i.v. and 1000-3000 µg/kg s.c. in severe **haemophilia A or B subjects**). Based on PK/PD modelling of nonclinical data, an i.v. dose of 250 µg/kg and an s.c. dose of 1000 µg/kg were considered the maximum dose to be administered to healthy subjects to avoid or limit target saturation. The prevention of TFPI-mediated FXa-inhibition by concizumab is expected to result in enhanced FXa generation followed by thrombin generation. FXa generates thrombin from prothrombin by cleaving off prothrombin fragments 1 and 2 (F1+2). Thus, F1+2 serves as a marker of thrombin generation. Thrombin catalyses the conversion of fibrinogen into fibrin. D-dimers are formed because of plasmin degradation of the cross-linked fibrin. In the process of fibrinolysis (break down of coagulation), plasmin is the central molecule in the process of fibrinolysis, where the tissue plasminogen activator (tPA) converts plasminogen into plasmin. Plasmin then degrades fibrin or fibrinogen into fibrin- or fibrinogen degradation products (FDPs). The rationale for the selection of TFPI (as residual functionality and as free compound) was considered an acceptable PD endpoint, as TFPI is the main PD marker of the MoA of concizumab, which is a monoclonal humanized IgG4 anti-tissue factor pathway inhibitor (anti-TFPI) antibody.

Residual TFPI functionality

Healthy subjects: With i.v. dosing, the mean residual TFPI functionality levels decreased after i.v. dosing at the highest dose (250 µg/kg) and were back to baseline levels after 24 hours. With s.c. dosing, residual TFPI functionality levels decreased at the highest dose (1000 µg/kg). The decrease was generally seen after 8 hours and levels increased gradually again after 48 hours.

Haemophilia subjects: With i.v. dosing, mean residual TFPI functionality also decreased. The time until the levels returned to baseline values varied. With s.c. dosing, residual TFPI functionality decreased in a dose-dependent manner at both doses administered (1000 and 3000 µg/kg). The decrease was generally seen after 4 hours and the levels gradually increased again after 6-7 days.

Total free TFPI plasma concentrations

Healthy subjects Following i.v. administration, total free TFPI plasma concentrations decreased in a dose-dependent manner and was most pronounced at i.v. doses ⩾ 50 µg/kg. Suppression of TFPI levels was dose-related and lasted for a mean period of 1−24 hours. Following s.c. administration, total free TFPI plasma concentrations decreased in a dose-dependent manner and was most pronounced at the highest dose (1000 µg/kg). The suppression of TFPI levels was dose-dependent with a mean period of 4 days at 1000 µg/kg.

Haemophilia subjects: Following i.v. administration, total free TFPI plasma concentrations were decreased at all i.v. dose levels (⩾250 µg/kg) in a clear dose-related manner. The suppression of TFPI levels lasted up to 14 days with highest dose of 9000 µg/kg, where after the levels gradually increased. Following s.c. administration, total free TFPI plasma concentrations were substantially decreased at both dose levels (1000 and 3000 µg/kg) in a dose-related manner. The suppression of TFPI levels varied from a mean period of 4

days at 1000 µg/kg up to 10 days at the highest s.c. dose of 3000 µg/kg, and thereafter increased gradually back to baseline values.

Coagulation-related safety parameters

- *Coagulation-related parameter - D-dimers*

Healthy subjects Increased levels of D-dimers were seen in healthy subjects following i.v. and s.c. administration at the highest dose s.c. (1000 µg/kg). D-dimer levels peaked at 48 hours post-dosing and returned to levels within normal reference range at Day 4−5 post-dosing, except for 1 subject, who had elevated levels throughout the whole trial period.

Haemophilia subjects Increased levels of D-dimers were seen following i.v. and s.c. administration. The D-dimer levels were slightly increased at both s.c. dose levels (1000 and 3000 µg/kg) in a dose-related manner. The mean D-dimer levels peaked at Day 3−4 post-dosing.

- *Coagulation-related parameter - Prothrombin fragment 1 and 2 (F1+2)*

Healthy subjects: An increase in prothrombin F1+2 levels was seen at the highest dose i.v. (250 µg/kg), and was seen at the highest dose s.c. (1000 µg/kg). The mean prothrombin F1+2 levels peaked at 48 hours postdosing and returned to levels within normal reference range at Day 4 post-dosing. With the lower doses, a few measurements were seen outside the reference range, but with no clear pattern.

Haemophilia subjects: The prothrombin F1+2 levels were increased at all i.v. dose levels ($\geqslant$ 250 µg/kg) in a dose-related manner. Following s.c., the prothrombin F1+2 levels were dose-dependently increased at both s.c. dose levels (1000 and 3000 µg/kg). The mean prothrombin F1+2 levels peaked at 48 hours postdosing and returned to levels within normal reference range at Day 14 post-dosing.

- *Coagulation-related parameter - Fibrinogen*

Healthy subjects: The reference range at the laboratory analysing samples from healthy subjects was 1.5−4 g/L. There was a tendency to transiently decreased levels in some healthy subjects at the highest dose levels.

Haemophilia subjects After i.v. administration, many of the fibrinogen values in haemophilia subjects were below normal reference range, also at baseline. However, the central laboratory, which tested fibrinogen samples from haemophilia subjects had an unusually high normal reference range (2.38−4.98 g/L). There was a tendency to transiently decreased levels in haemophilia subjects at the highest dose levels. The possible decrease was largely confounded by high intra- and inter-subject variation and firm conclusions could therefore not be made. The reason for this potential decreases was unknown. Also, for s.c. administration a possible, although weaker tendency to transiently reduced fibrinogen levels was noted in some haemophilia subjects at the highest dose levels.

Dose-dependent decreases in residual TFPI functionality and free TFPI in plasma were observed in healthy volunteers and patients after i.v. and s.c. administration. Especially in haemophilia patients free TFPI levels substantially decreased in a dose-dependently manner with at both doses administered (1 and 3 mg/kg), with no relevant differences in TFPI baseline levels between the study populations. The procoagulant effect of concizumab was demonstrated with dose-dependent increases in the coagulation-related parameters tested for safety (D-dimers and prothrombin F1+2) with peaks above the normal ranges. No anti-concizumab antibodies were detected during the trial, which is reassuring. No other relevant safety concerns have been identified, except one case of thrombophlebitis, which resolved spontaneously.

Regarding the PD parameter diluted PT (dPT) clot time, the first results of this parameter in the first-in-human trial were not interpretable, as a paradoxical prolongation of dPT upon in vitro addition of concizumab to one of the four baseline plasma samples was noted and the observation that the response in dPT did not correlate with the levels of concizumab. Therefore, it was decided to discontinue the assay in the clinical evaluation of concizumab.

The second single-dose **phase 1 study 3981 (Explorer 2)** used s.c. doses at two different dose levels 0.25 mg/kg or 1 mg/kg (250 µg/kg or 1000 µg/kg), in **healthy Japanese subjects**. PD parameters are similar to explorer 1.

As expected, a clear PD response was observed in residual TFPI functionality with 1 mg/kg. Further, a dose-dependent decrease after a single dose of 0.25 and 1 mg/kg in total free TFPI was shown, while coagulation-related parameters generally remained within the normal ranges with no relevant safety concerns.

Multiple dose studies

The **multiple-dose phase 1 study 3986 (Explorer 2)** investigated 0.25 mg/kg concizumab s.c every other day in **healthy subjects**. The trial was terminated prematurely, due to non-clinical safety findings. The two highest dose tiers (0.50 and 1 mg/kg) were never administered.
From the limited PD data collected, the residual TFPI functionality levels as well as total free TFPI in plasma decreased in all four healthy male subjects. Further, although high between-subject variability was observed, a PD response of the thrombin generation (TG) parameters was also demonstrated.

The **phase 1 multiple-dose study 4159 (Explorer 3)** investigated 0.25, 0.50 and 0.80 mg/kg concizumab s.c. every fourth day in **haemophilia A subjects**. This trial was also terminated earlier, as decided by the safety committee, since marked changes in coagulation-related parameters were observed outside of normal range with a dose of 0.80 mg/kg. A total of 24 patients were randomised and completed the trial.

A clear PD response was noted, as the concentration of free TFPI in plasma was decreased dose-dependently. This was supported by a decrease in residual TFPI functionality with a maximum effect with 0.5 mg/kg every fourth day. Further, a substantial change in coagulation parameters F1+2, fibrinogen, soluble fibrin, and D-dimers were observed mainly for the 0.80 mg/kg group, with some above the normal range, although no relevant AEs nor an increase in the number of bleeding episodes were observed. No ADAs were detected during this trial. No clinical consequences or serious adverse events were seen.

PD data in phase 2 studies

A summary of the PD results of phase 2 studies 4255 and 4310 are discussed here. An extensive discussion on the methods and further results are discussed under section 3.2 'dose-response studies' of this AR.

The first **phase 2 clinical proof-of-concept study 4310 (Explorer 4)** was an open-label, controlled trial in which a loading dose of 0.5 mg/kg concizumab was given as first dose, followed by daily s.c. injections of 0.15 mg/kg (with the possibility to escalate the dose to 0.20 mg/kg and 0.25 mg/kg if a patient experienced $\geqslant$3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab) in **male haemophilia A and B patients with inhibitors** for 24 weeks. Patients were randomised 2:1 to concizumab prophylaxis or on-demand treatment with eptacog alfa (rFVIIa).

In the main part of the study (24 weeks), 15 out of the 17 patients were randomised to concizumab stayed on 0.15 mg/kg, 2 patients escalated to 0.20 mg/kg and none escalated to 0.25 mg/kg.

Free TFPI levels decreased with increasing concizumab concentrations. As expected, no change to free TFPI was observed with eptacog alfa (rFVIIa) on-demand. The endogenous thrombin generation potential remained within the normal reference range but were higher in the concizumab groups in comparison to the eptacog alfa group. Further, increased levels of D-dimers and F1+2 were seen with increasing concizumab dose levels. For remaining coagulation parameters (fibrinogen, PT, INR, APTT and AT) no clinically significant changes were seen. Three of 17 patients had anti-concizumab ADAs and two of these developed treatment-induced ADA post-baseline, but this was considered a transient response as all subsequent results were negative for these patients and no clinical relevant effect has been observed in these patients.

The second **phase 2 clinical proof-of-concept study 4255 (Explorer 5)** was a single-arm study evaluating the same concizumab dose regimen for 24 weeks as in study 4310 in **patients with severe haemophilia A without inhibitors**. In the main part of the study (24 week of treatment) 21 patients stayed on 0.15 mg/kg, 7 patients on 0.20 mg/kg and 8 patients on 0.25 mg/kg concizumab.

Similar to results PD results obtained in phase 2 study 4310, the level of free TFPI was decreased with the use of concizumab for all three dose levels after 24 weeks of concizumab treatment. No dose-dependent manner has been observed. The thrombin generation parameters were brought in normal range and remained within the normal reference range, for all three dose levels after 24 weeks of concizumab treatment. As for coagulation related parameters assessed, elevated D-dimers and prothrombin fragments F1+2 were seen with higher concizumab dose. For remaining coagulation parameters (fibrinogen, PT, INR, APTT and AT) no clinically significant changes were seen. Three out of the 36 patients had ADAs (8%). One patient developed treatment-induced ADA post-baseline, but this was considered a transient response, as all subsequent results were negative for this patient. No clinically relevant effect of these ADAs on treatment has been observed in these patients.

PD in phase 3 studies

Also, in the pivotal phase 3 studies 4311 in HAwI and HBwI and study 4307 in HA and HB patients without inhibitors, PD results were obtained and are discussed here. An extensive discussion on the methods and further results are discussed under section 3.3 'main studies' of this AR.

Phase 3 pivotal study 4311 was a prospective, multicentre, open-label trial with 4 arms in **patients with haemophilia A or B with inhibitors**. Patients were randomised to concizumab PPX (arm 2) or no PPX (arm 1) or assigned to non-randomised concizumab treatment (arms 3 or 4), based on their treatment regimen before entering the trial. The treatment was temporarily paused, since 5 thromboembolic events were reported in 3 patients (2 patients in trial 4307, and 1 patient in trial 4311). Upon restart of the trial, the new dosing regimen was similar to the SmPC dose recommendations: a loading dose of 1 mg/kg and an initial daily dose of 0.20 mg/kg. Within an initial 5−8-week dose adjustment period on 0.20 mg/kg concizumab, the patients can be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab; this will be based on the concizumab exposure level at the week 4 visit.

The PD results of the study with the new dose regimen:

- Free TFPI concentration plasma levels were reduced immediately (within 24 hours) after the first dose of concizumab and remained stable for patients on concizumab PPX at all visits after baseline. A decrease from a geometric mean value of 88.3 ng/mL at baseline to 10.7 ng/mL was seen at week 24 for patients on concizumab PPX (arms 2−4), while the geometric mean levels remained similarly high with 76.0 ng/mL at week 24 for patients on no PPX (arm 1), as compared with levels at baseline.

- Thrombin peak levels increased into the range of normal plasma values and remained stable for patients on concizumab PPX, while no effect was seen on patients not on concizumab.
- Other thrombin generation parameters, such as lag time, velocity index, endogenous thrombin potential (ETP), ETP ratio and time to thrombin peak were also brought within the range of normal plasma with the use of concizumab. No clinically relevant differences were observed between arms 2, 3 and 4.
- In total, during and/or after the treatment pause 33/127 (26%) patients tested positive at one or more visits for anti-concizumab antibodies, of whom 8 (6.3%) who developed treatment-induced ADAs. No apparent impact on bleeding pattern, AEs, PK or PD data was observed for the ADAs. **Pivotal phase 3 study 4307** was a multicentre, 4-armed open-label clinical trial in **adult and adolescent patients with haemophilia A or B without inhibitors** of similar design as phase 3 study 4311 in HAwI and HBwI patients in which the same dose-regimen was used. Also, this trial was paused due to the reported non-fatal thromboembolic events. PD data showed:
- The geometric mean pre-dose free TFPI levels decreased from 84.8 ng/mL at baseline to 11.4 ng/mL at week 24 for HA and HB patients on concizumab PPX (arms 2−4). After the initial decrease, which started after the first administration, the levels remained stable over time to week 24, while there was no effect seen in arm 1 (patients not on concizumab).
- Further, the geometric mean pre-dose thrombin peak levels increased from 23.2 nmol/L at baseline to 81.1 nmol/L (which is considered within the range of normal plasma) at week 24 for HA and HB patients on concizumab PPX (arms 2−4). After the initial increase, the levels remained stable over time. Patients not on concizumab remained with thrombin peak levels below the lower limit of normal.
- Also, the other thrombin generation parameters, such as thrombin lag time, velocity index, ETP, ETP ratio and time to thrombin peak were brought within the ranges of normal plasma for patients on concizumab PPX (arms 2−4) at week 24.
- 18/151 (11.9%) patients were ADA-positive at 1 or more visits after first exposure to concizumab. Of these patients, 5 (3.3%) were positive for in vitro neutralising ADAs. There was no apparent clinical impact of ADAs on bleeding patterns, AEs or PK/PD. Of note, the key PD parameters were free TFPI (i.e. not bound to concizumab) and thrombin generation (thrombin peak, endogenous thrombin potential, endogenous thrombin potential ratio, time to thrombin peak, lag time and velocity index). Key PD endpoints are considered adequate and were agreed in EMA Scientific Advice. Yet, determination of free TFPI has limitations as plasma TFPI accounts for only approximately 7% of the total TFPI, which is mainly present on endothelial cells (~92%) and to some extent on platelets (~1%). Therefore, measuring free plasma TFPI provides only a snapshot of the true effect of concizumab on TFPI levels and coagulation. In addition, TFPI may also be bound to coagulation factor FVIIa via the Kunitz-type inhibitory domain 1 (K1) [Wood JP, et al. Biology of tissue factor pathway inhibitor. Blood 2014; 123 (19): 2934–2943], which is still available for FVIIa binding after concizumab binding specifically to K2. Following concizumab treatment, mean free TFPI values were close to the LLOQ and a notable number of patients had free TFPI plasma measurements below LLOQ. Therefore, any changes over time in this low range may not be detectable for individual patients and need to be interpreted with caution. Considering the limitations of free TFPI as PD marker, the importance of assessing a more functional parameter, i.e. thrombin generation, is highlighted. Although mean thrombin peak levels were within the range of normal plasma, levels of individual patients may be above the upper limit of normal. As stated in SmPC section 5.1, possible transiently elevated thrombin peak levels were reported in 37.6% of patients with no associated safety concerns.

PD data in children (CUP)

From the limited data available in the 7 children in the compassionate use programme (CUP), two patients (aged 13 and 17 years old) were exposed for the first time to concizumab and had pre- and post-dose PD data available. The free TFPI levels were reduced at week 4 to levels similarly seen in previous studies including adult and other adolescent patients and remained stable over time. Also, increased plasma concentrations of D-dimer and prothrombin fragment 1+2 were observed from week 4, which remained stable? above the normal reference range, as was also seen with the higher concizumab dose regimens and plasma concentration levels. In one patient (6 years of age), who had already received concizumab for 1 year and 3 months on an individual patient basis, the pre-dose free TFPI was already low and when entering the CUP, the TFPI and other PD parameters showed a similar pattern over time as noted in the 2 newly treated patients.

2.6.4. Conclusions on clinical pharmacology

In **healthy male subjects** (phase 1 studies 3813, 3981, 3986), higher doses of concizumab resulted in a clear PD response shown by a dose-dependent decrease of residual TFPI functionality and free TFPI levels in plasma, Free TPFI plasma levels over time exhibited an inverse correlation to concizumab plasma levels, as increasing concizumab dose levels resulted in decreasing levels of free TFPI and increased duration of free TFPI suppression.

The coagulation-related parameters D-dimers, prothrombin F1+2, PT and aPTT were used to give additional information about the procoagulant effect of concizumab. The procoagulant effect of the compound was shown by increased levels of D-dimers and prothrombin F1+2. The increase in both parameters was dose-dependent and was generally seen at i.v. doses $\geqslant$ 250 µg/kg and s.c. doses $\geqslant$ 1000 µg/kg, with healthy subjects responding more to the same dose level (mainly for D-dimers) than haemophilia patients. This finding was expected and was considered to reflect the pharmacological action of blocking TFPI in healthy subjects with a normal coagulation system. The dose-dependent increases in the coagulation-related parameters remained generally within the normal reference ranges.

In **haemophilia A or B subjects without inhibitors**, similar findings were observed for residual TFPI functionality and free TFPI levels in phase 1 studies (3813, 3986 and 4159). However, a substantial change above the normal range in coagulation parameters were observed mainly for the 0.80 mg/kg group (4159). As mentioned above, the procoagulant effect of the compound was shown by increased levels of D-dimers and prothrombin F1+2, but less pronounced as seen in healthy volunteers. In the two phase 2 clinical proof-of-concept studies (4255 and 4310) in which a loading dose of 0.5 mg/kg concizumab was given as first dose, followed by daily s.c. injections of 0.15 mg/kg (with the possibility to escalate the dose to 0.20 mg/kg and 0.25 mg/kg if a patient experienced $\geqslant$3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab) also an decrease in free TFPI was observed. The thrombin generation potential of concizumab (tested by endogenous thrombin potential (area under the curve), peak thrombin generation and velocity index) were brought within the normal range and remained within the normal reference range for both dose levels after 24 weeks of concizumab treatment. As to coagulation related parameters tested as safety parameter, D-dimers. F1+2 were shown to increase with increasing concizumab plasma concentration. For remaining coagulation parameters (fibrinogen, PT, INR, APTT and AT) no clinically significant changes were seen. PD results of the pivotal phase 3 study (4307) with a dose regimen in line with the SmPC recommendations showed the same results and remained stable over time to week 24.

In **haemophilia A or B subjects with inhibitors** (4311), who were dosed following the SmPC (a loading dose of 1 mg/kg and an initial daily dose of 0.20 mg/kg was implemented with the option to increase or decrease the dose to 0.25 mg/kg or 0.15 mg/kg concizumab), comparable PD data were shown with reduced free TFPI concentration levels and thrombin generation parameters brought within the normal range over a period of 24 weeks. Section 5.1 of the SmPC includes information on possible transiently elevated thrombin peak levels.

From the limited data available in **children** (CUP), free TFPI levels (in 2 patients aged 13 and 17 years with HBwI) were reduced to levels similarly seen in adults and other adolescent patients. No data were available in children <12 years of age. Further, marked increases above normal for D-dimer and prothrombin fragment 1+2 levels were seen, comparable with the higher concizumab dose regimens and plasma levels in adults/adolescents.

Clinical pharmacology parameters and pharmacodynamics markers have been adequately studied and relevant information has been reflected in SmPC sections 4.2, 4.4 and 5.2.

2.6.5. Clinical efficacy

Clinical development program

An overview of the trials contributing to the efficacy evaluation is provided in the table below.

Table 33: Overview of clinical trials contributing to the efficacy evaluation of concizumab

Trial ID	Trial description and duration	Population (age)	Concizumab dose and route of administration	Status
Phase 3				
4311	*Efficacy, PK, PD and safety* Randomised, OL, controlled, multiple-dose 160 weeks	N = 133 HAwI: 80 HBwI: 53 (≥12 years)	Day 1: Single s.c. loading dose of 1 mg/kg concizumab. Day 2 and onwards: Initial daily s.c. dose of 0.20 mg/kg. Individual maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure level after 4 weeks of treatment[a]	Primary analysis cut-off[b] and 56-week cut-off[c] reached. Extension part ongoing
4307	*Efficacy, PK, PD and safety* Randomised, OL, controlled, multiple-dose 160 weeks	N = 156[d] HA: 90 HB: 66 (≥12 years)	Day 1: Single s.c. loading dose of 1 mg/kg concizumab. Day 2 and onwards: Initial daily s.c. dose of 0.20 mg/k g. Individual maintenance dose set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment[a]	Confirmatory analyses cut-off[e] reached. Extension part ongoing
Phase 2				
4310	*Efficacy and safety* Randomised, OL, controlled, multiple-dose ≥76 weeks	N = 26 HAwI: 16 HBwI: 10 (≥18 years)	Day 1: Single s.c. loading dose of 0.5 mg/kg concizumab. Day 2 and onwards: Daily s.c. dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks.	Completed

Trial ID	Trial description and duration	Population (age)	Concizumab dose and route of administration	Status
4255	*Efficacy and safety* OL, multiple-dose ≥76 weeks	N = 36 HA (≥18 years)	Daily s.c. dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks.	Completed
Non Interventional Study				
4322	*Background population* Non-interventional; patients treated according to routine clinical practice[f] ≤115 weeks	N = 231 HA: 75 HB: 72 HAwI: 53 HBwI: 31 (≥12 years)	NA	Completed

Notes: [a]Prior to the treatment pause, the dosing regimen in trials 4311 and 4307 consisted of a loading dose of 1 mg/kg at Day 1 followed by a daily dose of 0.25 mg/kg from Day 2. The dose could be increased once to 0.35 mg/kg during the extension part of the trials at the investigator's discretion based on bleeding criteria. [b]The primary analysis cut-off (PACO) is defined as when all patients in arm 1 had completed visit 9/9a (or withdrawn) and all patients in arm 2 had completed visit 10a (or withdrawn).
[c]The 56-week cut-off is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment).
[d]When concizumab treatment restarted after the pause, 148 patients in total were randomised/allocated to treatment (no PPX or concizumab PPX) in trial 4307 and were included in the FAS which was primarily used for the efficacy evaluation.
[e]The confirmatory analyses cut-off (CACO) is defined as the point in time when all patients in arm 1 have completed the 24-week visit (visit 9a) or withdrawn and all patients on concizumab PPX (in arms 2 and 4) have completed the 32-week visit (visit 10a) or withdrawn. [f]Patients in study 4322 were not treated with concizumab.

The cut-off date for inclusion of data from completed and ongoing trials as well as compassionate use in the application was 30 August 2022.

Concizumab treatment pause

Phase 3 clinical trials were initiated in October 2019. Concizumab treatment in trials 4307, 4311 (and dose-response study 4255) was paused in March 2020 due to the occurrence of non-fatal thromboembolic events in 3 patients enrolled in the phase 3 programme, and the trials were subsequently put on clinical hold by the FDA. Analysis of the thromboembolic events and all available data led to implementation of changes to the phase 3 trial protocols as detailed below, in agreement with health authorities. The clinical hold was lifted in August 2020, whereafter treatment was reinitiated.

Primary mitigating actions. A new guidance was included for treatment of mild and moderate breakthrough bleeds with specific guidance for use of the lowest dose of factor product or bypassing agent while on concizumab PPX. Further, the request for the patients to contact the study site prior to treating a suspected bleed was added.

Additional mitigating actions. These included a new concizumab dosing regimen consisting of a loading dose of 1.0 mg/kg (unchanged from initial dosing regimen) and an initial daily dose of 0.20 mg/kg concizumab (decreased from 0.25 mg/kg). Based on concizumab exposure levels at the week 4 visit after initiating treatment, the daily maintenance dose can be increased to 0.25 mg/kg or decreased to 0.15 mg/kg. Further, elective major surgery was no longer allowed in trial and the Trial stopping rule was adapted, requiring urgent evaluation by the Novo Nordisk Safety Committee and consultation with the DMC in case of one (instead of two) significant thromboembolic events, DIC, TMA or death of trial patient which may be related to the trial product.

Enrolment/randomisation. When concizumab treatment was paused, 80% (i.e., 41 out of 51) of the planned number of randomised patients in trial 4311 had been enrolled. In agreement with health authorities, the randomisation of patients already included in the trial was kept the same and new patients were allocated according to the original randomisation list in order to meet the protocol targeted sample size. This approach aimed to use all gathered data to the extent possible, to retain already included patients in the trial and to maintain the randomised nature of the trial to the extent possible. For trial 4307, only 12% (i.e. 7 out of 60) of the planned number of randomised patients had been enrolled when concizumab treatment was paused. It was agreed with health authorities to re-start the randomisation into arms 1 and 2 with new patients enrolled after the treatment pause, while patients randomised to arms 1 and 2 before the pause were to enter arm 4 when restarting the trial. The implications of the treatment pause, and the changes implemented to the 4311 and 4307 trial designs for the primary statistical analyses, were investigated through sensitivity analyses.

2.6.5.1. Dose response studies

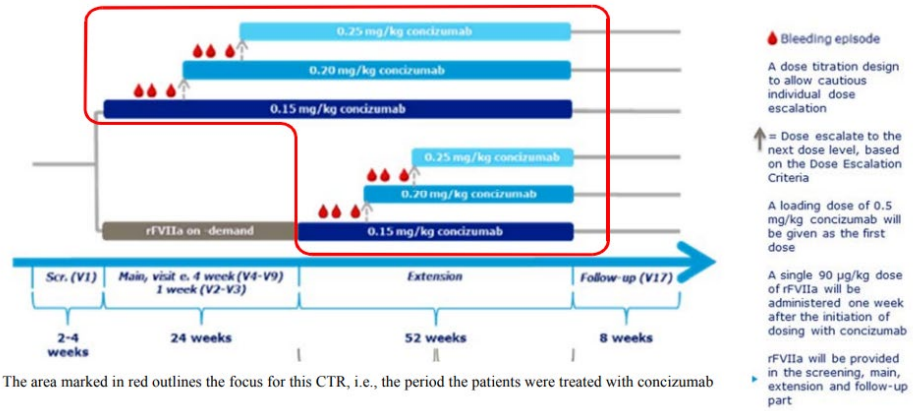
Study 4310 (Explorer 4, proof-of-concept study)

Methods - study 4310

Study design. Phase 2 study 4310 (explorer 4) was a multi-national, multi-centre, randomized (2:1) open-label, active controlled, multiple-dose study to compare efficacy and safety of concizumab as prophylaxis (PPX) to eptacog alfa (recFVIIa) as on-demand treatment in adult patients with HAwI (n=17) or HBwI (n=9) over a duration of at least 24 weeks. Further, to assess safety when eptacog alfa is provided for treatment of breakthrough bleeding episodes in patients treated with concizumab.

The trial consisted of a 2-weeks screening period, a main part of 24 weeks, an extension part of 52-94 weeks treatment period and an 8-week follow up period (Figure 50). The main part of the trial ended when the last patient in the concizumab arm had completed a minimum of 24 weeks of dosing, hence the duration of the main part differs from one patient to another in concizumab arm. For the patients in the eptacog alfa arm, the main part of the trial ended when all patients completed 24 weeks of treatment. In the concizumab arm, all available data up to and including the last scheduled visit before or at the time point where the main part ended was used.

Figure 50: Trial design study 4310.



The area marked in red outlines the focus for this CTR, i.e., the period the patients were treated with concizumab

Dose selection. A loading dose of 0.5 mg/kg concizumab was given s.c. as the first dose at visit 2, followed by daily s.c. injections at doses of 0.15 mg/kg, self-administered using the NovoPen 4 injector (with the

possibility to escalate the dose to 0.20 mg/kg and 0.25 mg/kg, if a patient experienced ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab). The first 2 weeks of the treatment with concizumab 0.15 mg/kg were considered as a run-in period and bleeding episodes occurring during this period did not influence a dose escalation decision.

Breakthrough bleeding episodes occurring from visit 2 (first administration of concizumab) to the end-of-trial visit were to be treated with eptacog alfa (rFVIIa).

Dose rationale. The dosing regimen was chosen because a post-hoc analysis from explorer 3 (trial 4159) indicated exposure-response in terms of fewer bleeding episodes at exposures above 100 ng/mL concizumab. The starting dose of 0.15 mg/kg concizumab was predicted to lead to plasma concentrations around 100 ng/mL for the majority of the patients. Further dose escalations to 0.20 and 0.25 mg/kg concizumab were permitted, based on the number of spontaneous bleeding episodes. Daily dosing was proposed to allow for an increase in trough levels and thus better efficacy was expected with a lower dose.

Control group. Patients in the comparator arm received eptacog alfa (rFVIIa) on-demand as i.v. injections for treatment of breakthrough bleeding episodes with a dose regimen at the discretion of the investigator. After completion of the main part of the trial (24 weeks), patients continued the trial in the extension part and switched to prophylactic treatment with 0.15 mg/kg s.c. daily administration of concizumab (with potential dose-escalation).

Rationale for the control group. A comparator arm was included to assess if concizumab was superior to on-demand treatment. Furthermore, the trial would give a possibility to assess safety of co-administration of eptacog alfa (rFVIIa) to the patients exposed to the concizumab treatment.

Treatment of breakthrough bleeding episodes. During the screening period (visit 1 to visit 2) treatment with any bypassing agent was allowed (e.g., eptacog alfa (rFVIIa), FEIBA) up to a period of 24 hours (for eptacog alfa) or 48 hours (for FEIBA) prior to first concizumab administration at visit 2.

Breakthrough bleeding episodes during the main (and extension) part of the study had to be treated with eptacog alfa at a dose not exceeding 90 mcg/kg. If a single dose of eptacog alfa was not sufficient to stop a bleeding episode, the patient had to inform the site and in agreement with the investigator might administer a second dose of eptacog alfa not higher than 90µg/kg 2−3h after the first dose had been administered. This could be repeated for a third dose, and then, if the bleeding was not stopped, the patient had to go to the treatment site.

One week after initiation of dosing with concizumab, a single 90 µg/kg dose of eptacog alfa was administered in a non-bleeding state at the trial site under medical supervision to assess 24h PK/PD and safety of treatment with eptacog alfa in patients exposed to concizumab treatment (visit 3 for the concizumab group, and visit 9.1 for those initially randomised to eptacog alfa).

Participants

Key inclusion criteria: Male haemophilia A or B patients with inhibitors, aged ⩾ 18 years currently treated on-demand with a minimum of six bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening currently in need of treatment with bypassing agents. Documented history of high-titer inhibitors towards FVIII or FIX, defined as ⩾ 5 Bethesda Units.

Key exclusion criteria: Platelet count below 50x10^9/L at screening; history or current signs of thromboembolic disease, significant infection or systemic inflammation condition requiring systemic treatment, hepatic dysfunction (ALT>3ULN) or renal impairment (eGFR<=60 ml/min/1.73m^2).

Rationale trial population: The most important reason for choosing the trial population, haemophilia with inhibitors, was that there is a significant unmet medical need in this patient population for more effective treatment and a treatment which reduces treatment burden. In addition, this trial population was considered the most suitable for assessing the safety of administering eptacog alfa to patients in whom plasma TFPI levels were inhibited, since most of these patients are likely to have been treated with eptacog alfa before. Finally, the trial population reflected the patient population that would be selected in a potential subsequent confirmative phase 3 trial.

Study objectives

Primary objective

- To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in haemophilia A and B patients with inhibitors

Secondary objectives

- To assess the long-term efficacy of concizumab in haemophilia patients with inhibitors
- To assess the safety of concizumab in haemophilia patients with inhibitors
- To assess the safety of administering recombinant factor VIIa (rFVIIa) to haemophilia patients with inhibitors that are exposed to concizumab
- To assess the immunogenicity of concizumab in haemophilia patients with inhibitors.

Outcomes/ Endpoints

Primary endpoint

- The number of bleeding episodes during at least 24 weeks from treatment onset

Supportive secondary efficacy endpoints

- The number of *spontaneous* bleeding episodes during at least 24 weeks from treatment onset

Exploratory endpoints - Exploratory patient-reported outcome endpoints included change in Hemophilia Treatment Experience Measure (Hemo-TEM), 36-Item Short Form Health Survey (SF-36v2), Sheehan Disability Scale (SDS), Treatment Satisfaction Questionnaire for Medication (TSQM), and injection site reaction questionnaire-self-injection assessment questionnaire (SIAQ-ISRQ) at 24 weeks.

Pharmacokinetic endpoints (see PK section) consisted of concentration of concizumab prior to the last dose administration at 24 weeks.

Pharmacodynamics endpoints (see PD section) consisted of plasma free TFPI concentration and parameter of thrombin generation parameters prior to the last dose administration at 24 weeks.

Safety endpoints (see PD and safety section) consisted of number of treatment-emergent AEs (TEAEs) during at least 24 weeks from treatment onset, number of TEAEs within 24 hours of rFVIIa administration, and occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset. Further change from baseline of fibrinogen, D-dimer and prothrombin fragment 1 + 2 (F1 + 2) during 24 weeks from treatment onset were evaluated.

Sample size. The sample size was determined taking the small patient population into account. Sufficient inference on bleeding episodes for the primary CPoC criterion was judged to be accommodated by 16 patients in the concizumab arm and 8 in the comparator arm.

Randomization and blinding. All patients included in the screening period and eligible for the trial entered the trial and were randomised at visit 2 in a 2:1 allocation to either concizumab prophylaxis arm or eptacog alfa (rFVIIa) on-demand arm.

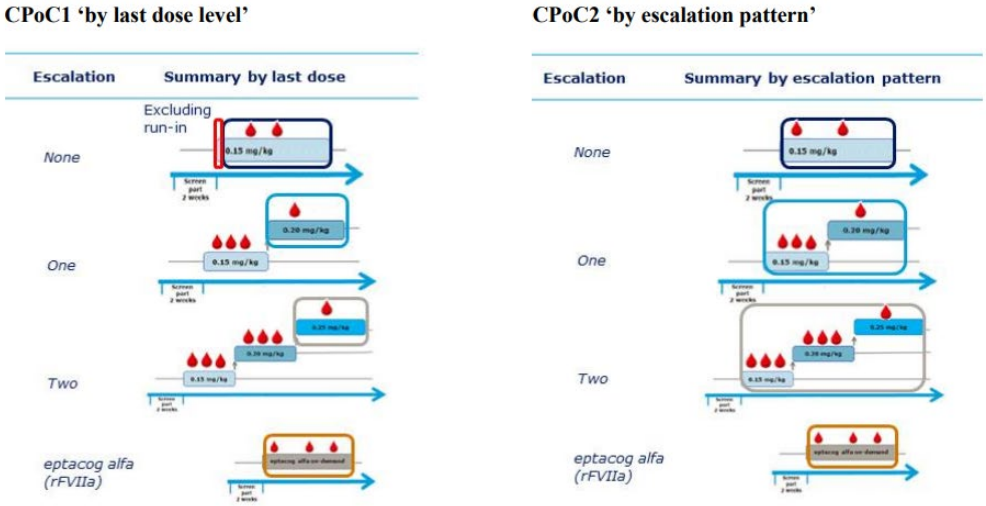
Statistical methods

Analysis Set. For the main part of the study, all randomised patients were included in the full analysis set (used for efficacy endpoints) as well as in the safety analysis set (used for safety endpoints).

Primary analysis- *Analysis of primary endpoint.* The reporting of efficacy endpoints was done with two approaches. Two criteria were evaluated in a hierarchical fashion:

- The primary CPoC (CPoC1) criterion aimed at evaluating the effect of concizumab at the last dose level reached for a patient (left part of Figure 51). Hence, for this evaluation, only observations from the period where patients were on their last dose level at the time of analysis contributed to the analysis
- The secondary CPoC (CPoC2) criterion aimed at evaluating the effect of concizumab when given as an escalation regimen (right part of Figure 51). This analysis included all bleeding episodes; i.e., from the entire treatment period.

Figure 51: Schematic diagram of the two clinical proof of concept analyses.



Note: The left part of the figure shows CPoC1 assessing the effect of concizumab at the last dose level reached for a patient. The right part of the figure shows CPoC2 aiming to evaluate the effect of concizumab during the entire treatment period.

The **estimand for the primary endpoint** is the "if all patients had adhered" estimand. The treatment ratio between s.c. concizumab prophylaxis and on-demand i.v. eptacog alfa (rFVIIa) during at least 24 weeks for all randomised patients if all patients adhered to trial drug and did not initiate alternative treatment options. To initiate alternative treatment options in this respect was defined as stopping concizumab or eptacog alfa on-demand treatment and initiating alternative treatment options.

This estimand is a de jure estimand assessing the expected added benefit a patient can achieve if continuing treatment with prophylactic s.c. concizumab as compared to on-demand i.v. eptacog alfa (rFVIIa) under similar conditions as observed in this trial.

The estimand for the primary endpoint was estimated using negative binomial regression with log of exposure time in the included observational period of the main part as offset and regimen as factor. The offset for first CPoC criterion of patients in concizumab arm was the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for patients on 0.15 mg/kg. The offset for the second criterion of patients in concizumab arm is the log of the individual exposure time in the main part. For patients in the on-demand arm regardless of criterion, the offset was the log of the exposure time in the main part. The analysis provides an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval and also actual estimate of the ABR with corresponding 95% confidence interval for each regimen. This analysis had the underlying assumption that the missing data mechanism is "missing at random", i.e. MAR.

Additional analysis. An additional evaluation of the primary endpoint was made, including actual concizumab dose level (interpreted as the patient's last dose level) as additional factor in the primary analysis model specified above. Point estimates and 95% confidence interval was provided for the ABR at the different dose levels of concizumab (0.15, 0.20 and 0.25 mg/kg).

Sensitivity analysis. To evaluate the robustness of the MAR assumption implied in the primary analysis, a modified tipping point analysis was performed where patients having discontinued before finalization of the main part were assumed to have a worse outcome compared to what was observed during the main part of the trial. This was done by adding a value Δ to the observed bleeding episodes in the main part of the trial before analysing the data. The offset was maintained as being the exposure during the main part since it was not possible to identify the amount of missing observation time. The degree of worsening, Δi, would gradually be increased to evaluate at which point concizumab prophylaxis no longer was superior to on-demand eptacog alfa (rFVIIa). The results of the primary analysis were considered robust if the tipping point was above what was considered clinically plausible.

The secondary CPoC criterion evaluating the effect of concizumab when given as an escalation regimen included observations from the 2-week run-in period. Therefore, an additional sensitivity analysis for CPoC criterion 2 was described where observations for the first 2 weeks of treatment are excluded. Since this could affect the ABR, an additional sensitivity analysis was performed where the secondary CPoC criterion was evaluated as described for the primary endpoint but without including observations from the 2-week run-in period and using log of exposure time excluding those days as the offset.

The primary endpoint was assessed using all treated bleeding episodes including those recorded as post-surgery or caused by surgical or other medical or dental procedures. Since the inclusion of bleeding episodes recorded as post-surgery or caused by surgical or other medical or dental procedures could affect the ABR, an additional sensitivity analysis was performed excluding these bleeding episodes from the primary and secondary CPoC criteria.

The supportive secondary efficacy endpoints were summarised descriptively by treatment regimen.

Results main part (24 weeks)

Recruitment and Patient flow. The trial initiation date was 10 August 2017. Primary completion date was 19 September 2018. A total of 28 patients, all males were screened in the trial, of which 2 of them were screening failures. A total of 26 patients were randomised and exposed in the trial. One (1) patient withdrew from the trial due to withdrawal of consent. A total of 25 patients completed the treatment during the main part of the trial.

Baseline data

Demographics and Baseline Characteristics. At baseline, 54% of patients had family history of haemophilia, mean (SD) age was 36.5(12.7) years, mean body weight was 71.2(13.9) kg and mean BMI was 24.2(4.2) kg/m2. All the patients came from an on-demand treatment regimen, and 4 of the patients (2/17 in the concizumab subgroup, 2/9 in the eptacog alfa group) also received prophylaxis within a year prior to screening. The ABR (median, range) during the prophylaxis treatment period prior to inclusion (n=4) was 14.8 (0-365). The ABR (median, range) during on-demand treatment (n=26) was 18 (6-120). At baseline, 20 out of 26 patients were reported to have at least one target joint. The target joint location for these 20 patients included ankle, elbow, hip, knee, shoulder and wrist. The mean number of bleeds in specified joint within 1-year prior to screening was 7.5 (range 3−30 bleeds).

Numbers analysed. The FAS included all the 26 patients who were randomised during the trial.

Exposure/dosing. In the main part of the study, out of the 17 patients randomised to concizumab, 15 patients stayed on 0.15 mg/kg, 2 patients escalated their dose to 0.20 mg/kg and none escalated to 0.25 mg/kg. Based on each patient's last dose level, the exposure time was 10.1 years in the patients who stayed on 0.15 mg/kg and 1.6 years in the patients who escalated to 0.20 mg/kg, giving a total exposure time to concizumab of 11.7 years. A total of 16 out of 17 patients in the concizumab arm were exposed beyond 24 weeks. The exposure time in the eptacog alfa arm was 3.9 years.

Outcomes and estimation

Primary efficacy endpoint: number of bleeding episodes during at least 24 weeks from treatment onset

When assessing each patient's last dose level in the concizumab arm, 15 patients (88%) reported 47 bleeding episodes during the main part of the trial. The bleeding episodes were equally divided into spontaneous (51%) and traumatic (49%) episodes; none were surgical. Most were joint bleeds (72%) and muscular bleeds (21%). In the eptacog alfa (rFVIIa) on-demand arm, 9 patients (100%) reported 77 bleeding episodes during the main part of the trial. Most of these were spontaneous (90%), while 9% were traumatic and 1% was surgical. Most were joint bleeds (77%) and muscular bleeds (19%). Two (2) bleeding episodes in this treatment arm were assessed as severe by the investigator.

Table 12: Treated bleeding episodes in main phase – bleeds occurring on last dose level - FAS

	Last dose level			Total	
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Concizumab	Eptacog alfa
Number of subjects	15	2	0	17	9
Number of subjects with no treated bleeding episodes, N (%)	2 (13.33)	0	0	2 (11.76)	0
Number of subjects with treated bleeding episodes, N (%)	13 (86.67)	2 (100.0)	0	15 (88.24)	9 (100.0)
Number of treated bleeding episodes	38	9		47	77
Cause of bleeding episodes, E (%)					
Spontaneous	19 (50.00)	5 (55.56)	0	24 (51.06)	69 (89.61)
Traumatic	19 (50.00)	4 (44.44)	0	23 (48.94)	7 (9.09)
Surgical	0	0	0	0	1 (1.30)
Missing	0	0	0	0	0
Location of bleeding episodes, E (%)					
Joint	28 (73.68)	6 (66.67)	0	34 (72.34)	59 (76.62)
Muscular	8 (21.05)	2 (22.22)	0	10 (21.28)	15 (19.48)

Skin	2 (5.26)	0	0	2 (4.26)	4 (5.19)
Gastrointestinal	0	1 (11.11)	0	1 (2.13)	1 (1.30)
Mouth, gums, nose	0	0	0	0	0
Urinary system	0	0	0	0	2 (2.60)
Central nervous system	0	0	0	0	0
Other	0	0	0	0	1 (1.30)
Missing	0	0	0	0	0
Classification of bleeding episode, E (%)					
Mild/moderate	38 (100.0)	9 (100.0)	0	47 (100.0)	75 (97.40)
Severe	0	0	0	0	2 (2.60)
Missing	0	0	0	0	0
Location of severe bleeding episodes, E (%)					
Joint	0	0	0	0	2 (2.60)
Muscular	0	0	0	0	0
Skin	0	0	0	0	0
Gastrointestinal	0	0	0	0	0
Mouth, gums, nose	0	0	0	0	0
Urinary system	0	0	0	0	0
Central nervous system	0	0	0	0	0
Other	0	0	0	0	0
Missing	0	0	0	0	0

N: number of subjects, %: percentage of subjects, E: number of bleeding episodes. A bleed can have multiple locations. Last dose level is the individual highest dose level at time of analysis and hence, previous dose levels and run-in are disregarded.

Annualised bleeding rates during main phase (24 weeks) primary CPoC criterion

In the concizumab arm, the estimated ABR on the last dose level for each patient was 4.5 with a 95% CI of [3.2; 6.4]. In the eptacog alfa (rFVIIa) on-demand arm, the estimated ABR was 20.4 with a 95% CI of [14.4; 29.1]. The ABR ratio was 0.22 with a 95% CI of [0.13; 0.36] and as the upper limit of the ABR ratio 95% CI was below 1, the primary CPoC criterion was met.

There was 1 year of exposure time on last dose level for patients who escalated their dose to 0.20 mg/kg compared to 9.5 years among the patients who stayed on 0.15 mg/kg during the main part of the trial. Note that the ABRs for 0.15 mg/kg vs 0.20 mg/kg concizumab represent different selections of patients, and therefore cannot be compared directly.

Table 13: Annualised bleeding rates during main phase – bleeds occurring by last dose Level – summary and analysis – full analysis set.

	Last dose level			Total	
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Concizumab	Eptacog Alfa
Number of subjects	15	2	0	17	9
Annualised bleeding rate					
N	15	2		17	9
Mean (SD)	3.9 (2.3)	8.6 (9.0)		4.5 (3.5)	21.1 (11.7)
Min ; Max	0.0 ; 7.0	2.2 ; 15.0		0.0 ; 15.0	6.6 ; 36.5
Median	4.5	8.6		4.5	19.7
P25 ; P75	2.4 ; 5.6	2.2 ; 15.0		2.4 ; 5.6	8.6 ; 33.0
N	15	2		17	9
Number of bleeding episodes	38	9		47	77
Duration (in years)	9.5	1.0		10.5	3.9
Primary analysis (CPoC1)*					
ABR estimate**				4.5	20.4
95% CI				3.2 ; 6.4	14.4 ; 29.1
ABR ratio**				0.22	
95% CI				0.13 ; 0.36	
P-value				<0.001	
Additional Analysis***					
ABR estimate**	4.0	8.9			
95% CI	2.7 ; 5.8	3.9 ; 20.5			

N: number of subjects, SD: standard deviation, P25/75 is the 25th/75th percentile, Min: minimum, Max: maximum, ABR: annualised bleeding rate, CI: Confidence interval, CPoC: Clinical proof of concept. Last dose level is the individual highest dose level at time of analysis and hence, previous dose levels and run-in are disregarded. Duration is the period where subjects are on their last dose at time of analysis. * Based on a negative binomial regression with log of exposure time in main part as offset and treatment arm as factor. ** Lsmeans estimates of ABR and ratio to the ABR of eptacog alfa subjects. *** Including actual concizumab dose level as additional factor in the primary analysis model. Two-sided p-value for test of ratio between arm different from 1.

Secondary clinical proof of concept (CPoC2)

In the concizumab arm, 15 patients (88%) reported 63 bleeding episodes during the entire treatment period (see below). The percentage of spontaneous (54%) and traumatic bleeding episodes (46%) were similar; none were surgical. Most were joint bleeds (71%) and muscular bleeds (22%). No bleeding episodes were assessed as severe by the investigator. For the eptacog alfa (rFVIIa) on-demand arm, the bleeding pattern was as described under 'First clinical proof of concept'.

Table 14 Treated bleeding episodes during main phase–all bleeds occurring by escalation pattern-FAS

	Last dose level			Total	
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Concizumab	Eptacog alfa
Number of subjects	15	2	0	17	9
Number of subjects with no treated bleeding episodes, N (%)	2 (13.33)	0	0	2 (11.76)	0
Number of subjects with treated bleeding episodes, N (%)	13 (86.67)	2 (100.0)	0	15 (88.24)	9 (100.0)
Number of treated bleeding episodes	43	20		63	77
Cause of bleeding episodes, E (%)					
Spontaneous	22 (51.16)	12 (60.00)	0	34 (53.97)	69 (89.61)
Traumatic	21 (48.84)	8 (40.00)	0	29 (46.03)	7 (9.09)
Surgical	0	0	0	0	1 (1.30)
Missing	0	0	0	0	0
Location of bleeding episodes, E (%)					
Joint	31 (72.09)	14 (70.00)	0	45 (71.43)	59 (76.62)
Muscular	10 (23.26)	4 (20.00)	0	14 (22.22)	15 (19.48)
Skin	3 (6.98)	0	0	3 (4.76)	4 (5.19)
Gastrointestinal	0	1 (5.00)	0	1 (1.59)	1 (1.30)
Mouth, gums, nose	0	1 (5.00)	0	1 (1.59)	0
Urinary system	0	0	0	0	2 (2.60)
Central nervous system	0	0	0	0	0
Other	0	0	0	0	1 (1.30)
Missing	0	0	0	0	0
Classification of bleeding episode, E (%)					
Mild/moderate	43 (100.0)	20 (100.0)	0	63 (100.0)	75 (97.40)
Severe	0	0	0	0	2 (2.60)
Missing	0	0	0	0	0

N: number of subjects, %: percentage of subjects, E: number of bleeding episodes.
A bleed can have multiple locations.

The estimated ABR during the entire treatment period (CPoC2) in the concizumab arm was 5.4 with a 95% CI of [3.8; 7.6]. In the eptacog alfa (rFVIIa) on-demand arm, the estimated ABR was 20.6 with a 95% CI of [13.7; 30.8]. The ABR ratio was 0.26 with a 95% CI of [0.15; 0.44] and as the upper limit of the ABR ratio 95% CI was below 1, the secondary CPoC criterion was met.

Table 15: Annualised bleeding rates during main phase – summary and analysis – full analysis set

	Main At least 24 weeks	
	Concizumab	Eptacog Alfa
Number of subjects	17	9
annualised bleeding rate		
N	17	9
Mean (SD)	5.3 (4.6)	21.1 (11.7)
Min ; Max	0.0 ; 20.4	6.6 ; 36.5
Median	4.3	19.7
P25 ; P75	3.2 ; 6.5	8.6 ; 33.0

N	17	9
Number of bleeding episodes	63	77
Duration (in years)	11.7	3.9
secondary analysis (CPoC2)*		
ABR estimate**	5.4	20.6
95% CI	3.8 ; 7.6	13.7 ; 30.8
ABR ratio**	0.26	
95% CI	0.15 ; 0.44	
P-value	<0.001	

N: number of subjects, SD: standard deviation, P25/75 is the 25th/75th percentile, Min: minimum, Max: maximum, ABR: annualised bleeding rate, CI: Confidence interval, CPoC: Clinical proof of concept. All data after enrolment contribute to this analysis. * Based on a negative binomial model with log of exposure time in main phase as offset and treatment arm as additional factor. ** Lsmeans estimates of ABR and ratio to the ABR of eptacog alfa subjects. Two-sided p-value for test of ratio between arm different from 1.

Sensitivity analysis. A planned sensitivity analysis was performed excluding the surgical bleeding episodes since the inclusion of bleeding episodes recorded as post-surgery or caused by surgical or other medical or dental procedures could affect the ABR. It was noted that excluding the surgical bleeds from the analysis did not change the overall results.

Secondary efficacy endpoints

Spontaneous bleeding episodes on last dose level

The estimated spontaneous annualised bleeding rate (sABR) in the concizumab arm was 2.3 with a 95% CI of [1.4; 3.6]. The estimated sABR for the eptacog alfa (rFVIIa) on-demand arm was 18.5 with a 95% CI of [12.4; 27.6]. That gives a sABR ratio of 0.12 with a 95% CI of [0.07; 0.23]. The median sABRs were 2.2 and 17.5, for the concizumab arm and eptacog alfa (rFVIIa) on-demand arm, respectively.

Spontaneous bleeding episodes during main part

The estimated sABR in the concizumab arm was 2.9 with a 95% CI of [1.9; 4.4]. The estimated sABR for the eptacog alfa (rFVIIa) on-demand arm was 18.6 with a 95% CI of [12.0; 28.6]. That gives a sABR ratio of 0.15 with a 95% CI of [0.08; 0.28]. The median sABRs were 2.2 and 17.5, for the concizumab arm and eptacog alfa (rFVIIa) on-demand arm, respectively.

Exploratory endpoints: patient-reported outcomes

- The change from baseline in mean Hemo-TEM total score was -15.3 in the concizumab arm but there was no change in Hemo-TEM total score in the eptacog alfa arm; a similar improvement was observed at least after 76 weeks (visit 16) as well
- Improvement from baseline to at least 76 weeks (visit 16) was observed in all SF-36v2 scores particularly with the items covered by the physical component summary being more pronounced

Summary of Safety results 24 week period (main part)

Adverse events

- A total 13 of 17 patients treated with concizumab reported 43 AEs and 7 of 9 patients treated on-demand reported 18 AEs.
- A total of 4 patients experienced 5 AEs which were evaluated by the investigator as probably/possibly related to concizumab. All the AEs were reported in patients while treated with 0.15 mg/kg concizumab.

The 5 PTs were prothrombin level increased (2 events), Fibrin D dimer increased, injection site erythema and headache. All the events were mild and the patients recovered from the events.

  - No deaths or thromboembolic events were reported.
  - No AEs led to permanent treatment discontinuation or withdrawal from the trial.
  - Four (4) patients treated with concizumab (23.5%) reported 12 injection site reactions.
- Three (3) patients had binding anti-concizumab antibodies with no apparent effect.

A total of 140 bleeding episodes were treated during the main part of the study, 63 in the concizumab-subgroup (43 events in 13 subjects with last-dose 0.15 mg/kg and 20 events in 2 subjects with last dose 0.20 mg/kg), and 77 in the on-demand-subgroup.

- No AEs were reported within 24 hours of administering eptacog alfa (rFVIIa) to concizumab-treated patients at the PK visit. Furthermore, no safety issues were identified for the treatment of breakthrough bleeding episodes with rFVIIa during the trial.

Study 4255 (Explorer 5)

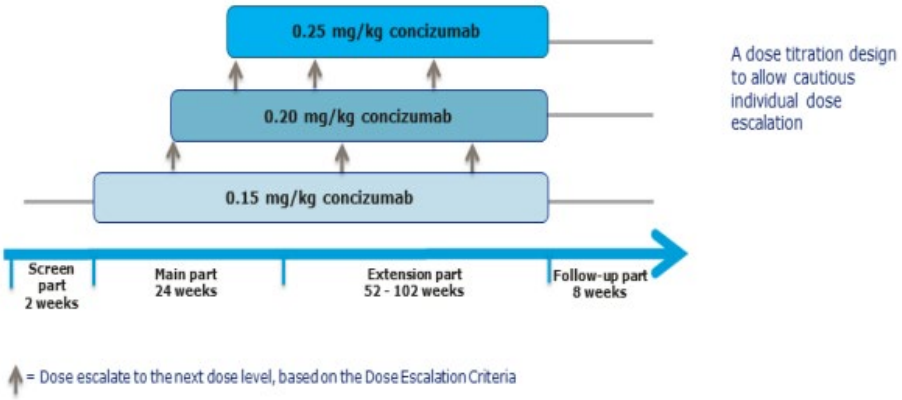
Methods - study 4255

Study design. Phase 2 study 4255 (Explorer 5) was a multi-national, multicentre, single-arm, multiple dose efficacy and safety trial of concizumab prophylactic treatment 0.15 mg/kg (with potential dose escalation to 0.20 and 0.25 mg/kg) administered daily s.c. in patients with severe haemophilia A without inhibitors.

The main rationales of this trial were to assess efficacy and safety, to obtain clinical proof of concept for concizumab, as well as to provide sufficient information to guide the design of the confirmatory phase 3 concizumab trials.

The trial consisted of 2-weeks screening period, a subsequent main part which lasted at least 24 weeks for all patients in the trial and an extension part which would be at least 102 weeks.

Figure 52: Design study 4255.



Dose selection. Initial maintenance dose of concizumab dose was 0.15 mg/kg, administered daily s.c. (Novopen 4), with potential dose escalation to 0.20 and 0.25 mg/kg (if a patient experienced ≥3 spontaneous bleeding episodes within the preceding 12 weeks of treatment with concizumab). The first 2-weeks of the treatment with concizumab 0.15 mg/kg was considered as a run-in period.

Rationale dose: The dosing regimen was chosen because a post-hoc analysis from study 4159 (Explorer 3) indicated exposure-response in terms of fewer bleeding episodes at exposures above 100 ng/mg concizumab. The daily dosing with 0.15 mg/kg was predicted by PK modelling to ensure steady-state levels of concizumab plasma concentrations around 100 ng/mL for most of the patients.

Treatment of breakthrough bleeding episodes. Breakthrough bleeding occurring from visit 1 to end-of-trial visit were treated by the patients at home with FVIII at the discretion of the investigator, either turoctocog alfa/Novoeight (rFVIII) (provided by Novo Nordisk) or other non-modified FVIII products (not provided by Novo Nordisk). The investigator chose dose levels, but any given single dose was not to exceed 50 IU/kg.

Participants

Key inclusion criteria: Male patients with severe HA (fVIII<1%) based on medical records or results at screening, aged >=18 years were eligible who were treated on-demand or with prophylaxis were eligible for the trial. For patients being treated on-demand with FVIII replacement therapy, minimum six documented and treated bleeding episodes during the 24 weeks (or twelve bleeds during 52 weeks) prior to screening was required.

Key exclusion criteria: A history of current signs of thromboembolic disease, major surgery conducted within one month prior to the initiation of trial activities or planned during the trial, significant infection or systemic inflammation condition requiring systemic treatment, hepatic dysfunction (ALT>3ULN), renal impairment (eGFR<=60 ml/min/1.73m^2), platelet count <= 100X10^9/l or previous history of presence of fVIII inhibitors (neutralizing antibodies).

Study objectives

Primary objective:

- To assess the efficacy of concizumab administered s.c. once daily in preventing bleeding episodes in patients with severe haemophilia A without inhibitors

Secondary objectives:

- To assess the longer-term efficacy, efficacy, and immunogenicity of concizumab in patients with severe haemophilia A without inhibitors

Outcomes/endpoints

Primary endpoint

- The number of bleeding episodes during at least 24 weeks from treatment onset

Secondary efficacy endpoint

- The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset

Supportive secondary pharmacokinetic endpoints (see PK section) consist of concentration of concizumab prior to the last dose administration at 24 weeks

Supportive secondary pharmacodynamics endpoints (See PD Section) consist of plasma free TFPI concentration and parameters of Thrombin generation prior to the last dose administration at 24 weeks

Safety endpoints include number of treatment-emergent AEs (TEAEs) and occurrence of anti-concizumab antibodies during at least 24 weeks from treatment onset, change from baseline of fibrinogen, D-dimer and prothrombin fragment 1 + 2 during 24 weeks from treatment onset

Sample size. The sample size has been determined taking the small patient population into account. Sufficient inference on bleeding episodes for the primary CPoC criterion was judged to be accommodated by 30 patients.

Statistical analysis. All dosed patients were included in the full analysis set (used for efficacy endpoints) as well as in the safety analysis set (used for safety endpoints).

The statistical analysis of the collected data aimed to establish CPoC that concizumab is efficacious in preventing bleeding episodes in haemophilia A patients without inhibitors.

- The primary CPoC (CPoC1) criterion aimed at evaluating the effect of concizumab at the last dose level reached for a patient. Hence, for this evaluation, only observations from the period where patients were on their end dose at the time of analysis contributed to the analysis.
- The secondary CPoC (CPoC2) criterion aimed at evaluating the effect of concizumab when given as an escalation regimen. This analysis included all bleeding episodes; i.e., from the entire treatment period.

The comparisons were made using a negative binomial model with log of exposure time in the included observational period of the main part as offset and regimen as factor. The offset for CPoC1 criterion is the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2-weeks run-in period for patients on 0.15 mg/kg. The offset for CPoC2 is the log of the individual exposure time in the main part.

For each criterion, evidence of effect was concluded if the 95% confidence interval of the estimated ABR was below 12. The value of 12 bleeds per year reflects conservatively a 50% reduction from the bleeding rate during on-demand treatment, which in previous trials typically has been reported to be above 30 bleeds per year (Applicantlangu, Blood 2014; Valentino, J Thromb Haest 2012; Manco-Johnson, J Thromb Haest 2013). In addition, a confidence limit lower than 12 was considered to substantiate that the prophylactic efficacy of concizumab may be similar to that of FVIII replacement therapy where an estimated mean of 6.5 bleeds per year was observed (Lentz, Haemophilia 2013).

The remaining endpoints were presented using descriptive statistics only.

Results main part (24 weeks)

Recruitment. Initiation date: 16 August 2017. Primary completion date: 22 June 2018. Trial completion: 03 June 2020. At the start of the treatment pause due to thromboembolic events in 2020, all of the subjects had completed the main part of the study, thereby the results of study 4255 are not compromised. The trial was conducted at 26 sites in 11 countries.

Patient flow. A total of 36 male patients were included and exposed to concizumab. Four patients withdrew before the end of main part (withdrawal of consent in two cases at 21 and 80 days on treatment, withdrawn from treatment in one case at 49 days, and patient experienced lack of efficacy in one case at day 11).

Baseline data

Demographics and Baseline Characteristics. At baseline, mean (SD) age was 36.9 (12.9) years, mean (SD) body weight was 77.0 (20.4) kg and mean (SD) BMI was 24.9 (5.1) kg/m^2.

The mean (SD) time from diagnosis of haemophilia A was 34.4 (12.1) years. A total of 31 patients reported prophylactic treatment during the 12 months prior to screening, with some patients on both prophylactic and on-demand treatment regimens. The ABR during the prophylaxis treatment period prior to inclusion (n=31) was 5.2 (9.7; range 0-52). The ABR during on-demand treatment (n=9) was 17.5 (15.4; range 4-47). At

baseline, 14 out of 36 patients were reported to have at least one target joint at some point before screening. The target join location for these 14 patients included ankle, elbow, knee and wrist. Mean number of bleeds in specified joint in the one-year period prior to screening was 8.3 (range 0-47 bleeds).

Numbers analysed. In the main part of the study, a total of 21 patients were treated with 0.15 mg/kg throughout the main part of the trial, 7 patients were escalated to 0.20 mg/kg and another 8 patients were escalated to 0.25 mg/kg at the cut-off for main part. The exposure time for these 3 dose levels was 10.2 years, 3.4 years and 3.6 years, respectively, total 17.2 years.

Outcomes and estimation (main part = 24 weeks of treatment)

Primary efficacy endpoint: the number of bleeding episodes during at least 24 weeks from treatment onset

Primary clinical proof of concept (CPoC1). Based on each patient's last dose level, a total of 23 patients reported 70 bleeding episodes during the main part of the trial (Table 38**:**). There were more traumatic (61.43%) than spontaneous (37.14%) bleeding episodes, and 1 bleeding episode (1.43%) was surgical. The majority of bleeds were joint bleeds (44 episodes, 62.86%), followed by muscular bleeds (18 episodes, 25.71%). There were 3 (4.29%) severe bleeding episodes and the remaining 67 (95.71%) were mild/moderate in severity.

Table 16 Treated bleeding episodes during main phase - bleeds occurring on last dose level - summary - full analysis set.

	Last dose level			
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Total
Number of subjects	21	7	8	36
Number of subjects with no treated bleeding episodes, N (%)	6 (28.57)	2 (28.57)	4 (50.00)	12 (33.33)
Number of subjects with treated bleeding episodes, N (%)	14 (66.67)	5 (71.43)	4 (50.00)	23 (63.89)
Number of treated bleeding episodes	43	13	14	70
Cause of bleeding episodes, E (%)				
Spontaneous	16 (37.21)	8 (61.54)	2 (14.29)	26 (37.14)
Traumatic	26 (60.47)	5 (38.46)	12 (85.71)	43 (61.43)
Surgical	1 (2.33)	0	0	1 (1.43)
Missing	0	0	0	0
Location of bleeding episodes, E (%)				
Joint	22 (51.16)	8 (61.54)	14 (100.0)	44 (62.86)
Muscular	14 (32.56)	4 (30.77)	0	18 (25.71)
Skin	4 (9.30)	0	0	4 (5.71)
Gastrointestinal	1 (2.33)	0	0	1 (1.43)
Mouth, gums, nose	1 (2.33)	1 (7.69)	0	2 (2.86)
Urinary system	1 (2.33)	0	0	1 (1.43)
Central nervous system	0	0	0	0
Other	2 (4.65)	1 (7.69)	0	3 (4.29)
Missing	0	0	0	0
Classification of bleeding episode, E (%)				
Mild/moderate	43 (100.0)	10 (76.92)	14 (100.0)	67 (95.71)
Severe	0	3 (23.08)	0	3 (4.29)
Missing	0	0	0	0
Location of severe bleeding episodes, E (%)				
Joint	0	2 (15.38)	0	2 (2.86)
Muscular	0	2 (15.38)	0	2 (2.86)
Skin	0	0	0	0
Gastrointestinal	0	0	0	0
Mouth, gums, nose	0	0	0	0
Urinary system	0	0	0	0
Central nervous system	0	0	0	0
Other	0	0	0	0
Missing	0	0	0	0

N: number of subjects, %: percentage of subjects, E: number of bleeding episodes.
A bleed can have multiple locations. Last dose level is the individual highest dose level at time of analysis and hence, previous dose levels are disregarded.

The estimated ABR on each patient's last dose level (CPoC1) was 7.0 with 95% CI [4.6; 10.7]. The median ABR was 4.5. As the upper limit of 95% confidence interval was below 12, the CPOC1 criterion was met.

Table 17 Annualised bleeding rates during main phase - bleeds occurring by last dose level - summary and analysis - full analysis set.

	Last dose level			Main
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	At least 24 weeks
Number of subjects	21	7	8	36
Annualised bleeding rate				
N	20	7	8	35
Mean (SD)	7.5 (12.1)	9.3 (8.9)	8.6 (10.7)	8.1 (11.0)
Min ; Max	0.0 ; 52.2	0.0 ; 23.6	0.0 ; 26.7	0.0 ; 52.2
Median	4.3	8.6	3.2	4.5
P25 ; P75	0.0 ; 7.1	0.0 ; 15.3	0.0 ; 17.9	0.0 ; 14.3
N	20	7	8	35
Number of bleeding episodes	43	13	14	70
Duration (in years)	9.4	1.4	0.9	11.7
Primary analysis (CPoC1)*				
ABR estimate**				7.0
95% CI				4.6 ; 10.7
P-value				0.0064
Additional Analysis***				
ABR estimate**	4.9	9.1	13.8	
95% CI	3.1 ; 7.7	4.1 ; 20.5	6.1 ; 31.3	

N: number of subjects, SD: standard deviation, P25/75 is the 25th/75th percentile, Min: minimum, Max: maximum, CI: confidence interval, CPoC: clinical proof of concept, ABR: annualised bleeding rate. Last dose level is the individual highest dose level at time of analysis and hence, previous dose levels are disregarded. Duration is the period where subjects are on their last dose at time of analysis. * Based on a negative binomial model with log of exposure time in main phase as offset. Observations from the two-week run-in are not included. ** Lsmeans estimates of Annualised Bleeding Rate. *** Including actual concizumab dose level as additional factor in the primary analysis model specified above. One-sided p-value for tests of upper confidence limit below 12.

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The mean ABR was 7.5 in the 0.15 mg/kg, 9.3 in the 0.20 mg/kg and 8.6 in the 0.25 mg/kg dose level. There was less exposure time on last dose level for the patients who escalated to 0.20 mg/kg (1.4 years) and for those who escalated to 0.25 mg/kg concizumab (0.9 years) compared to the patients who stayed on 0.15 mg/kg (9.4 years) during the main part of the trial. The ABRs for the three different concizumab dose groups represent different selections of the patients, and therefore cannot be compared directly.

Secondary clinical proof of concept (CPoC2). During the entire treatment period of main part, a total of 31 patients reported 199 bleeding episodes during the main part of the trial. There were more spontaneous (122 episodes, 61.31%) than traumatic bleeding episodes (74 episodes, 37.19%), and 3 bleeding episodes (1.51%) were surgical. Most of the bleeds were joint bleeds (138 episodes, 69.35%) and muscular bleeds (44 episodes, 22.11%). Five (2.51%) bleeding episodes were severe; the remaining 194 (97.49%) were mild or moderate. The estimated ABR during the entire treatment period (CPoC2) was 13.9 with a 95% CI of [9.5; 20.3]. As the upper limit of the 95% confidence interval was not below 12, the CPoC2 criterion was not met. The median ABR was 9.5.

Table 40: Treated bleeding episodes during main phase - all bleeds occurring by escalation regimen - summary - full analysis set.

	Last dose level			
	0.15 mg/kg	0.20 mg/kg	0.25 mg/kg	Total
Number of subjects	21	7	8	36
Number of subjects with no treated bleeding episodes, N (%)	5 (23.81)	0	0	5 (13.89)
Number of subjects with treated bleeding episodes, N (%)	16 (76.19)	7 (100.0)	8 (100.0)	31 (86.11)
Number of treated bleeding episodes	51	45	103	199
Cause of bleeding episodes, E (%)				
Spontaneous	23 (45.10)	33 (73.33)	66 (64.08)	122 (61.31)
Traumatic	27 (52.94)	12 (26.67)	35 (33.98)	74 (37.19)
Surgical	1 (1.96)	0	2 (1.94)	3 (1.51)
Missing	0	0	0	0
Location of bleeding episodes, E (%)				
Joint	27 (52.94)	24 (53.33)	87 (84.47)	138 (69.35)
Muscular	16 (31.37)	16 (35.56)	12 (11.65)	44 (22.11)
Skin	5 (9.80)	5 (11.11)	11 (10.68)	21 (10.55)
Gastrointestinal	1 (1.96)	0	0	1 (0.50)
Mouth, gums, nose	1 (1.96)	2 (4.44)	4 (3.88)	7 (3.52)
Urinary system	1 (1.96)	0	0	1 (0.50)
Central nervous system	0	0	0	0
Other	2 (3.92)	2 (4.44)	1 (0.97)	5 (2.51)
Missing	0	0	0	0
Classification of bleeding episode, E (%)				
Mild/moderate	51 (100.0)	40 (88.89)	103 (100.0)	194 (97.49)
Severe	0	5 (11.11)	0	5 (2.51)
Missing	0	0	0	0
Location of severe bleeding episodes, E (%)				
Joint	0	3 (6.67)	0	3 (1.51)
Muscular	0	3 (6.67)	0	3 (1.51)
Skin	0	0	0	0
Gastrointestinal	0	0	0	0
Mouth, gums, nose	0	0	0	0
Urinary system	0	0	0	0
Central nervous system	0	0	0	0
Other	0	0	0	0
Missing	0	0	0	0

N: number of subjects, %: percentage of subjects, E: number of bleeding episodes.
A bleed can have multiple locations.

Secondary efficacy endpoint:

- The estimated spontaneous annualised bleeding rate (sABR) on each patient's last dose level was 2.5 with a 95% CI of [1.5; 4.3]. Improvement from baseline to week 24 was observed in the bodily pain domain of SF-36v2 and the effectiveness and the convenience domains of TSQM**.**

Summary of Safety

Adverse events during main part of the study with at least 24 weeks of treatment

A total of 29 patients reported 130 adverse events; 2 patients reported 2 SAEs between database cut-off and partial database lock.

- No AE lead to permanent treatment discontinuation or to withdrawal from the trial
- No deaths or thromboembolic events were reported
- Fourteen (14) patients (38.9%) reported 25 injection site reactions

In this study, a total of 232 bleeding episodes in 29 subjects were treated using breakthrough bleeding treatment (either rFVIII or other non-modified FVIII products), without safety issues including thrombo-embolic events.

Three (3) patients had anti-concizumab binding antibodies with no apparent effect

New dose regimen evaluations performed during treatment pause

The concizumab phase 3 clinical trials were initiated in October 2019. Concizumab treatment in phase 3 trials 4307, 4311 and phase 2 trial 4255 was paused in March 2020 due to the occurrence of 5 non-fatal thromboembolic events in 3 patients enrolled in the phase 3 programme, and the trials were subsequently put on clinical hold by FDA. Findings from investigations of the thromboembolic (TE) events and all available data at that time have led the applicant to implement changes to trial protocols to reduce the risk that additional patients treated with concizumab will experience thromboembolic events. Investigations of the TE events were presented, and mitigating actions were agreed with health authorities. The clinical hold was lifted by the FDA in August 2020, whereafter treatment in phase 3 trials was reinitiated.

Overview of non-fatal thromboembolic events in 3 patients

Five thromboembolic events in 3 patients enrolled in the phase 3 programme (Table 41) occurred. All events were non-fatal serious adverse events, deemed by the investigators as possibly or probably related to concizumab. In all 3 cases, the patient was using breakthrough bleed treatment for (definite or suspected) intercurrent bleeding events, in 2 patients with HA without inhibitors factor VIII (in one patient a single dose of 67 IU/kg, and in 1 patient 35 IU/kg almost every day during the study), and in HBwI factor rVII NovoSeven for 4 days (initially 89 mcg/kg TID, followed by 130 mcg/kg TID on day 4) preceding the TE events. Concizumab was permanently discontinued in all cases.

Table 41: Overview of 3 cases of non-fatal thromboembolic events

Case #/ Subject ID/ Trial ID/	TE description (preferred term)	Onset date/ Trial day	Severity	Causality	Action taken	Outcome
Case 1/	Acute myocardial infarction		Severe	Possible	Drug withdrawn	Recovered/resolved
Case 2/	Renal infarct		Severe	Possible	Drug withdrawn	Not recovered/not resolved
Case 3/	1. Deep vein thrombosis 2. Pulmonary embolism 3. Venous thrombosis		1. Moderate 2. Moderate 3. Mild	Probable *(all 3 events)*	Drug withdrawn *(all 3 events)*	Not recovered/ not resolved *(all 3 events)*

Note: based on available data as of 06 May 2020.

Details of breakthrough bleed treatment just before onset of the TE event

All 3 patients had used breakthrough bleed treatment just before the onset of symptoms for thromboembolic event. In 2 of the patients, either a relatively high dose or prolonged concomitant treatment with factor product occurred:

- Case 1 had treated a left knee joint bleed with Advate (67 IU/kg).
- Case 2 had treated a left wrist bleed with NovoSeven using one dose of 89 µg/kg on February 20, 3 doses of 89 µg/kg (every 8h) on February 21 and 3 doses of 130 µg/kg (every 8h) on February 22 and 23.

- Case 3 had treated with Advate (35 IU/kg) daily (with only 3 exceptions) throughout the trial and until event onset. After the first event the patient continued concizumab and treatment until onset of the second event, pulmonary embolism, on trial day 92.

Management of breakthrough bleed treatment

Concizumab is being developed for routine prophylaxis, and concizumab treatment alone is not to be used for management of breakthrough bleeds. Bleeding episodes requiring treatment will be managed according to the patient's hemophilia type. Patients with HA without inhibitors will be treated with factor VIII-containing products, patients with HB without inhibitors will be treated with factor IX-containing products and patients with hemophilia with inhibitors will be treated with Bypassing Agents (rFVIIa, aPCC or ByClot).

Concizumab has been shown to normalize the thrombin generation potential in the majority of treated hemophilia patients. Addition of FVIII, FIX, FVIIa or aPCC further increased the thrombin generation potential of plasma from concizumab treated patients or in plasma spiked with concizumab. It appears that the TE events observed during concizumab treatment could be related to this further increase in procoagulant activity, and that treatment of bleeding episodes in patients receiving concizumab prophylaxis could require less procoagulant compound compared to patients not receiving prophylaxis.

The applicant has conducted *in vitro* and *ex vivo* studies to further investigate the thrombin generation potential when combining concizumab and procoagulant agents, and results from both previous and new studies. The available *in vitro* and *ex vivo* human data did not show any signs of exaggerated pharmacology, as seen for emicizumab in combination with aPCC, when adding FVIII, FIX, rFVIIa or aPCC to concizumab-containing plasma. For rFVIIa and concizumab this is supported by results from a cuticle bleeding model in rabbits (see non-clinical AR). The *in vitro* and *ex vivo* data supported the following:

- For FVIII dosing at conditions where the free TFPI is suppressed by concizumab, data suggested that a more than 2-fold reduced dose of FVIII would be sufficient to obtain the same thrombin generation capacity in the plasma as a standard dose FVIII in the absence of concizumab.
- For FIX dosing in the presence of concizumab, data suggested that a 2-fold reduced dose of FIX would be enough to obtain the same thrombin generation capacity in the plasma as obtained with 1.0 IU/mL FIX in the absence of concizumab.
- Drug-drug interaction effects up to 40% were observed when rFVIIa was combined with concizumab. This should be considered when administering rFVIIa to patients on concizumab PPX.
- If the aPCC concentration was reduced 2-fold in the presence of concizumab, the same thrombin generation capacity in the plasma is obtained as with a standard concentration of aPCC in the absence of concizumab. This supported a 2-fold reduction of aPCC dosing in patients on concizumab PPX. Furthermore, drug-drug interaction contributed with an effect up to 23% when combining concizumab and aPCC. This should be considered when administering aPCC to patients on concizumab PPX.

Revised recommendations for treatment of mild to moderate breakthrough bleeding

- As the 2 TE events in HA patients without inhibitors in phase 3 study 4307 occurred with extensive regular use of FVIII concomitantly with concizumab PPX in case 3 and shortly after a relatively high FVIII dose (67 IU/kg in case 1), the recommended dosing of FVIII for the revised phase 3 protocols will be in line with the lower end of the WFH dosing recommendations, and prolonged dosing will be monitored.
- No data on management of bleeds in haemophilia B without inhibitors with FIX during daily concizumab PPX is currently available, as data from the phase 3 trials are blinded to Novo Nordisk personnel to avoid

bias. Like for haemophilia A without inhibitors a cautious approach will be used recommending FIX dosing level in the lower end of the WFH dosing recommendations.

- Based on the clinical experience as well as data presented, the recommended dose of rFVIIa in the revised phase 3 protocols will be 90 µg/kg, and not higher doses that may be approved outside the US.
- The clinical experience with co-administration of aPCC and concizumab is currently too limited to provide clinically based dosing guidance for aPCC. The dosing guidance for aPCC in the revised phase 3 protocols will be based on the in vitro data presented.
- In connection with the 3 TE events none of the patients had used antifibrinolytics.

The below guidance (Table 42) for treatment of mild and moderate bleeding episodes with FVIII, FIX, rFVIIa and aPCC, provides a more cautious approach to treatment of breakthrough bleeds than previously recommended for the concizumab phase 3 trials in order to minimize the risk of thrombotic events. In addition, PPX with factor replacement therapy for the first two weeks of concizumab treatment in trial 4307 will no longer be allowed.

Table 42: (revised) Guidance on management of mild and moderate bleeds during concizumab PPX.

Protocol	FVIII SHL	FVIII EHL	FIX SHL	FIX EHL	rFVIIa	aPCC**	ByClot®***
Contact centre (PI)	The patient should contact the centre before initiating treatment of a bleeding episode. If more doses are needed, the patient should contact the centre before each dose.						
First dose *	20 IU/kg	20 IU/kg	30 IU/kg	30 IU/kg	90 µg/kg	Single dose must not exceed 50 U/kg, and not exceed 100 U/kg within 24 hours	Single dose must not exceed 60 µg/kg ByClot®, and not exceed 90 µg/kg ByClot® within 24 hours
Second dose	20 IU/kg	20 IU/kg	30 IU/kg	At investigator's discretion	90 µg/kg	At investigator's discretion	Additional dose can be given at an interval of 8 hours or longer
Dose interval	Time between first and second dose must not be shorter than stated in local labelling****						
Anti-fibrinolytics	Local/topical use is allowed. Use of single systemic doses is allowed after careful benefit-risk evaluation					Not recommended	Not recommended

*Lowest dose in accordance with local labelling. **For treatment of bleeds, the dose must not exceed a single dose of 50 U/kg FEIBA®, and not exceed 100 U/kg within 24 hours. The first treatment should be at the hospital, with observation of the patient for a minimum of 24 hours. If there are no safety concerns, the patient can continue with FEIBA® treatment for breakthrough bleeds at home. Single dose home treatment must not exceed 50 U/kg. If an additional dose is needed, the patient must come to the site.
***For treatment of bleeds, the dose must not exceed 60 µg/kg ByClot®, and not exceed 90 µg/kg ByClot® within 24 hours. Additional dose can be given at an interval of 8 hours or longer. The first treatment should be at the hospital, with observation of the patient for a minimum of 24 hours. If there are no safety concerns, the patient can continue with ByClot® treatment for breakthrough bleeds at home. Single dose home treatment must not exceed 60 µg/kg. If an additional dose is needed, the patient must come to the site.
****The interval between the two doses could be increased based on clinical case-by-case judgment keeping in mind that early breakthrough bleed control remains crucial. Abbreviations: SHL=standard half-life, EHL=extended half-life

Severe and life-threatening bleeding episodes

In the rare event of a severe (life-threatening) bleed the patient should be in immediate and close contact to the investigator and be treated with relevant doses of factor containing products at the discretion of the investigator.

Surgery

Elective, planned major surgery will not be allowed during the revised phase 3 trials. This is justified by a cautious approach as major surgery 'per se' is a well-established thrombotic risk factor and major surgery is often requiring several days of intense factor replacement therapy in the perioperative period. Given the 3 thromboembolic events and very limited experience with major surgeries in concizumab-treated patients, a conservative approach minimizing the risk of thrombotic events is suggested. Minor surgery, that in many ways resembles a mild bleeding episode and often requires one or two doses of factor replacement therapy, will be allowed during phase 3. More than 30 minor surgeries including dental procedures were performed during the phase 2 trials without any observed safety issues.

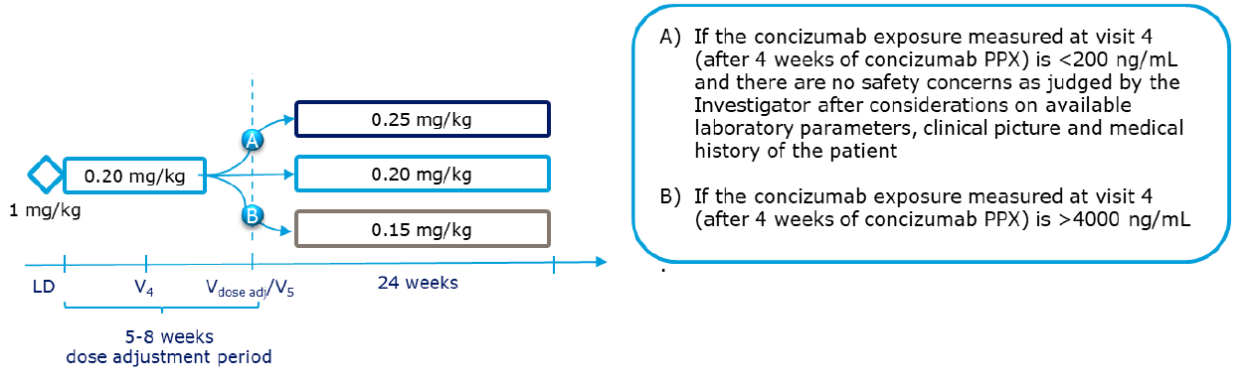
Investigator interactions and training

Investigator interactions are essential in creating a more controlled, structured and safe environment in the management of bleeds. Therefore, the need for close contact between patient and investigator will be more strongly emphasized in the phase 3 protocols. It was emphasised that it is the investigator that is deciding on the dose level if a bleed needs to be treated. Furthermore, it is important that patients are trained in the management of bleeds, and the applicant will therefore provide additional training to site staff and develop new patient material. Additionally, clear guidance on involvement of investigators during prolonged treatment of bleeding episodes will be established to eliminate unnecessary prolonged dosing.

Dosing level investigations

The applicant proposes a new concizumab dosing regimen with a loading dose of 1 mg/kg and an initial daily dose of 0.20 mg/kg. Within an initial 5−8-week dose adjustment period on 0.20 mg/kg concizumab, the patients can be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab; this will be based on the concizumab exposure level at the week 4 visit. The single loading dose of 1 mg/kg concizumab is unchanged and is included to decrease the time to steady state, see Figure 53**:**:

Figure 33 Proposed concizumab dosing regimen upon restart of phase 3 trials

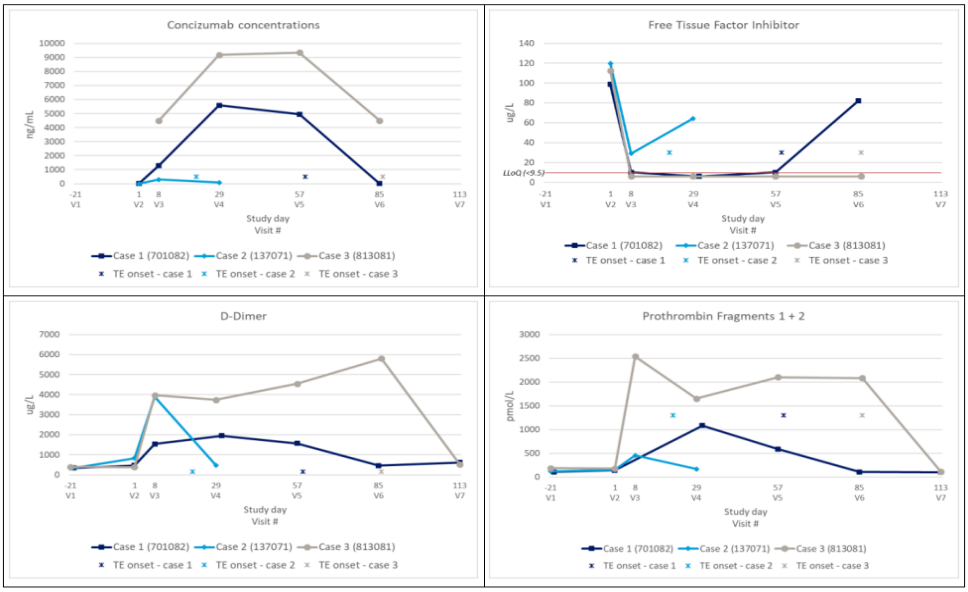


The decrease in the daily concizumab dose is based on 2 of 3 patients experiencing TE events were among the patients with concizumab exposure at the higher end of those observed in phase 2 studies, and the

general observation that the concizumab exposures observed in phase 3 were higher than expected based on the observed phase 2 main part data and the population PK model predictions.

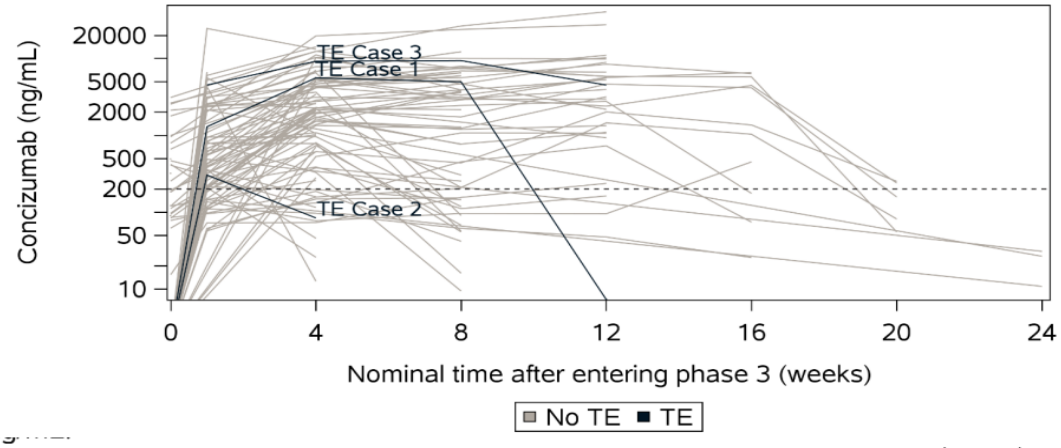
Exposure to concizumab and PD parameters in 3 subjects with TE events. Two (2) of the 3 patients (case 1) and patient (case 3) had concizumab exposure levels in the higher end (>5000 ng/ml) of these seen in the main part of the phase 2 trials together with free-TFPI levels <LLOQ. In line with observations in other patients and what had previously been published for the phase 2 trials, elevated D-dimer and prothrombin fragments 1+2 (F1+2) levels were observed after trial entry (Figure 54**:**). Other coagulation parameters were as expected in this population (APTT, PT and INR). Platelets, fibrinogen, antithrombin were normal, as were hematologic parameters, liver enzymes and creatinine.

Figure 34 Plots of selected laboratory parameters for the 3 patients with thrombotic events.



Further, the concizumab exposures observed in phase 3 were higher than expected based on the observed phase 2 main part data and the population PK model prediction (Figure 55**:**)

Figure 35 Observed exposure of concizumab after loading dose 1 mg/kg and daily maintenance dose of 0.25 mg/kg for patients with thrombotic events vs those without (trials 4311 and 4307).



nn7415/nn7415-exploratory/nheot005
12MAY2020:15:42:26 - f-czm-sp-fas.sas/f-czm-sp-ph3-fas.png

Abbreviations: TE = thromboembolic event. Note: The cut-off date for these results is April 27, 2020. The horizontal dashed line indicated the target concizumab exposure level above 200 ng/mL.

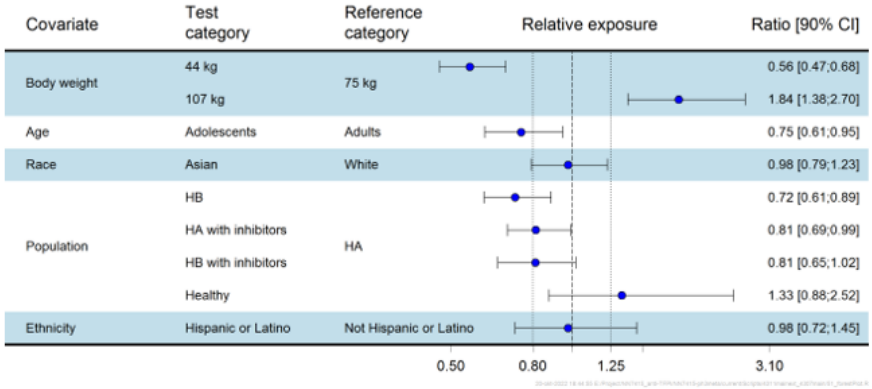
Population PK modelling. Two population PK models were developed. The first model was developed based on phase 1 data only, while the second model also used phase 2 data. The new, phase 2 PK model was better able to predict exposure and showed that exposure was underpredicted in the first model. The phase 2 model was used to support the phase 3 dosing regimen, including the loading dose of 1.0 mg, the initial maintenance dose (0.20 mg/kg) and the maintenance doses (0.15, 0.20 or 0.25 mg/kg) based on concizumab exposure at week 4.

The aim of re-evaluating the MM PK model was to use pooled phase 1 (all dose levels included) and phase 2 main part data to provide a generally applicable model to describe the PK of concizumab. This was accomplished by fitting a target-mediated drug disposition (TMDD) model to all available data. To get the most accurate description of the concizumab PK, the TMDD PK model was initially developed based on richly sampled PK data from the phase 1 trials, which ensured stability of the model. The main changes between the MM and the TMDD population PK models were (1) the addition of concizumab binding to TFPI at the endothelium and elimination via endocytosis, instead of the non-linear clearance pathway. Also, (2) delayed absorption through a transit compartment has been implemented instead of a split absorption with parallel fast and slow absorption pathways, (3) the increase in bioavailability with dose has been removed, and (4) all dose levels were included in the TMDD model, whereas in the MM model, doses below 0.25 mg/kg in the single-dose trial 3813 were not included.

The PK of concizumab in phase 3 was described by a 2-compartment model with combined linear clearance and TMDD based on data from all phases 1 and 2, data obtained up until the 56-week cut-off in trial 4311 in HAwI and HBwI patients and data obtained up until the confirmatory analyses cut-off in trial 4307 in HA and HB patients. A total of 366 participants with 6,710 PK samples were included in the population analysis.

The concizumab PK model was used to evaluate covariate effects on concizumab exposure, the impact of maintenance dose setting on concizumab exposure and the effect of changing timing intervals between doses based on predicted steady-state average concizumab plasma concentration. The effect of different covariates was investigated relative to a reference subject (non-Hispanic or Latino, White, adult male ≥ 18 years, body weight 75 kg) based on simulated steady-state exposure for 0.20 mg/kg concizumab in all subjects. The most important covariate for predicting concizumab exposure was body weight, with exposure increasing with increasing body weight. However, due to the maintenance dose setting after 4 weeks of treatment, patients with low (or high exposure) should increase (or decrease) dose, resulting in more similar exposure across patients. Further, exposure-response analysis showed that, due to the steep exposure-response curve, close to the maximum effect of concizumab is reached already at 200 ng/mL. Most patients had exposure above 200 ng/mL, and differences in exposure above this level have little clinically relevant impact on the effect of concizumab.

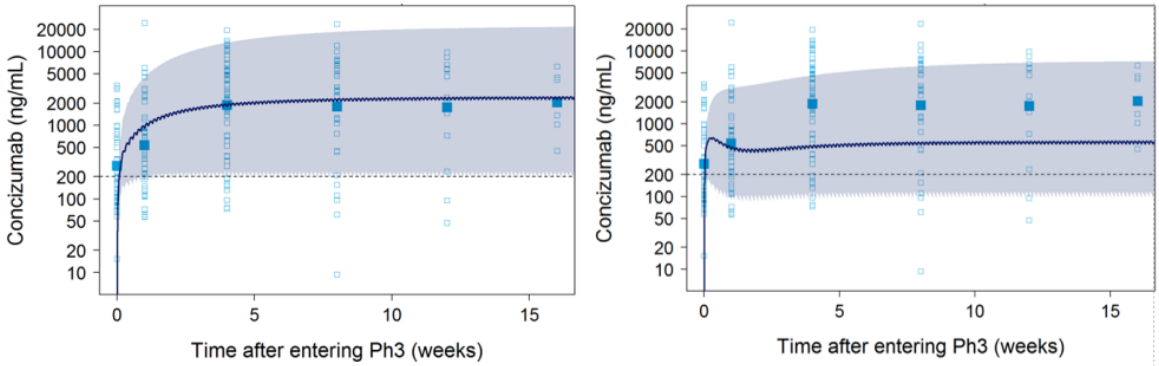
Figure 36 Forest plot of covariate effects on concizumab exposure (0.20 mg/kg).



Notes: Data is expressed as steady-state average concizumab concentrations (C_{avg}) following administration of 0.20 mg/kg relative to the reference subject profile, based on the full population PK model. The reference subject profile was non-Hispanic or Latino, White, adult male (≥18 years), with a body weight of 75 kg not enrolled in phase 3. The points and bars (the column on the right) show point estimates (based on the maximum likelihood estimates) and 90% confidence intervals based on SIR relative to the reference subject. The reference body weight of 75 kg corresponds to the approximate median in the population. Body weight test categories (44 and 107 kg) represent the 5% and 95% percentiles, respectively in the data set. Vertical dotted lines indicate the [0.80;1.25]-limits.
Abbreviations: HA: Haemophilia A, HB: Haemophilia B.

A good fit was seen between the observed phase 3 exposure results (blue squares), and the TMDD model predictions (solid blue line and shaded area, Figure 57**:**). The MM model underpredicted the mean exposure and the variability in data. Note that limited phase 3 exposure results were available after week 8.

Figure 37 TMDD (left) and MM (right) population PK model predictions of the concizumab exposure following a loading dose of 1 mg/kg and a daily maintenance dose of 0.25 mg/kg concizumab.

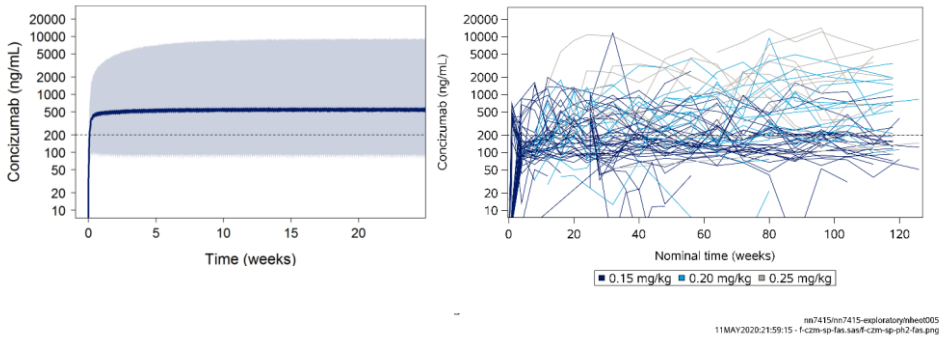


Note: the dark blue line represents the geometric mean, and the shaded area is the 90% prediction interval. The blue squares represent the observed phase 3 results from trials 4311 and 4307 with the solid symbols showing the geometric mean and the open symbols showing the individual, observed data points.

The higher predicted exposure by the TMDD model, together with the observation that 2 out of the 3 patients with thrombotic events were among the patients with the highest concizumab exposure, has led to the choice to restart all patients on the initial daily dose of 0.20 mg/kg instead of 0.25 mg/kg concizumab.

The predicted exposure level with the proposed dosing regimen, i.e a loading dose of 1 mg/kg concizumab followed by an initial daily dose of 0.20 mg/kg concizumab, is shown in Figure 58**:** -left panel and specific values for exposure-related key parameters are shown in Table 43. The observed exposure range in the phase 2 trials (trials 4310 and 4255) covers the predicted exposure in phase 3 following a daily dose of 0.20 mg/kg concizumab. Therefore, the phase 2 results are used to support the safety and provide information on the efficacy of the initial daily dose of 0.20 mg/kg concizumab.

Figure 38 Predicted exposure of concizumab in phase 3 trials (left) and observed exposure in the phase 2 trials 4310 and 4255 (right).



Notes: In the left side figure, the predicted geometric mean exposure is shown by the solid blue line, and the shaded area designated the 90% PI. Predictions are based on the PK model with TMDD, for the phase 3 population dosed with a loading dose of 1 mg/kg followed by once-daily doses of 0.2 mg/kg. In the right side figure, the observed exposure in the phase 2 trials is shown by dose level. The horizontal dashed line indicated the target concizumab exposure level above 200 ng/mL.

Safety of 0.20 mg/kg concizumab. Based on the two phase 2 trials, concizumab treatment was safe and well tolerated. No deaths or thromboembolic events have occurred. No AEs led to withdrawal. Additionally, few SAEs have been reported; all except for 1 (atypical pneumonia) have been assessed as unlikely related to concizumab (see safety section for details on safety).

PD parameters. In the main parts of trials 4310 and 4255, increasing concizumab exposure was associated with lower free TFPI and normalized thrombin generation potential; this was observed for all concizumab dose levels and all three hemophilia subtypes (HA, HAwI, HBwI).

Elevated D-dimers and prothrombin fragments 1+2 (F1+2) were observed in patients treated with concizumab indicating the procoagulant effect of concizumab. D-dimers and F1+2 seemed to increase with increasing concizumab plasma concentrations. For other coagulation laboratory parameters (e.g. fibrinogen, PT, INR, APTT and AT), no clinically significant changes were seen among the different concizumab dose groups and their level remained the same.

Efficacy of 0.20 mg/kg concizumab. In the main + extension parts of trial dose-response trial 4310 (explorer 4), 25 patients have been exposed to concizumab. All patients had an initial daily dose of 0.15 mg/kg, that could be escalated in case a patient experienced ≥ 3 spontaneous treated bleeding episodes within the preceding 12 weeks, to either 0.20 or (in a second escalation step) 0.25 mg/kg t concizumab. In trial 4310, a total of 9 patients had 0.20 mg/kg concizumab as their last dose level. The mean (SD) ABR for this group, only including the time they were on 0.20 mg/kg concizumab, was 3.2 (4.1), and the median ABR was 1.6.

In trial 4255, a total of 9 patients had 0.20 mg/kg concizumab as their last dose level. The mean (SD) ABR for this group, only including the time they were on 0.20 mg/kg concizumab, was 5.0 (6.8), and the median ABR was 1.9.

It is recognized that these data could contain some bias for the 0.20 mg/kg dose because the patients who are not sufficiently protected against bleeds are escalated to the highest dosing level.

Based on the safety and efficacy results presented above, 0.20 mg/kg was identified as an appropriate starting dose for all patients, with the possibility to make one dose adjustment based on the exposure level to bring the maximum number of patients within the expected target window for concizumab exposure.

Criteria for increasing or decreasing the concizumab maintenance dose of 0.20 mg/kg. Evaluation of concizumab exposure is performed after 4 weeks on the initial daily dose. Concizumab exhibits target mediated drug disposition (TMDD), which is associated with a high within- and between-patient variability in drug exposure. The non-linear pharmacokinetics leads to a faster target-mediated clearance mainly at lower concentration when the target is unsaturated. With higher target saturation, the clearance is lower, and the half-life becomes longer. Therefore, evaluation of exposure is performed after 4 weeks on the initial daily dose. This is considered an appropriate timeframe for evaluating exposure since most patients are expected to have reached their steady state exposure level while also ensuring safety.

Increasing maintenance dose. The daily maintenance of concizumab can be *increased to 0.25 mg/kg* if the concizumab exposure measured after 4 weeks of concizumab PPX is <200 ng/ml and there are no safety concerns by the Investigator after considerations on available laboratory parameters, clinical picture and medical history of the patient. Around 28% of patients on 0.20 mg/kg are predicted by the TMDD population PK model to have a measurement below 200 ng/mL of whom 24% can still, occasionally, be below this level despite increasing the dose to 0.25 mg/kg.

The target of concizumab exposure levels above 200 ng/mL emanates from an exploratory exposure-response analysis performed based on the phase 2 (trials 4255 and 4310) main part data. The individual PK profiles over time were well predicted for the phase 2 main part patients using the MM population PK model, thus the individual concizumab concentration at the time of a bleed could be estimated. Only the time patients were on 0.15 mg/kg was included to avoid any bias from the higher dose levels since these patients were pre-selected as frequent bleeders. Thus, the exposure-response shows that above 200 ng/mL, there is a trend towards a lower bleeding rate (Table 433).

Table 43: Predicted annualised bleeding rates for different concizumab exposure intervals based on main parts results from trials 4255 and 4310.

Concizumab exposure (ng/mL)	Number of subjects	Subjects with bleeds	Number of bleeds	Total exposure years	ABR
0–100	53	30	71	6.64	10.7
100–200	47	29	88	8.96	9.82
200–500	25	11	19	5.05	3.77
500–1000	13	5	9	2.32	3.88
>1000	8	3	5	1.04	4.81

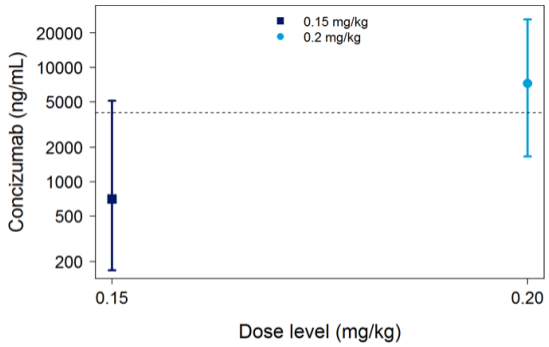
Abbreviation: ABR = annualized bleeding rate

Decreasing the maintenance dose. The daily maintenance of concizumab must be *decreased to 0.15 mg/kg* if the concizumab exposure measured after 4 weeks of concizumab PPX is above 4000 ng/mL. This is predicted to be the case for around 9–12% of patients on 0.20 mg/kg concizumab. Approximately 7% of patients, who were initially above 4000 ng/mL, are still expected to have occasional exposure levels above 4000 ng/mL after decreasing the daily dose to 0.15 mg/kg concizumab. In combination with the cautious approach to breakthrough bleed treatment, this is considered acceptable.

Two of the 3 patients with thrombotic events in phase 3 trials showed exposure levels above 5000 ng/ml. The data do not show that high exposure per se is causative of thrombotic events, but the observation suggests that the concizumab exposure in combination with other risk factors could contribute to thrombosis. Therefore, to avoid patients reaching constant very high concizumab exposure levels, a cut-off of 4000 ng/mL at week 4 was chosen. Based on the TMDD population PK model predictions, decreasing the maintenance dose from 0.20 mg/kg to 0.15 mg/kg for the patients who are predicted to present with concizumab exposure levels above 4000 ng/mL at week 4, leads to the majority of patients having steady-state exposure well below 4000 ng/mL. Due to the high variation in concizumab exposure, individual patient

exposure levels can occasionally be above 4000 ng/mL during the trial; this should not trigger a reduction in dose, since exposure levels above 4000 ng/mL were observed in phase 2 without any safety concerns.

Figure 39: Steady-state exposure for subpopulation above 4000 ng/mL after 4 weeks of concizumab PPX if staying on 0.20 mg/kg(right) vs if decreasing daily maintenance dose to 0.15 mg/kg.

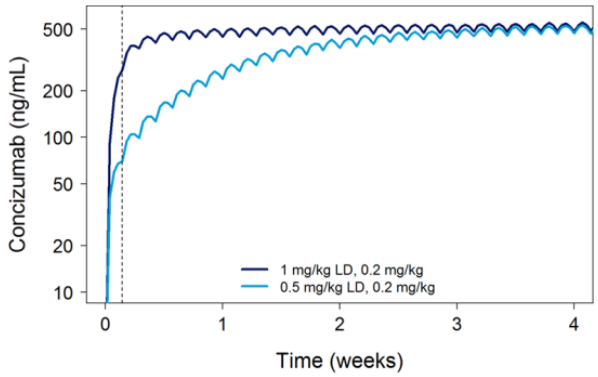


Notes: The point designates the geometric mean, and the error bars shown the 90% prediction interval for the steady-state exposure on a logarithmic scale.

Additional parameters (e.g., free TFPI, bleeds, D-dimers and prothrombin F1+2) have been considered for the adjustment of the concizumab maintenance dose. However, based on the currently available data, these were found to increase the complexity while not substantially contributing to increasing the patients' safety. Thus, the increase or decrease of the daily concizumab maintenance dose is based solely on concizumab exposure level. In haemophilia clinical practice, dose adaptation based on a laboratory parameter (e.g., FVIII dosing with trough level) is standard of care, but it should be as simple as possible and infrequent.

Loading dose. A single loading dose of 1 mg/kg is still considered appropriate with a daily dose of 0.20 mg/kg and is included to decrease the time to steady state. In the TMDD population PK model, the bioavailability is independent of the dose. Based on this model, a loading dose of 1 mg/kg leads to a similar exposure as steady-state exposure after daily maintenance doses of 0.20 mg/kg. Using a loading dose of 0.5 mg/kg would delay the time to the steady-state exposure of 0.20 mg/kg concizumab (Figure 60**:**). Furthermore, this loading dose is considered safe based on concizumab phase 1 results where single doses up to 9 mg/kg i.v. and 3 mg/kg s.c. were assessed, resulting in much higher exposures, without any safety concerns.

Figure 60: Comparison of loading doses of 0.5 mg/kg and 1 mg/kg followed by daily maintenance doses of 0.2 mg/kg using the TMDD population PK model.



Abbreviation: LD = loading dose

Note: the dark blue line shows the geometric mean exposure using a loading dose of 1 mg/kg, followed by a maintenance dose of 0.20 mg/kg concizumab. The light blue line shows the geometric mean exposure using a loading dose of 0.5 mg/kg, followed by a maintenance dose of 0.20 mg/kg concizumab

2.6.5.2. Main studies

Treatment pause March 2020 of studies 4311, 4307, 4255

The concizumab phase 3 clinical trials were initiated in October 2019. Concizumab treatment in trials 4307, 4311 and 4255 was paused in March 2020 as discussed in the dose response study section 2.6.5.1 (New dosing regimen evaluation performed during treatment pause). After implementing mitigating actions and changes to trial protocols the clinical hold was lifted by the FDA in August 2020, whereafter treatment in phase 3 trials was reinitiated.

The two phase 3 studies **Study 4311 (Explorer 7)** and **Study 4307 (Explorer 8)** are considered the main studies. Since study 4311 included the target population with HawI or HbwI, this is considered the pivotal study. The designs and efficacy data of these studies are discussed here.

Study 4311 – Explorer 7

Methods

Study design. Trial 4311 is a 4-armed multi-national, multi-centre, open-label, confirmatory trial in adolescent and adult patients with HAwI or HBwI, of which the randomised part of this study, arm 1 and arm 2, is designed to compare the effect of concizumab PPX to no PPX (on demand treatment with intravenous replacement with factor-containing products) in reducing the number of bleeding episodes. Arm 3 and arm 4 consist of patients allocated to concizumab PPX treatment only, that primarily contribute with additional safety and PK/PD data. The study design is presented below.

Trial 4311 was global and had sites in the following countries: Algeria, Australia, Austria, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Czech Republic, Denmark, Estonia, France, Germany, Hungary, India, Israel, Italy, Japan, Lithuania, Malaysia, Mexico, Poland, Portugal, Republic of Korea, Russian Fed., Serbia, South Africa, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, United Kingdom and United States.

Updated trial design after the treatment pause

Below the updated trial design after the concizumab treatment pause and treatment restart. For the details on the original trial design and treatment arms before the concizumab treatment pause it is referred to [Protocol version 2.0].

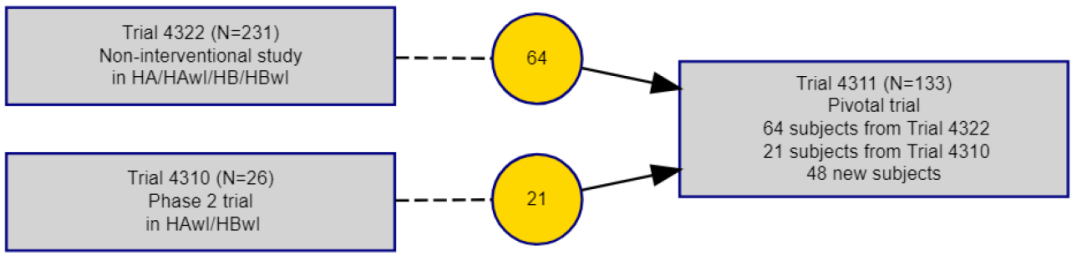
The trial consisted of a 3 week screening period, a main part (24-32 weeks treatment period), an extension part (128-136 weeks treatment period) and a 7 week follow-up period.

The trial consists of the following 4 arms:

- Arms 1 and 2 consisted of patients previously treated on demand who were randomised to Arm 1: On demand administration with i.v. replacement with factor-containing products and Arm 2: Concizumab PPX treatment. Eligible for randomization to arm 1 or 2 were participants from study 4322 (NIS study, see below), or subjects previously treated on demand, with at screening >= 6 documented treated bleeds in the last 24 weeks or >= 12 treated bleeds in the last 52 weeks.

- Arm 3 consisted of HAwI and HBwI patients enrolled into the concizumab phase 2 trial 4310 (explorer 4)) who were offered enrolment into arm 3 of trial 4311 (approx. 25 patients). All patients from study 4310 were transferred to the phase 3 trial 4311. Patients were on concizumab PPX up until enrolment into the trial. They continued concizumab PPX and had a combined visit 1 and 2.
- Arm 4 included approximately 60 patients previously on prophylaxis with by-passing agents as well as any on demand patients who were screened at a timepoint where the required number of patients in arms 1 and 2 had been randomised.

Figure 61: Patient flow from study 4322 and trial 4310 to trial 4311.



Trial population. In total, 136 patients were expected to be enrolled in this trial. It included patients enrolled before as well as after the concizumab treatment pause. The aim was to have approximately 15 unique HAwI and HBwI adolescent patients defined as patients between ≥12 to<18 years at trial start.

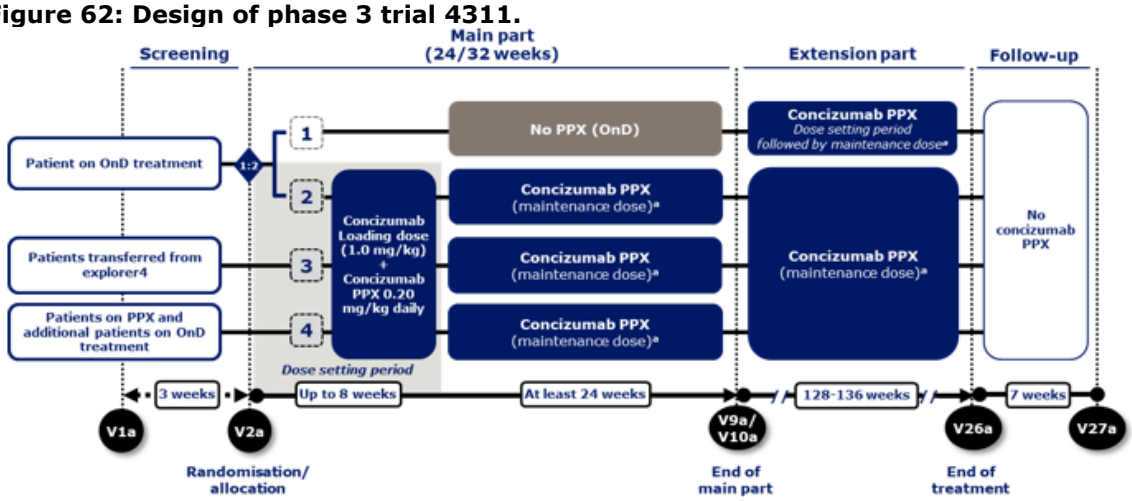
Table 18: Planned randomisation/enrolment overview

	Number of patients planned to be randomised/enrolled			
	Arm 1	**Arm 2**	**Arm 3**	**Arm 4 (PPX or on demand)**
HAwI	9	18	Up to 15	60
HBwI	8	16	Up to 10	

Main study part. In the design of the study before the treatment pause, no dose setting period was included and the main part of the study was 24 weeks for all arms. After treatment pause, a **dose-setting period of up to 8 weeks** for subjects on concizumab PPX was introduced (see Treatment discussion further below). The main part of the trial was completed after completion of at least 24 weeks of participation (screening period not included) for patients in arm 1 or at 32 weeks of participation (screening period not included, but with the additional dose setting period) for patients in arms 2, 3 and 4. The longer duration of main part for arms 2, 3 and 4 was due to the 8 week dose adjustment period in these arms.

Extension part. After the main part of the trial, all patients were offered to continue in the extension part of the trial and receive treatment with concizumab for up to an additional 128 weeks (arms 2-4) or 136 weeks (arm 1, including an 8 weeks dose setting period), see figure below.

Figure 62: Design of phase 3 trial 4311.



Notes: [a]The individual maintenance dose will be either 0.15, 0.20 or 0.25 mg/kg concizumab (see Section 1.3.6). Explorer4 = trial 4310. **Abbreviations**: OnD: on demand, PPX: prophylaxis, V: visit.

The primary analysis cut-off (PACO) at 24 weeks. PACO was to be performed when all patients in arm 1 have completed visit 9/9a (or withdrawn) and all patients in arm 2 have completed visit 10a (or withdrawn), corresponding to at least 24 weeks of treatment (end of main part).

Furthermore, a **56 week cut-off** is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment).

Choice of comparator. Comparison to on demand treatment was considered relevant as not all countries use PPX as standard of care for patients with inhibitors even though recommended by the WFH2 (for HBwI no good PPX treatment exists, and for HAwI not all countries have access to emicizumab). Therefore, inclusion of the no PPX arm serves as randomised control in this setting. Based on these considerations, comparison of PPX and no PPX serves as a scientifically as well as ethically justified control to demonstrate the effect of concizumab.

Choice of open-label design The trial was open label, as double-blinding the s.c. concizumab treatment and i.v. on demand treatment would require a double-dummy approach. In patients with haemophilia, injections with placebo are considered unethical due to the increased risk of haematoma.

- **Study Participants**

Key inclusion criteria were males aged ⩾12 years, with congenital Haemophilia A or B of any severity with documented history of inhibitor (⩾0.6 BU), who had been prescribed, or in need of, treatment with bypassing agents in the last 24 weeks prior to screening (for patients not previously enrolled in phase 2 study 4310 (Explorer 4)). Further, body weight >25 kg at screening.

Additional inclusion criteria for randomized arm 1 and 2 were >= 6 documented treated bleeds in the last 24 weeks or >= 12 treated bleeds in the last 52 weeks prior to screening.

Key exclusion criteria were known inherited or acquired coagulation disorder other than congenital haemophilia. Further, history of thromboembolic disease, current clinical signs of, or treatment for thromboembolic disease and patients who in the judgement of the investigator were considered at high risk of thromboembolic events. Further, ongoing or planned Immune Tolerance Induction treatment.

Only male patients were included. Females have not been included in the concizumab development programme, as female patients with moderate or severe haemophilia are rare. According to the WFH 2020 survey, 3.4% of the HAwI population and 5.4% of the HBwI population are female. Among patients with severe or moderate haemophilia admitted to treatment centres in the US, females account for a small proportion of patients, ranging from less than 0.5% to a little more than 1%. The number of female patients diagnosed with congenital haemophilia with inhibitor development worldwide is therefore expected to be very low. One female patient is receiving compassionate use of concizumab on an individual patient basis.

Discontinuation of concizumab. Discontinuation from trial product was required in case of a significant thromboembolic event, Disseminated Intravascular Coagulation (DIC), Thrombotic Microangiopathy (TMA), of an event of severe or serious hypersensitivity reaction related to concizumab.

Temporary discontinuation of concizumab was required in case a patient tested positive for COVID-19, and restarted only after the patient tested negative for COVID-19 or had fully recovered. If a randomised patient due to the COVID-19 pandemic was prevented from restarting the new dosing regimen, data from the patient would no longer be used to determine the primary analysis cut-off. However, this exception did not affect the actual cut-offs.

Surgery. Minor surgical procedures were allowed during the trial. During the perioperative period, patients continued daily concizumab prophylaxis. Planned major surgery was not allowed. For more information it is referred to section Surgery in Ancillary analysis.

- **Treatments**

Concizumab dose regimen **before** treatment pause

The dosing regimen was a loading dose of 1.0 mg/kg concizumab s.c. on the first day of treatment, followed by a maintenance dose of 0.25 mg/kg concizumab given as daily s.c. injections from the second day and onwards. A single dose escalation to 0.35 mg/kg/day concizumab was permitted, but only during the extension part of the trial, if an individual patient experience ≥2 bleeding episodes during a period of 6 consecutive months of concizumab prophylaxis.

Concizumab is administered by subcutaneous injection to the abdomen or thigh, using a a ready to administer pre-filled multidose pen-injector (PDS290 pen-injector).

*Rationale of dose regimen **before** treatment pause*

The initial dosing regimen was supported by integrated analyses of PK, PD, effect and safety data from the completed main parts of the phase 2 trials 4310 (explorer 4) and 4255 (explorer 5). It also was supported by modelling using data collected in the entire clinical development programme. The safety of 0.25 and 0.35 mg/kg/day concizumab was further justified based on non-clinical studies. In addition, results from prior clinical trials, where higher single doses of concizumab have led to exposures well above or in the same range as the exposures predicted for daily doses of 0.35 mg/kg concizumab, did not lead to raised safety concerns.

Treatment instructions during and after treatment pause

Arm 1: Patients randomised to arm 1 (on-demand treatment) before the treatment pause were instructed to continue their on-demand treatment during the pause and report data until treatment was restarted. Patients included prior to the treatment pause, restarted the trial at visit 9a. After restart patients used on demand treatment up to at least 24 weeks (main part). Upon completion of the main part, arm 1 patients started the

new concizumab dosing regimen in the extension part of the trial and were planned to receive up to 136 weeks of concizumab PPX.

Arm 2: Patients who were randomised to arm 2 before the treatment pause were instructed to discontinue their concizumab treatment during the pause. These patients received available standard of care treatment during the pause. Upon restart, patients received the new concizumab dosing regimen from visit 2a.

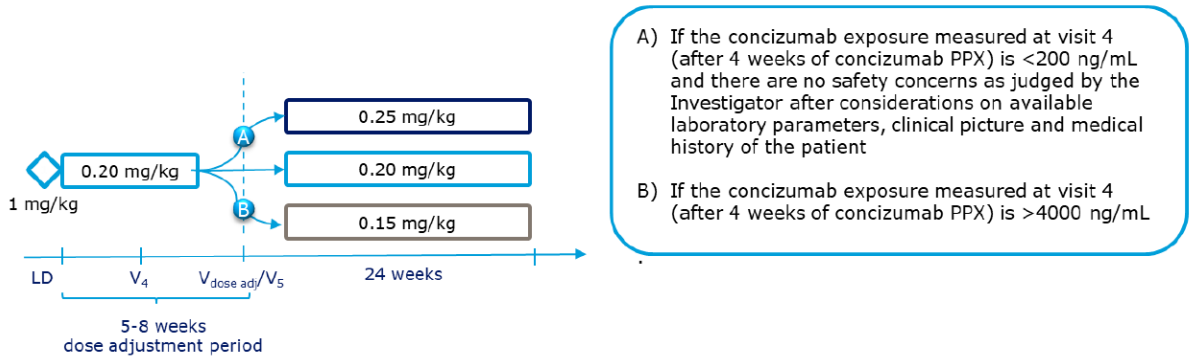
Arm 3: All patients in arm 3 were transferred to trial 4310 (phase 2 dose-response study, explorer 4) before the treatment pause. Upon restart, these patients received the new concizumab dosing regimen from visit 2a.

Arm 4: Patients enrolled into arm 4 before the pause discontinued their concizumab treatment during the treatment pause and received available standard of care treatment during the pause. Patients restarting in arm 4 as well as new patients allocated to arm 4 received the new concizumab dosing regimen from visit 2a.

Concizumab dose regimen **after** treatment pause

A new concizumab dosing regimen was applied with a loading dose of 1 mg/kg and an initial daily dose of 0.20 mg/kg. Within an initial 5–8-week dose adjustment period on 0.20 mg/kg concizumab, the patients can be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab; this will be based on the concizumab exposure level at the week 4 visit. The single loading dose of 1 mg/kg concizumab is unchanged and is included to decrease the time to steady state, see Figure 63::

Figure 40 Proposed concizumab dosing regimen upon restart of phase 3 trials.



The schematic dosing regimen is:

- Day 1: a single loading dose of 1 mg/kg.
- Day 2 once daily dosing of 0.20 mg/kg until individual maintenance dose setting at 4 weeks
- 4 weeks after initiation of treatment: measurement of concizumab pre-dose plasma concentration by concizumab enzyme-linked immunoassay (ELISA)
- individual maintenance dose is set once based on concizumab plasma concentration as indicated below (Table 45).

Table 19: Dose adjustment based on concizumab exposure level.

Concizumab exposure level	Type of visit	Visit window[a]	Acti
>4000 ng/mL	Site or phone visit allowed	2 working days from receipt of the laboratory report on the concizumab exposure level to patient contact	The investigator must decrease the daily maintenance dose to 0.15 mg/kg
200-4000 ng/mL	Phone visit	1 week from receipt of the laboratory report on the concizumab exposure level.	The patient must be informed that no dose adjustment was needed. Also, the investigator must document that the report from the central laboratory was received and that no action was needed.
<200 ng/mL	Site visit required	1 week from receipt of the laboratory report on the concizumab exposure level. Note: this visit cannot be earlier than 6 weeks after the previous dispensing visit 2a (arms 2–4) or 9a (arm 1).	The investigator can increase the daily maintenance dose to 0.25 mg/kg concizumab, if there are no safety concerns based on available laboratory parameters, clinical picture and medical history of the patient.

[a]Visit window for 4a.1/9a.3 must not exceed the timing of visit (weeks) and visit window (days) defined in the flowchart in Section 2

For the *rationale for the new dose regimen* after treatment pause, please refer to the dose response study section 2.6.5.1. - New dosing regimen evaluation performed during treatment pause.

Concizumab medicinal product. Investigational medicinal product consisted of the drug constituent (concizumab C 40 mg/mL and 100 mg/mL) and a device constituent (a PDS290 pen-injector). Only the Prefilled pen-injector, Concizumab PDS290 pen-injector, is to be used for administration of concizumab, in this trial. Only needles provided by Novo Nordisk must be used for administration of trial product.

Investigational medical device (in vitro diagnostic device). The concizumab-ELISA is an enzyme-linked immunosorbent assay (ELISA) intended to quantitate the concentration of concizumab in human citrated plasma from patients included in the concizumab clinical trials. The concizumab-ELISA has been used throughout the clinical development programme for measuring concizumab exposure (PK). The concentration of concizumab in human citrated plasma measured by this assay will also be used as the point of reference for dose adjustments in the phase 3 clinical trials for concizumab. All other samples will be analysed using the concizumab-ELISA. FDA has approved an investigational device exemption for concizumab-ELISA measurements to be used for dose adjustment.

On demand treatment (arm 1)

Patients randomised to arm 1 continued their previous on demand treatment prior to inclusion.

Guidance for treatment of bleeding episodes after treatment pause

Any bleeds occurring in the trial were treated with the patient's usual factor-containing product according to the treatment guidance provided in the protocol. Prophylactic treatment with concizumab was to continue independent of bleeding episodes and their treatment, i.e. the original dosing schedule was maintained unless the investigator judged otherwise.

Given the experiences gathered from the TE events that occurred in the phase 3 trials, it is important to ensure that bleeding episodes are carefully managed while on regular concizumab PPX. Therefore, the applicant recommends the below guidance for treatment of mild and moderate bleeding episodes with rFVIIa, aPCC, and Byclot providing a more cautious approach to treatment of breakthrough bleeds than previously recommended for the concizumab phase 3 trials to minimise the risk of thrombotic events.

Severe and life-threatening bleeding episodes

In the rare event of a severe (life-threatening) bleed the patient should be in immediate and close contact to the investigator and be treated with relevant doses of factor containing products at the discretion of the investigator.

Key criteria for discontinuation of Concizumab were a significant thromboembolic event, an event of Disseminated Intravascular Coagulation (DIC), an event of Thrombotic Microangiopathy (TMA) or an event of severe or serious hypersensitivity reaction related to concizumab.

For venous thromboembolic events where treatment of concizumab has been discontinued, re-initiation of concizumab can be considered by the investigator in the extension part of the trial, after the patient has fully recovered. The investigator must contact and agree with Novo Nordisk before reinitiating concizumab treatment.

During the trial, in case a patient tested positive for COVID-19, concizumab was paused immediately and not restarted until the patient tested negative again or had fully recovered from COVID-19 as judged by the investigator. In the interim period, patients were treated as per judgement of the investigator.

Prohibited medication included heparin, except for sealing of central venous access, vitamin K-antagonists, DOACs, emicizumab and anti-fibrinolytics, except for local use.

- **Objectives**

Primary objective

- To compare the effect of concizumab prophylaxis to no prophylaxis (on-demand treatment with bypassing agents) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A or B with inhibitors

Secondary objectives

- To compare the patient-reported outcomes (PROs) after treatment with concizumab prophylaxis vs no prophylaxis in adult and adolescent patients with haemophilia A or B with inhibitors
- To investigate the safety of concizumab prophylaxis in adult and adolescent patients with haemophilia A or B with inhibitors
- To investigate the PK and PD parameters of concizumab prophylaxis in adult and adolescent patients with haemophilia A or B with inhibitors

- **Outcomes/endpoints**

Primary endpoint

- The number of treated spontaneous and traumatic bleeding episodes (for on demand (arm 1) from randomisation (week 0) up until start of concizumab treatment (at least 24 weeks), for concizumab (arm 2) from start of the new concizumab dosing regimen (week 0) up until the primary analysis cut-off (at least 32 weeks).

Key secondary endpoints

- Change in SF36v2 bodily pain and physical functioning (from start of treatment (week 0) until week 24)

Supportive secondary endpoints

- Number of treated bleeding episodes differentiated for spontaneous, spontaneous and traumatic joint, or spontaneous and traumatic target joint treated bleeds.
- number of thromboembolic events, number of hypersensitivity type reactions, number of injection site reactions, number of patients with antibodies to concizumab,
- pre-dose (trough) concizumab plasma concentration (Ctrough), pre-dose thrombin peak, pre-dose free TFPI concentration, maximum concizumab plasma concentration (Cmax), area under the concizumab plasma, concentration-time curve (AUC)

Explorative endpoints

- Patient preference assessed by questionnaire (Hemo-TEM, PROMIS short form, Haem-A-QoL, Patient Global Impression PGI)
- Change in time spent in moderate to vigorous activity (MVPA)

Bleeding rate definitions. Bleeding rate is defined as the number of bleeds over the respective observation periods (Table 46,Table 47**:**,Table 48**:**). As a general rule a treated bleed is defined as any bleed where a factor containing product is reported between the start and stop time of a bleed. A re-bleed is defined as a bleeding episode within 72 hours after stopping treatment at the same anatomical location. If a bleeding episode occurs in the same location 72 hours after stopping treatment, the bleed is defined as a new bleeding episode.

At baseline, current target joints, including number of bleedings during the last 12 months, were registered. A target joint is defined as three or more spontaneous bleeds into a single joint within a consecutive 6-month period.

Table 20: Definitions of bleeding episodes (cause of bleed).

Category	Definition
Spontaneous	Not linked to a specific, known action or event
Traumatic	Caused by a specific, known action or event (e.g. injury or exercise)
Post-surgical	Bleeding episodes after surgery from the surgical wound. Bleeding episodes during surgery do not fall under this category

Table 21 Definition of bleeding episode severity.

Category	Definition
Mild/Moderate	Examples: uncomplicated musculoskeletal bleeds (joint, muscular bleeds without compartment syndrome), mucosal- or subcutaneous bleeds Mild/moderate bleeds may occur in other anatomical locations
Severe	Examples: intracranial, retroperitoneal, iliopsoas and internal neck bleeds; muscle bleeds with compartment syndrome; bleeds associated with a significant decrease in the haemoglobin level (>3g/dl) Severe bleeds may occur in other anatomical locations Bleeding episodes that require hospitalisation All life-threatening bleeding episodes

Table 22 Definition of stop of bleed.

Stop time is:	When the patient/parent or LAR experiences/observes signs of cessation of the active bleed such as; pain relief, no increase in swelling/limitation of motion and improvement in other objective signs of the bleeding episode.
Stop time is not:	When pain and objective signs of the bleeding episode are completely resolved.

- **Sample size**

The sample size calculation of the randomised arms was based on the estimand for the primary endpoint. The trial was powered for confirming superiority of the concizumab prophylaxis versus no prophylaxis (on demand) using a significance level of 5%. The power for concluding superiority of concizumab prophylaxis over no prophylaxis (on demand) treatment for the estimand was at least 88% having 42 patients, allocated in a 2:1 manner to either concizumab prophylaxis (n=28) or no prophylaxis (on demand) (n=14) to the trial and assuming a yearly overdispersion of 13, an ABR of 18 during on demand treatment and an ABR of 3 to 5 on the new concizumab regimen. Of note, expected differences in observation periods and efficacy in patients exposed before the pause was not accounted for in the sample size calculations.

ABR assumptions. For the on-demand inhibitor patients, an average ABR of 18 is considered appropriate, based on previous trials (see Table 49).

Table 23: Annualised bleeding rate assumptions for inhibitor patients treated on demand

Regimen	Compound	Study	N	ABR
On demand	Novoseven	NN1731-3562[a]	72	17.1
	Novoseven	NN7128-1907[b]	23	29.8
	Novoseven	NN7025-3601[c]	51	7.9[e]
	NovoSeven	NN7415-4310[d]	9	21

aNN1731-3562 CTR. bNN7128-1907 CTR. cNN7025-3601 CTR. dNN7415-4310 (explorer4) main part internal result meeting presentation.
eThe ABR is estimated: mean number of bleeding episodes per patient per 19.6 months ((12.9/19.6)*12=7.9).

Also, considering that a median ABR 28.7 was found in the on-demand arm of the randomised FEIBA prophylaxis trial (Antunes, 2014), an assumed ABR of 18 seems reasonable and conservative for the inhibitor on demand population. An ABR for concizumab prophylaxis of approximately 3−5 bleeds/year was expected.

Over-dispersion assumptions. A yearly over-dispersion of 13 deemed realistic based on experience from previous trials.

Power. Assuming an ABR of 18 for the on demand arm and an ABR between 3 and 7 for the concizumab arm (arm 2), a yearly over-dispersion varying between 11 and 15 and performing 10,000 simulations of each group produced different scenarios of power for superiority tabulated in Table 50 below:

Table 50: Power for superiority for 42 patients randomised 2:1 assuming an ABR for the on-demand treatment of 18.

Power	Yearly over-dispersion		
ABR concizumab	11	13	15
3	98%	97%	94%
4	96%	93%	90%
5	92%	88%	83%
6	86%	80%	75%
7	78%	70%	65%

When evaluating the power of the negative binomial analysis with logarithm of exposure time as offset and treatment as factor, annual bleeding rates of 18 and 3-5 were assumed for the on-demand patients and concizumab exposed patients, respectively. Assuming further a yearly over-dispersion of 13, the power for concluding superiority of concizumab prophylaxis became at least 88% with 28 patients in the concizumab arm and 14 in the comparator arm.

After the treatment pause, the treatment duration was set to 24 weeks for patients in arm 1 and 32 weeks for patients in arm 2 for a renewed sample size calculation. The power for concluding superiority of concizumab prophylaxis over no prophylaxis (on-demand) treatment for the primary endpoint was at least 88% having 42 patients, allocated in a 2:1 manner to either concizumab prophylaxis (n=28) or no prophylaxis (on-demand; n=14).

Expected withdrawal pattern. Since treatment options for haemophilia patients with inhibitors are limited, the completion rate for this trial was expected to be high with less than 15% withdrawing or discontinuing treatment prematurely. In treatment arm 1 and 2, approximately 51 patients (27 HAwI and 24 HBwI), previously treated on demand, were planned to be randomised 1:2 to either no PPX or concizumab PPX.

- **Randomisation and Blinding (masking)**

Patients meeting the randomisation criteria were centrally randomised using Integrated web response system (IWRS) and assigned to the next available treatment according to the randomisation schedule. Stratification of the randomised on demand patients into treatment arms 1 and 2 was performed in IWRS. The stratification variables were haemophilia subtype (HAwI, HBwI), and bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ≥9 bleeding episodes)

Randomisation after treatment pause

Patients who were screen-failed at sponsor's decision due to the treatment pause and who were re-screened at treatment restart received a new unique patient number. These patients were not counted as screening failures.

At the moment of **treatment pause**, 41/51 (80%) of planned subjects were enrolled. For subjects remaining in the study, the randomization was kept unchanged, and after restart of the study treatment, concizumab was restarted at the new dosing scheme. Fifteen (15) out of 114 subjects on concizumab PPX withdrew from the study before restart of the study.

This was an open-label trial.

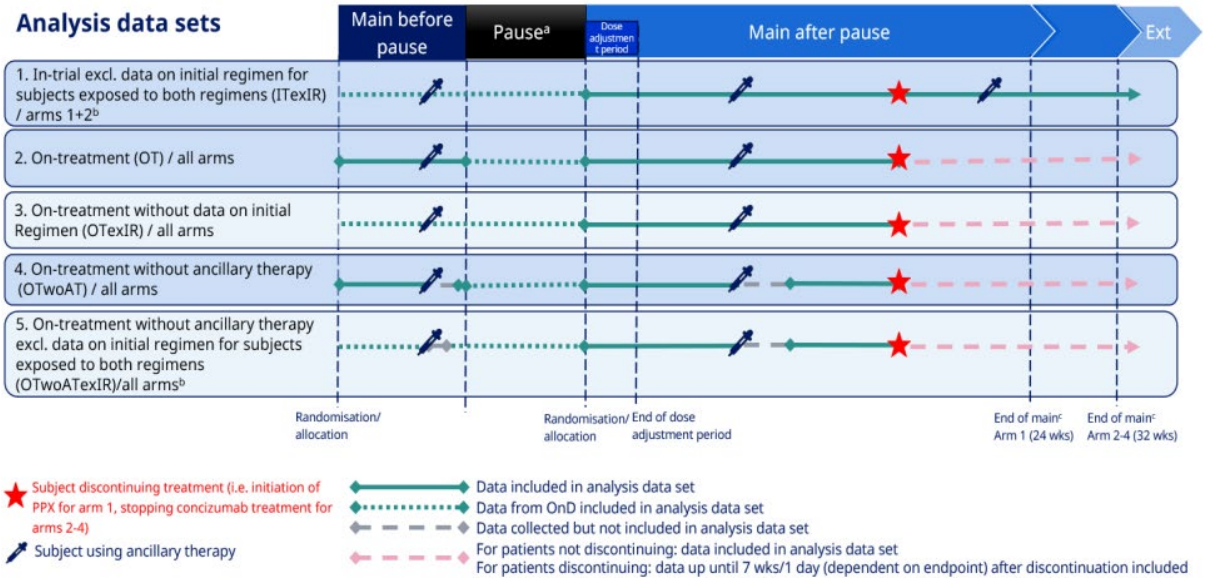
- **Statistical methods**

The following patient **analysis sets** were defined (**Figure 64:**).

- Full analysis set (FAS): All patients randomised to concizumab PPX or no PPX or allocated to arm 3 or 4. Patients from arms 1 and 2 will contribute to the evaluation 'as randomised'.
- Safety analysis set (SAS): All patients exposed to concizumab PPX or randomised to no PPX. All patients will contribute to the evaluation 'as treated'.

Different data analysis data sets describing specific observation periods were used for different endpoints. For the primary endpoint, the FAS and the 'on-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens' analysis data set was used. This reflects the observation period in which patients are exposed to either on demand treatment or the new concizumab dosing regimen (or the initial concizumab dosing regimen if patients were not exposed to the new dosing regimen). Periods with use of ancillary therapy (defined as use of factor containing products not related to treatment of a bleed, except when used for surgery and medical procedures) are not included.

Figure 41 Defined analysis data set



The **primary estimand** was defined as follows:

Population: HAwI and HBwI patients treated on demand prior to entering trial NN7415-4311.

Endpoint: On demand (arm 1): The number of treated spontaneous and traumatic bleeding episodes from randomisation (week 0) up until start of concizumab treatment (at least 24 weeks); Concizumab (arm 2): The number of treated spontaneous and traumatic bleeding episodes from start of the new concizumab dosing regimen (week 0) up until the primary analysis cut-off (at least 32 weeks)

Treatment condition: Arm 1: on demand treatment with intravenous replacement with factor-containing products; or arm 2: PPX treatment regimen with subcutaneous concizumab consisting of an initial loading dose of 1.0 mg/kg, followed by an initial daily dose of 0.20 mg/kg (during the maintenance dose setting period), followed by a maintenance dose of either 0.15, 0.20 or 0.25 mg/kg where breakthrough bleeds are treated with intravenous replacement with factor-containing products.

Intercurrent event strategy:

Permanent treatment discontinuation. For this intercurrent event, the data from the period after permanent discontinuation of trial treatment are not included. It is to be noted that for patients in the on-demand arm, permanent treatment discontinuation will mean initiation of PPX.

Temporary treatment discontinuation after restart of the trial. For this intercurrent event the 'treatment policy' strategy is used meaning that the data from this period are included.

Use of factor products not related to treatment of a bleed. For this intercurrent event, the data during this period are not included*.

Minor surgery. For this intercurrent event the 'treatment policy' strategy is used.

Population-level summary: The treatment ratio of the ABRs between the two treatment regimens.

The main analytical approach or the **primary endpoint** compared the number of treated bleeds between arms 1 and 2 based on the FAS and the 'on-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens' analysis data set. The statistical analysis used a negative binomial regression with the patient's number of bleeds analysed as a function of the randomized treatment regimen, type of haemophilia (HAwI or HBwI) and bleeding frequency (<9 or ⩾ 9 bleeding episodes during the past 24 weeks prior to screening) and the logarithm of the length of the observation period included as an offset in the model.

Furthermore, an ABR will be calculated at an individual basis as

$$ABR = \left(\frac{\text{Number of treated spontanous or traumatic bleeds}}{\text{Number of days in the analysis data set}}\right) x\ 365.25$$

In order to investigate the robustness of the primary endpoint analysis to not using the bleed data on the initial dosing regimen of 0.25 mg/kg/day several **sensitivity analyses** were performed: 1) using multiple imputation for the number of treated bleeds based on treated bleeds observed on the initial dosing regimen; 2) tipping point analysis by modelling patients that were only exposed to the initial dosing regimen with an increasing bleeding rate until the conclusion of superiority is changed, 3) repeating the primary analysis using all concizumab exposure, irrespective of the dosing regimen; and 4) a statistical analysis including an interaction term between treatment and a factor differentiating between patients randomised before and after the pause.

In order to investigate the effect of excluding observed data after intercurrent events, the primary analysis was repeated in a **supplementary analysis** handling intercurrent events by use of the treatment policy strategy.

In order to investigate the dependence on model assumptions, a non-parametric Van Elteren test was implemented.

No formal **interim analyses** were planned.

The **key secondary endpoint analyses** based on SF-36v2 were performed including all patients in the FAS using the 'on-treatment without data on initial regimen' analysis dataset. Due to the low number of patients in arms 1 and 2 contributing data both at baseline and post-baseline, the pre-planned multiple imputation (MI) analyses for key secondary endpoint based on SF-36 could not be performed as planned, post hoc the statistical method was changed to a mixed model for repeated measurements (MMRM) including the changes in SF-36v2 scores from week 0 to weeks 4, 8, 16 and 24, with treatment, type of haemophilia (HAwI or

HBwI) and bleeding frequency (<9 or ⩾9 bleeding episodes during the past 24 weeks prior to screening) as factors, and baseline SF-36v2 as a covariate, all nested within week (week 4, week 8, week 16 and week 24). An unstructured covariance matrix was used to describe the variability for the repeated measurements for a patient. The change in the model meant that only patients who had filled out the questionnaire at both baseline and at least one post-baseline visit where included in the analysis instead of all in the original analysis.

As sensitivity Analysis this was repeated in the 'in-trial excl. data on initial regimen data' analysis data set.

The bleed related **supportive secondary endpoints** were evaluated in the same way as the primary endpoint. The endpoints related to SF-36v2, PROMIS, Haem-A-QoL and Hemo-TEM were scored according to their respective scoring algorithms taken into account missing item(s). The ActiGraph data were analysed separately for patients with HA or HB using an ANCOVA model with treatment and bleeding frequency (<9 or ⩾9 bleeding episodes during the past 24 weeks prior to screening) as fixed effects and the respective baseline value as a covariate

Results

- **Recruitment and participant flow**

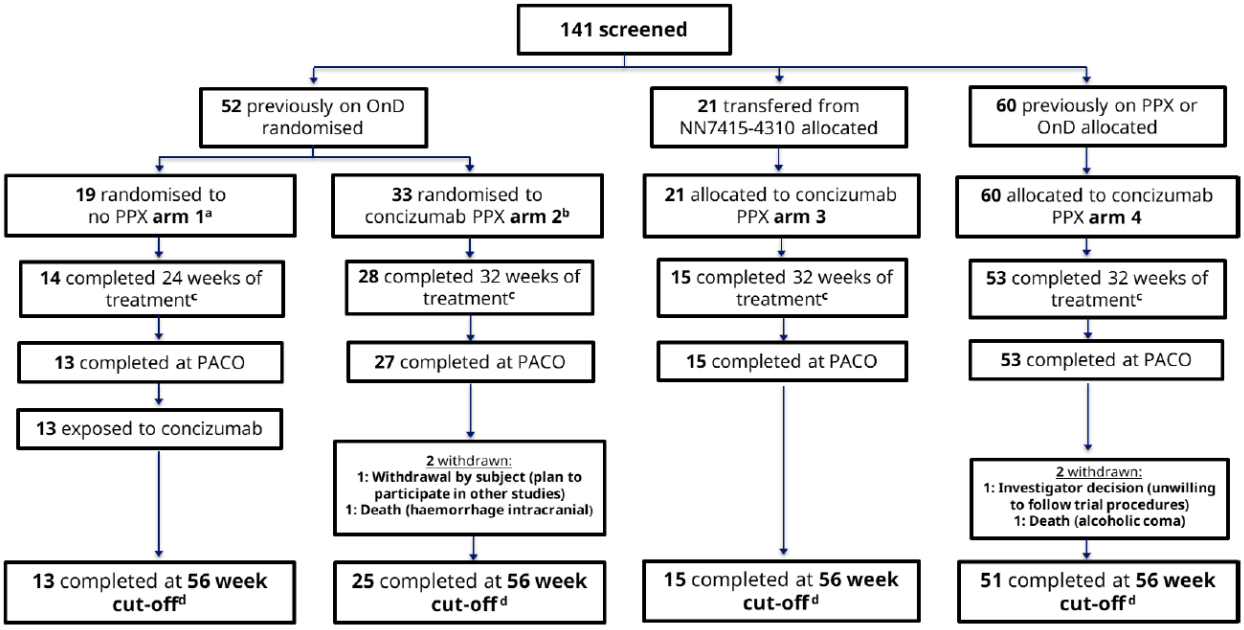
Results – Study 4311 – Explorer 7

A total of 141 male patients were screened. Screening failed in 8 patients, 3 due to inclusion/exclusion criteria and 5 due to withdrawn of consent. A total of 80 subjects were enrolled before the treatment pause, 13, 28, 21 and 18 subjects in arm 1, 2, 3 and 4, respectively. A total of 53 subjects were enrolled after the treatment pause, 6, 5, 0 and 42 subjects in arm 1, 2, 3 and 4, respectively. A total of 133 patients (100%) were randomised/allocated, with 114 patients exposed to concizumab in the main part of the trial.

Randomized arms 1 and 2
At the moment of treatment pause, 41/51 (80%) of planned subjects for the randomized arms 1 and 2 were enrolled. Of the 19 patients randomised to no PPX (arm 1), 13 patients were randomised before the restart and 6 were randomised after restart. Of the 33 patients randomised to the concizumab PPX arm 2, 28 patients were randomised before the restart and 5 were randomised after the restart. For subjects remaining in the study, the randomization was kept unchanged, and after restart of the study treatment, concizumab was restarted at the new dosing scheme.

By the end of the (primary analysis cut-off) PACO main part at 24/32 weeks, 110 patients (82.7%) had completed treatment, see Figure 65:.

Figure 42 Patient disposition at PACO and 56-week cut-off - trial 4311.



Notes: a Of the 19 patients randomised to no PPX (arm 1), 13 patients were randomised before the restart and 6 were randomised after restart. b Of the 33 patients randomised to the concizumab PPX arm 2, 28 patients were randomised before the restart and 5 were randomised after the restart. c Main part of the trial is completed when patients have completed at least 24 weeks of participation (arm 1) or 32 weeks of participation (arms 2, 3 and 4). d Randomised/ allocated patients who did not discontinue concizumab treatment prior to the 56-week cut-off. The 56-week cut-off is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment). Abbreviations: OnD = on-demand; PACO = primary analysis cut-off; PPX = prophylaxis.

A total of 25 patients (18.8%, arms 1−4) withdrew or discontinued treatment before the PACO. Six (6)/25 patients were randomised to no PPX (arm 1) and were not exposed to concizumab. Nineteen (19)/25 patients were on concizumab (arms 2-4), 5 of whom patients discontinued treatment due to an AE, 3 patients discontinued treatment at the discretion of investigator, and 11 patients discontinued treatment due to other reasons. In 15 out of these 19 subjects, the permanent treatment discontinuation occurred before the treatment restart, see Table 51 below.

Reason for withdrawal in 6/33 (18.2%) subjects randomized to concizumab PPX in arm 2 were: withdrawal by subject due to AE (n=1), and due to "other" (n=1) , physician decision (n=1), and death (n=3). A total of 6/19 (31.6%) patients were randomised to no PPX, and study withdrawal was due to withdrawal of consent in 5 subjects and death in 1 subject (trial day 75).

In subjects on concizumab PPX in arm 3 and 4, 13 subjects were withdrawn, due to physician decision (n=2), death (n=1), and withdrawal by subject (n=10).

Table 51: Subject disposition - summary - HAwI+HBwI - all subjects.

	Previous OnD treatment		Concizumab Non-naive	Concizumab Naive	
	No PPX (arm 1) N (%)	Concizumab PPX (arm 2) N (%)	Concizumab PPX (arm 3) N (%)	Concizumab PPX (arm 4) N (%)	Total N (%)
Screened					141
Screening failures					8
Randomised/allocated	19 (100.0)	33 (100.0)	21 (100.0)	60 (100.0)	133 (100.0)
Exposed		33 (100.0)	21 (100.0)	60 (100.0)	114 (100.0)
Completed treatment at 24/32 weeks [a]	14 (73.7)	28 (84.8)	15 (71.4)	53 (88.3)	110 (82.7)
Discontinued treatment		6 (18.2)	6 (28.6)	7 (11.7)	19 (16.7)
Adverse Event		2 (6.1)	2 (9.5)	1 (1.7)	5 (4.4)
Protocol deviation		0	0	0	0
Lack of efficacy		0	0	0	0
Lost to follow-up		0	0	0	0
Technical problems		0	0	0	0
Discretion of Investigator		1 (3.0)	2 (9.5)	0	3 (2.6)
Other		3 (9.1)	2 (9.5)	6 (10.0)	11 (9.6)
Withdrawn from trial	6 (31.6)	6 (18.2)	6 (28.6)	7 (11.7)	25 (18.8)
Withdrawal of consent [b]	5 (26.3)	2 (6.1)	3 (14.3)	7 (11.7)	17 (12.8)
Lost to follow-up	0	0	0	0	0
Investigator decision	0	1 (3.0)	2 (9.5)	0	3 (2.3)
Death	1 (5.3)	3 (9.1)	1 (4.8)	0	5 (3.8)
Full analysis set	19 (100.0)	33 (100.0)	21 (100.0)	60 (100.0)	133 (100.0)
Safety analysis set	19 (100.0)	33 (100.0)	21 (100.0)	60 (100.0)	133 (100.0)

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors.
N: number of subjects, %: Percentage of randomised/allocated subjects, PPX: Prophylaxis, OnD: on-demand.
[a]: Randomised/allocated subjects who did not discontinue treatment prior to week 24/32 (depending on arm).
[b]: withdrawal of consent by subject, subject's parent or subject's legally acceptable representative (LAR).
Subjects in arm 4 were previously on prophylaxis with by-passing agents or treated on-demand.

- **Conduct of the study**

Major protocol amendments. The original protocol was finalized on 6 June 2019. The initiation date of the study was 27 October 2019. Concizumab treatment was paused on 19 March 2020 due to the occurrence of 5 thrombo-embolic events in study 4311 and 4307. A modified trial protocol (version 4.0) was finalized on 8 July 2020. Concizumab treatment was restarted in August 2020. The latest updated protocol (version 7.0) was finalized on 18 June 2021. The protocol was amended to reflect changes to the definition of the primary analysis cut-off, establishing that after the last patient would have been randomised, any patient that due to the COVID-19 pandemic was prevented from restarting the new dosing regimen would no longer be used to determine the primary analysis cut-off and the 56-week cut-off. This modification was done in order to ensure continuity of the overall concizumab development programme despite the COVID-19 pandemic.

Protocol compliance. In total, there were 307 important PDs reported before the cut-off date 15 February 2022. The important PDs comprised 5 trial level PDs, 1 country level PDs, 50 site level PDs and 251 patient level PDs. The important PDs are summarised by deviation category in Table 52. Overall, the PDs were not considered to have an impact on the safety of the subjects and the integrity of the trial. However, the PDs related to PROs impacted the planned analysis of the PRO data.

Table 52: Summary of important protocol deviations at trial site and patient level.

Protocol deviation category	Site level (number of PDs)	Patient level (number of PDs)
Concomitant medication	1	14
Inclusion/Exclusion criteria	2	17
Informed consent	1	10
Privacy and data protection	3	8
SAE notification/Safety procedure	0	14
Subject visit schedule	3	22
Treatment Administration	8	40
Trial procedures/Assessment	32	126
Total	**50**	**251**

- **Baseline data**

Table 53: Demographics and baseline characteristics - subjects enrolled before the pause - descriptive statistics - HAwI+HBwI - OT - full analysis set.

	No PPX	Concizumab PPX			Total
	Arm 1	Arm 2	Arm 3	Arm 4	
Number of subjects	13	28	21	18	80
Age (years)					
N	13	28	21	18	80
Median	27.0	19.0	35.0	30.0	29.0
P25 ; P75	16.0 ; 46.0	14.5 ; 40.0	27.0 ; 47.0	15.0 ; 38.0	16.0 ; 41.5
Mean (SD)	34.2 (19.4)	26.5 (14.9)	37.9 (12.0)	30.1 (16.5)	31.5 (15.8)
Min ; Max	15.0 ; 67.0	12.0 ; 61.0	20.0 ; 61.0	12.0 ; 79.0	12.0 ; 79.0
Height (m)					
N	13	28	21	18	80
Median	1.8	1.7	1.7	1.7	1.7
P25 ; P75	1.6 ; 1.8	1.6 ; 1.7	1.7 ; 1.8	1.6 ; 1.8	1.6 ; 1.8
Mean (SD)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Min ; Max	1.5 ; 1.9	1.4 ; 1.9	1.5 ; 1.8	1.3 ; 1.8	1.3 ; 1.9
Body weight (kg)					
N	13	28	21	18	80
Median	62.3	61.4	69.4	62.6	64.4
P25 ; P75	54.4 ; 77.8	50.2 ; 74.6	59.4 ; 81.0	53.3 ; 82.0	54.3 ; 79.8
Mean (SD)	68.9 (21.3)	64.6 (19.6)	72.7 (15.2)	70.7 (25.9)	68.8 (20.4)
Min ; Max	44.1 ; 103.0	38.3 ; 115.3	52.5 ; 107.7	31.2 ; 127.1	31.2 ; 127.1
BMI, (kg/m^2)					
N	13	28	21	18	80
Median	21.5	21.8	24.2	21.9	23.2
P25 ; P75	18.7 ; 26.2	19.7 ; 26.2	22.5 ; 27.0	20.0 ; 28.7	20.0 ; 26.8
Mean (SD)	23.6 (6.0)	23.5 (6.3)	24.8 (4.8)	24.5 (6.6)	24.1 (5.9)
Min ; Max	16.3 ; 36.5	15.1 ; 42.4	17.4 ; 35.2	17.4 ; 41.0	15.1 ; 42.4

Demographics and baseline characteristics of total population after restart

Demographics and baseline characteristics for all patients randomised to arm 1 or treated with the new concizumab regimen (including the new patients after restart) based on the OTexIR analysis data set, are summarised in Table 54:. For the randomized comparison (arm 1 vs. arm 2), mean (SD) baseline age was 32.3 (17.6) yrs for 19 subjects on No PPX (arm 1) and 24.8 (14.4) yrs for 29 subjects on concizumab PPX (arm 2). The proportion of adolescents and adults in the randomised arms (22 vs 25) is acceptable, though it is noted that the proportion of adolescents enrolled in arm 2 (concizumab PPX) was higher than in arm 1 (no PPX), 16/29 (55.2%) vs 6/19 (31.6%.

Table 24 Demographics and baseline characteristics - summary - HAwI+HBwI - OTexIR – FAS.

	No PPX	Concizumab PPX			Total
	(arm 1) N (%)	(arm 2) N (%)	(arm 3) N (%)	(arm 4) N (%)	N (%)
Number of subjects	19	29	15	55	118
Age group (years)					
Adolescents (12-17 years)	6 (31.6)	16 (55.2)	0	18 (32.7)	40 (33.9)
Adults (18-64 years)	12 (63.2)	13 (44.8)	15 (100)	37 (67.3)	77 (65.3)
Elderly/very elderly (65-84 years)	1 (5.3)	0	0	0	1 (0.8)
Ethnicity					
Hispanic or Latino	1 (5.3)	3 (10.3)	0	2 (3.6)	6 (5.1)
Not Hispanic or Latino	16 (84.2)	25 (86.2)	15 (100)	52 (94.5)	108 (91.5)
Not Reported	2 (10.5)	1 (3.4)	0	1 (1.8)	4 (3.4)
Race					
American Indian or Alaska Native	1 (5.3)	1 (3.4)	0	1 (1.8)	3 (2.5)
Asian	6 (31.6)	13 (44.8)	4 (26.7)	12 (21.8)	35 (29.7)
Black or African American	1 (5.3)	4 (13.8)	0	3 (5.5)	8 (6.8)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
White	9 (47.4)	9 (31.0)	11 (73.3)	38 (69.1)	67 (56.8)
Not Reported	2 (10.5)	2 (6.9)	0	1 (1.8)	5 (4.2)
Country					
Algeria	0	0	0	9 (16.4)	9 (7.6)
Australia	0	1 (3.4)	0	2 (3.6)	3 (2.5)
Croatia	1 (5.3)	0	1 (6.7)	0	2 (1.7)
Czechia	0	0	0	1 (1.8)	1 (0.8)
Denmark	0	0	2 (13.3)	0	2 (1.7)
France	2 (10.5)	1 (3.4)	0	1 (1.8)	4 (3.4)
India	2 (10.5)	10 (34.5)	0	3 (5.5)	15 (12.7)
Italy	3 (15.8)	2 (6.9)	0	3 (5.5)	8 (6.8)
Japan	1 (5.3)	1 (3.4)	1 (6.7)	3 (5.5)	6 (5.1)
Malaysia	1 (5.3)	1 (3.4)	3 (20.0)	1 (1.8)	6 (5.1)
Mexico	1 (5.3)	1 (3.4)	0	1 (1.8)	3 (2.5)
Poland	1 (5.3)	1 (3.4)	0	5 (9.1)	7 (5.9)
Portugal	0	0	0	1 (1.8)	1 (0.8)
Russian Federation	1 (5.3)	1 (3.4)	0	2 (3.6)	4 (3.4)
Serbia	0	0	0	1 (1.8)	1 (0.8)
South Africa	1 (5.3)	4 (13.8)	0	2 (3.6)	7 (5.9)
Korea, Republic of	1 (5.3)	1 (3.4)	0	0	2 (1.7)
Spain	0	1 (3.4)	3 (20.0)	4 (7.3)	8 (6.8)
Sweden	0	0	1 (6.7)	1 (1.8)	2 (1.7)
Thailand	0	0	0	5 (9.1)	5 (4.2)
Turkey	0	0	0	4 (7.3)	4 (3.4)
Ukraine	3 (15.8)	2 (6.9)	3 (20.0)	2 (3.6)	10 (8.5)
United Kingdom of Great Britain and Northern Ireland	0	0	0	2 (3.6)	2 (1.7)
United States of America	1 (5.3)	2 (6.9)	1 (6.7)	2 (3.6)	6 (5.1)

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen.
N: number of subjects, %: percentage of subjects, PPX: Prophylaxis. Baseline is defined as the latest measurement before first dose with new regimen or before randomisation for arm 1.
Note: information on age, ethnicity and race are according to local regulations.

Baseline disease characteristics for the OTexIR

Haemophilia details. In the OTexIR data set, a total of 26 subjects with HawI and 22 subjects with HbwI were randomized to treatment arms 1 (9 HawI, 10 HbwI) and 2 (17 HawI, 12 HbwI), respectively. Inhibitors levels >= 5 BU were reported in 10/19 (62.5%) of subjects with HawI and 13/29 (50.0%) of subjects with HbwI. Approximately 40% of subjects had a family history of haemophilia. Details on haemophilia are provided in the table below.

Table 25: Haemophilia details - summary - HAwI+HBwI - OTexIR - full analysis set.

	No PPX	Concizumab PPX			Total
	(arm 1) N (%)	(arm 2) N (%)	(arm 3) N (%)	(arm 4) N (%)	N (%)
N in FAS	19	33	21	60	133
N in FAS and ADS	19	29	15	55	118
Classification of haemophilia type					
N	19 (100.0)	29 (100.0)	15 (100.0)	55 (100.0)	118 (100.0)
Haemophilia A	9 (47.4)	17 (58.6)	8 (53.3)	37 (67.3)	71 (60.2)
Haemophilia B	10 (52.6)	12 (41.4)	7 (46.7)	18 (32.7)	47 (39.8)
Inhibitor test result [1]					
N	16 (100.0)	26 (100.0)	15 (100.0)	49 (100.0)	106 (100.0)
< 0.6 BU	3 (18.8)	3 (11.5)	2 (13.3)	7 (14.3)	15 (14.2)
>= 0.6 and < 5 BU	4 (25.0)	11 (42.3)	5 (33.3)	18 (36.7)	38 (35.8)
>= 5 BU	10 (62.5)	13 (50.0)	15 (100.0)	30 (61.2)	68 (64.2)
Family history of haemophilia					
N	19 (100.0)	29 (100.0)	15 (100.0)	55 (100.0)	118 (100.0)
Yes	8 (42.1)	12 (41.4)	8 (53.3)	30 (54.5)	58 (49.2)
No	8 (42.1)	12 (41.4)	7 (46.7)	21 (38.2)	48 (40.7)
Unknown	3 (15.8)	5 (17.2)	0 (0.0)	4 (7.3)	12 (10.2)
Family history of prothrombotic disorders					
N	19 (100.0)	29 (100.0)	15 (100.0)	55 (100.0)	118 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (42.1)	8 (27.6)	11 (73.3)	23 (41.8)	50 (42.4)
Unknown	11 (57.9)	21 (72.4)	4 (26.7)	32 (58.2)	68 (57.6)
Family history of thromboembolism					
N	19 (100.0)	29 (100.0)	15 (100.0)	55 (100.0)	118 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	8 (42.1)	8 (27.6)	11 (73.3)	23 (41.8)	50 (42.4)
Unknown	11 (57.9)	21 (72.4)	4 (26.7)	32 (58.2)	68 (57.6)
Family history of inhibitors					
N	19 (100.0)	29 (100.0)	15 (100.0)	55 (100.0)	118 (100.0)
Yes	3 (15.8)	4 (13.8)	2 (13.3)	14 (25.5)	23 (19.5)
No	11 (57.9)	17 (58.6)	11 (73.3)	31 (56.4)	70 (59.3)
Unknown	5 (26.3)	8 (27.6)	2 (13.3)	10 (18.2)	25 (21.2)

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen.
N: number of subjects, %: percentage of subjects, FAS: Full analysis set, 05, PPX: Prophylaxis, SD: standard deviation, P25/P75 is the 25th/75th percentile, Min: minimum, Max: maximum.
[1] Subjects can have more than one inhibitor test result, therefore percentage do not add upto 100%.

Previous haemophilia treatment and bleed history for the OtexIR data set.

For the randomized groups, previous treatment regimen for arm 1 (on-demand treatment) was on demand treatment for 17/19 (89.5%) of patients for a mean (SD) time of 20.7 (24.6) months and prophylaxis in 1/19 (5.3%) patient for 7.7 months. For arm 2 (concizumab PPX), previous treatment regimen was on demand treatment for 27/33 (81.8%) for a mean (SD) time of 24.1 (33.5) months and prophylaxis in 3/33 (9.1%) patients for a mean (SD) time of 8.9 (5.8) months.

Mean ABR (SD) was 26.5 (41.5) for all patients previously on on demand treatment regimen, and 37.2 (76.5) for patients previously on prophylaxis.

Table 26: Haemophilia treatment and bleed history - summary - HAwI+HBwI - OTexIR - FAS.

	No PPX	Concizumab PPX			Total
	(arm 1)	(arm 2)	(arm 3)	(arm 4)	
N in FAS	19	33	21	60	133
N in FAS and ADS	19	29	15	55	118
Type of previous treatment, N (%)					
N	17 (100.0)	28 (100.0)	15 (100.0)	52 (100.0)	112 (100.0)
On demand	17 (100.0)	27 (96.4)	15 (100.0)	28 (53.8)	87 (77.7)
Prophylaxis	1 (5.9)	3 (10.7)	1 (6.7)	31 (59.6)	36 (32.1)
Time on prophylaxis, (months)					
N	1	3	1	25	30
Median	7.7	12.0	0.0	20.3	14.0
P25 ; P75	7.7 ; 7.7	2.3 ; 12.5	0.0 ; 0.0	12.2 ; 37.0	11.8 ; 32.6
Mean (SD)	7.7	8.9 (5.8)	0.0	34.7 (35.1)	30.0 (33.7)
Min ; Max	7.7 ; 7.7	2.3 ; 12.5	0.0 ; 0.0	3.6 ; 124.0	0.0 ; 124.0
Time on on demand, (months)					
N	8	22	15	21	66
Median	15.9	12.0	12.0	18.3	12.0
P25 ; P75	9.9 ; 25.8	9.0 ; 18.7	7.2 ; 12.0	7.7 ; 69.0	8.2 ; 24.0
Mean (SD)	20.7 (24.6)	24.1 (33.5)	10.7 (4.8)	57.5 (78.5)	31.3 (51.8)
Min ; Max	-11.7 ; 73.7	1.4 ; 128.3	3.1 ; 23.7	0.1 ; 244.2	-11.7 ; 244.2
Number of bleeding episodes during the prophylaxis treatment period					
N	1	3	1	31	36
Median	56.0	23.0	1.0	9.0	9.5
P25 ; P75	56.0 ; 56.0	5.0 ; 32.0	1.0 ; 1.0	5.0 ; 23.0	5.0 ; 23.5
Mean (SD)	56.0	20.0 (13.7)	1.0	27.6 (48.8)	27.0 (45.8)
Min ; Max	56 ; 56	5 ; 32	1 ; 1	0 ; 200	0 ; 200
ABR during the prophylaxis treatment period					
N	1	3	1	25	30
Median	87.4	26.1	365.3	5.5	8.0
P25 ; P75	87.4 ; 87.4	23.0 ; 30.8	365.3 ; 365.3	1.5 ; 16.6	1.9 ; 30.0
Mean (SD)	87.4	26.6 (3.9)	365.3	23.3 (47.6)	37.2 (76.5)
Min ; Max	87.4 ; 87.4	23.0 ; 30.8	365.3 ; 365.3	0.0 ; 196.4	0.0 ; 365.3
Number of spontaneous bleeding episodes during the prophylaxis treatment period					
N	1	3	1	30	35
Median	56.0	9.0	1.0	8.0	9.0
P25 ; P75	56.0 ; 56.0	2.0 ; 12.0	1.0 ; 1.0	3.0 ; 24.0	2.0 ; 24.0
Mean (SD)	56.0	7.7 (5.1)	1.0	25.0 (44.1)	23.7 (41.6)
Min ; Max	56 ; 56	2 ; 12	1 ; 1	0 ; 180	0 ; 180

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen.
N: number of subjects, %: percentage of subjects, FAS: Full analysis set, ADS: Analysis data set, PPX: Prophylaxis, SD: standard deviation, P25/P75 is the 25th/75th percentile, Min: minimum, Max: maximum, ABR: annualised bleeding rate.
The negative duration of on-demand treatment is caused by a reporting of the end date prior to the start date..

At baseline, 60 patients (50.8%) reported having at least 1 target joint, including 10/19 subjects in arm 1 and 12/29 subjects in arm 2, with a similar distribution across treatment arms. The most frequent target joint locations were knee 32.2%, elbow 20.3%, and ankle 12.7%. The mean (SD) number of bleeds in the specified joint within 12 months prior to screening was 6.8 (4.9), see Table 57:below.

Table 27 Target joints at baseline - summary - HAwI+HBwI - OTexIR - full analysis set.

	No PPX	Concizumab PPX			Total
	(arm 1)	(arm 2)	(arm 3)	(arm 4)	
N in FAS	19	33	21	60	133
N in FAS and ADS	19	29	15	55	118
Number of subjects having at least one target joint, N (%)	10 (52.6)	12 (41.4)	8 (53.3)	30 (54.5)	60 (50.8)
Target joint location, N (%) E					
Ankle	0	3 (10.3) 3	2 (13.3) 2	10 (18.2) 13	15 (12.7) 18
Elbow	4 (21.1) 4	4 (13.8) 6	3 (20.0) 3	13 (23.6) 17	24 (20.3) 30
Hip	1 (5.3) 1	0	1 (6.7) 1	2 (3.6) 2	4 (3.4) 4
Knee	9 (47.4) 10	8 (27.6) 8	2 (13.3) 3	19 (34.5) 22	38 (32.2) 43
Shoulder	1 (5.3) 1	2 (6.9) 2	2 (13.3) 2	3 (5.5) 3	8 (6.8) 8
Body position of joint, N (%) E					
Left	7 (36.8) 7	7 (24.1) 8	7 (46.7) 7	25 (45.5) 29	46 (39.0) 51
Right	6 (31.6) 9	10 (34.5) 11	3 (20.0) 4	20 (36.4) 28	39 (33.1) 52
Number of bleeds in specified joint within 12 months					
E	16	19	11	57	103
Median	5.0	6.0	4.0	6.0	6.0
P25 ; P75	4.0 ; 7.5	4.0 ; 7.0	3.0 ; 6.0	4.0 ; 8.0	4.0 ; 7.0
Mean (SD)	7.2 (5.3)	5.4 (1.9)	4.3 (1.5)	7.7 (5.7)	6.8 (4.9)
Min ; Max	3.0 ; 22.0	3.0 ; 10.0	3.0 ; 7.0	3.0 ; 30.0	3.0 ; 30.0

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen.
N: number of subjects, %: percentage of subjects, FAS: Full analysis set, PPX: Prophylaxis, E: number of target joints, SD: standard deviation, P25/P75 is the 25th/75th percentile, Min: minimum, Max: maximum.
Target joint are defined as having three or more spontaneous bleeds into a single joint within a consecutive 6-month period. Baseline is defined as the latest measurement before first dose with new regimen or before randomisation for arm 1 Subjects can have more than one targ et joint, thus the percentage do not add up to 100.

- **Numbers analysed**

The safety analysis set and the full analysis set were identical and consisted of all 133 randomised/ allocated patients.

The main basis for the efficacy evaluation are results available at the primary analysis cut-off (PACO) defined as when all patients on no PPX (arm 1) have completed the 24-week visit (or withdrawn) and all patients on concizumab PPX (arm 2) have completed the 32-week visit (or withdrawn). Accordingly, results for patients in arm 1 cover treatment with no PPX (for 24 weeks) and concizumab PPX (until PACO). These results are presented in the dose response section 2.6.5.1.

For the primary endpoint as well as the secondary endpoints, the FAS and the 'on-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens' (OTwoATexIR) analysis data set was used.

Primary analysis set (OTwoATexIR) The primary analysis set was based on on-treatment without ancillary therapy and excluding data on initial regimen for subjects exposed to both regimens (OTwoATexIR). This reflects the observation period in which patients are exposed to either on demand treatment or the new concizumab dosing regimen (or the initial concizumab dosing regimen if patients were not exposed to the new dosing regimen). Periods with use of ancillary therapy (defined as use of factor-containing products not related to treatment of a bleed, except when used for surgery and medical procedures) are not included. Data collected after permanent treatment discontinuation are not included. Additional intercurrent events are accounted for as described in the estimand. For patients in arm 2, who were exposed to both the initial and the new concizumab dosing regimen, the data from the initial dosing regimen are not included.

Exposure and dosing. A total of 114 patients were exposed to concizumab in the main part of the trial (both initial and new regimen). At the time of PACO, 127 patients had been exposed to concizumab (including 13 subjects from arm 1 who continued in the extension part).

The concizumab exposure time for patients in the primary analysis set (OTwoATexIR (On-treatment without ancillary treatment excluding data on initial regimen) was 9.3 and 24.2 patients years in treatment arms 1, and 2, respectively. The total concizumab exposure time was 92.8 patient years (all arms).

In total, in the OTexIR analysis data set, there were 99 exposed patients (arms 2, 3 and 4). Two (2) patients withdrew from the trial and did not dose adjust. Of the remaining 97 patients, 72 patients (74.2%) remained on the 0.20 mg/kg dose level, 24 patients (24.7%) increased to 0.25 mg/kg and 1 patient (1.0%) decreased to 0.15 mg/kg. Dose level distribution was similar across treatment arms.

- **Outcomes and estimation**

Bleeding episodes (spontaneous and traumatic) in the randomised part:
For patients in arm 2 on concizumab PPX, 15 (45.5%) patients reported 59 treated bleeding episodes. For patients on no PPX (arm 1), 17 patients (89.5%) reported 167 treated bleeding episodes up until PACO (Table 58:). The distribution of spontaneous or traumatic bleeding episodes for arm 1 or 2 was similar, 73.7% vs 67.8% and 25.1% vs 30.5%, respectively. Bleeding episodes tended to be classified more severely in subjects on concizumab PPX (in 8.4% vs 23.7% , arm 1 vs arm 2).

The proportion of patients with HAwI and HBwI with zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment, irrespective of whether they completed 24 weeks of treatment, was 63.6% on concizumab PPX (arm 2) and 10.5% on no PPX (arm 1), see Table 58:.

Table 28 Bleeding episodes - all treated - summary - HAwI+HBwI - OTwoATexIR - full analysis set.

	No PPX	Concizumab PPX									
	Arm 1	Arm 1		Arm 2		Arm 3		Arm 4		Arms 2-4		Total	
	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]
N in FAS	19		13		33		21		60		114		127	
N in FAS and ADS	19(100)		13(100)		33(100)		21(100)		60(100)		114(100)		127(100)	
Zero treated bleeds*	1(5.3)		5(38.5)		14(42.4)		5(23.8)		27(45.0)		46(40.4)		51(40.2)	
Treated bleeding episodes	17(89.5)	167[100]	8(61.5)	25[100]	15(45.5)	59[100]	11(52.4)	47[100]	28(46.7)	152[100]	54(47.4)	258[100]	62(48.8)	283[100]
Cause of bleeding episodes														
Spontaneous	17(89.5)	123[73.7]	6(46.2)	10[40.0]	13(39.4)	40[67.8]	8(38.1)	19[40.4]	24(40.0)	112[73.7]	45(39.5)	171[66.3]	51(40.2)	181[64.0]
Traumatic	11(57.9)	42[25.1]	6(46.2)	12[48.0]	7(21.2)	18[30.5]	8(38.1)	28[59.6]	18(30.0)	40[26.3]	33(28.9)	86[33.3]	39(30.7)	98[34.6]
Surgical	1(5.3)	1[0.6]	2(15.4)	3[12.0]	0		0		0		0		2(1.6)	3[1.1]
Missing	1(5.3)	1[0.6]	0		1(3.0)	1[1.7]	0		0		1(0.9)	1[0.4]	1(0.8)	1[0.4]
Location of bleeds														
Treated bleeds	17(89.5)	182[100]	8(61.5)	26[100]	15(45.5)	66[100]	11(52.4)	49[100]	28(46.7)	160[100]	54(47.4)	275[100]	62(48.8)	301[100]
Joint	16(84.2)	128[70.3]	7(53.8)	19[73.1]	13(39.4)	52[78.8]	9(42.9)	23[46.9]	24(40.0)	123[76.9]	46(40.4)	198[72.0]	53(41.7)	217[72.1]
Target joint	7(36.8)	28[15.4]	1(7.7)	1[3.8]	5(15.2)	12[18.2]	2(9.5)	3[6.1]	12(20.0)	62[38.8]	19(16.7)	77[28.0]	20(15.7)	78[25.9]
Muscular	9(47.4)	32[17.6]	2(15.4)	4[15.4]	4(12.1)	4[6.1]	8(38.1)	17[34.7]	9(15.0)	30[18.8]	21(18.4)	51[18.5]	23(18.1)	55[18.3]
Skin	4(21.1)	4[2.2]	0		0		4(19.0)	7[14.3]	6(10.0)	6[3.8]	10(8.8)	13[4.7]	10(7.9)	13[4.3]
Gastrointestinal or Stomach/gut	0		0		2(6.1)	8[12.1]	0		0		2(1.8)	8[2.9]	2(1.6)	8[2.7]
Mouth, gums or nose	3(15.8)	5[2.7]	2(15.4)	3[11.5]	1(3.0)	1[1.5]	0		0		1(0.9)	1[0.4]	3(2.4)	4[1.3]
Urinary system	1(5.3)	2[1.1]	0		1(3.0)	1[1.5]	0		1(1.7)	1[0.6]	2(1.8)	2[0.7]	2(1.6)	2[0.7]
Central nervous system	0		0		0		0		0		0		0	
Other	5(26.3)	11[6.0]	0		0		2(9.5)	2[4.1]	0		2(1.8)	2[0.7]	2(1.6)	2[0.7]
Classification of bleeding episodes														
Mild/moderate	16(84.2)	153[91.6]	8(61.5)	25[100]	13(39.4)	45[76.3]	10(47.6)	45[95.7]	26(43.3)	138[90.8]	49(43.0)	228[88.4]	57(44.9)	253[89.4]
Severe	5(26.3)	14[8.4]	0		7(21.2)	14[23.7]	2(9.5)	2[4.3]	9(15.0)	14[9.2]	18(15.8)	30[11.6]	18(14.2)	30[10.6]

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens. N: number of subjects, (%): percentage of subjects, E: number of bleeding episodes, [%]: percentage of bleeding episodes, FAS: Full analysis set, ADS: Analysis data set, PPX: Prophylaxis. * Subjects that do not complete 24 weeks without permanent treatment discontinuation will be counted as not having zero bleeds. Also, all treated bleeds with either of the four causes (spontaneous, traumatic, surgical or missing) will be counted when checking whether subject had any bleeds in this table. Bleeding episodes with multiple locations are counted in all of these locations. For location of bleeds and severe bleeds the E represents the number of bleeds and [%] is the percentage of bleeds.

Across all arms, a number of bleeding episodes which were classified as severe, seem to not meet the criteria of severe bleeding episodes as predefined. For example, the majority of severe bleeding episodes were treated with 1 or 2 injections of haemostatic medication, which is uncommon for severe bleeding episodes. Also, the vast majority of severe bleeding episodes were located in joints, target joints, muscles and skin, which according to the predefined criteria does not unambiguously classify them as severe. Thus, Novo Nordisk believes these bleeding episodes to be incorrectly classified as severe. No statistical analyses were impacted by this.

Primary analysis - Number of treated spontaneous and traumatic bleeding episodes

The primary endpoint was the number of treated spontaneous and traumatic bleeding episodes from randomisation (week 0) up until start of concizumab treatment (at least 24 weeks) for arm 1, and from the start of the new concizumab dosing regimen (week 0) up until the PACO (at least 32 weeks) for arm 2.

For patients on concizumab PPX (arm 2) the median ABR was 0.0, and for patients on no PPX (arm 1), the median ABR was 9.8 (Table 59:).

Table 29 Bleeding episodes - descriptive statistics - HAwI+HBwI - OTwoATexIR - full analysis set.

	No PPX	Concizumab PPX					
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2–4	Total
N in FAS and ADS	19	13	33	21	60	114	127
Person years of exposure in ADS	11.6	9.3	24.2	17.9	41.3	83.4	92.8
Treated spontaneous and traumatic bleeding episodes							
Number of bleeding episodes ABR	166	22	59	47	152	258	280
Median	9.8	1.9	0.0	0.8	0.0	0.0	0.0
Mean (SD)	18.4 (24.7)	2.1 (1.9)	3.8 (11.7)	2.1 (3.3)	3.2 (7.8)	3.2 (8.5)	3.1 (8.1)
Min ; Max	0 ; 94.7	0 ; 4.7	0 ; 66.4	0 ; 13.2	0 ; 47.4	0 ; 66.4	0 ; 66.4
P25 ; P75	6.5 ; 20.2	0 ; 3.9	0 ; 3.3	0 ; 3.3	0 ; 3.6	0 ; 3.3	0 ; 3.6

Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HAwI = haemophilia A with inhibitors; HBwI = haemophilia B with inhibitors; max = maximum; min = minimum; N = number of patients; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; P25/75 = 25th/75th percentile; PPX = prophylaxis; SD = standard deviation.
Cross-reference: Modified from Trial 4311 PACO (M5.3.5.1), TFL Table 14.2.19

Using a negative binomial regression model, the estimated mean ABR was 1.7 (95%CI 1.0-2.87) for patients on concizumab PPX (arm 2) and 11.8 (95%CI 7.03-19.86) for patients on no PPX (arm 1) (Table 600). The estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.14 (95%CI 0.07-0.29; p<0.001), corresponding to an 86% reduction in ABR for patients on concizumab PPX (arm 2) compared to no PPX (arm 1). Superiority of concizumab PPX (arm 2) over no PPX (arm 1) was confirmed for the primary endpoint.

Table 60: Statistical analyses of bleeding episodes – HAwI+HBwI - full analysis set – trial 4311 at the PACO (OTwoATexIR).

	No PPX (arm 1) Estimated mean ABR [95% CI]	Concizumab PPX (arm 2) Estimated mean ABR [95% CI]	ABR ratio [95% CI]
Primary endpoint Treated spontaneous and traumatic bleeding episodes	11.8 [7.03; 19.86]	1.7 [1.01; 2.87]	0.14 [0.07; 0.29] p<0.001
Treated spontaneous bleeding episodes	9.4 [5.20; 16.99]	1.3 [0.71; 2.31]	0.14 [0.06; 0.30]
Treated spontaneous and traumatic joint bleeding episodes	9.1 [5.13; 16.05]	1.4 [0.77; 2.46]	0.15 [0.07; 0.32]
Treated spontaneous and traumatic target joint bleeding episodes	1.1 [0.25; 5.20]	0.1 [0.02; 0.85]	0.12 [0.02; 0.84]
All treated and untreated spontaneous and traumatic bleeding episodes	13.3 [7.89; 22.51]	4.4 [2.84; 6.86]	0.33 [0.17; 0.64]

Abbreviations: ABR: annualised bleeding rate, CI: Confidence interval, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens, PPX = prophylaxis.

The estimated ABRs within arms in the phase 3 trials were obtained with the LSMEANS statement in SAS PROC GENMOD procedure, assuming a population with balanced characteristics with regard to the number of HAwI and HBwI patients and number of patients with low and high bleeding frequency during the past 24 weeks prior to screening. In addition, estimated ARBs based on OBSMARGIN (i.e. based on covariate distribution present in the study population) were calculated for the primary endpoint by using the characteristics as given in the study arms (haemophilia type and bleeding frequency). These are considered more realistic. The estimated ABR ratios and corresponding 95% CIs stayed unchanged compared to the initial calculations, while the estimated ABRs within arms changed slightly towards the direction of observed mean ABRs within each arm (Table 61).

Table 61: Bleeding episodes - statistical analysis - treated spontaneous and traumatic bleeding episodes - HAwI + HBwI - OTwoATexIR - full analysis set - trial 4311 (PACO) based on OBSMARGIN

	No PPX		Concizumab PPX
N in FAS	19		33
N in FAS and ADS	19		33
Treated spontaneous and traumatic bleeding episodes			
ABR estimate based on the covariate distribution	14.8		2.1
95% CI	[8.96;24.35]		[1.32;3.46]
ABR ratio		0.14	
95% CI		[0.07;0.29]	
% reduction		86	
p-value		<.001	

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors. OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens. N: number of subjects, ADS: analysis data set, FAS: Full analysis set, ABR: annualised bleeding rate, CI: Confidence interval, PACO: Primary analyses cut-off, PPX: Prophylaxis. Bleeding endpoints are analysed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment, type of haemophilia and bleeding frequency prior to screening as factors; and including the OBSMARGIN option in the estimates.

Since estimated ABRs based on OBSMARGIN are only provided for the primary endpoints, and results are similar, estimated ABRs based on LSMEAN statement are reported in the Overview, unless stated otherwise. Upon request, the clinical data presented in section 5.1 of the Product Information were changed to the results based on the OBSMARGIN option.

Sensitivity and supplementary analyses. The impact of potential bias introduced by the treatment pause was investigated with four sensitivity analyses addressing the robustness of the primary analysis. Fourty-one (41) patients in arms 1 and 2 were randomised before the treatment pause (13 patients in arm 1; 28 patients in arm 2). Four (4) patients in arm 2 did not restart.

Sensitivity analysis 1. Imputing the missing information on the new concizumab dosing regimen for the 4 patients in arm 2 who did not restart (by multiple imputation of bleed data on the initial dosing regimen to allow for an uncertainty of the missing information) did not impact the results or conclusion of the primary analysis. The estimated mean ABR was 1.6 (95%CI 0.92-2.88) for patients on concizumab PPX (arm 2) and 11.7 (95%CI 6.93-19.90) for patients on no PPX (arm 1). The estimated ABR ratio was **0.14** (95%CI 0.07-0.29; p<0.001).

Sensitivity analysis 2. Including all information in arm 2 up until the primary analysis cut-off, irrespective of the dosing regimen, did not impact the results or conclusion of the primary analysis. The estimated mean ABR was 1.7 (95%CI 1.03-2.83) for patients on concizumab PPX (arm 2) and 11.8 (95%CI 7.03-19.66) for patients on no PPX (arm 1). The estimated ABR ratio was **0.14** (95%CI 0.07-0.29; p<0.001).

Sensitivity analysis 3**.** The treatment effects in patients randomised before and after the concizumab treatment pause were comparable. For patients on concizumab PPX (arm 2), the estimated mean ABR was 1.9 (95%CI 1.07-3.30) for patients randomised before the pause, and 0.8 (95%CI 0.14-4.26) for patients

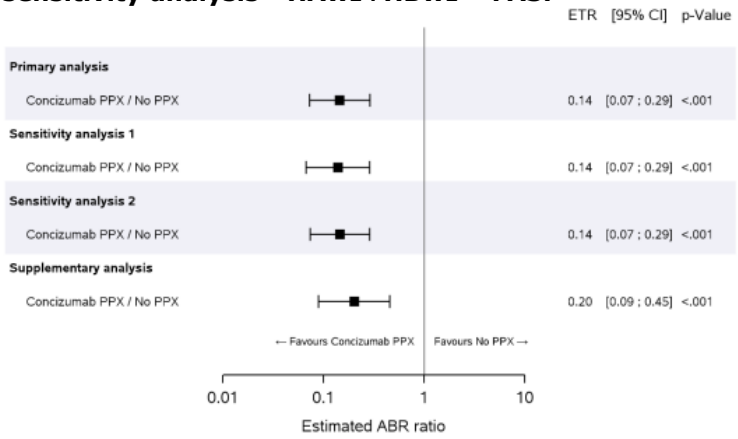
randomised after restart. For patients on no PPX (arm 1), the estimated mean ABR was 11.7 (95%CI 6.34-21.45) for patients randomised before the pause, and 13.0 (95%CI 5.14-32.62) for patients randomised after restart. The estimated ABR ratio was 0.16 (95%CI 0.08-0.35) for patients randomised before the pause, and 0.06 (95%CI 0.01-0.42) for patients randomised after restart.

Sensitivity analysis 4. The increase in the number of bleeding episodes (the penalty added to the imputed bleeding episode data in sensitivity analysis 1 when modelling bleeding episode data for the 4 patients in arm 2 who did not restart) required to tip the superiority conclusion of the primary analysis was 25. The magnitude of this penalty was considered implausible, thereby supporting the robustness of the superiority conclusion of the primary analysis.

Supplementary analysis 1. An estimand was investigated that followed the treatment policy strategy, by repeating the primary analysis while including all information collected after treatment discontinuation and during periods with use of ancillary therapy. The analysis showed that including observed data after permanent treatment discontinuation (the first intercurrent event) and during unallowed use of ancillary therapy (the third intercurrent event) did not impact the conclusion of the primary analysis. The estimated mean ABR was 2.8 (95% CI 1.67-4.65) for patients on concizumab PPX (arm 2) and 13.8 (95%CI 7.16-26.75) for patients on no PPX (arm 1). The estimated ABR ratio was 0.2 (95%CI 0.09-0.45; p<0.001).

Supplementary analysis 2. A non-parametric Van Elteren test comparing the mean ABRs in patients on concizumab PPX (arm 2) and no PPX (arm 1) demonstrated a statistically significant difference in mean ABRs between the two treatment groups, indicating that this difference is not dependent on the model assumptions of the parametric approach used for the primary analysis.

Figure 43 Bleeding episodes - treated spontaneous and traumatic - forest plot - primary analysis and sensitivity analysis - HAwI+HBwI – FAS.



HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors
ETR: estimated treatment ratio, CI: Confidence interval, PPX: Prophylaxis.
Sensitivity analysis 1: Multiple imputations based on the initial dosing regimen.
Sensitivity analysis 2: Analysis irrespective of the dosing regimen.

Number of treated spontaneous and traumatic bleeding episodes - by haemophilia subtype

Using a negative binomial regression model, the estimated mean ABR for patients on concizumab PPX (arm 2) was 1.6 (95%CI 0.89-2.83) for patients with HAwI and 2.2 (95%CI 0.76 - 6.52) for patients with HBwI. The estimated mean ABR for patients on no PPX (arm 1) was 18.3 (95%CI 10.18-32.87) for patients with HAwI and 7.2(95%CI 2.61-20.06) for patients with HBwI. Although trial 4311 was not powered to detect statistically significant differences within the separate haemophilia subtypes, for patients with HAwI there was a statistically significant difference between patients on concizumab PPX (arm 2) and no PPX (arm 1) in

the number of treated spontaneous and traumatic bleeding episodes, with an estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) of 0.09 (95%CI 0.04-0.18; p<0.001). For patients with HBwI, the estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.31 (95% CI 0.07- 1.36; p=0.12).

Key secondary endpoint - Change in SF-36 v2 bodily pain

The mean baseline score was 43.7 for patients on concizumab PPX (arm 2) and 37.6 for patients on no PPX (arm 1). The observed increase was greater for patients on concizumab PPX (arm 2) compared to patients on no PPX (arm 1). At week 24, around 75% of the patients on concizumab PPX (arm 2) had an improvement in bodily pain score compared to baseline, while around 45% of patients on no PPX (arm 1) had an improvement in bodily pain score compared to baseline. The estimated mean change in the bodily pain score from baseline to week 24 was 9.2 (95%CI 5.06- 13.2) for patients on concizumab PPX (arm 2) compared to 2.2 (95%CI -5.14- 9.52) for patients on no PPX (arm 1), yielding a difference estimate at week 24 of 6.96 (95%CI -1.64-15.57; p= 0.109).

Sensitivity analysis. Due to the low number of patients in arms 1 and 2 contributing with data, the pre-planned sensitivity analyses could not be performed.

An increase of at least 6.2 in SF-36 bodily pain score was pre-specified as the threshold for a clinically meaningful within-patient change. Based on the number of patients in arm 1 and 2 filling out the questionnaire both at baseline and at week 24 the observed proportion of responders at week 24 was 50.0% for patients on concizumab PPX (arm 2) and 16.7% for patients on no PPX (arm 1). No statistically significant difference in the odds estimate for achieving at least 6.2-point increase in the SF-36 bodily pain score at week 24 was observed between patients on concizumab PPX and patients on no PPX (arm 1), with odds estimates of 1.1 (95%CI 0.36-3.08) and 0.3 (95%CI 0.04-1.65), respectively. The estimated odds ratio (concizumab PPX (arm 2) / no PPX (arm 1)) was 4.12 (95%CI 0.54-31.71; p=0.174).

Key secondary endpoint - Change in SF-36 v2 physical functioning

The mean baseline score was 38.2 for patients on concizumab PPX (arm 2) and 36.3 for patients on no PPX (arm 1). The estimated mean change in the physical functioning score from baseline to week 24 was 4.5 (95%CI 0.77-8.19) for patients on concizumab PPX (arm 2) compared to 1.2(95%CI -4.76-7.10) for patients on no PPX (arm 1), yielding a difference estimate at week 24 of 3.30(95%CI -3.76-10.36; p=0.347). The statistical analysis is based on data from the 23 patients on concizumab PPX (arm 2) and 9 patients on no PPX (arm 1) contributing with data both at baseline and at least 1 visit post baseline.

Sensitivity analysis. Including all data collected after treatment discontinuation in the model does not change the overall conclusion of lack of effect from the main analysis. The results indicate a point estimate on treatment difference at week 24 of 3.92 (95%CI -3.36-11.20) which does not reach statistical significance (p=0.28).

An increase of at least 4.3 in SF-36 physical functioning score was pre-specified as the threshold for a clinically meaningful within-patient change. Based on the number of patients in arm 1 and 2 filling out the questionnaire both at baseline and at week 24 the observed proportion of responders at week 24 was 37.5% for patients on concizumab PPX (arm 2) and 25.0% for patients on no PPX (arm 1). No statistically significant difference in the estimated odds for achieving at least 4.3-point increase in the SF-36 physical functioning score at week 24 was observed between patients on concizumab PPX (arm 2) (odds estimate: 0.7 (95%CI 0.26-1.86)) and patients on no PPX (arm 1) (odds estimate: 0.9 (95%CI 0.1- 4.63]95%CI)). The estimated odds ratio (concizumab PPX (arm 2) / no PPX (arm 1)) was 0.78 (95%CI 0.1- 4.95; p= 0.796).

Supportive secondary outcomes – bleeding related endpoints

The supportive secondary outcomes related to number of treated bleeding episodes, including either spontaneous bleeding episodes, or spontaneous and traumatic joint bleeding episodes, or spontaneous and traumatic target joint bleeding episodes, all were consistent with the results obtained for the primary endpoint, with an estimated ABR ratio between patients on concizumab PPX (arm 2) vs no PPX (arm 1) of 0.14 (95%CI 0.06-0.30), 0.15 (95%CI 0.07- 0.32; p<0.001), and 0.21 (95%CI 0.04, 1.17 p=0.074), respectively. The analysis of the target joint bleads was based on 10 out of 19 subjects in arm 1 and 15 out of 33 subjects in arm 2, who had target joints at baseline. Comparable results were observed for the supportive secondary outcome of all treated and untreated spontaneous and traumatic bleeding episodes, the estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.33 (95%CI 0.17-0.64; p<0.001).

Additional bleeding-related results

Patients with zero bleeding episodes during the first 24 weeks of treatment

Of the 33 patients on concizumab PPX (arm 2), 21 patients (63.6%) had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment. Of the 19 patients on no PPX (arm 1), 2 patients (10.5%) had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment. Patients who discontinued before 24 weeks were counted as having more than zero bleeding episodes in this analysis.

The odds of having zero treated spontaneous and traumatic bleeding episodes during the first 24 weeks of treatment was increased in patients receiving concizumab PPX (arm 2) compared to no PPX (arm 1). Using a logistic regression model, the odds estimate was 1.3 (95%CI 0.58- 2.71) for patients on concizumab PPX (arm 2) and 0.1 (95%CI 0.01-0.41) for patients on no PPX (arm1). The estimated odds ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 23.42 (95%CI 2.63-208.87; p=0.005).

Haemostatic medication

Descriptive statistics of the consumption of haemostatic medication per bleed and per year is presented in Table 62. Most frequently used was rFVIIa, in 15/33 subjects on concizumab PPX and 13/19 subjects on on-demand treatment. In total, 283 bleeds were treated during concimant concizumab PPX in 62 subjects. Number of treated bleeds by using rFVII, FVIII, FVIIa+FX, and aPCC were 252, 9, 1 and 29. Mean consumption of rFVII to treat a bleed was 336.5 (902.2) IU/kg for subjects on on-demand treatment (arm 1) and 305.3 (459.2) IU/kg for subjects on concizumab PPX (arm 2). For aPCC mean consumption to treat a bleed was 190.4 (206.8) IU/kg for 8 subjects on on-demand treatment (arm 1) and 437.4 (790.6) IU/kg for 4 subjects on concizumab PPX in arm 4 (no treated events in arm 2 and 3). Mean consumption of rFVII per injection was 83.6 (126.2)IU/kg for subjects on on-demand treatment and 61.9 (25.5) IU/kg for subjects on concizumab.

Table 62: Haemostatic medication - consumption to treat bleeding episodes - descriptive statistics - HAwI+HBwI - OTwoATexIR - full analysis set

	No PPX	Concizumab PPX				
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arm 2-4	Total
N in FAS	19	13	33	21	60	114	127
N in FAS and ADS	19	13	33	21	60	114	127
PYE in ADS	11.6	9.3	24.2	17.9	41.3	83.4	92.8
N with a treated bleed	17	8	15	11	28	54	62
Number of treated bleeds	167	25	59	47	152	258	283
FVIII in IU/kg							
N(%) using product	1 (5.9)		1 (6.7)		5 (17.9)	6 (11.1)	6 (9.7)
Number of treated bleeds	1		1		8	9	9
Mean (SD)(consumption per year)	240.2		16.3		1433.8 (2830.1)	1197.6 (2596.6)	1197.6 (2596.6)
Mean (SD)(consumption per bleed)	48.0		10.0		535.4 (943.4)	477.0 (899.7)	477.0 (899.7)
Mean (SD)(consumption per injection)	48.0		10.0		428.3 (639.7)	390.3 (619.8)	390.3 (619.8)
Min; Max (consumption per injection)	48.0 ; 48.0		10.0 ; 10.0		16.0 ;1500.0	10.0 ;1500.0	10.0 ;1500.0
rFVIIa in ug/kg							
N(%) using product	13 (76.5)	7 (87.5)	15 (100.0)	11 (100.0)	22 (78.6)	48 (88.9)	55 (88.7)
Number of treated bleeds	114	23	59	47	123	229	252
Mean (SD)(consumption per year)	5457.6 (7645.2)	537.7 (513.6)	3220.3 (8696.7)	1212.9 (2125.9)	2295.9 (4536.4)	2336.6 (5764.6)	2107.6 (5414.7)
Mean (SD)(consumption per bleed)	336.5 (902.2)	131.2 (196.7)	305.3 (459.2)	302.8 (417.4)	266.3 (439.3)	283.8 (438.6)	269.9 (424.4)
Mean (SD)(consumption per injection)	83.6 (126.2)	50.3 (53.6)	61.9 (25.5)	87.3 (71.5)	107.4 (78.7)	85.6 (65.1)	83.0 (64.9)
Min; Max (consumption per injection)	0.1 ;2240.0	0.1 ; 300.0	0.3 ; 130.0	18.0 ; 810.0	0.1 ; 859.0	0.1 ; 859.0	0.1 ; 859.0
FVIIa+FX in ug/kg							
N(%) using product			1 (6.7)			1 (1.9)	1 (1.6)
Number of treated bleeds			1			1	1
Mean (SD)(consumption per year)			149.5			149.5	149.5
Mean (SD)(consumption per bleed)			160.0			160.0	160.0
Mean (SD)(consumption per injection)			40.0 (23.1)			40.0 (23.1)	40.0 (23.1)
Min; Max (consumption per injection)			20.0 ; 60.0			20.0 ; 60.0	20.0 ; 60.0
aPCC in IU/kg							
N(%) using product	8 (47.1)	2 (25.0)			4 (14.3)	4 (7.4)	6 (9.7)
Number of treated bleeds	60	5			24	24	29

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens.
N: number of subjects, FAS: Full analysis set, ADS: Analysis data set, PPX: Prophylaxis, PYE: patient years of exposure.
Classification of hemostatic medication is done by Novo Nordisk.

Pain relief during bleeding episodes

Of the 58 treated spontaneous and traumatic bleeding episodes recorded in patients on concizumab PPX (arm 2) up until PACO, 13 bleeding episodes (22.4%) were associated with reported pain. Of the 165 treated spontaneous and traumatic bleeding episodes recorded in patients on no PPX (arm 1) up until PACO, 66 bleeding episodes (40%) were associated with reported pain.

Exploratory endpoints – patient reported outcome

The following exploratory PRO questionnaires were included:

- 36 Item Short Form Health Survey (SF-36 v2)
  - Key secondary endpoint: Change in SF-36 v2 bodily pain
  - Key secondary endpoint: Change in SF-36 v2 physical functioning
- Haemophilia Quality of Life Questionnaire for Adults (Haem-A-QoL)
- Patient Global Impression of Severity (PGI-S) on physical functioning
- Patient Global Impression of Change (PGI-C) on physical functioning
- Haemophilia Patient Preference Questionnaire (H-PPQ)
- Haemophilia Treatment Experience Measure (Hemo-TEM)

Across all PROs (including the key secondary endpoints), a considerable proportion of patients did not fill out the questionnaires. The main reasons were lack of confirmation of visits in the StudyWorks system or patients not completing the required practice diary on Visit 2a, in which case the baseline value was lost.

SF-36 v2 health scale scores. At baseline (using the OTexIR analysis data set) the SF-36 v2 health scale scores were generally slightly higher in patients on concizumab PPX (arm 2) versus patients on on-demand treatment (arm 1). For patients on concizumab PPX (arm 2) there was an observed improvement from baseline to week 24 for all individual health scales as well as the physical and mental health component scores. For patients on no PPX (arm 1), there was an observed worsening from baseline to week 24 for General Health, Vitality, Role – Emotional, Mental Health, as well as the Mental health component score.

PROMIS Numeric Rating Scale. In the PROMIS Numeric Rating Scale v. 1.0 Pain Intensity 1a, patients rate their average pain in the past seven days on a scale from 0 (No Pain) to 10 (Worst imaginable pain). Higher scores indicate more pain intensity. From baseline to week 24 scores decreased in all arms, indicating reduced pain intensity across treatment groups, observed both for patients on concizumab PPX (arm 2) and no PPX (arm 1). PROMIS Short Form v2.0 -Upper Extremity 7a evaluate the status of physical functioning, containing 7 questions on physical functioning in upper extremities. From baseline to week 24 scores increased in all arms with patients on concizumab PPX (arms 2, 3 and 4) while it decreased for patients on no PPX (arm 1), indicating an improvement in physical functioning for patients on concizumab PPX.

Haem-A-QoL total score. The Haem-A-QoL total score decreased from baseline to week 24 for patients on concizumab PPX, as compared with an increase for patients on no PPX. A reduction in physical health domain score from baseline to week 24 was observed both for patients on concizumab PPX (arm 2) and no PPX (arm 1), indicating an improvement in health related QoL for both groups. The observed improvement was greater in magnitude for patients on concizumab PPX (arm 2).

Patient preference assessed by questionnaire. In the Haemophilia Patient Preference Questionnaire (H-PPQ) patients are asked about their treatment preference. Out of the 23 patients on concizumab PPX (arm 1) who responded, 21 (91.3%) preferred concizumab PPX to their previous treatment. 1 patient had no preference, and 1 patient preferred the previous treatment to concizumab PPX. 6 patients did not respond.

Change in patient's treatment burden using Hemo-TEM. The Hemo-TEM questionnaire contains questions related to treatment experience within the domains "Injection difficulties", "Physical impact", "Interference", "Treatment bother" and "Emotional impact". Data from 19/33 of subjects on concizumab PPX (arm 2) and 6/19 subjects on no PPX were available for analysis. At baseline (using the OTexIR analysis data set) mean scores differed among treatment groups, patients on concizumab PPX (arm 3) having lower scores for all domains compared to the other treatment arms, suggestive of a lower treatment burden. Patients on concizumab PPX (arm 2) achieved a mean improvement of 16.3 points in the Hemo-TEM total score from baseline to week 24, while patients on no PPX (arm 1) experienced a mean deterioration of 1.0 point. An 8.0-point responder threshold reflects whether a patient achieved a clinically meaningful improvement in the Hemo-TEM total score. The observed proportion of responders for the Hemo-TEM total score at week 24 was 11/19 (57.9%) for patients on concizumab PPX (arm 2) and 1/6 (16.7%) for patients on no PPX (arm 1).

Moderate or vigorous physical activity relative to awake time. Endpoints and/or assessments related to physical activity are presented using the FAS and the OTexIR analysis data set. Physical activity data was collected with a wrist-worn ActiGraph physical activity tracker. Missing patient assessments are likely related to use or availability of the ActiGraph tracker. Data for analysis were available for 22/33 subjects on concizumab PPX and 9/19 subjects on no PPX (arm 1). Using an analysis of covariance for the change from baseline to end of the main part for time spent in MVPA relative to awake time per day was increased by an estimated 4.4% points for patients on concizumab PPX (arm 2) compared to patients on no PPX (arm 1), corresponding to approximately 0.5 hrs at a mean awake time of 12 hrs.

Table 63: Statistical analyses of physical activity parameters in patients on concizumab PPX (arm 2) compared to patients on no PPX (arm 1) for the main part tracked by ActiGraph - descriptive statistics - HAwI+HBwI - OTexIR - full analysis set

Parameter	Difference estimate [95% CI]	P-value
Moderate or vigorous activity relative to awake time (%)	4.41 [0.38, 8.44]	0.033
Moderate activity relative to awake time (%)	4.19 [0.15, 8.24]	0.043
Vigorous activity relative to awake time (%)	0.14 [-0.63, 0.91]	0.717

CI: confidence interval.

Study 4311- extension part

After the end of the main part of study 4311, patients entering the extension-part were all treated with concizumab PPX. The extension part of study 4311 lasted up to week-56 cut-off.

Methods

Objectives, endpoints and assessments. No specific objectives which relate to the 56-week cut-off have been defined. The details of the exploratory efficacy endpoints, assessments and time frames for the week 56-week cut-off are outlined in the table below.

Table 30: Exploratory efficacy endpoints and assessments.

Title	Time frame	Unit
Bleed-related assessments		
The number of treated spontaneous and traumatic bleeding episodes	**For all 5 types of assessments:** **On demand (arm 1)** • From randomisation (week 0) up until start of concizumab treatment (at least 24 weeks) **Concizumab (arm 1)** • From start of the new concizumab dosing regimen up until the 56-week cut-off **Concizumab (arms 2–4)** • From start of the new concizumab dosing regimen (week 0) up until the 56-week cut-off	Count
The number of treated spontaneous bleeding episodes		Count
The number of treated spontaneous and traumatic joint bleeding episodes		Count
The number of treated spontaneous and traumatic target joint bleeding episodes		Count
The number of all spontaneous and traumatic bleeding episodes (treated and untreated)		Count

Statistical methods planned and determination of sample size

Definition of analysis sets and observation period. The following patient analysis sets were defined the 56-week cut-off, prior to unblinding:

- *Full analysis set.* The FAS was defined as all patients randomised to concizumab PPX or on-demand treatment or allocated to arms 3 or 4. Patients from arms 1 and 2 contributed to the evaluation 'as randomised'.
- *Safety analysis set*. The SAS was defined as all patients exposed to concizumab PPX or randomised to on-demand treatment. All patients contributed to the evaluation "as treated".

Statistical methodology and analysis. At the 56-week cut-off for the present trial, descriptive statistics were implemented on all arms. The 56-week cut-off was defined as when all patients in arms 2, 3 and 4 had completed the 56-week (visit 13a) assessments (or permanently discontinued treatment). For the analyses related to the 56-week cut-off, no statistical hypotheses were tested. Therefore, no adjustment for multiplicity was needed.

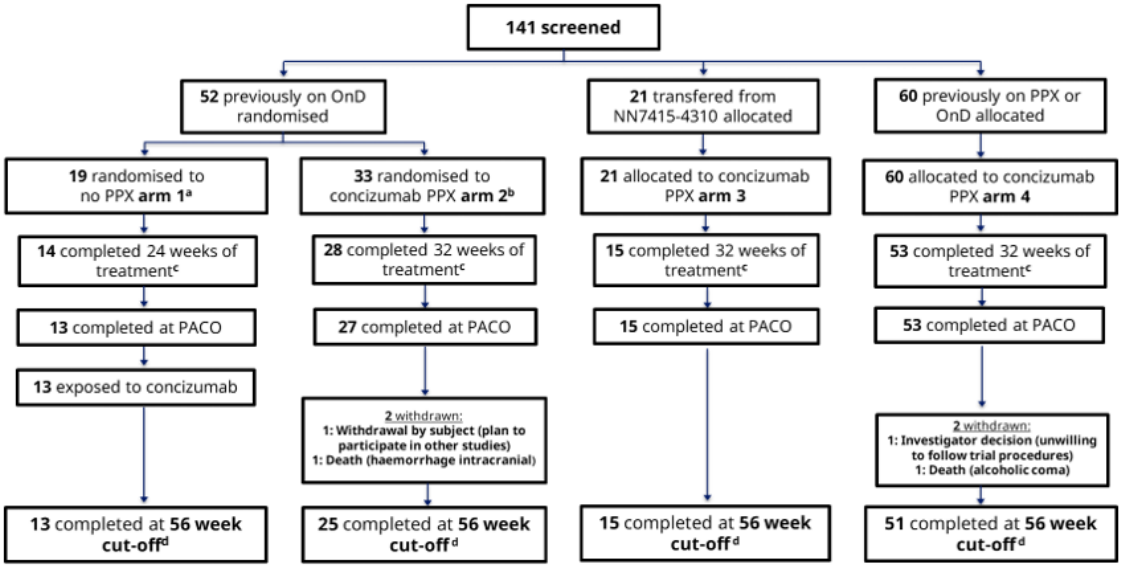
Exploratory efficacy analysis - Bleed-related assessments. Descriptive statistics were implemented for the bleed-related assessments up until week 56: treated bleeds, zero treated bleeds, cause of bleeds, anatomical location of bleeds, classification of bleeds and location of severe bleeds, presented by treatment arms and by a 'total concizumab' arm, as well as by haemophilia subtypes (HAwI and HBwI). The analysis data sets used for the bleed-related assessments were the FAS and the OtwoATexIR. The data collected while patients were

treated with the initial regimen are included for patients that did not restart in order not to invalidate the randomisation.

Results

Patient disposition. In the extension part, 13 of the 19 patients previously randomised to no PPX (arm 1), were exposed to concizumab (arm 1 PPX) (Fig XX)). A total of 114 patients were exposed to concizumab PPX in arms 2, 3 or 4. Hence, a total of 127 patients were exposed to concizumab.

Figure 44 Patient disposition at the PACO and 56-week cut-off – HawI+HBwI – trial 4311.



Notes: [a]Of the 19 patients randomised to no PPX (arm 1), 13 patients were randomised before the restart and 6 were randomised after restart. [b]Of the 33 patients randomised to the concizumab PPX arm 2, 28 patients were randomised before the restart and 5 were randomised after the restart. [c]Main part of the trial is completed when patients have completed at least 24 weeks of participation (arm 1) or 32 weeks of participation (arms 2, 3 and 4). [d]Randomised/ allocated patients who did not discontinue concizumab treatment prior to the 56-week cut-off. The 56-week cut-off is defined as when all patients in arms 2, 3 and 4 have completed visit 13a (or permanently discontinued treatment).

A total of 29 patients withdrew from the trial (25 before the PACO, 4 between PACO and 56-week cutoff) 18 patients due to withdrawal of consent, 7 patients due to death, and 4 patients due to investigators decision. Of the 29 patients withdrawn from the trial, 23 patients permanently discontinued concizumab treatment, 6 patients due to an AE (including 3 of the above deaths), 3 patients at the discretion of the investigator, 1 patient due to a protocol deviation, and 13 patients due to other reasons (including 3 of the above deaths).

A total of 91 patients from PPX arms 2-4 and 13 patients from arm 1 PPX had completed treatment at the 56-week cut-off.

Exposure and dosing

Exposure. At the 56-week cut-off, 127 patients had been exposed to concizumab and were included in the OT and OTwoATexIR analysis data sets. Across concizumab PPX arms, 76 patients with HAwI and 51 patients

with HBwI were exposed to concizumab. In total, 85 of the exposed patients were adults and 42 were adolescents (aged 12–17 years).

For patients in the OTwoATexIR analysis data set, the total concizumab exposure time across all concizumab arms was 140.6 patient years. Median (range) exposure per patient was 64 (2.0-88.7) weeks. Exposure of 19 patients in arm 1 to on-demand treatment (no PPX) was 11.6 person years, with a median (range) exposure of 31.1 (3.9-72.9) weeks.

Dosing. In total in the OTexIR analysis data set, 112 patients were exposed to concizumab across arms 1–4 (Table 65). Two patients withdrew from the trial and did not dose adjust. Of the remaining 110 patients, 79 patients (71.8%) remained on the 0.20 mg/kg dose level, 30 patients (27.3%) increased the dose to 0.25 mg/kg and 1 patient (0.9%) decreased the dose to 0.15 mg/kg.

Table 31: Concizumab maintenance dose level - summary - HAwI+HBwI - OTexIR - safety analysis set.

	Concizumab PPX				Total
	(arm 1) N (%)	(arm 2) N (%)	(arm 3) N (%)	(arm 4) N (%)	N (%)
Number of patients	13	29	15	55	112
Maintenance dose level					
N	13	28	15	54	110
0.15 mg/kg	0	0	1 (6.7)	0	1 (0.9)
0.25 mg/kg	6 (46.2)	8 (28.6)	2 (13.3)	14 (25.9)	30 (27.3)
0.20 mg/kg	7 (53.8)	20 (71.4)	12 (80.0)	40 (74.1)	79 (71.8)

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen.
N: number of patients, %: percentage of patients, PPX: Prophylaxis.
The following patients missed the maintenance dose: (Arm 4), (Arm 2).

Efficacy results up to 56 weeks-cut-off

The FAS and the SAS were identical and consisted of all 133 patients with HAwI or HBwI who were randomised/allocated and exposed to treatment. For the no PPX arm (arm 1), the results at the 56-week cut-off for patients in arm 1 who switched to concizumab PPX from on-demand treatment after at least 24 weeks are also presented.

Treated bleeding episodes up to week 56

For patients on concizumab PPX (arms 1−4), 72 patients (56.7%) reported 408 treated bleeding episodes up until week 56 (Table 66**:**). Most of these bleeding episodes (65.9%) were spontaneous, 32.6% were traumatic and 1.2% were surgical. Most bleeding episodes (90.0%) were classified as mild/moderate, while 10.0% were classified as severe. Bleeds constituting these bleeding episodes were most frequently located in joints (72.3%) or muscle (16.5%).

Table 32 Bleeding episodes - all treated - summary - HAwI+HBwI - OTwoATexIR - full analysis set.

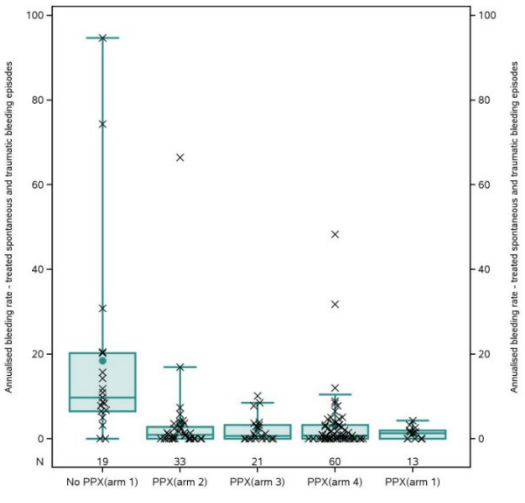
	No PPX	Concizumab PPX									
	Arm 1	Arm 1		Arm 2		Arm 3		Arm 4		Arms 2-4		Total	
	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]	N (%)	E [%]
N in FAS	19		13		33		21		60		114		127	
N in FAS and ADS	19(100)		13(100)		33(100)		21(100)		60(100)		114(100)		127(100)	
Zero treated bleeds*	1(5.3)		5(38.5)		10(30.3)		4(19.0)		22(36.7)		36(31.6)		41(32.3)	
Treated bleeding episodes	17(89.5)	167[100]	8(61.5)	27[100]	19(57.6)	89[100]	12(57.1)	70[100]	33(55.0)	222[100]	64(56.1)	381[100]	72(56.7)	408[100]
Cause of bleeding episodes														
Spontaneous	17(89.5)	123[73.7]	6(46.2)	11[40.7]	16(48.5)	65[73.0]	10(47.6)	36[51.4]	26(43.3)	157[70.7]	52(45.6)	258[67.7]	58(45.7)	269[65.9]
Traumatic	11(57.9)	42[25.1]	6(46.2)	13[48.1]	9(27.3)	23[25.8]	9(42.9)	33[47.1]	22(36.7)	64[28.8]	40(35.1)	120[31.5]	46(36.2)	133[32.6]
Surgical	1(5.3)	1[0.6]	2(15.4)	3[11.1]	0		1(4.8)	1[1.4]	1(1.7)	1[0.5]	2(1.8)	2[0.5]	4(3.1)	5[1.2]
Missing	1(5.3)	1[0.6]	0		1(3.0)	1[1.1]	0		0		1(0.9)	1[0.3]	1(0.8)	1[0.2]
Location of bleeds														
Treated bleeds	17(89.5)	182[100]	8(61.5)	28[100]	19(57.6)	96[100]	12(57.1)	72[100]	33(55.0)	234[100]	64(56.1)	402[100]	72(56.7)	430[100]
Joint	16(84.2)	128[70.3]	7(53.8)	20[71.4]	17(51.5)	74[77.1]	11(52.4)	42[58.3]	27(45.0)	175[74.8]	55(48.2)	291[72.4]	62(48.8)	311[72.3]
Target joint	7(36.8)	28[15.4]	1(7.7)	1[3.6]	6(18.2)	18[18.8]	3(14.3)	7[9.7]	14(23.3)	91[38.9]	23(20.2)	116[28.9]	24(18.9)	117[27.2]
Muscular	9(47.4)	32[17.6]	2(15.4)	4[14.3]	4(12.1)	5[5.2]	8(38.1)	20[27.8]	9(15.0)	42[17.9]	21(18.4)	67[16.7]	23(18.1)	71[16.5]
Skin	4(21.1)	4[2.2]	0		0		4(19.0)	7[9.7]	6(10.0)	12[5.1]	10(8.8)	19[4.7]	10(7.9)	19[4.4]
Gastrointestinal or Stomach/gut	0		0		2(6.1)	9[9.4]	0		0		2(1.8)	9[2.2]	2(1.6)	9[2.1]
Mouth, gums or nose	3(15.8)	5[2.7]	2(15.4)	3[10.7]	2(6.1)	2[2.1]	1(4.8)	1[1.4]	2(3.3)	2[0.9]	5(4.4)	5[1.2]	7(5.5)	8[1.9]
Urinary system	1(5.3)	2[1.1]	0		1(3.0)	1[1.0]	0		2(3.3)	2[0.9]	3(2.6)	3[0.7]	3(2.4)	3[0.7]
Central nervous system	0		0		1(3.0)	1[1.0]	0		0		1(0.9)	1[0.2]	1(0.8)	1[0.2]
Other	5(26.3)	11[6.0]	1(7.7)	1[3.6]	2(6.1)	4[4.2]	2(9.5)	2[2.8]	1(1.7)	1[0.4]	5(4.4)	7[1.7]	6(4.7)	8[1.9]
Classification of bleeding episodes														
Mild/moderate	16(84.2)	153[91.6]	8(61.5)	26[96.3]	16(48.5)	68[76.4]	12(57.1)	66[94.3]	32(53.3)	207[93.2]	60(52.6)	341[89.5]	68(53.5)	367[90.0]
Severe	5(26.3)	14[8.4]	1(7.7)	1[3.7]	9(27.3)	21[23.6]	3(14.3)	4[5.7]	10(16.7)	15[6.8]	22(19.3)	40[10.5]	23(18.1)	41[10.0]

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens.N: number of patients, (%): percentage of patients, E: number of bleeding episodes, [%]: percentage of bleeding episodes, FAS: Full analysis set, ADS:Analysis data set, PPX: Prophylaxis.* Patients that do not complete 56 weeks without permanent treatment discontinuation will be counted as not having zero bleeds. Also, all treated bleeds with either of the four causes (spontaneous, traumatic, surgical or missing) will be counted when checking whether patient had any bleeds in this table. Bleeds with multiple locations are counted in all of these locations. For location of bleeds and severe bleeds the E represents the number of bleeds and [%] is the percentage of bleeds.

The number of treated spontaneous and traumatic bleeding episodes up to 56 weeks cut-off

Individual ABRs for each patient for the treated spontaneous and traumatic bleeding episodes are presented as descriptive statistics and plotted in the Figure 68.

Figure 45: Bleeding episodes - treated spontaneous and traumatic - box plot - HAwI+HBwI - OTwoATexIR - full analysis set.



HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens.
N: number of patients, PPX: prophylaxis.
The filled circle represents the mean, the top/bottom of the box outline is the first/third quartile, the line in the middle of the box is the median and whiskers represent 5 and 95 percentiles. The x symbols represent the individual values that are summarised in the box plot.

The overall median ABR for treated spontaneous and traumatic bleeding episodes for the 127 patients on concizumab PPX (arms 1−4) at the 56-week cut-off was 0.8 (Table 67**:**). For the 13 patients in arm 1 who

switched from no PPX to concizumab PPX after at least 24 weeks, the median ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 1.3. For the 19 patients on no PPX (arm 1), the median ABR at the PACO was 9.8.

Table 33 Bleeding episodes - descriptive statistics - HAwI+HBwI - OTwoATexIR - full analysis set.

	No PPX	Concizumab PPX				
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4	Total
N in FAS	19	13	33	21	60	114	127
N in FAS and ADS	19	13	33	21	60	114	127
Person years of exposure in ADS	11.6	14.9	36.3	24.6	64.8	125.7	140.6
Weeks of exposure in ADS							
Median	31.1	72.0	64.1	80.0	56.4	64.0	64.0
P25 ; P75	16.3 ; 43.9	32.6 ; 79.9	56.1 ; 72.0	16.4 ; 80.1	56.1 ; 64.7	56.1 ; 72.3	56.0 ; 73.1
Mean (SD)	31.9 (18.3)	59.7 (22.5)	57.3 (23.5)	61.2 (32.6)	56.4 (20.1)	57.5 (23.6)	57.8 (23.5)
Min ; Max	3.9 ; 72.9	25.1 ; 80.6	3.1 ; 80.7	3.6 ; 88.7	2.0 ; 88.3	2.0 ; 88.7	2.0 ; 88.7
Treated spontaneous and traumatic bleeding episodes							
Number of episodes	166	24	89	69	221	379	403
ABR							
Median	9.8	1.3	0.9	0.7	0.7	0.7	0.8
P25 ; P75	6.5 ; 20.2	0.0 ; 2.0	0.0 ; 2.8	0.0 ; 3.2	0.0 ; 3.2	0.0 ; 3.2	0.0 ; 3.2
Mean (SD)	18.4 (24.7)	1.4 (1.4)	3.9 (11.7)	2.2 (3.1)	3.1 (7.6)	3.1 (8.4)	3.0 (8.0)
Min ; Max	0.0 ; 94.7	0.0 ; 4.3	0.0 ; 66.4	0.0 ; 10.1	0.0 ; 48.3	0.0 ; 66.4	0.0 ; 66.4
Treated spontaneous bleeding episodes							
Number of episodes	123	11	65	36	157	258	269
ABR							
Median	8.4	0.0	0.0	0.0	0.0	0.0	0.0
P25 ; P75	3.9 ; 14.3	0.0 ; 1.3	0.0 ; 2.2	0.0 ; 1.8	0.0 ; 1.9	0.0 ; 1.9	0.0 ; 1.8
Mean (SD)	13.3 (16.3)	0.6 (0.7)	3.4 (11.7)	1.2 (1.8)	2.2 (5.9)	2.4 (7.6)	2.2 (7.2)
Min ; Max	0.0 ; 58.2	0.0 ; 1.6	0.0 ; 66.4	0.0 ; 7.2	0.0 ; 35.2	0.0 ; 66.4	0.0 ; 66.4
Treated spontaneous and traumatic joint bleeding episodes							
Number of episodes	124	19	69	41	166	276	295
ABR							
Median	6.5	1.3	0.7	0.6	0.0	0.0	0.0
P25 ; P75	3.2 ; 13.1	0.0 ; 1.6	0.0 ; 2.8	0.0 ; 2.0	0.0 ; 2.2	0.0 ; 2.4	0.0 ; 2.4
Mean (SD)	14.9 (22.5)	1.0 (1.1)	3.5 (11.5)	1.4 (2.1)	2.2 (5.8)	2.4 (7.5)	2.3 (7.1)
Min ; Max	0.0 ; 81.2	0.0 ; 3.3	0.0 ; 66.4	0.0 ; 7.2	0.0 ; 34.6	0.0 ; 66.4	0.0 ; 66.4
Treated spontaneous and traumatic target joint bleeding episodes							
Number of episodes	28	1	18	7	89	114	115
ABR							
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
P25 ; P75	0.0 ; 2.2	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
Mean (SD)	3.7 (11.8)	0.1 (0.2)	1.8 (8.7)	0.2 (0.5)	1.2 (3.5)	1.2 (5.3)	1.1 (5.0)
Min ; Max	0.0 ; 51.7	0.0 ; 0.7	0.0 ; 49.8	0.0 ; 1.8	0.0 ; 21.5	0.0 ; 49.8	0.0 ; 49.8
All treated and untreated spontaneous and traumatic bleeding episodes							
Number of episodes	181	28	185	85	297	567	595
ABR							
Median	10.9	1.6	2.4	1.3	1.9	1.9	1.9
P25 ; P75	6.5 ; 20.2	0.0 ; 3.2	0.7 ; 4.9	0.0 ; 3.9	0.0 ; 5.3	0.0 ; 5.0	0.0 ; 4.3
Mean (SD)	19.4 (24.6)	1.9 (1.6)	6.7 (15.6)	2.7 (3.2)	4.1 (7.7)	4.6 (10.2)	4.3 (9.7)
Min ; Max	0.0 ; 94.7	0.0 ; 4.3	0.0 ; 83.0	0.0 ; 10.1	0.0 ; 48.9	0.0 ; 83.0	0.0 ; 83.0

N: number of patients, SD: standard deviation, P25/P75 is the 25th/75th percentile, Min: minimum, Max: maximum.
FAS: Full analysis set, ADS: Analysis data set, PPX: Prophylaxis, ABR: annualised bleeding rate.
HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens.
All endpoints other than 'Treated spontaneous bleeding episodes' include bleeding episodes with missing cause.

Haemophilia subtype data up to 56 weeks cut-off

Bleeding patterns overall were comparable between patients with HAwI and HBwI on concizumab PPX (arms 1−4).

Out of 76 patients with HAwI, 43 patients (56.6%) reported 190 treated bleeding episodes up until the 56-week cut-off. Most of these bleeding episodes (62.6%) were spontaneous, while 35.8% were traumatic and 1.1% were surgical. Most bleeding episodes (85.8%) were classified as mild/moderate, while 14.2% were classified as severe. Bleeds constituting these bleeding episodes were most frequently located in joints (74.8%) or muscle (15.8%). For patients with HAwI on concizumab PPX (arms 1−4), the median ABR for treated spontaneous and traumatic bleeding episodes was 0.7.

Out of 51 patients with HBwI, 29 patients (56.9%) reported 218 treated bleeding episodes up until the 56-week cut-off. Most of these bleeding episodes (68.8%) were spontaneous, while 29.8% were traumatic and 1.4% were surgical. Most bleeding episodes (93.6%) were classified as mild/moderate, while 6.4% were

classified as severe. Bleeds constituting these bleeding episodes were most frequently located in joints (70.2%) or muscle (17.1%). The corresponding median ABR for patients with HBwI on concizumab PPX (arms 1−4) was 1.1.

The number of bleeding episodes up to 56 weeks cut-off differentiated for cause, location or treatment indication.

The observed ABR for treated bleeding episodes, including either spontaneous bleeding episodes, or spontaneous and traumatic joint bleeding episodes, or spontaneous and traumatic target joint bleeding episodes, in general demonstrated a comparable persistent reduction in bleeding frequency at 56 week-cut-off (Table 68**:**).

Patients with zero bleeding episodes up to 56 weeks cut-off

For the 127 patients on concizumab PPX (arms 1−4), 41 patients (32.3%) had zero treated bleeding episodes up until the 56-week cut-off. For the 13 patients in arm 1 who switched from no PPX to concizumab PPX after at least 24 weeks, 5 patients (38.5%) had zero treated bleeding episodes while on concizumab PPX up to the 56-week cut-off. For the 19 patients on no PPX (arm 1), 1 patient (5.3%) who completed the first 24 weeks of treatment had zero treated bleeding episodes while on no PPX.

Target joints up to 56 weeks cut-off

In trial 4311, resolution of target joints was evaluated at the 56-week cut-off. At baseline, 60 (50.8%) of subjects reported at least one target joint, including 10/19 subjects in arm 1 and 12/29 subjects in arm 2. Most frequent target joint locations were knee (32.2%), elbow (20.3%) and ankle (12.7%).

For patients on concizumab PPX (arms 1-4) reporting pre-existing target joints at baseline, the majority (91.8%) of these target joints were resolved at 12 months or soon thereafter, which was the earliest possible time for evaluation of resolution of target joints. Four (4) patients on concizumab PPX reported 5 newly developed target joints during trial 4311.

Table 34 Resolution of baseline target joints - summary - HAwI+HBwI - OTexIR - 56-week cut-off - FAS - trial 4311.

	No PPX	Concizumab PPX				
	(arm 1)	(arm 1)	(arm 2)	(arm 3)	(arm 4)	Total PPX
N in FAS	19	13	33	21	60	127
N in FAS and ADS	19	13	29	15	55	112
Number of patients having at least one target joint, N (%)	10 (52.6)	5 (38.5)	12 (41.4)	8 (53.3)	30 (54.5)	55 (49.1)
Number of patients having at least one target joint and in OTexIR for at least 12 months, N (%)	0	3 (23.1)	10 (34.5)	8 (53.3)	28 (50.9)	49 (43.8)
Target joint getting resolved?						
E	0	4	17	11	53	85
Yes	0	4 (100.0)	17 (100.0)	11 (100.0)	46 (86.8)	78 (91.8)
No	0				7 (13.2)	7 (8.2)
If resolved, when (month)						
E	0	4	17	11	46	78
Median	0	12.0	12.0	12.0	12.0	12.0
P25 ; P75	0	12.0 ; 12.0	12.0 ; 12.0	12.0 ; 12.0	12.0 ; 12.0	12.0 ; 12.0
Mean (SD)	0	12.0 (0.0)	12.0 (0.0)	12.2 (0.6)	12.2 (1.2)	12.2 (1.0)
Min ; Max	0	12.0 ; 12.0	12.0 ; 12.0	12.0 ; 14.0	12.0 ; 20.0	12.0 ; 20.0

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen, N: number of patients, E: number of target joints.
When there have been <= 2 bleeding episode in the joint during the previous 12 months, it is no longer considered a target joint. When there have been >=3 spontaneous bleeding episodes in the joint during the previous 6 months, it is considered as a new target joint. One month is defined as 30 days. Only patients exposed to concizumab new dosing regimen for at least 12 months are included.

Pain relief during bleeding episodes up to 56 weeks cut-off

Of the 402 treated spontaneous and traumatic bleeding episodes recorded in patients on concizumab PPX (arms 1–4) up until the 56-week cut-off, 64 bleeding episodes (15.9%) were associated with reported pain. Of the 165 treated spontaneous and traumatic bleeding episodes recorded in patients on no PPX (arm 1) up until the PACO, 66 bleeding episodes (40.0%) were associated with reported pain.

Ancillary analysis

Subgroup analysis for haemophilia subtype (arm 1 vs arm 2)

Haemophilia subtype. For the primary endpoint of number of treated spontaneous and traumatic bleeding episodes, in HAwI, the observed median ABR was 1.6 for patients on concizumab PPX (arm 2) and 11.8 for patients on no PPX (arm 1). In HBwI, the observed median ABR was 0.0 for patients on concizumab PPX (arm 2) and 8.5 for patients on no PPX (arm 1). For all supportive secondary bleed-related endpoints, the observed median ABR was 0.0 both for patients with HAwI and HBwI on concizumab PPX (arms 1–4). The findings at the 56-week cut-off for comparison between patients with HAwI and HBwI, are consistent with the bleeding pattern observed at the PACO.

Table 35 Bleeding episodes - statistical analysis – HAwI and HBwI - full analysis set - trial 4311 at the PACO (OtwoATexIR).

Population	No PPX (arm 1) Estimated mean ABR [95% CI]	Concizumab PPX (arm2) Estimated mean ABR [95% CI]	ABR ratio [95% CI]
27 patients with HAwI	18.3 [10.18; 32.87]	1.6 [0.89; 2.83]	0.09 [0.04; 0.18]
25 patients with HBwI	7.2 [2.61; 20.06]	2.2 [0.76; 6.52]	0.31 [0.07; 1.36]

Abbreviations: ABR: annualised bleeding rate, CI: confidence interval, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens, PPX: prophylaxis.

Notes: Data is for treated spontaneous and traumatic bleeding episodes.

Given the rarity of HBwI, a separate superiority analysis for patients with HBwI alone was not considered feasible. There was no indication that the effect on bleeding events was driven solely by one haemophilia subtype.

Further, nine out of 18 (50.0%) patients with HAwI on concizumab PPX (arm 2) had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment vs none of the 9 patients on no PPX (arm 1). Twelve out of 15 (80.0%) patients with HBwI on concizumab PPX (arm 2), had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment vs 2 out of 10 (20.0%) of patients with HBwI on no PPX (arm 1).

Haemostatic medication to treat bleeding events up to the PACO in HAwI consisted of FVIII in 6 (6.2%) subjects, rFVIIa in 31(83.8%) subjects, FVIIa+FX in no subject and aPCC in 6(13.5%) subjects. For HBwI, these treatments were administered in 0(0%), 24 (96.0%), 1(4.0%) and 1(4.0%), respectively.

Across the PROs applied, there was a trend towards a benefit of concizumab PPX compared to no PPX for patient's health related quality of life in both haemophilia subtypes. Improvements were generally more pronounced in patients with HBwI compared to HAwI. A reduction in treatment burden was observed in both haemophilia subtypes.

Efficacy analysis across arms 2-4 (all patients on concizumab treatment)

Demographics and baseline disease characteristics. A total of 99 subjects were randomised or allocated to treatment according to the new concizumab regimen (arms 2-4) and were included in the OTexIR analysis data set. For arms 2-4, mean (SD) age was 31.5 (15.8) years.

Haemophilia details. In the OTexIR data set, the trial population consisted of male patients with congenital haemophilia A or B of any severity with a documented history of inhibitors. A total of 62 subjects with HawI

and 37 subjects with HbwI were included in arms 2-4. Inhibitors levels >= 5 BU were reported in 58 (58.6%) of subjects. A total of 50 (50.5%) subjects had a family history of haemophilia.

Previous treatment regimen was on demand treatment for 70 (70.7%) patients for a mean (SD) time of 31.3 (51.8) months and prophylaxis for 35 (35.4%) patients for a mean (SD) time of 30.0 (33.7) months. Mean ABR (SD) was 26.5 (41.5) for all patients previously treated with on demand treatment regimen, and 37.2 (76.5) for patients previously on prophylaxis.

Outcomes and estimation

Exposure in arms 2-4 (ADS) was 83.4 person years. For all patients on concizumab PPX (arms 2−4), 62 patients (48.8%) reported 283 treated bleeding episodes up until PACO. Most of these bleeding episodes (64.0%) were spontaneous, 34.6% were traumatic and 1.1% were surgical. Most bleeding episodes (89.4%) were classified as mild/moderate, while 10.6% were classified as severe. Bleeds constituting these bleeding episodes were most frequently located in joints (72.1%) and muscle (18.3%).

For the **primary endpoint** of treated spontaneous and traumatic bleeding episodes during the main part of the study, mean (SD) ABR was 3.2 (8.5). In arm 2 separately, the ABR was 3.8 (11.7).

In arms 2-4, 54 (47.4%) of subjects completing 24 weeks of concizumab treatment had zero bleeds. In arm 2, 17 (51.5%) of subjects had zero treated bleeds.

Patient reported outcomeSF-36 v2 bodily pain and physical functioning scores. At baseline (using the OTexIR analysis data set) the SF-36 v2 health scale scores were generally slightly higher in patients on concizumab PPX (arm 2-4) compared to patients on no PPX (arm 1). In general, results on patient-reported outcome for patients on concizumab PPX (arm 2-4) were in line with the results in arm 2.

Subgroup-analysis in subjects on concizumab treatment

The efficacy of concizumab in trial 4311 was explored by age group (adolescents [12−17 years] and adults [⩾18 years]), by race (Asian, Black or African American, White or other/not reported) and by ethnicity (not Hispanic or Latino, Hispanic or Latino, not reported).

The number of treated spontaneous and traumatic bleeding episodes for each subpopulation is presented in Table 70**:**. Results below are presented for concizumab PPX (arms 1−4) as some sub-populations are very small. Overall, the number of treated spontaneous and traumatic bleeding episodes in sub-populations were in line with results in the total trial population.

Table 70: Number of treated spontaneous and traumatic bleeding episodes – subpopulations - OTwoATexIR - trial 4311 at the PACO - full analysis set

		Concizumab PPX (arms 1–4)	
	N	Mean ABR (SD)	Median ABR (P25; P75)
Haemophilia subtype			
HAwI	76	2.2 (4.6)	0.0 (0.0; 3.7)
HBwI	51	4.3 (11.5)	0.0 (0.0; 3.3)
Age group			
Adolescents (12-17 years)	42	1.5 (2.1)	0.0 (0.0; 2.6)
Adults (≥18 years)	85	3.8 (9.7)	0.0 (0.0; 3.9)
Race			
Asian	34	2.8 (3.7)	1.5 (0.0; 3.9)
Black or African American	9	2.0 (2.9)	0.0 (0.0; 3.3)
White	76	3.6 (10.1)	0.0 (0.0; 3.7)
Other/not reported	8	0.0 (0.0)	0.0 (0.0; 0.0)
Ethnicity			
Hispanic or Latino	6	0.0 (0.0)	0.0 (0.0; 0.0)
Not Hispanic or Latino	117	3.3 (8.4)	0.9 (0.0; 3.7)
Not reported	4	0.0 (0.0)	0.0 (0.0; 0.0)

Notes: All endpoints other than 'Treated spontaneous bleeding episodes' includes bleeding episodes with missing cause.
Abbreviations: ABR = annualised bleeding rate; HAwI = haemophilia A with inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens; P25/P75 = 25th/75th percentile; PPX = prophylaxis; SD = standard deviation.
Cross-reference: modified from Summary 2.7.3, Appendix 7.1, Tables 3, 4, 8, 14 and 16

In adults, **haemostatic medication** used was rfVIIa, aPCC or FVIII in 88%, 12% and 3% of bleeding events respectively, as compared with 93%, 4.9 and 3.2% in adolescents.

Race. There was no indication that the effect of concizumab on ABR was mainly driven by patients of a specific race. At the PACO, across races, treated bleeding events were reported in 64.7%, 44.4% and 47.4% of Asian, Black/African American, or White patients.

Surgery

Minor surgical procedures were allowed during the phase 3 trials. Minor surgery is defined as an invasive operative procedure where only the skin, the mucous membranes or superficial connective tissue is manipulated. After the treatment pause, planned major surgery was not allowed. Up until the 56-week cut-off, a total of 5 major and 16 minor surgeries were reported in 15 patients in the OT analysis data set.

Minor surgical procedures

HA and HB patients with/without inhibitors undergoing minor surgical procedures were to be managed in accordance with local standard of care. Coagulation factor replacement therapy using either regular or extended half-life products were allowed and to be used in accordance with local label. Local/topical use of antifibrinolytics e.g. tranexamic acid was allowed. Use of single systemic doses was allowed after careful benefit-risk evaluation. During the perioperative period patients should continue daily concizumab prophylaxis. Of the minor surgeries, 14 were reported in 11 patients while on concizumab PPX (arm 1 extension; arms 2–4), while 2 were reported in 1 patient on no PPX (arm 1). A variety of minor surgeries were conducted. The number of surgery-related bleeding episodes was overall low, 5 treated surgical bleeding episodes in 4/127 subjects on concizumab PPX vs 1 treated surgical bleeding episode in 1/19 subjects on no PPX.

Major surgeries

Of the major surgeries, 4 were reported in 4 patients on concizumab PPX (arms 2–4): haemophilic arthropathy of the left hip; haematoma drainage in the head; right femoral neck fracture and osteoarthritis. One (1) of these surgeries (osteoarthritis) was only reported as an SAE. Concizumab treatment was interrupted prior to these major surgeries. In addition, one major surgery was reported in 1 patient on no PPX (arm 1). Details are described below:

Study 4311:

In one subject (arm 4), joint surgery due to haemarthos was performed. Concizumab was interrupted at 12 weeks prior to surgery and was restarted at 5 weeks after surgery.

In one subject (arm 2), haematoma drainage was performed. No data on interruption of concizumab are reported.

In one subject (arm 3), surgery for right femoral neck fracture was performed. Concizumab was interrupted at 4 days prior to surgery and restarted at 2 weeks after surgery.

The fourth major surgery was only reported as an SAE.

Study 4307:

In one subject (arm 2), major surgery of the right ankle was performed for arthropathy. Concizumab treatment was interrupted at one day prior to surgery and was restarted at 4 days after surgery.

In one subject (arm 2), laparotomy due to suspected intra-abdominal bleeding was performed. Concizumab was interrupted at 9 days before surgery and restarted at 9 days after surgery.

Impact of anti-concizumab antibody formation on efficacy

The impact of anti-concizumab antibody formation on concizumab efficacy was assessed by examining the pattern of treated spontaneous and traumatic bleeding episodes over time, in relation to ADA-status, in patients who tested positive for anti-concizumab antibodies at one or more timepoints during treatment.

The pattern of treated spontaneous and traumatic bleeding episodes for each patient was generally not different between times of presence or absence of anti-concizumab antibodies. Based on these results, there is no indication that formation of anti-concizumab antibodies impacts the effect of concizumab on preventing bleeding episodes in haemophilia patients. In 2 patients with ADAs with in vitro neutralising effects, impact on PK and efficacy cannot be excluded.

One (1) patient in trial 4310 showed ADA titres increasing from initial low levels 12 weeks after initiation of concizumab to high levels over the course of several months, after temporary discontinuation due to surgery for to traumatic bone fracture. The patient showed evidence of ADAs with in vitro-neutralising effects with restoration of free TFPI levels (at week 40). Concizumab treatment was discontinued permanently as no therapeutic effect was suspected due to restoration of the free TFPI back to baseline. The clinical impact of the ADAs was concluded to be inconclusive.

One (1) patient (compassionate use, treated on an individual patient basis for 2 years and 9 months up until the database lock date of 25 August 2022) had a single positive test for *in vitro*-neutralising anti-concizumab antibodies (taken 576 days after first concizumab dose) during a period where a reduced, though not absent, effect of concizumab was observed. The medical practitioner took no action to concizumab treatment, based on clinical judgement, after the positive anti-concizumab antibody test. It remains unclear if anti-concizumab antibodies impacted concizumab efficacy in this patient.

Study 4307 – Explorer 8

Methods - Study 4307 – Explorer 8

Study design. Trial 4307 is a 4-armed multi-national, multi-centre, open-label, confirmatory trial in adolescent and adult patients adult and adolescent patients with HA or HB without inhibitors, of which the randomised part of this study, arm 1 and arm 2, is designed to compare the effect of concizumab PPX to no PPX (on demand treatment with intravenous replacement with factor-containing products) in reducing the number of bleeding episodes. Arm 3 and arm 4 consist of patients allocated to concizumab PPX treatment only, that primarily contribute with additional safety. The study design is presented below, see Figure 69**:**.

Trial 4307 was global and had sites in the following countries: Algeria, Australia, Bosnia and Herzegovina, Bulgaria, Canada, Croatia, Denmark, Estonia, France, Germany, Hungary, India, Italy, Japan, Lithuania, Malaysia, Mexico, Poland, Portugal, Russia, Serbia, South Africa, South Korea, Spain, Sweden, Switzerland, Thailand, Turkey, Ukraine, United Kingdom, United States

Updated trial design after the treatment pause

The trial consists of a 3 week screening period, a main part (24-32 weeks treatment period), an extension part (128-136 weeks treatment period) and a 7 week follow-up period. The study design was similar to that of study 4311, with randomised inclusion in arms 1 and 2, a main part lasting 24 to 32 weeks, and extension phase of 128 to 136 weeks in patients with HA and HB without inhibitors. In Arm 1 and 2 HA and HB patients, previously treated on-demand were randomised to concizumab PPX (arm 2) versus no PPX (arm). Concizumab dose regimen was similar as applied in study 4311. Patients in arm 1 (no PPX) were to continue on-demand treatment with their usual replacement therapy. In (non-randomised) arm 3 patients were enrolled from trial 4255 prior to treatment pause, and in arm 4 patients enrolled included subjects from NIS study 4322 (enabling a within-patient comparison with factor-containing prophylaxis).

At the start of the **treatment pause**, only 12% (i.e. 7 out of 60) of the planned number of randomised patients had been enrolled. New patients could belong to the following categories: Patients entering from non-interventional study 4322, or Patients who previously participated in the phase 2 trial 4255, or Patients who were in the screening phase at the time of the treatment pause, or new patients coming from outside the concizumab programme.

A **confirmatory analyses cut-off** (**CACO**) was defined as when all patients on no PPX (arm 1) had completed the 24-week visit (visit 9a) or withdrawn and all patients on concizumab PPX (in arms 2 and 4) had completed the 32-week visit (visit 10a) or withdrawn.

Study participants. The patient population was defined based on severity of haemophilia because severity is known to correlate with the endogenous factor activity and the bleeding phenotype in patients without inhibitors. The intention was to select patients with a high medical need or a bleeding frequency of 5 bleeds every 24 weeks.

Key inclusion criteria were males aged ≥12 years with congenital severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%) with documented treatment with coagulation factor containing product in the last 24 weeks (not applicable for trial 4255 patients enrolled prior to the treatment pause) and with body weight >25 kg at screening.

Additional inclusion criteria for randomized arm 1 and 2 were either on-demand patient transferred from study 4322, or on-demand patient who had ⩾5 documented treated bleeds in the last 24 weeks or ⩾10 treated bleeds during 52 weeks before screening.

Stratification variables were Haemophilia subtype (HA, HB), and bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ⩾9 bleeding episodes).

Key exclusion criteria were comparable with study 4311.

Treatments

The applied dose regimen of concizumab, and treatment of breakthrough bleeding were similar to study 4311.

Objectives

Primary objectives

- To compare the effect of concizumab PPX to no PPX (on-demand treatment with factor) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A without inhibitors
- To compare the effect of concizumab PPX to no PPX (on-demand treatment with factor) in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia B without inhibitors

Secondary objectives

- To compare the effect of concizumab PPX to the patients' previous PPX treatment in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia A without inhibitors
- To compare the effect of concizumab PPX to the patients' previous PPX treatment in reducing the number of bleeding episodes in adult and adolescent patients with haemophilia B without inhibitors
- To investigate the safety of concizumab PPX in adult and adolescent patients with haemophilia A or B without inhibitors

The **sample size** calculation was determined based on the primary and confirmatory secondary endpoint analysis. For the primary endpoints, ABRs of 24 and 18 were assumed for the patients with HA and HB on no PPX, respectively. An ABR of between 3 and 5 was expected for concizumab PPX. Assuming a yearly over-dispersion of 13, the power for concluding superiority of concizumab PPX versus no PPX for patients with HA was estimated to be at least 82% with 21 patients (14 in the concizumab arm and 7 in the no PPX arm). The power for concluding superiority of concizumab PPX versus no PPX for patients with HB was estimated to be at least 79% with 33 patients (22 in the concizumab arm and 11 in the comparator arm).

For the confirmatory secondary endpoints , the assumptions for showing non-inferiority of concizumab PPX versus previous PPX in a within-patient comparison were: a concizumab ABR between 3 and 5; an ABR for previous PPX of 4; a non-inferiority margin of 2.0 on the relative scale; a yearly over-dispersion of 13; and patient's frailty for experiencing bleeds in the first period (on previous PPX) and the second period (on concizumab PPX) was fully correlated. With the above assumptions, the power to show non-inferiority for each haemophilia subtype was estimated to be at least 79%. A sample size of 30 subjects for each haemophilia subgroup was planned.

Randomisation and blinding

Patients were centrally randomised using an IWRS as well as stratification of the randomised on-demand patients into treatment arms 1 and 2 was performed in the IWRS. No-blinding, as this was an open-label trial.

Statistical methods

For analysis of the efficacy results data were used up until the confirmatory analyses cut-off (CACO) defined as the point in time when all patients in arm 1 had completed the 24-week visit or withdrawn and all patients on concizumab PPX (in arms 2 and 4) had completed the 32-week visit or withdrawn.

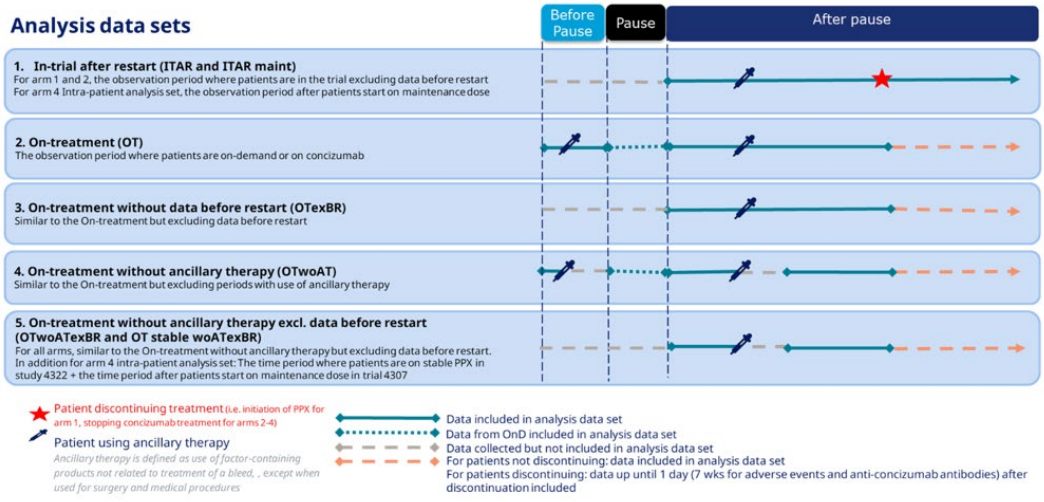
The following analysis data sets were defined for the efficacy evaluation:

Full analysis set (**FAS**). The FAS was defined as all patients randomised to the new concizumab PPX dosing regimen or on demand treatment after the treatment pause or allocated to arms 3 or 4 with the new concizumab PPX dosing regimen. Patients from arms 1 and 2 contributed to the evaluation 'as randomised'.

Intra-patient analysis set (**IPAS**). The IPAS was defined as patients in arm 4 who were on a stable PPX regimen for at least 24 weeks in study 4322 and who entered the maintenance period in the present trial.

- The On-treatment without data before restart (**OTexBR**) is the observation period after the restart of treatment where patients were considered to be affected by no PPX (on-demand treatment) or concizumab PPX with the new concizumab dosing (fig xx).
- On-demand treatment without ancillary therapy excluding data before restart (**OTwoATexBR**)

Figure 46 Defined analysis data sets trial 4307.



The **primary estimands** were addressed by use of a negative binomial regression model using the FAS and the 'OTwoATexBR' analysis data set. In the model, the logarithm of the length of the observation period was included (in years) as an offset with randomised treatment regimen and bleeding frequency (<9 or ≥9 bleeding episodes during the past 24 weeks prior to screening) included as factors.

From the statistical model, an estimate of the rate ratio of the ABR between the treatment regimens (concizumab PPX and no PPX) with the corresponding 95% CI and a p-value for the test for superiority were provided. Also, estimates of the actual ABRs with corresponding 95% CIs were provided for arms 1 and 2.

Primary sensitivity analyses. The implications of the concizumab treatment pause and the changes implemented to the trial design were investigated through sensitivity analyses for each haemophilia subtype.

Supplementary analyses. In order to investigate the effect of excluding observed data after permanent treatment discontinuation (the first intercurrent event) and during not allowed use of factor products not related to treatment of a bleed (the third intercurrent event).

Multiplicity adjustment. Tests of the statistical hypotheses were evaluated separately for the 2 populations of patients with HA or HB. Therefore, no multiplicity adjustment was required across the 2 populations. The type-I error for the 2 hypotheses within each population was controlled at a 5% significance level (2-sided) using a hierarchical (fixed sequence) testing procedure.

Confirmative secondary efficacy endpoints. The IPAS and the 'OT stable woATexBR' analysis data set were used. The analysis was similar to the primary analysis model. Non-inferiority was confirmed if the upper limit of the 95% CI was below 2.0.

Results- study 4307 – Explorer 8

Participant flow.

Patients enrolled after the treatment pause (relevant for efficacy evaluation)

When concizumab treatment restarted, 148 (82 HA and 66 HB) patients in total were randomised/allocated to treatment. Of the 82 patients with HA who were randomised/allocated to treatment after the treatment pause, 8 patients permanently discontinued concizumab PPX treatment and 5 patients also withdrew from the trial. Of the 66 patients with HB who were randomised/allocated to treatment after the treatment pause, 6 patients permanently discontinued concizumab PPX treatment. In addition, 1 patient in arm 1 (no PPX) withdrew from the trial after having completed 24 weeks of no PPX but before starting on concizumab treatment due to investigator decision The patient was diagnosed with myocardial ischaemia and was withdrawn by the investigator for safety reasons.

Conduct of the study. In protocol 3.0, dated 17 December 2019, the protocol was amended to lower the non-inferiority margin from 6 to 4, which was done in order to be more rigorous concerning the evidence needed to demonstrate efficacy of concizumab compared to previous prophylaxis. In protocol version 4.0, dated 6 July 2020, the protocol was amended to reflect the thromboembolic events seen in the phase 3 programme for concizumab and to include mitigating actions implemented to minimise the risk of additional thromboembolic events. The latest updated protocol (version 5.0) was finalized on 25 March 2021, with amendments on the concizumab ELISA in vitro diagnostic device.

Protocol deviations. There were 45 trial site level and 211 patient level important protocol deviations, that were not considered to have an impact on the safety of the patients, the integrity of the trial or interpretability of the trial data.

Baseline data. Of the 148 patients, 110 (74.3%) were adults and 38 (25.7%) were adolescents. The distribution of age, height, body weight, and BMI was similar across the treatment arms. Mean (SD) BMI was 25.2 (5.5) kg/m2 across the treatment arms.

Baseline HA/HB disease characteristics - prior treatment and mean ABR

For the randomized arms 1 and 2, 7/21 (33.3%) and 10/42 (23.%) of subjects were adolescents. A total of 10 (47.6) and 25 (59.5%) subjects in arm 1 and 2 had a family history of haemophilia.

For the randomized groups 1 and 2, prior to enrollment, all subjects with HA received on-demand treatment (9/9 (100%) and 18/18 (100%)), and prophylaxis in 3/9 (33.3%) and 1/18 (5.6%), respectively. The mean (SD) ABR was 20.4 (11.6) for HA patients previously on an on-demand treatment regimen and 5.6 (10.9) for patients previously on PPX. Prior to enrollment, subjects with HB received on-demand treatment in 11/12 (91.7%) and 22/24 (95.7%), respectively, and prophylaxis in 1/12 (8.3%) and 3/24 (13.0%). The mean (SD) ABR was 27.4 (38.6) for HB patients previously on an on-demand treatment regimen and 69.7 (310.8, median value 1.1) for patients previously on PPX.

Numbers analysed. In the OtwoATexBR analysis data set, for the randomised comparison of arm 1 (on demand treatment) versus arm 2 (concizumab PPX), 21 patients were randomised to arm 1 (9 patients with HA, 12 patients with HB) and 42 to arm 2 (18 patients with HA, 24 patients with HB). The mean (SD) patient years exposure to concizumab was 0.8 (0.3) years in 42 subjects in randomized arm 2.

The *intra-patient analysis set (IPAS)* consisted of 51 patients with HA (29) or HB (22) who were allocated to concizumab PPX in arm 4, reached the maintenance dose setting and had been on stable PPX for at least 24 weeks in study 4322. Note that the intended sample size of 30 patients with HA and 30 patients with HB was not reached. Mean (SD) patient years exposure was 1.0 (0.5) years.

Outcomes and estimation

Bleeding episodes (spontaneous and traumatic).

Patients with HA For the randomised comparison for subjects with HA, 6/18 (33%) of subjects on concizumab PPX (arm 2) reported no bleeding events versus 0/9 (0%) for subjects on on-demand treatment. On concizumab PPX, 12 subjects reported 65 bleeding events. Most of these bleeding episodes (69.2%) were spontaneous, 27.7% were traumatic. All bleeding episodes (100.0%) were classified as mild/moderate. Bleeds were most frequently located in joints (80.9%) and muscle (4.4%). On on-demand treatment, 9 subjects reported 122 bleeding events. Most of these bleeding episodes (69.7%) were spontaneous, 27.9% were traumatic. All bleeding episodes (100.0%) were classified as mild/moderate. Bleeds were most frequently located in joints (71.7%) and muscle (12.6%).

Patients with HB For the randomised comparison, for subject with HB, 6/24 (25.0%) subjects on concizumab PPX (arm 2) reported no bleeding events versus 1/12 (8.3%) of subjects on on-demand treatment. On concizumab PPX, 17 subjects reported 59 bleeding events. Most of these bleeding episodes (66.1%) were spontaneous, 28.8% were traumatic. All bleeding episodes (86.4%) were classified as mild/moderate, and 13.6% severe. Bleeds were most frequently located in joints (79.7%) and muscle (6.8%). On on-demand treatment, 11 subjects reported 97 bleeding events. Most of these bleeding episodes (85.6%) were spontaneous, 14.4% were traumatic. All bleeding episodes (88.7%) were classified as mild/moderate and 11.3% severe. Bleeds were most frequently located in joints (76.6%) and muscle (12.6%).

Median ABR

Patients with HA For HA patients on concizumab PPX (arm 2) the median ABR was 2.9, and for HA patients on no PPX (arm 1), the median ABR was 19.6. Superiority of concizumab PPX (arm 2) over no PPX (arm 1) was confirmed for the primary endpoint. Using a negative binomial regression model, the estimated mean ABR was 2.7 (95%CI 1.63-4.59) for HA patients on concizumab PPX (arm 2) and 19.3 (95%CI 11.25-33.03) for HA patients on no PPX (arm 1) (Table 71). The estimated ABR ratio between HA patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.14 (95%CI 0.07 - 0.29; $p<0.001$), corresponding to an 86% reduction in ABR for HA patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

Table 71: Bleeding episodes - treated spontaneous and traumatic - statistical analysis - HA - OTwoATexBR - full analysis set.

	No PPX (arm 1)		Concizumab PPX (arm 2)
N in FAS	9		18
N in FAS and ADS	9		18
Treated spontaneous and traumatic bleeding episodes			
ABR estimate	19.3		2.7
95% CI	[11.25; 33.03]		[1.63; 4.59]
ABR ratio		0.14	
95% CI		[0.07; 0.29]	
% reduction		86	
p-value		<0.001	

HA: haemophilia A, OTwoATexBR: On-treatment without ancillary therapy excluding data before restart, PPX: prophylaxis.
N: number of patients, FAS: Full analysis set, ADS: Analysis data set, ABR: annualised bleeding rate, CI: Confidence interval.
The endpoint includes bleeding episodes with missing cause. p-value is for two-sided test of no difference from 1. The endpoint is analysed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment and bleeding frequency prior to screening as factors.

Patients with HB For HB patients on concizumab PPX (arm 2) the median ABR was 1.6, and for HB patients on no PPX (arm 1), the median ABR was 14.9. Superiority of concizumab PPX (arm 2) over no PPX (arm 1) was confirmed for the primary endpoint. Using a negative binomial regression model, the estimated mean ABR was 3.1 (95%CI 1.91-5.04) for HB patients on concizumab PPX (arm 2) and 14.8 (95%CI 8.14-26.86) for HB patients on no PPX (arm 1) (Table 72). The estimated ABR ratio between HB patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.21 (95%CI 0.10- 0.45; p<0.001) corresponding to a 79% reduction in ABR for HB patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

Table 72: Bleeding episodes - treated spontaneous and traumatic - statistical analysis - HB - OTwoATexBR - full analysis set.

	No PPX (arm 1)		Concizumab PPX (arm 2)
N in FAS	12		24
N in FAS and ADS	12		24
Treated spontaneous and traumatic bleeding episodes			
ABR estimate	14.8		3.1
95% CI	[8.14; 26.86]		[1.91; 5.04]
ABR ratio		0.21	
95% CI		[0.10; 0.45]	
% reduction		79	
p-value		<0.001	

HB: haemophilia B, OTwoATexBR: On-treatment without ancillary therapy excluding data before restart, PPX: prophylaxis.
N: number of patients, FAS: Full analysis set, ADS: Analysis data set, ABR: annualised bleeding rate, CI: Confidence interval.
The endpoint includes bleeding episodes with missing cause. p-value is for two-sided test of no difference from 1.
The endpoint is analysed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment and bleeding frequency prior to screening as factors.

The estimated ABRs within arms in the phase 3 trials were obtained based on LSMEANS, assuming a population with balanced characteristics with regard to number of patients with low and high bleeding frequency during the past 24 weeks prior to screening. In addition, estimated ABRs based on OBSMARGIN (i.e. based on covariate distribution present in the study population) were calculated for the primary endpoint by using the characteristics as given in the study arms (haemophilia type and bleeding frequency). These are considered more realistic. The estimated ABR ratios and corresponding 95% CIs stayed unchanged compared to the initial calculations, while the estimated ABRs within arms changed slightly towards the direction of observed mean ABRs within each arm (Table 73).

Table 73: Bleeding episodes – statistical analysis – treated spontaneous and traumatic bleeding episodes – HA – OtwoATexBR – full analysis set – trial 4307 (CACO) based on OBSMARGIN

	No PPX		Concizumab PPX
N in FAS	9		18
N in FAS and ADS	9		18
Treated spontaneous and traumatic bleeding episodes			
ABR estimate based on the covariate distribution	24.5		3.5
95% CI	[14.50;41.48]		[2.18;5.54]
ABR ratio		0.14	
95% CI		[0.07;0.29]	
% reduction		86	
p-value		<.001	

HA: haemophilia A. OTwoATexBR: On-treatment without ancillary therapy excluding data before restart. N: number of subjects, ADS: analysis data set, FAS: Full analysis set, ABR: annualised bleeding rate, CI: Confidence interval, CACO: confirmatory analyses cut-off, PPX: Prophylaxis. Bleeding endpoints are analysed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment and bleeding frequency prior to screening as factors; and including the OBSMARGIN option in the estimates.

Table 36 Bleeding episodes - statistical analysis - treated spontaneous and traumatic bleeding episodes - HB - OTwoATexBR - full analysis set - trial 4307 (CACO) based on OBSMARGIN

	No PPX		Concizumab PPX
N in FAS	12		24
N in FAS and ADS	12		24
Treated spontaneous and traumatic bleeding episodes			
ABR estimate based on the covariate distribution	15.4		3.2
95% CI	[8.55;27.78]		[2.00;5.22]
ABR ratio		0.21	
95% CI		[0.10;0.45]	
% reduction		79	
p-value		<.001	

HB: haemophilia B. OTwoATexBR: On-treatment without ancillary therapy excluding data before restart. N: number of subjects, ADS: analysis data set, FAS: Full analysis set, ABR: annualised bleeding rate, CI: Confidence interval, CACO: confirmatory analyses cut-off, PPX: Prophylaxis. Bleeding endpoints are analysed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment and bleeding frequency prior to screening as factors; and including the OBSMARGIN option in the estimates.

Since estimated ABRs based on OBSMARGIN are only provided for the primary endpoints, and results are similar, estimated ABRs based on LSMEAN statement are reported in the Overview, unless stated otherwise.

Sensitivity and supplementary analysis. Sensitivity analysis 1 (tipping point analysis): when imputing the number of bleeding episodes for the 2 patients in arm 2 who permanently discontinued treatment prior to week 32, the results were supporting the robustness of the superiority conclusion of the primary analysis. Sensitivity analysis 2: re-running the primary analysis including patients from the initial randomisation (before the treatment pause) did not impact the results or conclusion of the primary analysis.

Confirmatory secondary endpoints- number of treated spontaneous and traumatic bleeding episodes (previous factor containing PPX vs concizumab PPX) within-patient comparison

These analyses compared the ABR in patients treated with concizumab PPX in trial 4307 arm 4 who were previously on stable factor containing PPX for at least 24 weeks in study 4322 (historical ABR).

For patients with HA, the median ABR was 2.3 on concizumab PPX (trial 4307) and 2.2 on previous PPX (study 4322)and for Patients with HB the median ABR was 1.4 on concizumab PPX (trial 4307) and 2.1 on previous PPX. Both for patients with HA and HB, for the additional bleed-related assessments in the intra-patient comparison (number of treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes and all treated and untreated spontaneous and traumatic bleeding episodes), median ABRs were numerically similar or lower with concizumab PPX (trial 4307) than with previous PPX (study 4322). However, non-inferiority of concizumab PPX (trial 4307) over previous PPX (study 4322) was not confirmed, as the upper limits of the 95% CI of the ABR ratios of concizumab PPX (trial 4307) over previous PPX (study 4322) were above the non-inferiority margin of 2.0.

Supportive secondary endpoints – bleeding related endpoints

In line with the primary endpoint results on treated bleeding events, additional analyses of all treated and untreated spontaneous and traumatic bleeding, including joint bleeding episodes showed statistically significant difference between patients on concizumab PPX (arm 2) and no PPX (arm 1) in both HA and HB patients. For target joint bleeding episodes, the treatment effect was statistically significant in HA patients, but did not reach statistical significance for HB patients.

- **Ancillary analyses**

Patients with zero bleeding episodes (No PPX vs concizumab PPX)

Patients with HA Of the 18 HA patients on concizumab PPX (arm 2), 6 patients (33.3%) had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment. Of the 9 HA patients on no PPX (arm 1), no patients had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment.

Patients with HB Of the 24 HB patients on concizumab PPX (arm 2), 11 patients (45.8%) had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment. Of the 12 HB patients on no PPX (arm 1), 1 patient (8.3%) had zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment.

Haemostatic medication

For HA, mean consumption of fVIII per injection to treat a bleeding event was 27.3 IU/kg, in line with the updated breakthrough bleed guidance of 20 IU/kg. The mean total consumption of fVIII to treat a bleeding episode was 28.6 (19.4) IU/kg on concizumab PPX (arm 2) vs 30.0 (17.3) IU/kg for on-demand treatment (arm 1). For HB, the mean consumption of fIX per injection to treat a bleeding event was 37.6 (21.0) IU/kg, in line with the updated breakthrough bleed treatment guidance of 30 IIU/kg. The mean total consumption of fIX to treat a bleeding episode was 45.9 (76.4) IU/kg on concizumab PPX (arm 2) vs 54.6 (45.9) IU/kg for on-demand treatment (arm 1).

Surgery

Up until the confirmatory analyses cut-off, a total of 13 minor surgeries were reported in 9 patients with HA, and 3 major and 12 minor surgeries were reported in 12 patients with HB, in the OT analysis data set.

Of the major surgeries in patients with HB, 2 were reported in 2 patients on concizumab PPX (arm 2): Right Ankle Arthropathy and Diagnostic laparoscopy with removal of blood from the abdominal cavity, and 1 was reported in a patient on no PPX (arm 1): liver transplant. Concizumab treatment was interrupted prior to these major surgeries. In addition, one major surgery was reported in a patient on no PPX (arm 1).

The haemophilia management in case of (unplanned or semi-elective) major surgery was not predefined, regarding period of interruption of concizumab PPX and monitoring of anticoagulation. This can be understood in view of the rarity of the occasions. In total, data on concizumab interruption are available in 5 of these cases. Prior to surgery, concizumab was interrupted for a period ranging from 1, 4 or 9 days and up to 12 weeks in a single case. After surgery, concizumab treatment was resumed after a period ranging from 4 days to 5 weeks. All cases were managed peri-operatively using haemostatic treatment consisting of FEIBA, fVII and nonacog alfa.

A variety of minor surgeries was conducted, and the number of surgery-related bleeding episodes was overall low, 8 treated surgical bleeding episodes in 8/144 subjects on concizumab PPX vs no treated surgical bleeding episode in subjects on no PPX.

- **Summary of main efficacy results**

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 37: Summary of efficacy for study 4311 (Explorer 7)

Title: Explorer 7: A phase 3 multi-national, multi-centre, randomised, open-label, confirmatory study, followed by a non-controlled extension period, to assess efficacy and safety of concizumab PPX vs no PPX (on demand treatment with intravenous replacement with factor-containing products) in reducing the number of bleeding episodes in adult and adolescent patients with HAwI or HBwI.		
Study identifier	Study NN7415-4311 (short title: Explorer 7), EudraCT: 2018-004889-34	
Design	Randomised (arms 1 and 2), controlled, open-label, parallel group, multicentre, global.	
	Duration dose-setting phase: Duration of main phase: Duration of Extension phase: Duration of Follow-up phase:	>= 8 weeks (concizumab PPX arms) >=24 weeks (32 incl. dose-setting period) 128 weeks (136 incl. dose-setting period) 7 weeks
Hypothesis	Superiority of concizumab PPX over no PPX (on-demand bleeding treatment with factor-containing products)	
Treatment groups	Concizumab PPX (arm 2)	Males aged >= 12 years with congenital HA or HB of any severity, with history of inhibitor (>= 0.6 BU) and ABR >= 12 episodes/yr Treatment: Concizumab, loading dose 1 mg/kg s.c., initial daily dose 0.20 mg/kg s.c., at 4 weeks followed by individual dose setting to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure Breakthrough bleeding treatment with bypassing agent (see below). Duration: 24 weeks at primary analysis cut-off (PACO), extension phase 56 weeks-cut off reached Number randomized: 33
	On-demand (arm 1)	Males aged >= 12 years with congenital HA or HB of any severity, with history of inhibitor (>= 0.6 BU) and ABR >= 12 episodes/yr

			Treatment: On demand breakthrough bleeding treatment with bypassing agent (see below). Duration: 24 weeks at primary analysis cut-off (PACO), extension phase 56 weeks-cut off reached Number randomized: 19
	<u>For both groups: Breakthrough bleeding treatment with bypassing agent:</u> • rFVIIa (dose 90 mcg/kg) • aPCC (FEIBA®), single dose <= 50 U/kg, daily dose <= 100 U/kg) • ByClot® (Plasma-derived factors VIIa and X mixtures), single dose <= 60 µg/kg, daily dose <=90 µg/kg		
Endpoints and definitions	**Primary endpoint**	ABR (estimated annual bleeding rate)	The number of treated spontaneous and traumatic bleeding episodes. • For concizumab (arm 2): from start of the new concizumab dosing regimen (week 0) up until the primary analysis cut-off (at least 32 weeks). • For on demand (arm 1): from randomisation (week 0) up until start of concizumab treatment (at least 24 weeks).
	Key secondary endpoints		• Change in SF36v2 bodily pain (from start of treatment (week 0) until week 24) • Change in SF-36v2 physical functioning (from start of treatment (week 0) until week 24)
	Supportive secondary endpoints	ABR	• Number of treated spontaneous bleeding episodes, • number of treated spontaneous and traumatic joint bleeds, • number of treated spontaneous and traumatic target joint bleeds
Database lock	27 December 2021		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Full analysis set (FAS, all patients randomised to concizumab PPX or no PPX) Time point: PACO, Primary analysis-cut-off • For endpoints related to bleeding episodes, the Analysis Data Set On-treatment without ancillary therapy exc. Data on initial regimen for subjects exposed to both regimens (OtwoATexIR) was used, reflecting the observation period in which patients are exposed to either on demand treatment or the new concizumab dosing regimen (or the initial concizumab dosing regimen if patients were not exposed to the new dosing regimen). • Statistical test: a negative binomial regression analysis with logarithm of exposure time as offset and treatment as factor • For endpoints related to PRO, the Analysis Data Set On-treatment without data on initial regimen (OtexIR) was used. • Statistical test: post-hoc MMRM		
Primary endpoint	Treatment group	On-demand (no PPX)	Concizumab PPX	Estimated ABR ratio (concizumab PPX / on-demand) (95% CI)

	Number of subjects	19	33	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes Mean (95% CI)	11.8 (7.03, 19.86)	1.7 (1.01,2.87)	0.14 (0.06, 0.30) (p<0.001)
				Difference at week 24
Key secondary endpoints[a, d]	Estimated mean Change in SF-36 v2 bodily pain (baseline to week 24) (95% CI)	2.2 (-5.14, 9.52)	9.2 (5.06, 13.25)	6.96 (-1.64, 15.57) P=0.109
	Estimated mean Change in SF-36 v2 physical functioning (baseline to week 24) (95% CI)	1.2 (-4.76, 7.10)	4.5 (0.77, 8.19)	3.30 (-3.76, 10.6) P=0.347
				Estimated ABR ratio (concizumab PPX / on-demand) (95% CI)
Explorative secondary endpoints	Estimated ABR for treated spontaneous bleeding episodes Mean (95% CI)	9.4 (5.20, 16.99)	1.3 (0.71, 2.31)	0.14 (0.06, 0.30)
	Estimated ABR for treated spontaneous and traumatic joint bleeding episodes Mean (95% CI	9.1 (5.13, 16.05)	1.4 (0.77, 2.46)	0.15 (0.07, 0.32)
	Estimated ABR for treated spontaneous and traumatic target joint bleeding episodes Mean (95% CI	2.5 (0.54, 11.91)	0.5 (0.07, 3.76)	0.21 (0.04, 1.17)
	Estimated ABR for all treated and untreated spontaneous and traumatic bleeding episodes Mean (95% CI)	13.3 (7.89, 22.51)	4.4 (2.84, 6.86)	0.33 (0.17, 0.64)
Sub-group analysis				
HAwI	number	9	17[b]	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes Mean (95% CI)	18.3 (10.18, 38.87)	1.6 (0.89, 2.83)	0.09 (0.04, 0.18) (p<0.001)[c]

HBwI	number	10	12[b]	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes Mean (95% CI)	7.2 (2.61, 20.06)	2.2 (0.76, 6.52)	0.31 (0.07, 1.36) P=0.12[c]
[a]: adapted post-hoc analysis using MMRM-model, due to high proportion of missing values. [b]: number of subjects in the OtwoATexIR analysis dataset (a total of 33 subjects with HawI and HbwI were randomized) [c]: Study was not powered to detect statistically significant differences for concizumab PPX vs on-demand within the separate haemophilia subtypes [d]: a change of >= 6.2 in SF-36v2 Bodily pain and >= 4.3 in SF-36v2 physical functioning were thresholds for a clinically meaningful within-patient change. The statistical model for the treated target joint bleeds is only fitted for the patients having target joints at baseline.				

Compassionate Use programme 4807 and individual patient basis

Concizumab has been provided for compassionate use both on an individual patient basis and in a compassionate use programme. The primary objective of the compassionate use programme was to provide expanded access to concizumab to patients with congenital haemophilia who could not be treated satisfactorily with authorized and marketed medicines, and who were not able to enroll in concizumab clinical trials.

Individual patient basis

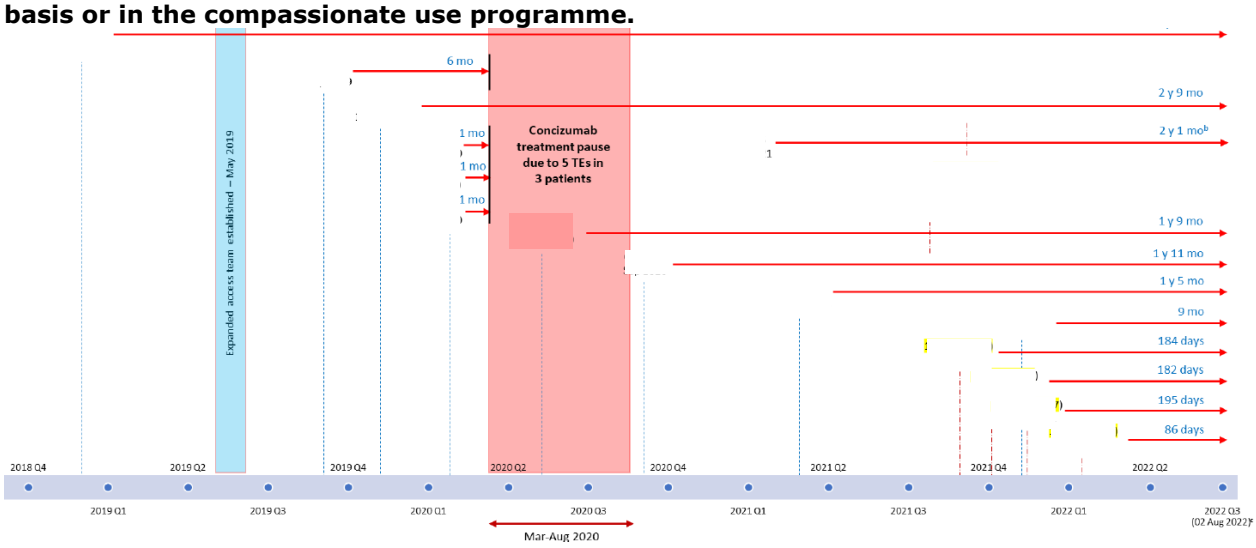
Novo Nordisk has granted compassionate use of concizumab on an individual patient basis after careful medical and safety evaluation. Accordingly, the American, French and Swedish health authorities have approved requests for the compassionate use of concizumab for several patients with congenital haemophilia who were not satisfactorily treated with approved medicines.

Compassionate use programme

Novo Nordisk developed a compassionate use programme covered by a specific protocol (NN7415-4807 and ClinicalTrials.gov Identifier: NCT04921956). The compassionate use programme provided patients of any age with the highest unmet medical need with concizumab for free, even though it is not yet approved by health authorities and allowed for a more structured collection of data to monitor the patients' safety and clinical benefit. Concizumab has not previously been studied in children below 12 years of age. As children constitute a vulnerable population, the increased monitoring of patients in the compassionate use programme was considered important for the safety of the patients.

Enrolment of patients. A total of 14 children and adolescents with HBwI have received concizumab up to the database lock date for the compassionate use report (25 August 2022) (Figure 70**:**0). Ten (10) patients had received concizumab on an individual patient basis, whereby health authority agreement is obtained to allow patients to receive unapproved medicinal products outside a clinical trial. Three (3) of the 10 patients went on to enroll in the CUP, and an additional 4 patients also enrolled in the CUP (i.e., a total of 7 patients enrolled in the CUP).

Figure 70: Concizumab total exposure for patients receiving concizumab on an individual patient basis or in the compassionate use programme.

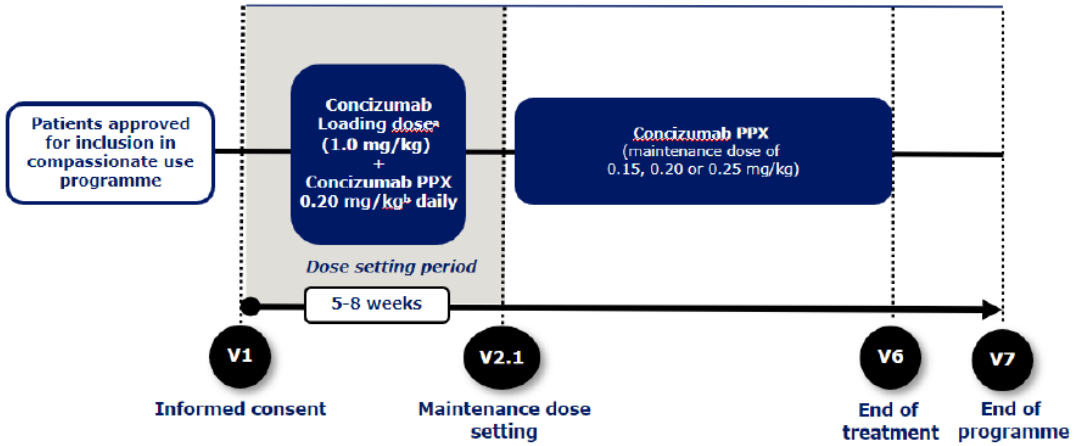


Notes: Patients receiving individual patient basis compassionate use have a patient ID starting with COM. Patients in the compassionate use programme receiving concizumab for >1 day, shown with yellow highlighting, have a 6-digit patient ID together with the programme number (4807). aPatient subsequently switched to the compassionate use programme and received concizumab for 1 day (01-Jul-2022). bIncluding treatment pause. cDatabase lock date for individual patient basis compassionate use was 25-Aug-2022. Abbreviations: ID: identifier; mo: months; TE: thromboembolic event; y: years.

The 10 patients (9 male, 1 female) who received concizumab on an individual patient basis were aged between 1 and 15 years and were exposed to concizumab for between 1 month and 3 years and 6 months up to the database lock date. Information on the patients was collected in the form of patient narratives provided by the patients' medical practitioners in emails as well as AEs reported to Novo Nordisk in accordance with local legislation. The medical practitioners were asked to provide a short statement on the overall condition related to haemophilia while the respective patient was on concizumab treatment and to provide a rating on their overall condition, considering efficacy, safety, and quality of life. This statement was unavailable for 2 of the 3 patients who switched to the CUP.

Design CUP study 4807. Approximately 10–20 patients were expected to enroll in the compassionate use programme, whose design is shown in the figure below.

Figure 71: Design CUP study 4807.



Notes: aLoading dose only applicable for concizumab-naïve patients; bStarting dose might be 0.25 mg/kg for patients already receiving concizumab on an individual patient basis prior to entering the compassionate use programme. Abbreviations: PPX: prophylaxis; V: visit.

Dosing regimen and maintenance dose setting. The dosing regimen for the compassionate use programme was identical to that applied in the phase 3 clinical trials for concizumab in adults and adolescents (NN7415-4311 and -4307) as well as the dosing regimen for the ongoing paediatric phase 3 trial 4616, which includes children below the age of 12 years. Patients already receiving concizumab on an individual patient basis did not receive a loading dose when entering the compassionate use programme.

Treatment of breakthrough bleeding episodes. The investigator instructed the patient and caregivers on how to treat breakthrough bleeds in accordance with the guidance in the protocol.

Endpoints

Individual basis: The patient's medical practitioner provided information in the form of a short statement and a rating on the patient's overall condition related to haemophilia while on concizumab treatment (considering efficacy, safety and quality of life). One of the following rating options was to be chosen: Much improved, Minimally improved, No change, Minimally worse, Much worse. SAEs reported by the patients who received concizumab on an individual patient base are presented.

Compassionate use (study 4807): Case narratives including observed ABR prior to and during concizumab PPX and treatment history.

Statistical plan (study 4807). No formal statistical analyses were planned. Only descriptive statistics were used for reporting. Evaluation of the collected assessments will be made on an individual patient level. AEs and bleeding episodes will be investigated across patients.

An ABR for all treated bleeding episodes and an ABR for treated joint bleeding episodes will also be calculated. Furthermore, the patient's individual historical ABR before starting on concizumab will be reported.

Results compassionate use on individual base

Participant flow. Concizumab was provided on a compassionate use basis in 14 children and adolescents with HBwI. Ten (10) patients received concizumab on an individual patient basis and 7 patients were included in the compassionate use programme, including 3 who switched to this programme after receiving concizumab on an individual patient basis.

Overall, the 14 patients were aged between 1 and 17 years when they first received concizumab and treatment exposure ranged between 1 month and 3 years and 6 months. Eleven (11) of the 14 patients were below the age of 12 years.

Exposure in CUP and Individual patient exposure Exposure information for each of the patients is provided in the table below and illustrated visually in the figure above.

Table 38: Concizumab exposure for patients receiving compassionate use of concizumab

Patient number	Date of first concizumab dose	Individual patient basis exposure	Exposure in 4807	Total exposure
		3 years and 6 months	1 day	3 years and 6 months
		6 months	NA	6 months
		1 month	NA	1 month
		1 month	NA	1 month
		1 year and 7 months[a]	196 days (~6.5 months)	2 years and 1 month[a]
		2 years and 9 months	NA	2 years and 9 months
		1 year and 5 months	NA	1 year and 5 months
		1 year and 3 months	175 days (~6 months)	1 year and 9 months
		1 year and 11 months	NA	1 year and 11 months
		9 months	NA	9 months
		NA	184 days (~6 months)	184 days (~6 months)
		NA	182 days (~6 months)	182 days (~6 months)
		NA	86 days (~3 months)	86 days (~3 months)
		NA	195 days (~6.5 months)	195 days (~6.5 months)

Notes: aIncluding treatment pause (Section 3.3). Cut-off date for individual patient basis compassionate use (patients with an ID starting with COM) was 25-Aug-2022. For patients in the compassionate use programme (4807; patients with a 6-digit patient ID), data were included up to the date of the last visit occurring at the latest on 02-Aug-2022 (see Table 4-2 for the last visit date). Abbreviations: ID: identifier; NA: not applicable**.**

In total, 7 children or adolescents with HBwI received concizumab in the compassionate use programme between 23-Aug-2021 (start date for the first patient) and 02-Aug-2022 (cut-off date for this report). Six (6) patients were recruited in the USA, and 1 patient from Bulgaria. Three (3) of the patients also received concizumab on an individual patient basis prior to enrolling in the compassionate use programme. The patients (all males) were aged between 1 and 17 years when they entered the compassionate use programme.

Ten (10) patients with HBwI received concizumab on an individual patient basis between 10-Dec-2018 (start date for the first patient) and 25-August-2022 (database lock date). The patients (9 males, 1 female) were aged between 1 and 15 years when they first received concizumab and they were exposed to concizumab for between 1 month and 3 years and 6 months see Table 77**:**.

Table 39 Patients receiving concizumab on an individual patient basis

Patient number	Country	Sex	Date of first concizumab dose	Age when first received concizumab (years)	Individual patient basis exposure
		Male			3 years and 6 months
		Male			6 months
		Male			1 month
		Male			1 month
		Male			1 year and 7 months[d]
		Male			2 years and 9 months
		Male			1 year and 5 months
		Male			1 year and 3 months
		Male			1 year and 11 months
		Female			9 months

Notes: aPatient later switched to the compassionate use programme. bPatient later switched to the compassionate use programme. cPatient later switched to the compassionate use programme. dIncluding treatment pause. Abbreviations: ID: identifier.

Outcome/ estimation narratives (rating scores) patients on individual treatment basis

The overall rating scores provided by the treating physician: "much improved" in 5 cases, "minimally improved" in 2 cases, "no change" in 1 case. No rating was provided in 2 cases. Both subjects were switched to study 4807.

One subject, initially responded well to concizumab treatment, but bleeding frequency increased after 15 months with recurrent joint bleeds and antibodies against concizumab were detected. The effect of concizumab was limited and the patient's quality of life was affected by pain, daily intravenous injections (NovoSeven), frequent hospital visits and limited possibilities to attend pre-school. The patient did experience some [beneficial] effect of concizumab treatment since he responded better to NovoSeven compared to before starting concizumab treatment. Therefore, he was continued on concizumab at the discretion of the treating physician.

Outcome/ estimation - CUP study 4807

Results regarding exposure, number of bleeding episodes and calculated ABR are presented below:

Table 40: Patients receiving concizumab in the compassionate use programme 4807

Patient number	Country	Age on entering 4807 (years)	Treated bleeds and calculated ABR in exposure period			Number of AEs
			Exposure in 4807 (days)	Number of treated bleeding episodes	Calculated ABR	
[redacted][a]	[redacted]	[redacted]	1	0	–	0
[redacted][b]			196	1	1.9	3[d]
[redacted][c]			175	0	0.0	4
[redacted]			184	1	2.0	10[e]
[redacted]			182	6	12.0	6
[redacted]			86	2	8.5	6[f]
[redacted]			195	1	1.9	0

Notes: aPatient previously received concizumab on an individual patient basis. bPatient previously received concizumab on an individual patient basis. cPatient previously received concizumab on an individual patient basis. dIncluding 2 SAEs. eIncluding 1 SAE. fIncluding 1 SAE. Abbreviations: ABR: annualised bleeding rate; AE: adverse event; ID: identifier; SAE: serious adverse event.

A summary of the medical history for each patient based on their medical practitioner's initial request for compassionate use of concizumab is provided together with a summary of the number of treated bleeding episodes and calculated ABR after receiving concizumab in the table below.

Table 41: Summary of patient medical history and treated bleeding episodes / calculated ABR after receiving concizumab

Patient number	Age on entering 4807 (years)	Summary of patient medical history prior to receiving concizumab	Number of treated bleeding episodes and calculated ABR after receiving concizumab
		Inhibitors developed at age 16 months. Initially treated with rFIX; bleeds nonresponsive at age 25 months. Bleeding managed with rFVIIa, which reduced but did not prevent the bleeds. ITI with rFIX and then albumin fusion rFIX started and eventually unsuccessful due to allergic symptoms; eventually discontinued. Greatly impacted quality of life. Limited treatment options.	'Much improved' medical practitioner rating after receiving concizumab on an individual patient basis. 0 treated bleeding episodes over a period of 1 day in the compassionate use programme.
		Inhibitors developed at age 1 year after treatment with rFIX Fc fusion protein, leading to anaphylaxis. Subsequent daily PPX with rFVIIa, but with breakthrough bleeding events and inadequate bleeding control. Considered a poor candidate for ITI therapy by medical practitioner, with prognosis of increasing morbidity, and increased risk of musculoskeletal and other serious complications.	1 treated bleeding episode (0 joint bleeds) over a period of 196 days in the compassionate use programme, corresponding to a calculated ABR of 1.9.
		Inhibitors developed at age 11 months after rFIX treatment. rFVIIa proved inadequate to control spontaneous bleeding. ITI therapy with desensitisation started, but long-term adverse effects developed. Further therapy with rFIX fusion protein, rFVIIa and ITI not considered appropriate due to risk of inhibitor reoccurrence, multiple spontaneous bleeds, or risk of anaphylaxis and nephropathy, respectively.	0 treated bleeding episodes over a period of 175 days in the compassionate use programme, corresponding to a calculated ABR of 0.
		Medical history of growth hormone and vitamin D deficiency, platelet delta storage pool disorder. Previously received ITI therapy but developed anaphylactic reactions. Began using rFVIIa, with increased frequency of joint bleeds and decreased efficacy by age 11 years. aPCC initiated, but inhibitor titres increased. ITI reinitiated, leading to anaphylactic reactions and use of desensitisation protocols. Plans for further ITI put on hold due to anaphylactic reactions; intercurrent bleeds treated with rFVIIa.	1 treated bleeding episode (0 joint bleeds) over a period of 184 days in the compassionate use programme, corresponding to a calculated ABR of 2.0.
		Treated with secondary FIX PPX since age of about 8 months due to an intracranial bleed. Undergone ITI therapy several times due to intermittent inhibitor development, with different treatments and to varying degrees of success. Developed anaphylaxis to FIX products during inhibitor development and also to the monoclonal antibody rituximab, given after desensitisation. Also previously been on aPCC.	6 treated bleeding episodes (3 joint bleeds) over a period of 182 days in the compassionate use programme, corresponding to a calculated ABR of 12.0.
		Previously experienced a life-threatening left exterior chest wall haemorrhage and developed severe anaemia requiring multiple blood transfusions. Subsequently received PPX with rFIX and various FIX treatments due to a mild increase in bleeding symptoms and repeated allergic reactions. Eventually diagnosed with inhibitors. rFVIIa was initiated but unsuccessful, with soft tissue haematomas and bleeds consistent with haemarthrosis several times.	2 treated bleeding episodes (1 joint bleed) over a period of 86 days in the compassionate use programme, corresponding to a calculated ABR of 8.5.
		Inhibitors to FIX first detected at age 1 year and 4 months; first joint bleed at age 2 years. Patient switched to rFVIIa treatment on demand, but joint health deteriorated including frequent bleeds. Switching to aPCC treatment resulted in systemic hypersensitivity reactions and a subsequent increase in inhibitor titres. Patient developed muscle atrophy of the left knee and right elbow.	1 treated bleeding episode (0 joint bleeds) over a period of 195 days in the compassionate use programme, corresponding to a calculated ABR of 1.9.

Abbreviations: ABR: annualised bleeding rate; aPCC: activated prothrombin complex concentrate; FIX: coagulation, factor IX; ITI: immune tolerance induction; PPX: prophylaxis; rFVIIa: recombinant activated coagulation factor VII; rFIX: recombinant coagulation factor IX.

2.6.6. Discussion on clinical efficacy

Efficacy in patients aged ≥ 12 years with HAwI and HBwI

The efficacy in the clinical development programme of concizumab in this indication is based on the efficacy data of one pivotal phase 3 study 4311 (Explorer 7) in patients ≥ 12 years with HAwI and HbwI. Importantly, this study is supported by a second phase 3 study 4307 (Explorer 8) with a similar design in patients aged ≥12 years with HA or HB without inhibitors. Further supportive studies were the phase 2 dose-finding and proof-of-concept study 4310 (Explorer 4) in patients with HawI and HbwI and uncontrolled dose-response study 4255 in in patients with HA without inhibitors (Explorer 5). All studies provided long-term uncontrolled extensions. Additionally, a non-interventional study (NIS) was performed providing baseline information on details of haemophilia and physical activity tracker over a period of 24 weeks from patients who would subsequently be offered screening for both phase 3a trials. Additionally, NIS provided historical ABR data for a within patient comparison in study 4307.

Rationale for the dosing used in the phase 3 clinical trials

The recommended dose regimen is a loading dose of 1 mg/kg and an initial daily dose of 0.20 mg/kg. Within an initial 5−8-week dose adjustment period on 0.20 mg/kg concizumab, the patients can be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab; this will be based on the concizumab exposure level at the week 4 visit. The rationale is presented below in the concizumab treatment pause section.

Concizumab treatment pause

Phase 3 clinical trials were initiated in October 2019. Concizumab treatment in trials 4307, 4311 and 4255 was put on clinical hold in March 2020 by the FDA due to the occurrence of 5 non-fatal thromboembolic events (TEs) in 3 patients enrolled in the phase 3 programme. These cases occurred in 1 patient in study 4311 and 2 in study 4307. All occurred during treatment with bypassing agents for breakthrough bleeding events, of whom one patient with HA without inhibitors concomitantly used FVIII with concizumab from the start of the study. Analysis of the TEs and all available data led to changes to the phase 3 trial protocols. Risk mitigation measures were implemented, and trial protocols were updated before resuming concizumab treatment. The main changes included a new dose regimen, and new guidance for treatment of mild and moderate breakthrough bleeds with specific guidance for use of the lowest dose of factor product or bypassing agent while on concizumab PPX based on the WFH guidelines. Additional mitigating actions included non-allowance of elective major surgery during the trial. The clinical hold was lifted in August 2020. These risk mitigations were evaluated and approved of in SA EMEA/H/SA/2178/1/FU/3/2020/PA/II.

Rationale for the dosing used in the phase 3 clinical trials

The initially used dose regimen for the phase 3 studies, a single loading dose of 1 mg/kg followed by a daily maintenance dose of 0.25 mg/kg sc was based on the results of phase I and II studies and on PK modelling. The dosing scheme was re-evaluated due to 5 TEs patients in study 4307.

After the treatment pause, a new concizumab dosing regimen with a loading dose of 1 mg/kg and an initial daily dose of 0.20 mg/kg was implemented with the option to increase or decrease the dose to 0.25 mg/kg or 0.15 mg/kg concizumab; this will be based on the concizumab exposure level at the week 4 visit. The single loading dose of 1 mg/kg concizumab is unchanged and is included to decrease the time needed to reach steady state. The decrease in the daily concizumab dose is based on the observations that in 2 of 3 patients a high exposure to concizumab up to approximately 5000 ng/ml was seen, and that concizumab exposures observed in phase 3 were higher than expected based on the observed phase 2 main part data and the

population PK model predictions. Additionally, the higher predicted exposure by the newly developed target mediated PK model supported a reduction of the initial daily maintenance dose from 0.25 mg/kg to 0.20 mg/kg. The presented efficacy and safety data in support of the 20 mg/kg dose collected from phase 2 studies can be considered sufficient support for this new initial maintenance dose of 0.20 mg/kg.

As concizumab exhibits target mediated drug disposition (TMDD), a large variation between subjects in concizumab exposure was seen at a similar dose level. Therefore, a dose setting step was introduced at 4 weeks after initiation (at steady state), with an upward or downward dose titration to 0.25 or 0.15 mg/kg/day if the concizumab level was < 200 or > 4000 ng/ml. The exposure interval ranging from 200 to 4000 ng/ml is wide. The lower exposure limit of 200 ng/mL is based on exposure-response analysis (based on main part results from trials 4255 and 4310) showing that above 200 ng/mL there was a trend towards a lower bleeding rate. This threshold is considered acceptable. An upper limit of exposure as precaution to prevent reaching constant high exposure levels is justified. The clinical relevance of the selected threshold for down-titration of 4000 ng/ml is considered sufficiently justifaced with below arguments:

- The upper exposure limit of 4000 ng/mL was added as an additional precaution to the lowered starting dose of 0.20 mg/kg as an extremely cautious approach to avoid patients reaching constant very high concizumab exposure levels (i.e., nearing NOAEL, corresponding to 82,600 ng/mL).
- Patients in trial 3813 have been exposed to very high concizumab plasma concentrations (>100,000 ng/mL) for approximately 48 hours with a Cmax of 239,053 ng/mL with no safety concerns.
- The geometric mean maximum human exposure (Cmax) for the dosing regimen used in phase 3 trial 4311 after restart (1167 ng/mL, Summary 2.7.2, Table 3-4) was more than 70-fold lower than the exposure at NOAEL.
- Concizumab exposure in individual patients was not observed above 10,500 ng/mL at any point in time during trial 4311 after restart and up until the 56-week cut-off.

With this dosing scheme, a mean exposure of concizumab of approximately 500 ng/ml was expected, and with the addition of a dose-setting step after 4-6 weeks of treatment the percentage of subjects outside this range, i.e. with exposure <200 ng/ml or >4000 ng/ml was estimated at approximately 7% and 0.6 to 0.8% of subjects, respectively based on the popPK model.

Concizumab exposure was not systematically determined during breakthrough bleeding episodes However, plots based on individual model predicted and observed concizumab exposure as well as treated bleeding episodes for patients experiencing treated bleeding episodes with high concizumab exposure (above 3000 ng/mL) were performed. The cut-off of 3000 ng/mL was chosen to investigate patients experiencing bleeding episodes while having concizumab exposure in the higher end of the observed exposure range in the phase 3 trials. The results suggested that treated bleeding episodes occurred at various concizumab exposure levels up to 7076.98 ng/mL. Breakthrough bleed treatment has therefore been administered across a range of concizumab exposures. In study 4311, 5 patients and in study 4307, 9 patients had documented concizumab exposure exceeding 3000 ng/ml at least on one occasion and were treated at least once for breakthrough bleeding events. The number of patients with high concizumab exposure and with treated bleeding events is limited, but in these cases no safety issues, including TE, were reported.

During the phase 3 studies, concizumab PPX was to be discontinued in case of thromboembolic/TMA or DIC events. No cases of discontinuation due to thrombo-embolic/ DIC/TMA event have occurred. According to the study-protocol, patients were allowed to restart on concizumab PPX after discontinuation for a TE-, TMA- or DIC-event, in the extension phase of the phase 3 studies. However, restart of concizumab PPX after a TE did not occur and therefore no data on safety in this situation are available. Section 4.2 of the SmPC states that:

'Treatment with rFVIIa should be discontinued at least 12 hours before starting concizumab therapy and treatment with aPCC should be discontinued at least 48 hours before' and provide recommendations on the posology to be followed. In addition, section 4.4 of the SmPC states that Concizumab therapy does not produce clinically meaningful changes in standard measures of coagulation including activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT). In case of suspicion of thromboembolic events, concizumab should be discontinued, and further investigations and appropriate medical treatment should be initiated.

Treatment of breakthrough bleeding episodes

In vitro and *ex vivo* studies have been performed to investigate the thrombin generation potential when combining concizumab and procoagulant agents. The available *in vitro* and *ex vivo* human data did not show any signs of exaggerated pharmacology, as seen for emicizumab in combination with aPCC, when adding FVIII, FIX, rFVIIa or aPCC to concizumab-containing plasma. For rFVIIa and concizumab this is supported by results from a cuticle bleeding model in rabbits. Based on these studies, a 2-fold reduced dose of FVIII, FIX and aPCC would be sufficient to obtain the same thrombin generation capacity. After the treatment pause, the recommendations were revised with implementing more restrictive dosing with regards to the use of breakthrough bleed treatment including rFVIIa, FEIBA, and ByClot, and are in line with the lower end of the WFH dosing recommendations. Further, additional training of investigators and patients had been implemented in the trials. In general, the dosages that are advised are the lowest according to the SmPC of these products. The use of bypassing agents during the study was monitored using a classification developed by Novo Nordisk and were in line with the advised dosages.

Design and conduct of the clinical studies

Pivotal study 4311 (Explorer 7)

Phase 3 study 4311 is a 4-armed multi-national, multi-centre, open-label, confirmatory trial in adolescent and adult patients with HAwI or HBwI, of which the randomised part of this study, arm 1 and arm 2, is designed to compare the effect of concizumab PPX to no PPX (on demand treatment with i.v. replacement with factor-containing products) in reducing the number of bleeding episodes. Arm 3 and arm 4 consist of patients allocated to concizumab PPX treatment only, that primarily contribute with additional safety and PK/PD data. After the main part of the trial, all patients were offered to continue in the extension part of the trial and receive treatment with concizumab for up to an additional 128 weeks (arms 2-4) or 136 weeks (arm 1, including an 8 weeks dose setting period).

For subjects with HBwI, on-demand treatment as comparator is justifiable, since the options for prophylactic treatment in HBwI are limited to FVIIa, as the use of aPCC is complicated by a high chance of severe hypersensitivity reactions. For HAwI, alternative prophylactic treatment with aPCC, FVIIa, or emicizumab is currently applied in clinical practice. Using on-demand treatment as comparator in study 4311 for subjects with HAwI was justified since prophylactic treatment is not standard-of-care in all countries due to lack of access to emicizumab. The use of on-demand treatment as comparator in subjects with haemophilia and inhibitors is in line with SA EMEA/H/SA/2178/3/2019/PA/III.

The open label design may lead to observation bias. However, since blinding would require injections with placebo which is considered unethical in haemophilia due to increased risk of haematoma, the open-label design can be endorsed and is in line with other studies in haemophilia, e.g. the HAVEN study with emicizumab (NEJM 2018). The duration of the randomized controlled phase of 24 to 32 weeks is acceptable and in line with the 4-armed HAVEN-studies with emicizumab.

Patients receiving ITI were not eligible to the study as ITI requires administration of long term frequent, high doses of FVIII, and safety of concomitant use of concizumab under these conditions has not been established. The lack of data on concomitant ITI has been adequately mentioned in section 4.2 of the SmPC.

During the study, a temporary discontinuation of concizumab was required in case a patient was tested positive for COVID-19. The following warning has been added in section 4.4 of the SmPC: In conditions in which tissue factor is overexpressed (e.g., advanced atherosclerotic disease, crush injury, cancer or septicaemia), there may be a risk of thromboembolic events or disseminated intravascular coagulation (DIC). In these situations, the potential benefit of treatment with concizumab should be weighed against the risk of these complications.

Efficacy endpoints. The primary analysis consisted of establishing superiority over no PPX for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes from randomisation (week 0) up until start of concizumab treatment (at least 24 weeks) for arm 1, and from the start of the new concizumab dosing regimen (week 0) up until the PACO (at least 32 weeks) for arm 2. The difference in exposure time is due to the concizumab PPX dose adaptation period of 8 weeks in arm 2. The selected primary endpoint is considered appropriate and in line with scientific advice (SA EMEA/H/SA/2178/3/2019/PA/II). The definition of re-bleed and new bleed is in in line with Blanchett et al 2014 and appears acceptable. Cause and severity of bleeding events as well as target joints are clearly defined, in line with ISTH guidelines (Blanchett, 2014) and in line with other recent studies, though e.g. in the HAVEN-studies bleeding events are not expressed as ABR but as number of patients with zero treated bleeds. The participants received specific instructions to recognise bleeding events.

Two key secondary endpoints were selected, i.e. SF36v2 of bodily pain and SF36v2 of physical functioning and are considered relevant. The applicability of SF36v2 in the assessment of haemophilia is recognised (Kempton, 2017), though a haemophilia-specific tool specially might have been more sensitive to detect improvement or worsening. However, additional PROs specifically validated for haemophilia patients were investigated as exploratory endpoints.

The **randomization procedure** (1:2 manner (no PPX vs. concizumab PPX)) and stratification related to haemophilia subtype and severity as expressed by bleeding frequency is acceptable. The random allocation sequence was generated by permuted block randomization, which is suitable to achieve balanced groups. Assumptions on bleeding event rates for the **sample size** estimation were based on previous trials and are considered reasonable. Sample size calculation cannot be followed, but discrepant results for sample size calculation obtained with nQuery might be explained by a different parametrisation, and further, power considerations are of minor importance after trial conduct. Considering potential withdrawal of patients, a sample size of 51 patients was to ensure a high likelihood of having at least 42 patients completing arms 1 and 2 main part.

The **primary estimand** is considered acceptable. However, as stated in scientific advice, considering the changes in the study design due to the treatment pause, and different definitions possible, it is difficult to define a single primary estimand and the importance of the validity of the assumptions made for estimation, alternative estimands and sensitivity analyses are vital. The investigation of the estimand, where all four considered intercurrent events (permanent treatment discontinuation, temporary treatment discontinuation, use of factor products and minor surgery) are handled by the treatment policy strategy, is considered central for the assessment, as the CHMP did not agree on the estimand defined for the primary analysis. It is understood, that the estimand based on the 'treatment policy' strategy is analysed using available data after intercurrent events, not applying imputation methods to compensate for missing data. In order to further investigate the robustness of the results, the applicant provided an additional analysis of this estimand based

on the treatment policy strategy, applying multiple imputation to account for missing data until PACO instead of restricting to available data. In addition, the applicant provided a supplementary analysis investigating an estimand using the hypothetical strategy for the intercurrent events 'permanent treatment discontinuation' and 'use of factor products'. The results from the two supplementary analyses were very similar to the result of the supplementary analysis 1 included in the initial submission. Data periods, where ancillary therapy not related to bleedings was used, were short compared to the total exposure time. Thus, excluding these time intervals for the primary analyses is not expected to have a substantial impact. Furthermore, the use of ancillary therapy seems to be roughly balanced between on-demand and PPX treatment, which is reassuring. Similarly, the conduct of minor surgeries was rare and balanced between groups. Temporary treatment discontinuation was more often recorded in patients on prophylaxis therapy than in on-demand patients, which was to be expected. Generally, the frequency of temporary as well as permanent treatment discontinuation is considered adequately low. Upon request, the applicant provided figures that visualise the time point of the PACO for each participant, which confirm that only few patients discontinued treatment before the PACO.

The **primary analysis set** was based on "on-treatment without ancillary therapy excluding data on initial regimen for subjects *exposed to both regimens"* (= OTwoATexIR analysis set). This reflects the observation period in which patients are exposed to either on demand treatment or the new concizumab dosing regimen (or the initial concizumab dosing regimen if patients were not exposed to the new dosing regimen), which is agreed. The **statistical analysis** of the primary endpoint uses a negative binomial model, including stratification factors and using the log of observation time as offset. This is considered standard for count endpoints and is acceptable. However, when describing negative binomial analyses for the bleeding endpoints, the applicant does not only give the estimated bleeding rate ratio but also presents estimates of the actual ABRs within arm 1 and arm 2.

The estimated ABRs within arms in the phase 3 trials were obtained with the LSMEANS statement, assuming a population with balanced characteristics with regards to number of patients with low and high bleeding frequency during the past 24 weeks prior to screening. In addition, estimated ABRs based on OBSMARGIN (i.e. based on covariate distribution present in the study population) were calculated for the primary endpoint by using the characteristics as given in the study arms (haemophilia type and bleeding frequency). These are considered more realistic. The estimated ABR ratios and corresponding 95% CIs stayed unchanged compared to the initial calculations, while the estimated ABRs within arms changed slightly towards the direction of observed mean ABRs within each arm. Since estimated ABRs based on OBSMARGIN are only provided for the primary endpoints, and results are similar, estimated ABRs based on LSMEAN statement are reported in the Overview, unless stated otherwise.

Periods with use of ancillary therapy (defined as use of factor-containing products not related to treatment of a bleed, except when used for surgery and medical procedures) are not included, since the use of ancillary therapy reduces the bleeding risk and thus interferes with concizumab PPX. In an alternative estimand, using a treatment policy strategy will allow to assess whether ignoring bleeding events after intercurrent events affected the results, which is acceptable.

Sensitivity analyses were performed to test missing data of patients that dropped out during the treatment pause, using multiple imputation and tipping point analyses as well as inclusion of the data before the treatment pause. Together these sensitivity analyses will allow assessment of the influence of ignoring events on concizumab in the initial treatment phase.

Due to high numbers of missing values, MMRM after imputation of missing values and the analysis of key secondary endpoints was changed in a post-hoc MMRM, analysing only patients who had filled out both a

baseline and a post-baseline questionnaire. This results in a kind of completers analysis, which may not be conservative in a subjective endpoint such as SF-36. However, considering that the results were not statistically significant, this was not further pursued.

Other secondary endpoints were generally analysed appropriately but are considered as exploratory. However, when analysing the binary endpoint of zero treated spontaneous and traumatic bleeds using logistic regression, patients who had discontinued treatment before week 24 were counted as having more than zero bleeding episodes. This approximation is considered acceptable given that the proportion of patients with zero treated spontaneous and traumatic bleeds who discontinued before week 24 is higher in Arm 2 (Concizumab PPX) than in Arm 1 (on-demand) as shown in Table 11-9 in the study report, i.e. the approximation should lead to a conservative estimate of the treatment effect.

Efficacy data and additional analyses pivotal study 4311

Regarding the **study disposition**, a total of 141 patients were screened, which failed in 8 patients, 3 due to inclusion/exclusion criteria and 5 due to withdrawal of consent. A total of 133 patients (100%) were randomised/allocated, with 114 patients exposed to concizumab in the main part of the trial, 80 subjects were enrolled before, and 53 subjects after the treatment pause.

Randomized arms 1 and 2. Of the 19 patients in no PPX (arm 1), 13 patients were randomised before and 6 were randomised after restart. Of the 33 patients in the concizumab PPX arm 2, 28 patients were randomised before and 5 were randomised after the restart. For subjects remaining in the study, the randomization was kept unchanged, and after restart of the study treatment, concizumab was restarted at the new dosing scheme. Due to the treatment pause, the patients in arm 1 (on-demand) and arm 2 (concizumab PPX) were not concurrently observed in the phase 3 trial 4311. No indication of bias due to time shift was detected from the comparison of ABR in patients randomized before and after the pause, comparison of results from trial 4311 and from trial 4307, where the controls were observed concurrently and comparison of results with and without inclusion of information prior to the pause (sensitivity analysis 2). Further, the treatment benefit demonstrated by the primary analysis was large enough to exclude that it might fully be explained by small temporal effects.

Conduct of the study. Treatment non-compliance was reported as protocol deviation in 3 subjects in arm 1 (no PPX) and 12 subjects in arm 2. Missed concizumab doses for a period ranging from 5 to 73 days was reported in 5 subjects, and incorrect dosing occurred in 7 subjects (including 2 subjects prior to treatment pause). The protocol deviations in general concerned missed or lower dose of concizumab and therefore are not expected to cause a type 1 error.
In the randomised arms, 6/33 subjects on concizumab PPX (arm 2) were withdrawn from the study, due to AE (n=1), other/physician decision (n=2) and death (n=3). None of the three deaths was related to a bleeding event or lack of efficacy. A total of 6/19 (31.2%) of patients on on-demand treatment (arm 1) were withdrawn, due to withdrawal of consent (n=5) and death (n=1).

There are some concerns whether the treatment of bleeds was handled similarly in arms 1 and 2 due to non-concurrent observation periods and consequently different impact of the pandemic restrictions. Thus, also results for the ABR based on untreated and treated bleeds are presented in the SmPC, as this endpoint is not affected from classification inconsistencies.

Baseline demographics. Overall, baseline demographics and disease characteristics are representative for the target population of subjects with HAwI or HBwI with an elevated bleeding tendency. Baseline characteristics generally were well-balanced between the study arms. All subjects were male, mean age was 31.5 (SD 15.8) years. Adolescents are well represented with 6 on no PPX (arm 1) vs 16 adolescents on

concizumab PPX (arm 2), respectively. No subjects aged >65 years were included in the concizumab PPX arms, thereby limiting data on treatment in elderly. However, a similar effect on frequency of bleeding episodes is expected based on the MoA. At rising age, the risk for a thromboembolic event might be increased, however, adequate warning on this concern has been mentioned in section 4.4 of the SmPC. In total, 26 subjects with HAwI and 22 subjects with HBwI were included in arm 1 and 2. For the randomized arms, previous treatment regimen included on-demand treatment in 44 (84.6%) patients and prophylaxis in 4 (7.7%) patients.

Previous haemophilia treatment and bleed history. For the randomized groups, previous treatment regimen for arm 1 (on-demand treatment) consisted of on demand treatment for 17/19 (89.5%) of patients for 20.7 months and prophylaxis in 1/19 (5.3%) patient for 7.7 months. For arm 2 (concizumab PPX), previous treatment was on demand treatment for 27/33 (81.8%) for a mean (SD) time of 24.1 months and prophylaxis in 3/33 (9.1%) patients 8.9 months. Mean ABR (SD) was 26.5 (41.5) for all patients previously on on demand treatment regimen, and 37.2 (76.5) for patients previously on prophylaxis. These baseline data indicate that ABR in both groups is well balanced, and in line with the additional inclusion criteria for randomized arm 1 and 2 of ≥ 6 documented treated bleeds in the last 24 weeks or ≥12 treated bleeds in the last 52 weeks prior to screening.

Total concizumab **exposure** time for 33 patients in treatment arm 2 in the OTwoATexIR analysis set was 24.2 patient years, with exposure per patient 0.9 (0.4) years. A total of 8 (28.6%) of subjects remained on the 0.20 mg/kg dose level, in 20 (71.4%) subjects the dose was increased to 0.25 mg/kg in none of the patient the dose was decreased to 0.15 mg/kg.

Primary endpoint. Mean annual bleeding rate (ABR) at 24/32 weeks in patients with HAwI or HBwI:

- The estimated mean ABR was 11.8 (95%CI 7.03-19.86) for patients on on-demand treatment (arm 1) and 1.7 (95%CI 1.0-2.87) for patients on concizumab PPX (arm 2), with an estimated ABR ratio of 0.14 (95%CI 0.07-0.29; p<0.001 for superiority). This corresponds to a 86% reduction in ABR for patients on concizumab PPX (arm 2) compared to on-demand treatment (arm 1).
- The impact of potential bias introduced by the treatment pause was investigated with four sensitivity analyses, and 2 supplementary analyses that all consistently confirmed the primary analysis, thereby supporting the robustness of the primary analysis outcome. Furthermore, the applicant presented two supplementary analyses, one addressing an estimand based on the treatment policy strategy and one using a non-parametric Van Elteren test, that were confirmative for the primarye analysis.

Haemophilia subtypes The estimated mean ABR by haemophilia subtype for treated spontaneous and traumatic bleeding episodes was comparable between patients with HAwI and HBwI, with no indication that the effect on bleeding events was driven solely by one haemophilia subtype.

- For patients with HAwI, the estimated mean ABR for treated spontaneous and traumatic bleeding episodes for patients on on-demand treatment 18.3 (95%CI 10.18-32.87) and on concizumab PPX (arm 2) was 1.6 (95%CI 0.89-2.83).
- For patients with HBwI the estimated ABR on on on-demand treatment was 7.2 (95%CI 2.61-20.06) and on concizumab PPX (arm 2) 2.2 (95%CI 0.76- 6.52).

Although not powered to detect statistically significant differences within the separate haemophilia subtypes, significancy was found for HAwI, with an estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) of 0.09 (95%CI 0.04-0.18; p<0.001). For patients with HBwI, the estimated ABR ratio was 0.31 (95% CI 0.07-1.36; p=0.12). The point-estimate of the ABR-ratio for concizumab PPX vs on-

demand treatment is more pronounced for HAwI than for HbwI. However, the ABR on concizumab PPX is similar for Hawi and HBwi, and the difference in ABR ratio is mainly due to a lower ABR for HBwi in the on-demand group. Further, the study was not powered to determine the effect of concizumab in both haemophilia subgroups separately, and the differences in ABR ratios might be a chance finding. Despite a potentially smaller reduction in ABR for HBwi, a reduction of 69% of bleeding events is still considered clinically relevant in view of the high unmet medical need.

Due to the low number of severe bleeding episodes, no statistical analysis related to severity of bleeding events has been conducted. Numerically, the reduction in ABR is seen for all grades of severity of bleeding episodes, though it seems to be more pronounced for mild/moderate severity than for severe bleeding events. On conzimuab PPX 14/59 (23.7%) of treated bleeding events in 7 out of 33 (21.2%) subjects were classified as severe, versus 14/167 (8.4%) severe bleeding events in 5 out of 19 (26.3%) subjects on on-demand treatment. On concizumab PPX, severe bleeding events were in joints (12/14 events), target joints (4/14 events), muscular (2/14 events), gastro-intestinal (1/14 events) and Central nervous system (1/14 events). During on-demand treatment, severe bleeding events were in joints (12/14 events), target joints (3/14 events), muscular (2/14 events) and other (1/14 events). In both groups, all events were treated with rFVIIa, requiring 1, 2 or >=3 injections in 10(71.4%), 2 (14.3%) and 2 (14.3%) severe bleeding events on concizumab PPX and in 7 (50.0%), 4 (28.6%) and 3 (21.4%) severe bleeding events on on-demand treatment. In one case on concizumab PPX also FX was administered. Fatal bleeding events have been reported due to intra-abdominal bleeding and intracranial bleeding. In conclusion, the data as they are provided, suggest that concizumab PPX results in a more pronounced reduction in bleeding rate for mild to moderate bleeding events than for severe bleeding events. Mechanistically this can be understood, since severe bleeding events likely requires further optimalisation of coagulation. However, a reduction of bleeding events is seen across all categories of severity.

Key secondary endpoints. No superiority for the key secondary endpoints of change in SF-36 v2 for the items bodily pain or physical functioning was demonstrated. However, for both items a numerical greater increase was noted in favour of concizumab, as well as greater proportions of responders at week 24.

In addition, various PRO (as explorative endpoints) by additional SF-36 v2 health scale scores (generalized health based QoL score)**,** Haem-A-QoL total score (haemophilia specific QoL), Hemo-TEM (measuring treatment burden) generally suggested beneficial trends for subjects in favour of concizumab PPX in comparison to no PPX. However, the high rate of missing values, the fact that patients were not concurrently treated, and different baseline situations in arm 2 (naïve and non naïve to the IP due to the treatment pause, limit the reliability of the results.

Supportive secondary outcomes- bleeding related endpoints. The supportive secondary outcomes related to number of treated bleeding episodes, differentiated for cause (spontaneous or traumatic), and specified for location (joint and target joint) were consistent with the outcomes for the primary endpoint. During evaluation, the applicant confirmed that one target joint in a certain participant was wrongly not assigned as target joint at baseline. However, as only two treated BEs (in this joint) were reported until the week-56 cut-off, the influence of this wrong assignment on the overall target joint ABR is considered very negligible.

Additional bleeding-related results. The lower number of patients with zero bleeding episodes for subjects on concizumab PPX (arm 2) of 21/33 (63.6%) vs 2/19 (10.56%) on on-demand treatment (arm 1), further supports the efficacy of concizumab in prevention of bleeding events.

Haemostatic medication for breakthrough bleeding events. The study participants used four different haemostatic medications to treat bleeds, mainly rFVIIa (76.5% in the on-demand arm, 88.7% in the PPX arms) but also aPCC (47.1% in the on-demand arm, 9.7% in the PPX arms), FVIII (5.9% in the on-demand arm, 9.7% in the PPX arms) and FVIIa+FX (ByClot in Japan, by a single patient in arm 2). For rFVIIa, the number of injections to treat the bleed was comparable for the concizumab PPX group (arm 2) and the on-demand group (arm 1), with 45.8 vs 50.9% of bleeds requiring 1 injection, 6.8 vs 12.3% requiring 2 injections, and 47.5 vs 36.8% requiring at least 3 injections. Mean consumption of rFVII to treat a bleed was 305.3 (459.2) IU/kg for subjects on concizumab PPX (arm 2) vs 336.5 (902.2) IU/kg for subjects on on-demand treatment (arm 1). These data suggest that a similar amount of rFVII is required to treat a bleeding event, regardless of the use of concizumab. No patients in arm 2 and arm 3 received aPCC for treatment of breakthrough bleeds. The mean [SD] consumption of aPCC per bleed was actually lower in the on-demand arm, with 190.4 [206.8] in arm 1 (on-demand phase), compared to 437.4 [790.6] for arm 1 (PPX phase) and arm 4 combined. Considering that only few patients used aPCC (n=8 in the on-demand arm, n=6 in the PPX arms, none in the randomised arm 2), the meaningfulness of this observed difference in aPCC use per bleed is limited.

In study 4311 **Extension Part** up to 56 weeks cut-off, the overall median ABR for treated spontaneous and traumatic bleeding episodes for 127 subjects on concizumab PPX was 0.8 (arm 1-4, median exposure 64 weeks), as compared with 9.8 in 19 patients on no PPX (arm 1, median exposure 31.1 weeks at the PACO). In addition, the number of subjects with zero bleeding episodes was higher in subjects on concizumab PPX (41/127 (32.3%) vs 1/19 (5.3%)). Similar results were seen for HAwI and HBwI. These results are in line with the results for the primary endpoint during the main part of the study in arm 2, and confirmative of maintenance of treatment effect of concizumab PPX on ABR during longer-term treatment up to 56 weeks. Due to the follow-up time needed, resolution of target joints could only be determined at the 56-week cut-off. Resolution of pre-existing target joints at baseline was reported in 78/85 (91.8%) of target joints in 49 subjects on concizumab (arm 1-4).

Supportive studies

Study 4307 (Explorer 8)

Phase 3 study 4307 is a 4-armed multi-national, multi-centre, open-label, confirmatory trial in adult and adolescent patients with HA or HB without inhibitors. The study **design** was similar to that of study 4311, with randomised inclusion in arms 1 and 2, a main part lasting 24 to 32 weeks, and extension phase of 128 to 136 weeks. Concizumab dose regimen was similar as applied in study 4311. In the randomized part (arm 1 + 2), patients in arm 1 (no PPX) were to continue on-demand treatment with their usual replacement therapy, and patients in arm 2 received concizumab. In (non-randomised) arm 3 patients were enrolled from trial 4255 prior to treatment pause, and in arm 4 patients enrolled included subjects from NIS study 4322 (enabling a within-patient comparison with historical ABR previously obtained with factor-containing prophylaxis).

A total of 82 subjects with HA and 66 subjects with HB were enrolled. A total of 27 subjects with HA were randomized to arm 1 (n=9, on-demand treatment) or arm 2 (n=18, concizumab PPX). A total of 36 subjects with HB were randomized to arm 1 and 2 (n=12 and n=24).

Primary endpoint. Superiority in reduction of the number of treated spontaneous and traumatic bleeding episodes on concizumab PPX as compared with on-demand treatment was demonstrated both for subjects with HA and subjects with HB:

- For patients with HA, the estimated ABR ratio between patients on concizumab PPX versus no PPX was 0.14 (95%CI 0.0- 0.29; p<0.001), corresponding to a substantial and clinically relevant 86% reduction in ABR.
- For patients with HB, superiority for the primary endpoint was demonstrated. The estimated ABR ratio between patients on concizumab PPX versus and no PPX was 0.21 (95%CI 0.10- 0.45; p<0.001) corresponding to a substantial and clinically relevant 79% reduction in ABR.

Sensitivity analyses and supplementary analyses consistently support the robustness of the primary analysis. The reduction in ABR of 86% in HA and 79% in HB is comparable with the reduction in ABR of 86% in HAwI/HBwI combined, seen in study 4311. These data were supported by secondary endpoints. Overall, these data support the treatment effect of concizumab prophylaxis on bleeding events in haemophilia, irrespective of the type of haemophilia.

The confirmatory secondary analysis does not provide evidence that concizumab is non-inferior to standard of care factor prophylaxis. The upper limits of the estimated 95% CI of the ABR ratios of concizumab PPX (trial 4307) over previous PPX (study 4322) were above the non-inferiority margin of 2.0. For the 29 patients with HA, the intra-patient ABR ratio was 1.39 [0.73; 2.63], for the 22 patients with HB, the intra-patient ABR ratio was 1.75 [0.81; 3.78].

Surgery. Minor surgery was allowed during the clinical trials and was reported in 14 subjects on concizumab PPX in study 4311, and 22 subjects in study 4307. The number of (associated) bleeding events was low, 4 and 8 treated surgical bleeding events in subjects on concizumab PPX in study 4311 and 4307, respectively. After the treatment pause, planned major surgery was not allowed during the study, but unplanned, acute major surgery in subjects on concizumab PPX occurred 6 times in study 4311 and 4307. Concizumab PPX treatment was interrupted prior to these major surgeries. The haemophilia management in case of (unplanned or semi-elective) major surgery was not predefined, regarding period of interruption of concizumab PPX and monitoring of anticoagulation. This can be understood in view of the rarity of the occasions. In total, data on concizumab interruption are available in 5 of 6 cases. Prior to surgery, concizumab was interrupted for a period ranging from 1, 4 or 9 days and up to 12 weeks in a single case. After surgery, concizumab treatment was resumed after a period ranging from 4 days to 5 weeks. All cases were managed peri-operatively using haemostatic treatment consisting of FEIBA, fVII and nonacog alfa. The proposed additional text in the SmPC with regards to major surgery clearly reflects the lack of clinical data. Based upon this limited clinical experience, it is advised to interrupt concizumab from at least 4 days before and up to 10 to 14 days after elective major surgery. It is advised to restart concizumab at the same maintenance dose without loading dose. This seems a prudent approach that is considered acceptable.

Supportive Phase 2 study 4310 (explorer 4) was a multi-national, multi-centre, randomized (2:1) open-label, active controlled, multiple-dose study to compare efficacy and safety of concizumab as prophylaxis (PPX) to eptacog alfa (recFVIIa) as on-demand treatment in adult patients with HAwI (n=17) or HBwI (n=9) over a duration of at least 24 weeks. Further, to assess safety when eptacog alfa is provided for treatment of breakthrough bleeding episodes in patients treated with concizumab.

The dose regimen was a loading dose of 0.5 mg and initial daily dose of 0.15 mg/kg, with potential dose escalation to 0.20 and 0.25 mg/kg if experiencing ≥3 spontaneous bleeding episodes within preceding 12 weeks. The estimated ABR on the last dose level for concizumab PPX was 4.5 (95%CI 3.2-6.4) vs 20.4 (95% CI 14.4- 29.1) on on-demand eptacog alfa. The estimated ABR during the entire treatment period for concizumab PPX was 5.4 (95% CI 3.8-7.6) vs 20.6 (95% CI 13.7-30.8) on on-demand eptacog alfa.

Supportive study 4255 (Explorer 5) was a phase 2 multi-national, multicentre, single-arm, multiple dose study investigating efficacy and safety of concizumab prophylactic treatment at similar dose regimen applied in study 4310. In 36 male patients with severe haemophilia A without inhibitors, Clinical Proof of Concept was demonstrated on the primary efficacy endpoint of ABR (all treated bleeding episodes over 24 weeks) on last dose level reached, with an estimated ABR of 7.0 (CI 95% 4.6-10.7). The secondary criterion, analysing all bleeding episodes from the entire treatment period, was not met, with an estimated ABR during the entire treatment period of 13.9 (95% CI 9.5-20.3). This lack of effect during the entire treatment period possibly reflects reduced efficacy of concizumab on bleeding events on lower dose-levels before dose-escalation. During the study, the initial daily dose of 0.15 mg/kg was escalated to 0.20 mg/kg in 7/21 subjects, and to 0.25 mg/kg in 8/21 subjects.

Development of antibodies. A total of 68/320 (21.3%) subjects treated with concizumab in phase 2 or 3 trials tested positive for binding anti-concizumab antibodies. For 97% of ADA-positive patients, the titres were low. In 17/320 (5.3%) subjects treated with concizumab, ADAs with in-vitro neutralizing effects were reported. No clear clustering of bleeding episodes is observed for periods with positive ADA or in vitro-neutralising ADA tests. In one subject 1 year of age on concizumab based on individual compassionate use, bleeding frequency after 15 months of treatment was increased and ADAs with in-vitro neutralizing effects were demonstrated once, followed by 4 negative tests for ADAs. Treatment was continued since patient's condition was considered improved on concizumab. In a single case of a phase 2 patient (study 4310) with ADAs with in vitro neutralizing effects, impact on PD (restoration of free TFPI back to baseline after treatment for 40 weeks) was demonstrated. The continuous increase in ADA titres to high levels was attributed to a combination of a boosted immune response after traumatic events experienced by the patient and re-initiation of concizumab treatment. A clinical impact of the anti-concizumab antibodies appeared unlikely since restoration of free TFPI levels to baseline were not accompanied by a significant worsening in bleeding patterns or occurrence of immunogenicity-related AEs. The immunogenicity information proposed to be included in section 5.1 of the SmPC is considered adequate.

Discontinuation – rebound. During treatment pause, median ABR for arms 2-4 of study 4311 increased to 11.8, comparable with ABR during on-demand treatment in arms 2-4 prior to inclusion (median ABR 13.8). With regard to free TFPI levels and thrombin peak levels, levels returned to baseline values upon discontinuation of concizumab. Further, during treatment pause no signals of rebound or withdrawal effects were detected for D-dimer, prothrombin fragments, fibrinogen and platelets.

Data provided on PD parameters and coagulation parameters were limited to a single timepoint, therefore, a detailed time course after discontinuation of concizumab is not established. However, levels of all clinical, PD and routine coagulation parameters that were reported return to baseline values and the data provided do not show a signal of rebound.

Compassionate use programme.

Compassionate use programme covered by a specific protocol (**study 4807**). The study was designed to provide concizumab PPX to paediatric patients with haemophilia and a high unmet medical need, allowing for a structured collection and analysis of data. The inclusion criteria of severe HA or moderate to severe HB without inhibitors, or haemophilia of any severity with inhibitors enable inclusion of the target population. The exclusion criteria as well as criteria for discontinuation of treatment are similar to the criteria for the other phase 2/3 clinical studies. The dosing regimen and treatment of breakthrough bleeds is similar to other phase 2/3 clinical trials.

No formal statistical analysis was performed, which is considered acceptable in view of the small population of patients who entered the study for unmet medical need due to rarity of the condition. AEs and bleeding events were investigated, using descriptive statistics, thereby yielding information on safety and efficacy.

Results. From august 2021, 7 subjects aged 1-17 years with HBwI were enrolled in CUP study 4807 and exposed to concizumab for 1 day up to 196 days. Prior to concizumab PPX, all subjects had frequent and severe bleeding events, despite prophylactic or on-demand treatment with rFVII or (r)FIX. Four (4) subjects had undergone ITI, complicated by severe hypersensitivity reactions.

All subjects in CUP study 4807 were treated according to the new dosing regimen, with a starting dose of 0.20 mg/kg/day. After initiation of concizumab PPX, the number of treated bleeds in these 7 subjects was 0, 0, 1, 1, 1, 2, 6, and the corresponding calculated ABR was 0, 0, 1.9, 1.9, 2.0, 8.5, 12. These limited results indicate that most patients had improvement in their number of bleedings as reflected in the low ABR. Further, though not clearly reported on, a treatment consisting of daily sc injection of concizumab might be considered less burdensome than iv factor-containing products every 24-48 hrs.

Though these data can be considered promising, the efficacy data available in patients < 12 years of age are currently too limited. Although the high unmet medical need for prophylactic treatment in children <12 years of age suffering from HB with inhibitors is acknowledged, the currently available efficacy (and safety, PK, and PD) data collected in a compassionate use setting are not sufficient for assessment of the B (and the risk) in this age group.

2.6.7. Conclusions on the clinical efficacy

Based on the current available data, with a completed efficacy data set from the pivotal study, a statistical significant and clinically relevant beneficial treatment effect of concizumab PPX has been demonstrated on number of bleeding episodes, as compared to on-demand treatment with bypassing agents in the target population of adult and adolescent patients with HAwI or HBwI. In general, explorative endpoints on patient reported outcome were supportive of improvement in aspects of health-related QoL and treatment burden. A combined analysis of HAwI and HBwI was performed due to the rarity of the conditions. A relevant reduction in bleeding episodes was seen in both HawI and HBwI, though numerically the reduction in estimated ABR was less for HBwI (69% vs 91%).

When given as prophylaxis, the benefit of Alhemo is the prevention of bleeding in patients with haemophilia A and FVIII inhibitors or haemophilia B and FIX inhibitors. This benefit was observed at 24 to 32 weeks of treatment in a superiority study that compared the effects of concizumab prophylaxis to no prophylaxis.

The efficacy results are supportive for the indication of prophylactic treatment of patients >= 12 years of age with HawI or HbwI.

2.6.8. Clinical safety

The evaluation of the safety of concizumab in this summary is based on safety results from all completed and ongoing trials as well as compassionate use with concizumab, as of the application cut-off date 30 August 2022 (see figure below).

The safety results are therefore provided from 8 completed trials in patients ≥ 12 years and older:

- 2 phase 3 trials: Trial 4307 in patients with HA and HB without inhibitors (up until the confirmatory analyses cut-off [CACO] date) and 4311 in patients with HAwI and HBwI (up until the 56-week cut-off date). The extension part is ongoing for both trials.
- 2 completed phase 2 trials: 4310 (main and extension part) and 4255 (main and extension part).
- 4 completed phase 1 trials (3813, 3981, 3986 and 4159).

Table 80: Overview of patient disposition by trial (trials 4311, 4310, 4307, 4255 and 4159).

Trial ID	4311 (HAwI and HBwI)		4310 (HAwI and HBwI)		4307 (HA and HB)		4255 (HA)	4159 (HA)[f]	
Treatment	Concizumab (arms 1–4)	No PPX (arm 1)	Concizumab	No PPX	Concizumab (arms 2–4)	No PPX (arm 1)	Concizumab	Concizumab	Placebo
Exposed patients	127	19	25	9	134	21	36	18	6
Patients completing treatment	104 (78.2%)[a]	14 (73.7%)[b]	22 (88.0%)[c]	8 (88.9%)[c]	116 (85.9%)[d]	21 (100.0%)[d]	30 (83.3%)[e]	18 (100%)	6 (100%)

Notes: a Randomised/allocated patients in concizumab PPX arms 1−4 (including 13 patients who switched from no PPX arm 1 to concizumab PPX arm 1 in the extension part) who did not discontinue concizumab treatment prior to the 56 weeks data cut-off. The proportion is based on the total number of patients randomised/allocated to concizumab PPX arms 2−4 and no PPX arm 1 (133 patients). b PACO completion status; defined as randomised patients who did not discontinue treatment prior to week 24. c For patients on PPX: patients completing treatment with concizumab PPX in the main and extension part of the trial (including 8 patients who switched from no PPX [eptacog alfa on demand] in the extension part). For patients on no PPX: patients completing treatment in the main part of the trial. d CACO completion status; defined as randomised/allocated patients who did not discontinue treatment prior to week 24/32 (depending on arm). For patients on concizumab PPX (arms 2−4), the proportion is based on 116 'treatment completers' and 135 patients randomised/allocated to concizumab PPX arms 2−4. e Patients completing treatment in the main and extension part of the trial. f For trial 4159, end-of-trial corresponds to visit 18 (week 11) (see Table 9-3 [flowchart] in the clinical trial report). Abbreviations: CACO: confirmatory analyses cut-off; PACO: primary analysis cut-off.

Paediatric indication

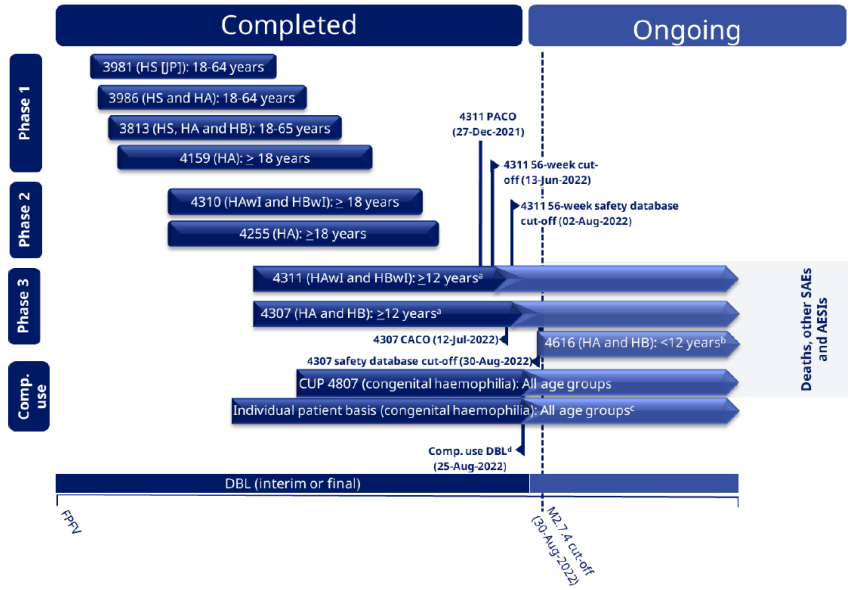
In support of a clinical indication with no age restrictions for patients with HBwI in the proposed label, results are also included from:

- Paediatric patients (aged 1-17 years) with HBwI who have received concizumab via the compassionate use programme (CUP; 4807). The dosing regimen for the CUP is identical to that in the two phase 3 trials 4311 and 4307.
- Individual patient basis.
- Narratives for deaths, other SAEs and adverse events of special interest (AESIs) reported in the ongoing phase 3 trial in paediatric patients aged (<12 years) with haemophilia A or B with or without inhibitors (trial 4616).

Long-term data

Narratives for deaths, other SAEs and adverse events of special interest (AESIs) reported in the ongoing extension part of trials 4311 (from the 56-week cut-off) and 4307 (from the CACO) and compassionate use (from the data cut-off dates for the compassionate use programme [4807] and individual patient basis) have been included with this application to further support the safety evaluation of concizumab.

Figure 73: Overview of clinical trials and compassionate use contributing with safety data.



Notes: a For the completed parts of trials 4311 and 4307, the 56-week cut-off and CACO, respectively, correspond to the clinical data cut-off dates. b For trial 4616, arm 1 includes patients <12 years, whereas arm 2 includes patients of any age previously treated with concizumab via compassionate use. c For compassionate use with concizumab via individual patient basis, AEs were collected according to local legislation. d The database lock date for inclusion of available data from both types of compassionate use (compassionate use programme [4807] and individual patient basis) was 25 Aug 2022. For each patient in the compassionate use programme (4807), available data were included up to the date of the last visit occurring at the latest on the cut-off date of 02 Aug 2022. Abbreviations: AESIs: adverse events of special interest; CACO: confirmatory analyses cut-off; Comp. use: compassionate use; CUP: compassionate use programme (4807); DBL: database lock; FPFV: first patient first visit; HA: haemophilia A without inhibitors; HAwI: haemophilia A with inhibitors; HB: haemophilia B without inhibitors; HBwI: haemophilia B with inhibitors; HS: healthy subjects; JP: Japanese patients; PACO: primary analysis cut-off.

Focus areas and data collection

The safety evaluation is based on standard assessments (e.g., serious and non-serious AEs, clinical safety laboratory evaluations, physical examination, vital signs, electrocardiograms (ECGs), and technical complaints) with in-depth evaluation of the safety focus areas listed in Table 81 below.

Table 81: Safety focus areas.

Safety focus areas	
Area	**Basis for the evaluation**
Thromboembolic events	MedDRA search performed on AE data Adverse event of special interest[a]
Hypersensitivity reactions	MedDRA search performed on AE data AEs with additional data collection[a]
Injection site reactions	MedDRA search performed on AE data AEs with additional data collection[a]
Medication errors	MedDRA search performed on AE data AEs with additional data collection[a]
Increased inflammatory response	MedDRA search performed on SAEs
Increased bleeding tendency	Laboratory assessment (fibrinogen)
Rare events	MedDRA search
Hepatic events	MedDRA search performed on AE data Laboratory assessment of ALT, AST, total bilirubin (including potential Hy's law)
Renal events	MedDRA search performed on AE data Laboratory assessment of eGFR and creatinine
Suspected transmission of an infectious agent	MedDRA search performed on AE data

Notes: aOnly applicable for trial-by-trial presentation, due to change in definitions of AE categories between trial 4159, where thromboembolic events, hypersensitivity reactions, injection site reactions and medication errors were collected in accordance to medical event of special interest [MESI] criteria, and trials 4255, 4307, 4310 and 4311 which reported these events as either AESI (thromboembolic event) or 'AE requiring additional data collection' (hypersensitivity reaction, injection site reaction and medication errors). Abbreviations: AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; eGFR = estimated glomerular filtration rate; MedDRA = medical dictionary for regulatory activities.

Data presentation

By trial

The main basis for the safety evaluation is the 5 multiple-dose trials in patients with haemophilia exposed to concizumab (trials 4311, 4310, 4307, 4255 and 4159). These trials represent the majority of the exposure to concizumab.

The phase 3 trial 4311 is the pivotal trial for the safety evaluation in patients with HAwI and HBwI. Safety results from trial 4311 are considered up until the 56-week cut-off date, defined as when all patients in concizumab PPX arms 2, 3 and 4 had completed 56-week visit (or permanently discontinued treatment).

The phase 3 trial 4307 is the pivotal trial for the safety evaluation in patients with HA and HB. Safety results from trial 4307 are considered up until the CACO date, defined as when all patients on no PPX (arm 1) had completed the 24-week visit or withdrawn and all patients on concizumab PPX (in arms 2 and 4) had completed the 32-week visit or withdrawn.

The phase 2 trials (4310 and 4255) provide supportive safety results for concizumab PPX.

The phase 1 trial (4159) in patients with severe HA without inhibitors supplements with separate safety results, providing an approximate 42-days comparison of dose-levels of concizumab PPX vs no concizumab PPX, i.e. on-demand treatment.

By haemophilia subtype – total safety pool

In addition to a by trial presentation of safety results, a pooling of safety data from the 5 multiple-dose trials in patients with haemophilia was also included in evaluation of the safety of concizumab.

The following safety pool and relevant groupings were defined as follows:

- The total **safety pool**, comprising all multiple-dose trials in patients with haemophilia exposed to at least one dose of concizumab (trials 4311, 4310, 4307, 4255 and 4159): to supplement an aggregated evaluation of the safety of concizumab PPX and increase the likelihood of detecting potential safety signals. Consistency across the trials in the pool was also evaluated to ensure that no safety issues were overlooked by pooling the trials.
- Haemophilia subtype group (HAwI, HBwI, HA, and HB): to detect potential differences in the safety profile between indications. Safety data from patients with HA (trials 4307, 4255 and 4159) were grouped and included as supportive data together with safety data from patients with HB (trial 4307).

As no substantial difference in the safety profile of concizumab has been observed across the multiple-dose trials completed in patients with haemophilia with and without inhibitors (trials 4159, 4255, 4310, 4311 and 4307), exposure and AE data from patients on concizumab in these trials have been pooled and referred to as the total 'safety pool'. The safety evaluation provided primarily focuses on the total 'safety pool' and groupings (haemophilia subtype HAwI, HBwI, HA, and HB) within this, to provide a comprehensive evaluation of the safety in patients with haemophilia when exposed to concizumab and to increase the likelihood of detecting potential safety concerns.

Comparison to on-demand treatment

The comparator arms across the trials comprising the safety pool have not been combined due to the inherent difference in the comparators (on demand in trials 4310, 4311 and 4307 and placebo in trial 4159) as well as to avoid a mixture of within- and between-patient comparison due to patients switching from on demand treatment (no PPX arm 1) to concizumab treatment (PPX arm 1) in the extension part of the trials. Therefore, no comparisons are made between the pooled concizumab results and the placebo or on demand treatment data from the trials.

Analysis sets

The following safety analysis set was defined based on the 5 multiple-dose trials:

The safety analysis set (SAS)

- Trial 4311 and 4307: all patients exposed to concizumab PPX or randomised to on-demand treatment. All patients contributed to the evaluation 'as treated'.
- Trial 4310, 4255 and 4159: all concizumab dosed patients.
- Trial 4159: all patients exposed to at least one dose of concizumab and analysed according to the received treatment.

All safety evaluations are based on the SAS.

For safety evaluations based on data from pivotal phase 3 trial 4311 and phase 3 trial 4307, two analysis data sets were defined:

- The on-treatment (OT) analysis data set: This analysis data set represents the entire OT period and includes data before the treatment pause (including 7 weeks follow up from last dose) as well as after the treatment pause, where patients were treated on demand or with concizumab, irrespective of concizumab dosing regimen.
- The on-treatment excluding data on initial regimen (OTexIR) analysis data set (trial 4311)
- The on-treatment without data before restart (OTexBR) analysis data set (trial 4307).

These OTexIR/OTexBR analysis data sets represent the OT period after concizumab treatment restart, where patients were treated on demand or according to the new concizumab dosing regimen and were added as analysis data set, to enable an evaluation of safety after treatment restart, when patients were treated according to the new concizumab dosing regimen, in addition to throughout the trial (OT period).

For both trials (4311 and 4307), different analysis data sets describing specific observation periods were used for different endpoints/assessments.

Implications of COVID-19 on trials included in the application

Overall, no safety concerns were observed in trials 4307, 4311 and 4255 due to the COVID-19 pandemic and the impact of COVID-19 on the interpretation of the trial results was considered limited. For the remaining multiple-dose trials in haemophilia (trial 4310 and 4159), DBL had already occurred at the time of the pandemic.

For trials 4311, 4307 and 4255, the lockdown conducted by local governments prevented some patients from coming to their respective trial sites and physical site visits were converted to phone or video contact at the investigator’s discretion. During the pandemic, even if patients were unable to visit the sites, site staff continued to collect all trial-related information/data in the patient's medical records, and all relevant data capture systems were updated in a timely manner (e.g., electronic data capture, interactive web response system) to the extent possible. Site visits converted to phone visits and missed laboratory assessments were captured as protocol deviations.

In pivotal trial 4311, out of 2080 visits in total in the trial, 8 visits were missed due to the pandemic (belonging to 2 patients, all visits before treatment pause) and 63 visits (belonging to 23 patients, 3 visits after the treatment pause and remaining visits before the treatment pause) were performed as phone visits instead of site visits. In phase 3 trial 4307, in total 80 on-site monitoring visits were converted to off-site monitoring visits.

For patients in trials 4311 and 4307 who tested positive for COVID-19, concizumab treatment was to be paused immediately and not restarted until the patient tested negative again or had fully recovered from COVID-19 as judged by the investigator.

2.6.8.1. Patient exposure

Dosing regimen

In the 5 multiple-dose trials in patients with haemophilia, concizumab PPX was administered s.c. either daily in trials 4311, 4310, 4307 and 4255). In trial 4159 (phase 1) every 4 days (trial 4159). For all trials, dosing by body weight was used.

In phase 3 trial 4311 and phase 2 trial 4310 in HAwI and HBwI and phase 3 trial 4307 in HA and HB, patients received an initial single loading dose of 1.0 mg/kg (4311 and 4307) or 0.5 mg/kg concizumab (4310), on the first day of trial product administration followed by an initial daily dose of 0.20 mg/kg or 0.15mg/kg, respectively, concizumab from treatment day 2.

According to the new dosing regimen after treatment pause in trials 4311 and 4307, patients had their individual maintenance dose set at 0.15, 0.20 or 0.25 mg/kg within an initial 5−8-week period on 0.20 mg/kg concizumab (at visit 4a.1 or 9a.3), based on the concizumab exposure level measured at the previous visit.

In phase 2 trials 4255 and 4310, dose escalation to 0.20 mg/kg (initially) and again to 0.25 mg/kg was allowed if patients experienced ≥3 spontaneous bleeding episodes within a preceding period of 12 weeks.

In phase 1 trial 4159, patients with HA received a total of 12 doses of concizumab 0.25, 0.5 or 0.80 mg/kg (or placebo). The initial 2 doses of concizumab were administered on 2 consecutive days, in order to rapidly reach steady state at the targeted plasma concentration. Hereafter, patients received concizumab every fourth day.

In the main part of trials 4310 and 4311, those patients who were randomised to on-demand treatment received intravenous (i.v.) eptacog alfa (rFVIIa) or on-demand treatment with their usual bypassing product, respectively, and treated according to local treatment practice.

In the main part of phase 3 trial 4307, patients randomised to arm 1 were to continue on-demand treatment with their usual replacement therapy.

Pivotal trial 4311 in patients with HAwI or HBwI (PACO and 56 weeks cut-off)

At PACO, in the OTexIR analysis data set, there were 99 exposed patients (arms 2, 3 and 4). Two patients withdrew from the trial and did not dose adjust. Of the remaining 97 patients, 72 patients (74.2%) remained on the 0.20 mg/kg dose level, 24 patients (24.7%) increased to 0.25 mg/kg and 1 patient (1.0%) decreased to 0.15 mg/kg. Dose level distribution was similar across treatment arms.

At the 56 weeks cut-off, in the OTexIR analysis data set, 112 patients were exposed to concizumab across arms 1–4. Two patients withdrew. Of the remaining 110 patients, 79 patients (71.8%) remained on the 0.20 mg/kg dose level, 30 patients (27.3%) increased the dose to 0.25 mg/kg and 1 patient (0.9%) decreased the dose to 0.15 mg/kg.

Trial 4307 in patients with HA or HB without inhibitors (CACO)

For patients with HA in the OTexBR analysis data set, 73 patients were exposed to concizumab in arms 2, 3 and 4 after the treatment restarted. Two patients in arm 3 withdrew. Of the remaining 71 patients, 54 (76.1%) remained on the 0.20 mg/kg dose level, 13 (18.3%) increased their dose to 0.25 mg/kg and 4 (5.6%) decreased their dose to 0.15 mg/kg.

For patients with HB in the OTexBR analysis data set, 54 patients were exposed to concizumab in arms 2, 3 and 4 after the treatment restarted. Four patients, 1 in arm 2 and 3 in arm 4, withdrew. Of the remaining 50 patients, 27 (54.0%) remained on the 0.20 mg/kg dose level, 18 (36.0%) increased their dose to 0.25 mg/kg and 5 (10.0%) decreased their dose to 0.15 mg/kg.

Exposure

By trial (trials 4311, 4310, 4307, 4255 and 4159)

The cumulative exposure to concizumab at the data cut-off date and comparators is presented by trial in Table 82 and Table 83 (trials 4311, 4310, 4307 and 4159), respectively. Note that differences in exposure time between patients on concizumab PPX and patients on no PPX (on-demand treatment) prevent a meaningful comparison between treatment groups in trials 4311, 4310 and 4307.

The pivotal phase 3 trials in HAwI and HBwI (4311) and in HA and HB (4307) contributed with most of the total exposure (160.0 PYE and 134.0 PYE, respectively), whereas mean exposure time was higher in the phase 2 trials (4255 and 4310), where also extension part data are included.

In total, 239 patients have been exposed to the new concizumab PPX dosing regimen in the pivotal phase 3 trials 4311 (HAwI or HBwI: 112 patients in concizumab PPX arms 1−4 [138.6 PYE]) and 4307 (HA or HB: 144 patients in concizumab PPX arms 1−4 [125.6 PYE]), whereof the majority of patients had their maintenance dose set at 0.20 mg/kg concizumab, following the initial 4-week period with a daily dose of 0.20 mg/kg concizumab.

Table 82: Concizumab exposure by trial (trials 4311, 4310, 4307, 4255 and 4159) – safety analysis set.

	Trial 4159	Trial 4255	Trial 4310		Trial 4307		Trial 4311		Total*
	HA	HA	HAwI	HBwI	HA	HB	HAwI	HBwI	HA+HB+HAwI+HBwI
Patient years of exposure									
N	18	36	15	10	87	64	76	51	320
Total	3.8	71.9	27.0	18.3	87.0	47.0	94.3	65.7	415.0
Median	0.2	2.4	1.8	1.9	0.6	0.6	1.2	1.4	1.1
P25 ; P75	0.2 ; 0.2	1.8 ; 2.4	1.6 ; 2.0	1.7 ; 2.2	0.6 ; 1.5	0.6 ; 1.0	1.1 ; 1.6	1.0 ; 1.8	0.6 ; 1.7
Mean (SD)	0.2 (0.003)	2.0 (0.748)	1.8 (0.233)	1.8 (0.433)	1.0 (0.577)	0.7 (0.419)	1.2 (0.485)	1.3 (0.603)	1.3 (0.996)
Min ; Max	0.2 ; 0.2	0.0 ; 2.7	1.4 ; 2.2	0.7 ; 2.2	0.2 ; 2.0	0.0 ; 1.9	0.1 ; 2.0	0.2 ; 2.2	0.0 ; 4.4

HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, N: number of subjects, P25/P75 is the 25th/75th percentile, SD: standard deviation, Min: minimum, Max: maximum. * Patients continuing from trial 4255 (phase 2) into trial 4307 (phase 3) and 4310 (phase 2) into trial 4311 (phase 3) will only count once in the total column with the total exposure in the two trials combined. Subjects exposed to concizumab are included. This means that placebo data from 4159, Eptacog alpha data from 4310, and on-demand data from 4307 and 4311 are excluded. For trial 4307 and 4311, the on-treatment (OT) analysis data set is used.

By haemophilia subtype – total safety pool

A total of 320 unique patients with HAwI, HBwI, HA and HB have been exposed to concizumab in the clinical trials 4311, 4310, 4307, 4255 and 4159, corresponding to a total of 415.0 PYE. Note that for ongoing clinical trials (trial 4311 and 4307), results on exposure are based on the 56-week cut-off date and CACO, respectively.

Across the concizumab clinical development programme, 261 (82%) of the pooled population were exposed to concizumab for at least 6 months, roughly corresponding to the duration of the main part in trials 4255, 4307, 4310 and 4311. Of the 261 patients, 189 patients were exposed for more than 12 months, and 49 patients have been exposed for more than 24 months (Table 83 below).

Table 83: Concizumab exposure – duration intervals - by trial and haemophilia subtype – safety analysis set - on-treatment – trials 4311, 4310, 4307, 4255 and 4159.

	Trial 4159	Trial 4255	Trial 4310		Trial 4307		Trial 4311		Total*
	HA	HA	HAwI	HBwI	HA	HB	HAwI	HBwI	HA+HAwI+HBwI
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
N in SAS	18	36	15	10	87	64	76	51	320
Duration interval (months)									
0 to <3	18 (100.0)	2 (5.6)	0	0	6 (6.9)	10 (15.6)	4 (5.3)	4 (7.8)	41 (12.8)
3 to <6	0	2 (5.6)	0	0	9 (10.3)	3 (4.7)	5 (6.6)	5 (9.8)	18 (5.6)
6 to <12	0	1 (2.8)	0	1 (10.0)	33 (37.9)	35 (54.7)	2 (2.6)	4 (7.8)	72 (22.5)
12 to <18	0	1 (2.8)	1 (6.7)	0	13 (14.9)	12 (18.8)	39 (51.3)	16 (31.4)	79 (24.7)
18 to <24	0	4 (11.1)	10 (66.7)	5 (50.0)	26 (29.9)	4 (6.3)	26 (34.2)	14 (27.5)	61 (19.1)
24 to <30	0	24 (66.7)	4 (26.7)	4 (40.0)	0	0	0	8 (15.7)	17 (5.3)
>= 30	0	2 (5.6)	0	0	0	0	0	0	32 (10.0)

HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, N: number of subjects, %: percentage of subjects. * Patients continuing from trial 4255 (phase 2) into trial 4307 (phase 3) and 4310 (phase 2) into trial 4311 (phase 3) will only count once in the total column with the total exposure in the two trials combined. Subjects exposed to concizumab are included. This means that placebo data from 4159, Eptacog alpha data from 4310, and on-demand data from 4307 and 4311 are excluded. For trial 4307 and 4311, the on-treatment (OT) analysis data set is used.

Paediatric population

Compassionate use

Ten patients were exposed to concizumab on an individual patient basis. Seven patients were exposed in the compassionate use programme, including 3 who switched to this programme after receiving concizumab on an individual patient basis.

Overall, the 14 patients were aged between 1 and 17 years when they first received concizumab and treatment exposure ranged between 1 month and 3 years and 6 months. Eleven of the 14 patients were below the age of 12 years.

Trial 4616

Further in trial 4616, 4 patients in trial 4616 had been exposed to concizumab, at the application cut-off date (30-Aug-2022).

2.6.8.2. Adverse events

Common adverse events

By trial (trials 4311, 4310, 4307, 4255 and 4159)

In this section, data across the five trials comprising the safety pool (4311, 4310, 4307, 4255 and 4159) are evaluated by trial, to ensure no safety issues are overlooked by pooling the trials. Results are based on the SAS and on-treatment period and include data up until the latest data cut-off date for the trial.

Patients on concizumab PPX

An overview of the proportion of patients with AEs and corresponding event rates in the 5 multiple-dose trials is provided in (Figure 74**:**).

The proportion of patients with AEs were comparable across the two phase 3 trials (trials 4311 [HAwI and HBwI] and 4307 [HA and HB]) and higher in the phase 2 (trials 4310 [HAwI and HBwI] and 4255 [HA]) and 1 (trial 4159 [HA]) trials. Across the phase 2 and 3 trials, similar AE rates were observed in trials 4311, 4310 and 4307, whereas a slightly higher AE rate was observed in trial 4255. This was mainly due to more non-

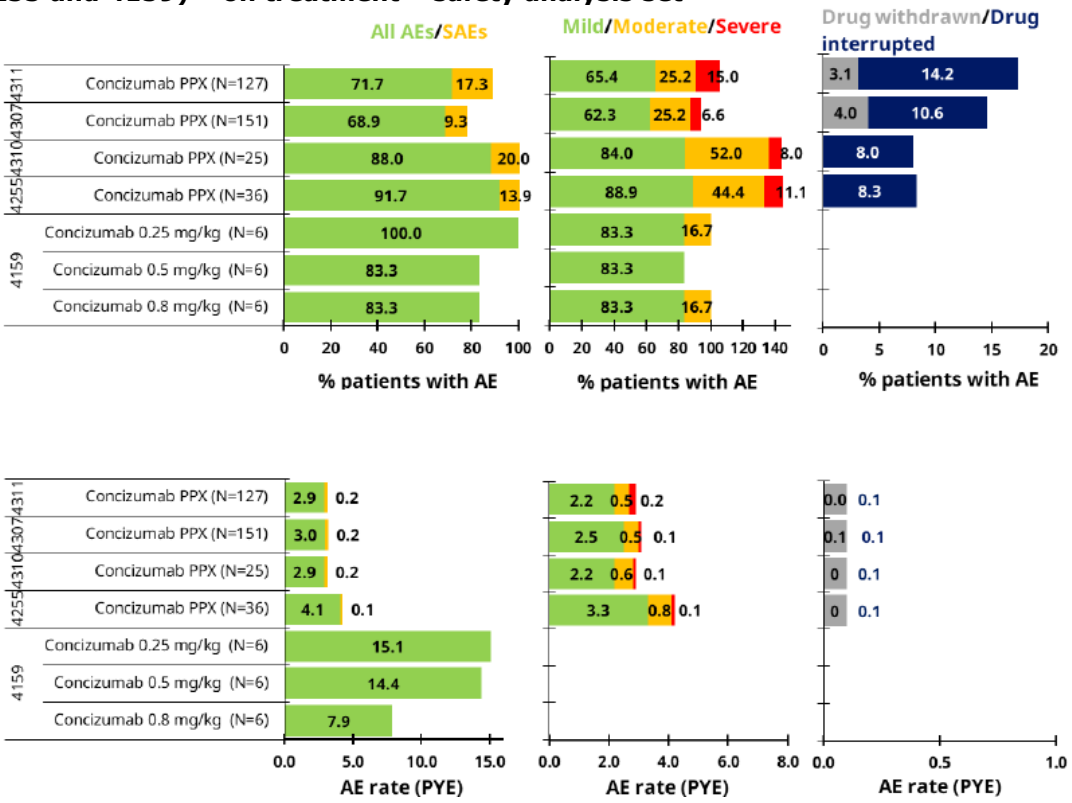
serious events reported across multiple SOCs in trial 4255. Across all trials, most AEs were mild in severity (range: 62.3% to 88.9% patients).

In the phase 1 trial (4159), the AE reporting rate for the two lowest doses (0.25 mg/kg [19 events in 6 patients] and 0.5 mg/kg [18 events in 5 patients]) were 2-fold the event rate in the highest dose group (0.8 mg/kg; 10 events in 5 patients). However, the event rate in the 0.8 mg/kg dose group was similar to that for placebo (7.9 and 7.1, respectively), thus, no apparent dose-relationship with respect to the numbers of AEs was observed. Importantly, no SAEs were reported in trial 4159 and the majority (54 of 56 AEs in 18 patients) were mild in severity.

The proportion of patients with SAEs ranged from 9.3% (trial 4307) to 20.0% (trial 4310). Across trials, most SAEs were unlikely related to concizumab, as judged by the investigator.

A comparable proportion of patients with AEs leading to permanent discontinuation was observed in the two phase 3 trials (4311 and 4307). No patients permanently discontinued trial product due to AEs in trials 4310, 4255 and 4159. The proportion of patients with AEs leading to temporary discontinuation of trial product ranged from 8.0% (trial 4310) to 14.2% (trial 4311). No patients temporarily discontinued trial product due to AEs in trial 4159.

Figure 47 Overview of AEs by trial for patients exposed to concizumab PPX (4311, 4310, 4307, 4255 and 4159) – on treatment – safety analysis set



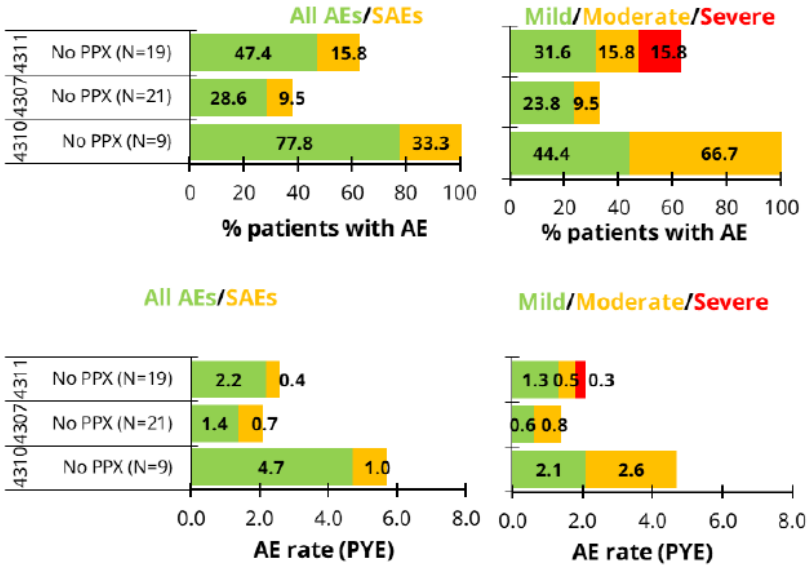
Notes: Figure shows the proportion of patients with AEs (top panels) and corresponding event rates (bottom panels). As some patients reported multiple AEs, the total percentage can exceed 100%. Data represent AEs reported across all concizumab dose-levels ('total') during the full trial (trials 4255 and 4310) and AEs reported in concizumab PPX arms 1−4 up until the confirmatory analyses cut-off (trial 4307) or the 56-week cut-off (trial 4311) using the on-treatment analysis data set. Only the overall AE rate is available from 4159. Drug interrupted: AEs leading to temporary treatment discontinuation. Drug withdrawn: AEs leading to permanent treatment discontinuation. Abbreviations: AE: adverse event; N: number of patients; PPX: prophylaxis; PYE: patient years of exposure; SAE: serious adverse event.

Patients on no PPX (trials 4307, 4310 and 4311)

For patients on no PPX, both the proportion of patients with AEs and corresponding AE rates were higher for patients with HAwI or HBwI (trials 4310 and 4311) as compared to patients with HA or HB (trial 4307). For SAEs, a higher proportion of patients reported SAEs in trials 4311 and 4310 as compared to trial 4307, though event rates were comparable between trials 4311 and 4307 and lower as compared with trial 4310. All events in patients on no PPX in trial 4310 were mild or moderate in severity and reported as resolved.

Across all trials, most AEs in patients on no PPX were mild or moderate in severity. Severe events were only reported in patients on no PPX in trial 4311. Action to trial product was not assessed in patients on no PPX (Figure 75**:**).

Figure 48 Overview of AEs by trial for patients on no PPX (4307, 4310 and 4311) – on treatment – safety analysis set.



Notes: Figure shows the proportion of patients with AEs (top panels) and corresponding event rates (bottom panels). As some patients reported multiple AEs, the total percentage can exceed 100%. Data represent AEs reported during the on-treatment period in patients on no PPX during the main part of trial 4310 and AEs reported up until the PACO (trial 4311) and CACO (trial 4307). For trial 4307, only AEs reported after treatment restart are included, hence 1 mild AE (PT: Gilbert's syndrome') with onset prior to the treatment pause is not counted. Abbreviations: AE: adverse event; CACO: confirmatory analyses cut-off; N: number of patients; no PPX: patients treated on demand; PACO: primary analysis cut-off; PYE: patient years of exposure; SAE: serious adverse event.

Trial 4311 – Phase 3 – HAwI and HBwI

Patients on concizumab PPX – up until the PACO

The event rate of AEs for concizumab PPX arms 2–4 was 3.3 events per PYE. In the no PPX arm 1, 8 (42.1%) patients reported 25 AEs, which was equal to 2.1 events per PYE.

The most frequently reported AEs (> 5%) by PT in concizumab PPX arms 2–4 were arthralgia, injection site erythema, upper respiratory tract infection and prothrombin fragment 1+2 increased. None of these PTs were reported in the concizumab PPX arm 1.

In total, 23 non-serious events of arthralgia were reported in 13 [11.4%] patients in concizumab PPX arms 2–4 (0.2 AEs per PYE). The majority of these patients (10 of 13) had underlying conditions within the SOC 'musculoskeletal and connective tissue disorders'. Most AEs (21 of 23 AEs) were of mild or moderate severity and judged as unlikely related to concizumab. One (1) patient reported 2 severe events of arthralgia judged

as possibly related to concizumab. The patient recovered with no actions to trial product. No events of arthralgia were reported in patients on no PPX (arm 1).

Nine (9 [7.9%]) patients on concizumab PPX (arms 2−4) reported 13 events of injection site erythema (0.1 events per PYE). All AEs were non-serious, of mild severity, did not lead to action to trial product and were reported as resolved. No events of injection site erythema were reported in patients on no PPX (arm 1).

Eight (8 [7 %]) patients on concizumab PPX (arms 2−4) and 1 patient on no PPX reported single AEs of upper respiratory tract infection, with an event rate of 0.1 events per PYE for both treatment groups. All AEs were non-serious, of mild severity, did not lead to action to trial product and were reported as resolved.

Seven (7 [6.1%]) patients on concizumab PPX (arms 2−4) reported 12 AEs of prothrombin fragment 1+2 increased (0.1 AEs per PYE). All were judged as probably or possibly related to trial product by the investigator. Most (11 of 12) AEs were non-serious and of mild or moderate severity.

One (1) SAE of severe prothrombin fragment 1+2 increased was reported (concizumab PPX arm 4) but did not lead to action to trial product and the patient recovered. No events of prothrombin fragment 1+2 increased were reported in the no PPX arm.

Patients on concizumab PPX - up until the 56-week cut-off

The safety profile of concizumab at the 56-week cut-off was consistent with that observed at the PACO (at 32 weeks) in terms of reported events, rates, severity, relation to concizumab and outcome. Overall, no new type of events or pattern of events were observed with prolonged treatment.

At the 56-week cut-off, a total of 91 (71.7%) patients reported 467 AEs (2.9 events per PYE) across concizumab PPX arms 1−4. Most AEs were non-serious, mild or moderate in severity, considered unlikely related to trial product and were reported as recovered. A total of 35 (27.6%) patients had not recovered from their AEs, all (73 events) non-serious, as of the 56-week cut-off date.

A summary of AEs by classification (seriousness; severity; temporary and permanent trial product discontinuation [drug interrupted and drug withdrawn, respectively]) is provided in the figure below. The most frequently reported AEs (>5%) by PT in concizumab PPX arms 1−4 (in descending order) included Arthralgia, COVID-19 and Pyrexia.

The most frequently reported (> 5%) possibly or probably related AEs in patients in concizumab PPX arms 1−4 [total], as judged by the investigator, in trial 4311 are provided in Table 84**:**. Of note, causality was judged only for patients on concizumab PPX in this trial.

Figure 49 Adverse events - by preferred term - most frequent (>=5%) in concizumab PPX (arms 1−4) - summary plot -HAwI+HBwI - OT - safety analysis set – trial 4311 (56-week cut-off).

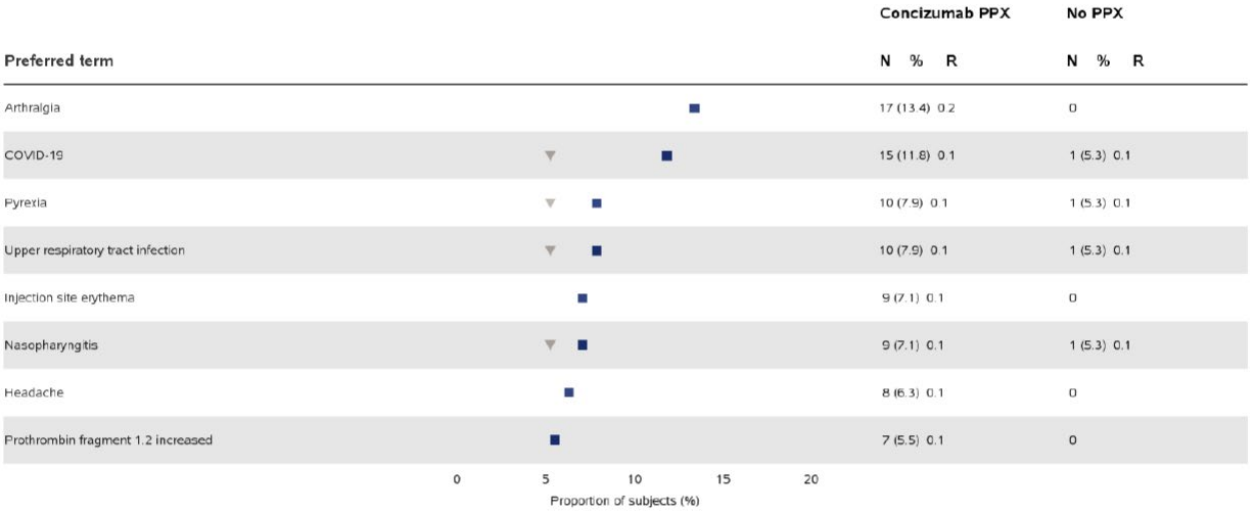


Table 42 Possibly or probably related AEs (≥5%) in concizumab PPX (arms 1−4) - by preferred term - HAwI+HBwI - OT - safety analysis set – trial 4311 (56-week cut-off).

	Concizumab PPX											
	Arm 1 N (%) E [R]		Arm 2 N (%) E [R]		Arm 3 N (%) E [R]		Arm 4 N (%) E [R]		Arms 2-4 N (%) E [R]		Total N (%) E [R]	
N in SAS	13		33		21		60		114		127	
N in SAS and ADS	13(100)		33(100)		21(100)		60(100)		114(100)		127(100)	
PYE	14.9		43.8		31.1		70.3		145.1		160.0	
Total events	1(7.7)	1[0.1]	9(27.3)	15[0.3]	4(19.0)	5[0.2]	20(33.3)	101[1.4]	33(28.9)	121[0.8]	34(26.8)	122[0.8]
General disorders and administration site conditions	1(7.7)	1[0.1]	6(18.2)	8[0.2]	2(9.5)	2[0.1]	16(26.7)	40[0.6]	24(21.1)	50[0.3]	25(19.7)	51[0.3]
Injection site erythema	0		1(3.0)	1[0.0]	1(4.8)	1[0.0]	7(11.7)	11[0.2]	9(7.9)	13[0.1]	9(7.1)	13[0.1]
Investigations	0		1(3.0)	2[0.0]	1(4.8)	2[0.1]	8(13.3)	24[0.3]	10(8.8)	28[0.2]	10(7.9)	28[0.2]
Prothrombin fragment 1.2 increased	0		1(3.0)	1[0.0]	1(4.8)	2[0.1]	5(8.3)	10[0.1]	7(6.1)	13[0.1]	7(5.5)	13[0.1]
Fibrin D dimer increased	0		1(3.0)	1[0.0]	0		5(8.3)	11[0.2]	6(5.3)	12[0.1]	6(4.7)	12[0.1]

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OT: On-treatment, On-treatment corresponds to the time period where patients are considered to be affected by on-demand treatment or concizumab treatment. N: number of patients with adverse event, %: percentage of patients with adverse event, E: number of adverse events, R: rate calculated as number of adverse events per patient years of exposure (E/total exposure time in trial), PYE: patient years of exposure, SAS: safety analysis set, ADS: Analysis data set, PPX: Prophylaxis. On-treatment corresponds to the time period where patients are considered to be affected by on-demand treatment or concizumab treatment.

Patients on no PPX (arm 1) – Up until the PACO

Of the 19 patients randomised to no PPX (arm 1) in the main part of the trial, 9 (47.4%) patients had a total of 26 AEs (2.2 AEs per PYE). Except for 3 AEs in 3 (15.8%) patients (Blood alkaline phosphatase increased; Lower limb fracture and Fibroma) all patients had recovered or were recovering from reported events. All AEs in the no PPX arm 1 were reported as single events in 1 patient, thereby reaching the threshold of 5%.

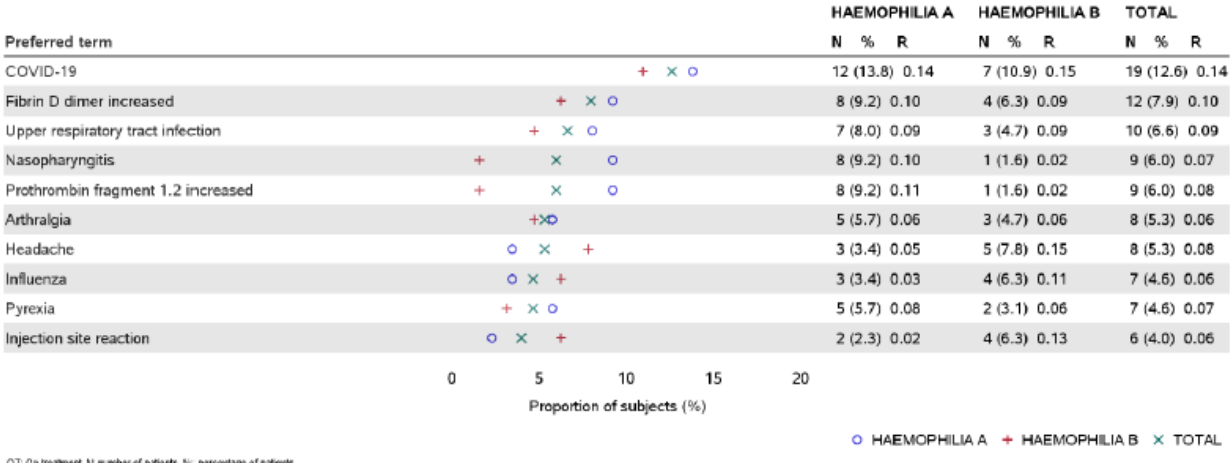
Trial 4307 – phase 3 – HA and HB

Patients on concizumab PPX – up until the CACO

A total of 104 (68.9%) patients reported 408 AEs (3.0 events per PYE) across concizumab PPX arms 1−4. Most AEs were non-serious, mild or moderate in severity, considered unlikely related to trial product and were reported as recovered. A total of 48 (31.8%) patients had not recovered from their AEs as of the cut-off date. All but 2 unresolved SAEs in 2 patients (Haemophilic arthropathy and Hemiparesis) were non-serious.

The most frequently reported AEs (>5%) by PT in concizumab PPX arms 1−4 (in descending order) were COVID-19, Fibrin D dimer increased and Upper respiratory tract infection (Figure **77:** below).

Figure 50 Adverse events - by preferred term - most frequent (>=5%) in concizumab PPX (arms 1−4) - summary plot - HA+HB - OT - safety analysis set – trial 4307.



The most frequently reported (≥5%) possibly or probably related AEs in patients with HA or HB on concizumab PPX arms 1−4, as judged by the investigator, in trial 4307 are provided in the table 85 below. Of note, causality was judged only for patients on concizumab PPX in this trial.

Table 43 Possibly or probably related AEs (≥5%) in concizumab PPX (arms 1−4) - by preferred term - HA+HB - OT - safety analysis set – trial 4307.

	Concizumab (arms 1-4)		
	HA	HB	Total
	N (%) E [R]	N (%) E [R]	N (%) E [R]
N in SAS	87	64	151
N in SAS and ADS	87 (100)	64 (100)	151 (100)
PYE	87.0	47.0	133.9
Total events	29 (33.3) 53 [0.6]	18 (28.1) 38 [0.8]	47 (31.1) 91 [0.7]
General disorders and administration site conditions	11 (12.6) 12 [0.1]	13 (20.3) 27 [0.6]	24 (15.9) 39 [0.3]
Injection site erythema	3 (3.4) 4 [0.0]	3 (4.7) 9 [0.2]	6 (4.0) 13 [0.1]
Injection site reaction	2 (2.3) 2 [0.0]	4 (6.3) 6 [0.1]	6 (4.0) 8 [0.1]
Investigations	12 (13.8) 23 [0.3]	5 (7.8) 6 [0.1]	17 (11.3) 29 [0.2]
Fibrin D dimer increased	8 (9.2) 9 [0.1]	2 (3.1) 2 [0.0]	10 (6.6) 11 [0.1]
Prothrombin fragment 1.2 increased	7 (8.0) 9 [0.1]	1 (1.6) 1 [0.0]	8 (5.3) 10 [0.1]

HA: haemophilia A, HB: haemophilia B, OT: On-treatment, PPX: prophylaxis. N: number of patients, %: percentage of patients, E: number of adverse events, R: rate calculated as number of adverse events per patient years of exposure (E/total exposure time in trial), SAS: safety analysis set, ADS: Analysis data set, PYE: patient years of exposure. On-treatment corresponds to the time period where patients are considered to be affected by on-demand treatment or concizumab treatment. Patients in the concizumab PPX group includes patients exposed to concizumab.

Patients on no PPX (arm 1) – Up until the CACO

Of the 21 patients randomised to no PPX (arm 1) after treatment restart, 6 (28.6%) patients had a total of 15 AEs (1.4 AEs per PYE]). All events were mild or moderate in severity. Seven (7) SAEs were reported in 2 (9.5%) patients. All events reported in patients on no PPX (after treatment restart) were reported as recovered or recovering. Prior to the treatment pause, 1 of 2 patients randomised to no PPX, experienced a mild AE (PT: Gilbert's syndrome) with outcome reported as 'not recovered'. All AEs in the no PPX arm 1 were reported as single events, thereby reaching the threshold of 5%.

By haemophilia subtype - total safety pool

An overview of AEs for the total safety pool and by haemophilia subtype is provided in Table 86**:**. Overall, the safety profile of concizumab was consistent across haemophilia subtypes. AE rates were slightly lower in patients with HAwI and HBwI than in patients with HA and HB. This was mainly due to more non-serious AEs reported across multiple SOCs in patients with HA and HB and no consistent pattern or clustering was associated with this. Across all haemophilia subtypes, most AEs were mild, non-serious and with outcome recovered.

Comparable event rates were observed for SAEs (range: 0.1-0.3 events per PYE) and severe (range: 0.1-0.2 events per PYE) AEs across haemophilia subtypes (HAwI, HBwI, HA and HB), though the proportion of patients with SAEs and severe events was higher in the HBwI group. This was mainly due to more singularly reported events judged as unlikely related to concizumab across multiple SOCs (mainly 'injury, poisoning and procedural complications' and 'musculoskeletal and connective tissue disorders') in the HBwI group.

Five (5; 1.6%) patients experienced fatal events (HA: 1 patient and HBwI: 4 patients). All but 1 fatal event were judged as unlikely related to concizumab by the investigator. Across all haemophilia subtypes, few patients permanently discontinued trial product due to AEs.

Table 44 Overview of AEs by haemophilia subtype - safety pool – HAwI, HBwI, HA and HB – on-treatment - safety analysis set - trials 4311, 4310, 4307, 4255 and 4159.

	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]
N	125			64			78			53			131			320		
PYE	162.7			47.0			121.3			84.0			205.3			415.0		
Total events	100	(80.0)	580 [3.6]	42	(65.6)	173 [3.7]	59	(75.6)	326 [2.7]	40	(75.5)	272 [3.2]	99	(75.6)	598 [2.9]	241	(75.3)	1351 [3.3]
Serious																		
Yes	12	(9.6)	17 [0.1]	7	(10.9)	10 [0.2]	9	(11.5)	12 [0.1]	17	(32.1)	24 [0.3]	26	(19.8)	36 [0.2]	45	(14.1)	63 [0.2]
No	99	(79.2)	563 [3.5]	39	(60.9)	163 [3.5]	57	(73.1)	314 [2.6]	38	(71.7)	248 [3.0]	95	(72.5)	562 [2.7]	233	(72.8)	1288 [3.1]
Severity																		
Severe	9	(7.2)	11 [0.1]	5	(7.8)	8 [0.2]	7	(9.0)	14 [0.1]	14	(26.4)	18 [0.2]	21	(16.0)	32 [0.2]	35	(10.9)	51 [0.1]
Moderate	35	(28.0)	95 [0.6]	17	(26.6)	27 [0.6]	20	(25.6)	68 [0.6]	19	(35.8)	46 [0.5]	39	(29.8)	114 [0.6]	91	(28.4)	236 [0.6]
Mild	94	(75.2)	474 [2.9]	36	(56.3)	138 [2.9]	56	(71.8)	244 [2.0]	35	(66.0)	208 [2.5]	91	(69.5)	452 [2.2]	221	(69.1)	1064 [2.6]
Relationship to trial product																		
Probable	33	(26.4)	83 [0.5]	13	(20.3)	29 [0.6]	14	(17.9)	39 [0.3]	14	(26.4)	37 [0.4]	28	(21.4)	76 [0.4]	74	(23.1)	188 [0.5]
Possible	32	(25.6)	54 [0.3]	8	(12.5)	9 [0.2]	12	(15.4)	49 [0.4]	9	(17.0)	10 [0.1]	21	(16.0)	59 [0.3]	61	(19.1)	122 [0.3]
Unlikely	94	(75.2)	440 [2.7]	37	(57.8)	133 [2.8]	55	(70.5)	235 [1.9]	37	(69.8)	216 [2.6]	92	(70.2)	451 [2.2]	223	(69.7)	1024 [2.5]
Missing	2	(1.6)	3 [0.0]	2	(3.1)	2 [0.0]	2	(2.6)	3 [0.0]	3	(5.7)	9 [0.1]	5	(3.8)	12 [0.1]	9	(2.8)	17 [0.0]
Outcome																		
Fatal	1	(0.8)	1 [0.0]	0			0			4	(7.5)	6 [0.1]	4	(3.1)	6 [0.0]	5	(1.6)	7 [0.0]
Not Recovered	39	(31.2)	69 [0.4]	18	(28.1)	37 [0.8]	20	(25.6)	47 [0.4]	17	(32.1)	36 [0.4]	37	(28.2)	83 [0.4]	94	(29.4)	189 [0.5]
Recovered with sequelae	4	(3.2)	4 [0.0]	0			1	(1.3)	1 [0.0]	1	(1.9)	1 [0.0]	2	(1.5)	2 [0.0]	6	(1.9)	6 [0.0]
Recovering	10	(8.0)	13 [0.1]	3	(4.7)	3 [0.1]	7	(9.0)	7 [0.1]	5	(9.4)	7 [0.1]	12	(9.2)	14 [0.1]	25	(7.8)	30 [0.1]
Recovered	96	(76.8)	492 [3.0]	40	(62.5)	132 [2.8]	58	(74.4)	271 [2.2]	38	(71.7)	222 [2.6]	96	(73.3)	493 [2.4]	232	(72.5)	1117 [2.7]
Unknown	1	(0.8)	1 [0.0]	1	(1.6)	1 [0.0]	0			0			0			2	(0.6)	2 [0.0]
Action taken to trial product																		
Drug withdrawn	4	(3.2)	6 [0.0]	2	(3.1)	2 [0.0]	1	(1.3)	1 [0.0]	3	(5.7)	3 [0.0]	4	(3.1)	4 [0.0]	10	(3.1)	12 [0.0]
Drug interrupted	14	(11.2)	18 [0.1]	5	(7.8)	5 [0.1]	12	(15.4)	16 [0.1]	8	(15.1)	9 [0.1]	20	(15.3)	25 [0.1]	39	(12.2)	48 [0.1]
Dose reduced	2	(1.6)	2 [0.0]	1	(1.6)	1 [0.0]	1	(1.3)	3 [0.0]	0			1	(0.8)	3 [0.0]	4	(1.3)	6 [0.0]
Dose increased	0			1	(1.6)	1 [0.0]	1	(1.3)	1 [0.0]	1	(1.9)	1 [0.0]	2	(1.5)	2 [0.0]	3	(0.9)	3 [0.0]
Dose not changed	91	(72.8)	500 [3.1]	36	(56.3)	147 [3.1]	48	(61.5)	279 [2.3]	36	(67.9)	228 [2.7]	84	(64.1)	507 [2.5]	211	(65.9)	1154 [2.8]
Unknown	0			0			0			0			0			0		
N/A	29	(23.2)	51 [0.3]	7	(10.9)	8 [0.2]	13	(16.7)	23 [0.2]	14	(26.4)	22 [0.3]	27	(20.6)	45 [0.2]	63	(19.7)	104 [0.3]
Missing	2	(1.6)	3 [0.0]	5	(7.8)	9 [0.2]	2	(2.6)	3 [0.0]	3	(5.7)	9 [0.1]	5	(3.8)	12 [0.1]	12	(3.8)	24 [0.1]

HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, N: number of subjects, %: percentage of subjects with adverse event, E: number of adverse events, R: rate calculated as number of adverse events per patient years of exposure, PYE: patient years of exposure. Subjects exposed to concizumab are included. This means that placebo data from 4159, Eptacog alpha data from 4310, and on-demand data from 4307 and 4311 are excluded. Treatment-emergent events from trials 4159, 4255 and 4310 are included. For trial 4307 and 4311, the on-treatment (OT) analysis data set is used.

Common AEs (>5%) by SOC and PT

The most frequently reported AEs (>5%) across haemophilia subtypes (in descending order by 'total' safety pool) were events common to the general population (SOC 'Infections and infestations' [mainly concerning PTs: Nasopharyngitis and COVID-19]), 'General disorders and administration site conditions' (mainly concerning PTs: Pyrexia and Injection site erythema) and events most likely to be the consequence of haemophilia (SOC 'Musculoskeletal and connective tissue disorders' [mainly concerning PT: Arthralgia]).

Amongst the most frequently reported SOCs, differences in the event rates were observed between HAwI and HBwI for the SOC of 'General disorders and administration site conditions' (primarily due to more patients with HBwI reporting non-serious injection site reactions as well as for the SOC 'Nervous system disorders' (primarily due to non-serious events of Headache and Migraine in few patients with HAwI, for which all but 3 AEs were resolved).

Differences in the event rate were also observed between patients with HA and HBwI for the SOC of 'Investigations', where also a higher proportion of patients with HA reported AEs (21.6% vs 13.2%). This mainly concerned events commonly reported in patients treated with concizumab (PTs: Fibrin D-dimer increased and Prothrombin fragment 1.2 increased).

No apparent difference in the event rates or proportion of patients with AEs for commonly reported SOCs were observed for patients in patients with HB as compared to patients with HAwI, HBwI and HA.

The AE pattern was considered expected for the patient population of haemophilia and the concizumab AE profile was, overall, consistent across the haemophilia subtypes with respect to the type of events reported and the most common AEs by PT (figure 78).

In the total safety pool, the most frequently reported AEs (reported in >5% of 'total') by PT were Nasopharyngitis (11.3%), COVID-19 (10.6%), Arthralgia (10.0%), Headache (9.1%), Fibrin D-dimer increased (8.8%), Upper respiratory tract infection (8.4%), Pyrexia (7.2%), Injection site erythema (5.9%) and Prothrombin fragment 1.2 increased (5.3%).

- All events of Nasopharyngitis (51 events in 36 [11.3%] patients were non-serious and reported across all haemophilia subtypes and was the most commonly reported PT in patients with HA, (35 AEs in 23 [18.4%] patients).
- All events of COVID-19 (36 events in 34 [10.6%] patients) were unlikely related to concizumab as judged by the investigator. Three (3) events in 3 patients were serious (1 fatal). In accordance with the protocol discontinuation criteria for trials 4311 and 4307, a total of 16 patients temporarily discontinued treatment with concizumab due to events of COVID-19, of which 15 patients had recovered. COVID-19 was reported across all haemophilia subtypes (though only in trials 4311 and 4307 due to the timing of the pandemic) and was the most commonly reported PT in patients with HB (7 AEs in 7 [10.9%] patients).
- All events of Arthralgia (47 events in 32 [10.0%] patients) were non-serious. and unlikely related to concizumab as judged by the investigator (42 in 30 [9.4%] patients). Events of Arthralgia are consistent with reported concomitant illness at screening, for which conditions within the SOC of 'musculoskeletal and connective tissue disorders' were most commonly reported across all haemophilia subtypes. Note that deteriorations in the musculoskeletal system were not observed for patients on concizumab PPX, based on physical examination. Arthralgia was reported across all haemophilia subtypes and was the most commonly reported PT in patients with HAwI (15 events in 8 [10.3%] patients) and HBwI (16 events in 11 [20.8%] patients).

Most common (>5%) AEs possibly or probably related to concizumab

In the total safety pool, 310 AEs reported in 112 (35.0%) patients (0.7 events per PYE) were evaluated as possibly or probably related to concizumab by the investigator. The most frequently possibly/probably related AEs (>5%) in the total safety pool were consistent with commonly reported AEs within the SOC of 'General disorders and administration site conditions' followed by 'Investigations' and mainly concerned injection site reactions and increases in coagulation-related parameters (D-dimer and prothrombin F1+2), respectively.

Across haemophilia subtypes event rates for possibly or probably related AEs were comparable (range 0.6-0.8 AEs per PYE), while the proportion of patients with possibly or probably related AEs was lower in the HAwI and HB groups, and higher in the HA and HBwI groups, as compared to the total safety pool.

A similar pattern of AEs with possible or probable relation to concizumab was observed between the individual haemophilia subtypes (HAwI, HBwI, HA and HB). The most common (>5%) possibly or probably related AEs (by PT) within each haemophilia subtype were:

- HAwI: Fibrin D-dimer increased (10 AEs in 5 [6.4%] patients), Prothrombin fragment 1.2 increased (9 AEs in 5 [6.4%] patients) and Injection site erythema (5 AEs in 4 [5.1%] patients)
- HBwI: Injection site erythema (9 AEs in 6 [11.3%] patients), Injection site reaction (3 AEs in 3 [5.7%] patients), Injection site urticaria (7 AEs in 3 [5.7%] patients) and Fibrin D-dimer increased (4 AEs in 3 [5.7%] patients)
- HA: Fibrin D-dimer increased (21 AEs in 16 [12.8%] patients), Prothrombin level increased (13 AEs in 8 [6.4%] patients) and Prothrombin F1.2 increased (10 AEs in 8 [6.4%] patients), injection site bruising (10 AEs in 6 [4.8%] patients) and Injection site erythema (7 AEs in 6 [4.8%] patients)
- HB: Injection site reaction (6 AEs in 4 [6.3%] patients) and Injection site erythema (9 AEs in 3 [4.7%] patients)

2.6.8.3. Serious adverse event/deaths/other significant events

Deaths

Deaths were reported in trials 4307 and 4311 only, why the following section will focus on these trials. An overview of deaths for the total safety pool is presented by haemophilia subtype in the table 87 below.

A total of 8 patients experienced events with fatal outcome during the concizumab PPX development programme, of which 6 deaths occurred during the on-treatment period (concizumab PPX: 5 [1.6%] patients and no PPX: 1 patient). All deaths are summarised below and listed by trial and treatment.

All but 1 death (Intra-abdominal haemorrhage) were unlikely related to concizumab, as judged by the investigator.

Table 45: Listing of deaths – trials 4311 and 4307

Trial/Period	Patient ID Case no.	Age (years)/ BMI (kg/m²)/ Haemophilia subtype	Preferred term	AE onset (study day)[a]/ Duration (days)	Causality
Concizumab PPX					
4311/Main (after treatment restart)		/HBwI	Road traffic accident Femur fracture Humerus fracture	Day 540/21 Day 540/21 Day 540/21	Unlikely Unlikely Unlikely
4311/Extension (after treatment restart)		/HBwI	COVID-19	Day 553/22	Unlikely
4311/Extension (after treatment restart)		/HBwI	Alcoholic coma	Day 375/4	Unlikely
4311/Extension (after treatment restart)		/HBwI	Haemorrhage intracranial	Day 345/8	Unlikely
4307/Follow-up (after treatment restart)		2/HA	Intra-abdominal haemorrhage	Day 276/1	Possible
No PPX					
4311/Main (before treatment restart)		/HAwI	Pneumonitis	NA; NA	Unlikely
Deaths reported outside the on-treatment period (concizumab PPX)[c]					
4311/Follow-up (treatment pause)		/HBwI	Haematoma[b]	Day 214/21	Unlikely
4311/Follow-up (treatment pause)		/HBwI	Gastrointestinal haemorrhage	Day 228/4	Unlikely

Notes: a Study day is calculated based on the treatment start date. b The haematoma was reported as "hematoma laterocervical and in mouth floor". c For a definition of analysis data sets and observation periods. Patient age and BMI are reported at baseline. Abbreviations: AE: adverse event; HA: haemophilia A without inhibitors; HAwI: haemophilia A with inhibitors; HBwI: haemophilia B with inhibitors; BMI: body mass index; HBwI: haemophilia B with inhibitors; ID: identifier; NA: not available; OT: on-treatment period; PPX: prophylaxis.

Trial 4311

Up until the 56-week cut-off date (13 Jun 2022), 7 deaths were reported of which 5 deaths were reported within the on-treatment period:

- Concizumab PPX (arms 1−4): 4 (3.1%) patients died due to:
    - Road traffic accident, Femur fracture and Humerus fracture (reported in the same patient);
    - COVID-19;
    - Alcoholic coma
    - Haemorrhage intracranial
- No PPX (arm 1): 1 (5.3%) patient died due to:
    - Pneumonitis

The remaining 2 patients were originally allocated to concizumab PPX but died during the treatment pause (more than 7 weeks after the treatment was discontinued) when patients were treated at the discretion of their treating physician. The 2 deaths with onset during the treatment pause were due to an event of Haematoma and Gastrointestinal haemorrhage, respectively. All deaths in the concizumab PPX arms in trial 4311 were judged as unlikely related to concizumab by the investigator. No additional deaths were reported between the 56-week cut-off and safety database cut-off date (30 Aug 2022).

Table 46: Adverse events with fatal outcome - HAwI+HBwI - safety analysis set.

Subject ID (case number)/ Age/BMI/ Haemophilia subtype	PT with fatal outcome/ Onset (study day[a]); End (study day)[a]/ Period	Other relevant details (investigator reported)
Concizumab PPX		
HBwI	Covid-19/ Day 553;Day 574/ Extension (after treatment restart)	The patient had cough (reported as onset of COVID-19 infection) and went to hospital for COVID-19 testing. The patient was admitted to hospital upon a positive test result for SARS-CoV-(22). After 22 days, the patient died from COVID-19 respiratory complication. The patient had a medical history of obesity and hypertension. Investigator-judged causality: unlikely.
HBwI	Femur fracture, humerus fracture, road traffic accident/ Day 540;Day 560/ Main after treatment restart	The patient was admitted to hospital following a motor vehicle accident caused by collision with an ox. Fractions of the femur and humerus bone were identified and the patient was treated with eptacog alfa (activated) and transferred for surgery. The patient's condition was reported as stable but after 21 days the patient felt ill and was declared dead in the ICU the same day. Autopsy was performed but the results are not available. Investigator-judged causality (all 3 fatal events): unlikely.
No PPX arm 1		
HAwI	Pneumonitis/ NA/ Main before treatment restart	The patient experienced mild fever and cough and was admitted to hospital, where the patient received oxygen therapy and antibiotics. A CT scan showed bilateral pneumonitis and lab results demonstrated severe anaemia leading to red blood cell transfusion and initiation of continuous treatment with rFVIIa. The patient developed respiratory failure and coma and died of cardiorespiratory failure. An autopsy was not performed. All COVID-19 tests performed were negative. The patient had a medical history of emphysema and chronic obstructive pulmonary disease. Investigator-judged causality: unlikely
Deaths reported outside the on-treatment period (concizumab PPX)		
HBwI	Haematoma/ Day 214;Day 234/ Follow-up (treatment pause)	Approximately 3 months after discontinuing treatment with concizumab PPX (study day 204) and while hospitalised for urinary tract obstruction (AE no. 1), the patient experienced haematoma latero-cervical and in mouth floor with respiratory compromise (AE no. 4). A temporary tracheotomy was performed and the patient was treated with eptacog alfa (activated). After 21 days from onset of the haematoma, the patient was transferred to ICU due to dyspnoea and abdominal distention and died the same day with the main and intermediate cause of death reported as 'severe hemophilia B with inhibitor' and 'retroperitoneal hematoma and hemoperitoneum', respectively. The patient's medical history included hepatic C virus-related hepatopathy and hypertension. During hospitalisation, the patient also experienced retinal vascular occlusion (AE no. 2) and vena cava thrombosis (AE no. 3) which he recovered from. Investigator-judged causality (all 4 SAEs): unlikely.
HBwI	Gastrointestinal haemorrhage/ Day 228/Day 231/ Follow-up (treatment pause)	Approximately 6 months after discontinuing treatment with concizumab PPX (study day 54), the patient experienced gastrointestinal bleeding at home and was admitted to hospital. The patient was administered eptacog alfa (activated) i.v. and also received blood transfusion for the gastrointestinal bleeding but died 3 days after onset of the event. Autopsy was not done. The patient had pre-existing anaemia and a medical history of gastrointestinal bleeding. Investigator-judged causality: unlikely.

Notes: Age: Age in years; aStudy day is calculated based on the treatment start date, either before the treatment pause (visit 2) for patients exposed to both the initial and new concizumab dosing regimen or after treatment restart (visit 2a) for patients exposed to only the new concizumab dosing regimen (see Section 9.5.1 for details). Abbreviations: AE: adverse event; HAwI: haemophilia A with inhibitors; BMI: body mass index (kg/m2); CT: computed tomography; HBwI: haemophilia B with inhibitors; ICU: intensive care unit; SAE: serious adverse event; PPX: prophylaxis; PT: preferred term.

Table 47: Adverse events with fatal outcome since PACO – HAwI+HBwI – safety analysis set.

Patient ID (case number)/ Age (years)/BMI (kg/m^2)/ Haemophilia subtype	PT with fatal outcome/ Onset (study day); End (study day)/ Period/Duration (days)	Other relevant details (investigator reported)
HBwI	Alcoholic coma/ Day 375; Day 378/ Extension/4	The patient had an alcoholic coma with respiratory arrest and was resuscitated after 45 minutes of cardiac massage followed by admission to the hospital in intensive care unit. Three (3) days later the patient died due to hypoxic cardiorespiratory arrest. The patient had relevant concomitant conditions of anxiety and depression, a failure to thrive (probably linked to growth factor deficiency), obsessive neurosis, mild intellectual deficit and hypogonadism. According to the investigator, the patient was not known to abuse alcohol. Investigator-judged causality: unlikely.
HBwI	Haemorrhage intracranial/ Day 345; Day 352/ Extension/8	The patient developed intense headache and repeated vomiting and was instructed by the investigator to go to the nearest ER, but the patient's mother did not follow the instructions. The following day, the mother was again instructed to take the patient to the hospital and the patient went to the ER. A CT scan was performed, and intracranial haemorrhage was observed that required surgical intervention with hematoma drainage. Surgery was performed the same day. Six (6) days following the surgery, the patient died after presenting tachycardia with hypotension and reporting cardio-respiratory arrest (death diagnosis: brain death). The patient's mother confirmed that it was a spontaneous bleeding. There was no family or personal history of intracerebral haemorrhage or aneurysms. Investigator-judged causality: unlikely.

Abbreviations: AE: adverse event; CT: computerised tomography; ER: emergency room; HAwI: haemophilia A with inhibitors; BMI: body mass index; HBwI: haemophilia B with inhibitors; PACO: primary analysis cut-off; PT: preferred term.

Trial 4307

Up until the CACO, 1 (0.7%) patient treated with concizumab PPX (arm 4) experienced an SAE with fatal outcome (Intra-abdominal haemorrhage). The event was judged as possibly related to concizumab PPX by the investigator, with alternative causality reported as 'underlying disease severe haemophilia A'. Event onset is unknown (the patient was found dead in his apartment). Of note, the patient was exposed to concizumab PPX in trial 4255 prior to continuing in trial 4307 with no reported bleeds in either trial.

No additional deaths were reported between the CACO and safety database cut-off date (30 Aug 2022).

Table 90: Adverse events with fatal outcome – safety analysis set.

Patient ID (case number)/ Age/BMI/ Haemophilia subtype	Preferred term / Onset;End (study day[a])/ Period	Other relevant details (investigator reported)
Concizumab PPX		
HA	Intra-abdominal haemorrhage/ Day 276;Day 276/ Follow-up (after treatment restart)	The patient was treated with concizumab PPX for approximately 8 months prior to event onset and was also treated with concizumab PPX in trial 4255.[b] The exact day of death is unknown, as the patient was found dead at home. Cause of death based on autopsy: 'bleeding to death by diffuse intraabdominal bleed of 1.7 L without a clearly localizable bleed source'. Alternative causality was reported as 'underlying disease severe haemophilia A'. There were no signs of venous or arterial thromboembolic event, no vascular rupture or dissection, no intestinal bleeding, no cerebral haemorrhage, no sign of traumatic effects, liver and spleen intact, no muscle or joint bleed. Current conditions: elevated blood pressure, haemophilic arthropathy both elbow joints, haemophilic arthropathy both ankle joints. Concomitant medications: Bisoprolol (since 2001) and COVID-19 vaccine. Investigator-judged causality: possible.

Serious adverse events

By trial (trials 4311, 4310, 4307, 4255 and 4159)

No SAEs were reported in phase 1 trial 4159 nor 'other' clinical pharmacology trials.

SAEs were reported in trials 4311, 4310, 4307 and 4255. A similar pattern of SAEs was observed across these trials in concizumab-treated patients with HAwI and HBwI (trials 4311 and 4310) and HA (trials 4307 and 4255) and HB (trial 4307).

Within each trial, all SAEs were recorded as single events in 1 or 2 patients and across different SOCs.

Trial 4311 – Phase 3 – HAwI and HBwI

Patients on concizumab PPX – up until the PACO

Overall, the number of SAEs were low and distributed across multiple SOCs and PTs with no apparent clustering. No SAEs (by PT) were reported in ≥5% patients across the concizumab PPX arms.

SAEs with onset during the on-treatment period are summarised by SOC and PT in Table 91**:** (note that the cases of SAEs with fatal outcome are also included in this summary table).

A total of 14 (12.3%) patients treated with concizumab PPX (arms 2–4) reported 18 SAEs with similar SAE event rates across arms. In 5 patients 7 possibly or probably related SAEs were reported, these concerned renal infarct, hypersensitivity, melaena and haematemesis (both PTs were reported in the same patient), dizziness, and fibrin d-dimer increased and prothrombin fragment 1+2 increased (both PTs were reported in the same patient). Three (3; 15.8%) patients on no PPX (arm 1) reported 5 SAEs, corresponding to an SAE event rate comparable to that for concizumab PPX arms 2–4 (0.4 and 0.2 SAEs per PYE, respectively). The non-fatal SAE of renal infarct reported in concizumab PPX arm 2 prior to the treatment pause led to permanent discontinuation of trial product.

Table 91: Serious adverse events by system organ class and preferred term – summary – HAwI+HBwI - OT – safety analysis set.

	No PPX	Concizumab PPX					
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4	Total
	N (%) E [R]	N (%) E [R]	N (%) E [R]	N (%) E [R]	N (%) E [R]	N (%) E [R]	N (%) E [R]
N in SAS	19	13	33	21	60	114	127
N in SAS and ADS	19(100)	13(100)	33(100)	21(100)	60(100)	114(100)	127(100)
PYE	12.0	9.3	31.7	24.3	46.4	102.5	111.8
Total events	3(15.8) 5[0.4]	0	6(18.2) 9[0.3]	1(4.8) 1[0.0]	7(11.7) 8[0.2]	14(12.3) 18[0.2]	14(11.0) 18[0.2]
Injury, poisoning and procedural complications	1(5.3) 2[0.2]	0	1(3.0) 3[0.1]	0	1(1.7) 1[0.0]	2(1.8) 4[0.0]	2(1.6) 4[0.0]
Road traffic accident	1(5.3) 1[0.1]	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Femur fracture	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Humerus fracture	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Ligament sprain	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Lower limb fracture	1(5.3) 1[0.1]	0	0	0	0	0	0
Infections and infestations	1(5.3) 1[0.1]	0	2(6.1) 2[0.1]	0	2(3.3) 2[0.0]	4(3.5) 4[0.0]	4(3.1) 4[0.0]
COVID-19	1(5.3) 1[0.1]	0	1(3.0) 1[0.0]	0	1(1.7) 1[0.0]	2(1.8) 2[0.0]	2(1.6) 2[0.0]
Catheter site infection	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Encephalitis	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Investigations	0	0	0	1(4.8) 1[0.0]	1(1.7) 2[0.0]	2(1.8) 3[0.0]	2(1.6) 3[0.0]
Fibrin D dimer increased	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Haemoglobin decreased	0	0	0	1(4.8) 1[0.0]	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Prothrombin fragment	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Gastrointestinal disorders	0	0	1(3.0) 2[0.1]	0	0	1(0.9) 2[0.0]	1(0.8) 2[0.0]
Haematemesis	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Melaena	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Musculoskeletal and connective tissue disorders	0	0	0	0	2(3.3) 2[0.0]	2(1.8) 2[0.0]	2(1.6) 2[0.0]
Haemarthrosis	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Muscle haemorrhage	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Immune system disorders	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Hypersensitivity	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Nervous system disorders	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Dizziness	0	0	0	0	1(1.7) 1[0.0]	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Renal and urinary disorders	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Renal infarct	0	0	1(3.0) 1[0.0]	0	0	1(0.9) 1[0.0]	1(0.8) 1[0.0]
Respiratory, thoracic and mediastinal disorders	1(5.3) 1[0.1]	0	0	0	0	0	0
Pneumonitis	1(5.3) 1[0.1]	0	0	0	0	0	0
Vascular disorders	1(5.3) 1[0.1]	0	0	0	0	0	0
Haematoma	1(5.3) 1[0.1]	0	0	0	0	0	0

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OT: On-treatment, On-treatment corresponds to the time period where subjects are considered to be affected by on-demand treatment or concizumab treatment. N: number of subjects with adverse event, %: percentage of subjects with adverse event, E: number of adverse events, R: rate calculated as number of adverse events per patient years of exposure (E/total exposure time in trial), PYE: patient years of exposure, SAS: safety analysis set, ADS: Analysis data set, PPX: Prophylaxis. On-treatment corresponds to the time period where subjects are considered to be affected by on-demand treatment or concizumab treatment.

Patients on concizumab PPX – up until 56-week cut-off

Overall, the number of SAEs was low and distributed across multiple SOCs and PTs with no apparent clustering of events. No SAEs (by PT) were reported in ≥5% patients across the concizumab PPX arms.

A total of 22 (17.3%) patients treated with concizumab PPX (arms 1–4) reported 27 SAEs (0.2 events per PYE) up until the 56-week cut-off. Most SAEs (20 of 27) reported in concizumab arms 1–4 (17 [13.4%] patients) were judged as unlikely related to concizumab and resolved.

Possibly or probably related SAEs (7 SAEs in 5 patients), were events of (PT): Renal infarct; Hypersensitivity, Melaena and Haematemesis [both SAEs were reported in the same patient]; Dizziness; and Fibrin D-dimer increased and Prothrombin fragment 1+2 increased [both SAEs were reported in the same patient]). Except for the event of 'Dizziness', which was moderate in severity, all possibly or probably related SAEs were severe and all were reported as recovered, except for the case of 'Renal infarct', which was reported as

'recovered with sequelae'. As per protocol discontinuation criteria, the events of Renal infarct and Hypersensitivity led to permanent discontinuation of trial product.

Patients on no PPX (arm 1) – up until the PACO

Three (3; 15.8%) patients on no PPX (arm 1) reported 5 SAEs corresponding to an SAE event rate of 0.2 SAEs per PYE: Road traffic accident, Lower limb fracture and COVID-19 (reported in the same patient); Pneumonitis (fatal) and Haematoma. For the events of Lower limb fracture and Road traffic accident, the outcome was 'not recovered' and 'recovered with sequalae', as the patient's multiple broken leg bone was not recovered and the patient may require additional surgery, respectively.

Trial 4307 – phase 3 – HA and HB without inhibitors

Patients on concizumab PPX – up until the CACO

Overall, the number of SAEs was low and the SAEs were distributed across multiple SOCs and PTs with no apparent clustering. No SAEs (by PT) were reported in ≥5% patients with HA or HB treated with concizumab PPX (arms 1–4).

In total, 22 SAEs (0.2 SAEs per PYE) were reported in 14 (9.3%) patients exposed to concizumab PPX (arms 1–4), with a similar proportion of patients with SAEs and similar event rates across HA and HB. Most SAEs reported in concizumab arms 1–4 were judged as unlikely related to concizumab (16 SAEs in 10 [6.6%] patients) and resolved (14 SAEs in 10 [6.6%] patients).

Possibly or probably related SAEs (6 SAEs in 4 patients) were events of (PT): Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis [reported in the same patient]; Acute myocardial infarction and 2 events of Intra-abdominal haemorrhage in 2 patients (of which 1 had fatal outcome). Both events of Intraabdominal haemorrhage and the event of Acute myocardial infarction were severe. Apart from the fatal event, remaining events were reported as recovered (2 SAEs in 2 patients) or recovering (3 SAEs in 1 patient). Five (5) related SAEs in 3 patients led to permanent discontinuation of concizumab. For the events of PT: Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis and Acute myocardial infarction, permanent discontinuation was per protocol discontinuation criteria).

Patients on no PPX - up until the CACO

No SAEs were reported in patients with HA on no PPX (arm 1). Seven (7) SAEs (1.2 SAEs per PYE) were reported in 2 (16.7%) patients with HB on no PPX. All SAEs were resolved.

By haemophilia subtype - safety pool

An overview of SAEs with onset during the on-treatment period and summary of SAEs by SOC and PT for the total pool and by haemophilia subtype is provided in Table 92. Note, that SAEs with fatal outcome are also included in these tables.

In total, 45 (14.1%) patients reported 63 SAEs [0.2 events per PYE), the majority of these (49 SAEs in 35 [10.9%] patients) were unlikely related to concizumab, as evaluated by the investigator.

A total of 9 SAEs in 7 (2.2%) patients led to permanent discontinuation of trial product (including 1 fatal event of COVID-19) and 18 SAEs in 15 (4.7%) patients led to temporary discontinuation of trial product.

For all haemophilia subtypes, the majority of SAEs were recorded as single events in 1 or 2 patients with no clustering of events across SOCs.

Event rates for SAEs were comparable across haemophilia subtypes (HAwI, HBwI, HA and HB), though a higher proportion of patients with HBwI reported SAEs (Table 92). This was primarily due to more patients with HBwI reporting SAEs judged as unlikely related to concizumab by the investigator under the SOC of 'Musculoskeletal and connective tissue disorders' (5 SAEs in 5 [9.4%] patients) and injuries under the SOC 'Injury, poisoning and procedural complications' (7 SAEs in 4 [7.5%] patients.

Table 92: SAEs on concizumab - overview - by haemophilia type - summary - HA, HAwI and HBwI - SAS - trials 4311, 4310, 4307, 4255 and 4159

	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]
N	125			64			78			53			131			320		
PYE	162.7			47.0			121.3			84.0			205.3			415.0		
Total events	12	(9.6)	17 [0.1]	7	(10.9)	10 [0.2]	9	(11.5)	12 [0.1]	17	(32.1)	24 [0.3]	26	(19.8)	36 [0.2]	45	(14.1)	63 [0.2]
Serious																		
Yes	12	(9.6)	17 [0.1]	7	(10.9)	10 [0.2]	9	(11.5)	12 [0.1]	17	(32.1)	24 [0.3]	26	(19.8)	36 [0.2]	45	(14.1)	63 [0.2]
No	0			0			0			0			0			0		
Severity																		
Severe	8	(6.4)	10 [0.1]	4	(6.3)	6 [0.1]	4	(5.1)	6 [0.0]	13	(24.5)	17 [0.2]	17	(13.0)	23 [0.1]	29	(9.1)	39 [0.1]
Moderate	4	(3.2)	5 [0.0]	3	(4.7)	3 [0.1]	4	(5.1)	5 [0.0]	5	(9.4)	6 [0.1]	9	(6.9)	11 [0.1]	16	(5.0)	19 [0.0]
Mild	2	(1.6)	2 [0.0]	1	(1.6)	1 [0.0]	1	(1.3)	1 [0.0]	1	(1.9)	1 [0.0]	2	(1.5)	2 [0.0]	5	(1.6)	5 [0.0]
Relationship to trial product																		
Probable	1	(0.8)	3 [0.0]	0			2	(2.6)	3 [0.0]	1	(1.9)	1 [0.0]	3	(2.3)	4 [0.0]	4	(1.3)	7 [0.0]
Possible	3	(2.4)	3 [0.0]	1	(1.6)	1 [0.0]	2	(2.6)	2 [0.0]	1	(1.9)	1 [0.0]	3	(2.3)	3 [0.0]	7	(2.2)	7 [0.0]
Unlikely	8	(6.4)	11 [0.1]	6	(9.4)	9 [0.2]	6	(7.7)	7 [0.1]	15	(28.3)	22 [0.3]	21	(16.0)	29 [0.1]	35	(10.9)	49 [0.1]
Outcome																		
Fatal	1	(0.8)	1 [0.0]	0			0			4	(7.5)	6 [0.1]	4	(3.1)	6 [0.0]	5	(1.6)	7 [0.0]
Not Recovered	1	(0.8)	1 [0.0]	1	(1.6)	1 [0.0]	0			1	(1.9)	1 [0.0]	1	(0.8)	1 [0.0]	3	(0.9)	3 [0.0]
Recovered with sequelae	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]
Recovering	2	(1.6)	4 [0.0]	0			0			1	(1.9)	1 [0.0]	1	(0.8)	1 [0.0]	3	(0.9)	5 [0.0]
Recovered	9	(7.2)	10 [0.1]	6	(9.4)	9 [0.2]	9	(11.5)	12 [0.1]	12	(22.6)	15 [0.2]	21	(16.0)	27 [0.1]	36	(11.3)	46 [0.1]
Unknown	0			0			0			0			0			0		
Action taken to trial product																		
Drug withdrawn	4	(3.2)	6 [0.0]	1	(1.6)	1 [0.0]	0			2	(3.8)	2 [0.0]	2	(1.5)	2 [0.0]	7	(2.2)	9 [0.0]
Drug interrupted	4	(3.2)	5 [0.0]	1	(1.6)	1 [0.0]	5	(6.4)	6 [0.0]	5	(9.4)	6 [0.1]	10	(7.6)	12 [0.1]	15	(4.7)	18 [0.0]
Dose reduced	0			0			0			0			0			0		
Dose increased	0			0			0			0			0			0		
Dose not changed	4	(3.2)	4 [0.0]	5	(7.8)	7 [0.1]	3	(3.8)	5 [0.0]	11	(20.8)	13 [0.2]	14	(10.7)	18 [0.1]	23	(7.2)	29 [0.1]
Unknown	0			0			0			0			0			0		
N/A	1	(0.8)	2 [0.0]	1	(1.6)	1 [0.0]	1	(1.3)	1 [0.0]	2	(3.8)	3 [0.0]	3	(2.3)	4 [0.0]	5	(1.6)	7 [0.0]

HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, N: number of subjects, %: percentage of subjects with adverse event, E: number of adverse events, R: rate calculated as number of adverse events per patient years of exposure, PYE: patient years of exposure. Subjects exposed to concizumab are included. This means that placebo data from 4159, Eptacog alpha data from 4310, and on-demand data from 4307 and 4311 are excluded. Adverse events on concizumab are included. Treatment-emergent events from trials 4159, 4255 and 4310 are included. For trial 4307 and 4311, the on-treatment (OT) analysis data set is used.

A total of 14 SAEs in 10 (3.1%) patients in the safety pool were judged as possibly or probably related to concizumab PPX by the investigator. Both the proportion of patients with possibly/probably related SAEs and SAE rates were similar across haemophilia subtypes (Table 93, see below).

- In HAwI (5 SAEs in 3 [3.8%] patients): Haematemesis and Melaena (same patient); Dizziness; and Fibrin D-dimer increased and Prothrombin F1.2 increased (same patient)
- In HBwI (2 SAEs in 2 [3.8%] patients): Renal infarct and Hypersensitivity

With the exception of the SAE of Renal infarct, which was reported as 'resolved with sequelae' (case which led to treatment pause), all patients with HAwI or HBwI with possibly or probably related SAEs had recovered. One (1) patient with HAwI permanently discontinued trial product due to a related SAE. No related SAEs in patients with HBwI led to permanent discontinuation of trial product.

- In patients with HA, 6 SAEs in 4 (3.2%) patients were judged as possibly or probably related to concizumab: Atypical pneumonia; Intra-abdominal haemorrhage (fatal) and Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis (same patient) and Acute myocardial infarction (case that led to treatment pause)

- 4 patients with HA, permanently discontinued treatment with concizumab PPX due to possibly or probably related SAEs. Except for the fatal event, remaining patients with HA with possibly or probably related SAEs were recovered or recovering.
- In patients with HB, 1 SAE in 1 (1.6%) patient was judged as possibly related to trial product: Intra-abdominal haemorrhage (alternative aetiology reported as 'suspected malignity'). The event was severe and led to permanent discontinuation of trial product. The patient was reported as recovered.

Table 93: Listing of SAEs possibly or probably related to concizumab PPX – by haemophilia subtype and trial - safety analysis set – trials 4311, 4307 and 4255

Trial ID/Patient ID (case no.)	Haemophilia type/ Age/ BMI	AE no.	Study day/ Duration (Days)	SOC / PT	Action / outcome
	HBwI/	2	21/205	Renal and urinary disorders/ Renal infarct	Drug Withdrawn/ Recovered/Resolved With Sequelae
	HBwI/	8	39/8	Immune system disorders/ Hypersensitivity	Drug Interrupted/ Recovered/Resolved
	HAwI/	1	8/78	Nervous system disorders/ Dizziness	Drug Interrupted/ Recovered/Resolved
	HAwI/	5	8/22	Investigations/ Fibrin D dimer increased	Dose Not Changed/ Recovered/Resolved
		6	8/22	Investigations/ Prothrombin fragment 1.2 increased	Dose Not Changed/ Recovered/Resolved
	HAwI/	1	368/11	Gastrointestinal disorders/ Haematemesis	Drug Interrupted/ Recovered/Resolved
		2	367/12	Gastrointestinal disorders/ Melaena	Drug Interrupted/ Recovered/Resolved
	HB/	1	3/48	Gastrointestinal disorders/ Intra-abdominal haemorrhage	Drug Withdrawn/ Recovered/Resolved
	HA/	2	276/1	Gastrointestinal disorders/ Intra-abdominal haemorrhage	Dose Not Changed/ Fatal
	HA/	4	59/15	Cardiac disorders/ Acute myocardial infarction	Drug Withdrawn/ Recovered/Resolved
	HA/	3	86/63	Vascular disorders/ Deep vein thrombosis	Drug Withdrawn/ Recovering/Resolving
		4	92/57	Respiratory, thoracic and mediastinal disorders/ Pulmonary embolism	Drug Withdrawn/ Recovering/Resolving
		5	92/57	Vascular disorders/ Superficial vein thrombosis	Drug Withdrawn/ Recovering/Resolving
	HA/	13	540/11	Infections and infestations/ Atypical pneumonia	Drug Interrupted/ Recovered/Resolved

Notes: Patient age and BMI are reported at baseline. Abbreviations: AE: Adverse event; SOC: system organ class; PT: preferred term.

Compassionate use (CUP) [4807] and individual patient basis data

In total, 12 SAEs have been reported in 14 children or adolescents (<18 years) with HBwI receiving concizumab via compassionate use.

Four (4) of the 10 patients who received concizumab on an individual patient basis reported a total of 8 SAEs: Haemarthrosis (3 events in 2 patients); Abdominal pain; Influenza; Injections site haematoma and Injection site swelling (same patient) and Muscle haematoma.

- 6 of 8 SAEs were unlikely related to concizumab as judged by the medical practitioner and did not lead to changes in concizumab dose. For the remaining 2 SAEs (Injection site haematoma and Injection site swelling [same patient]) relationship was not reported by the medical practitioner but the SAEs were considered to be possibly or probably related to concizumab treatment by Novo Nordisk.
- For 3 SAEs in 2 patients (Influenza and Muscle haematoma [same patient] and Haemarthrosis), outcome was not reported by the medical practitioner. The remaining 5 SAEs (in 3 patients) were resolved.

Three of the 7 patients in the compassionate use programme reported a total of 4 SAEs: Limb injury and Haemarthrosis (same patient); Intra-abdominal haematoma and COVID-19 infection.

- All SAEs were unlikely related to concizumab as judged by the investigator, did not lead to changes in concizumab dose and were reported as recovered.

During the evaluation, the applicant provided an update of all new deaths and SAEs reported across the clinical trial programme. The nature and frequency of the SAEs and AESIs observed until the cut-off of 14 June 2023 across the clinical trial programme do not give rise to concern. However, the late breaking information of one event of ischemic cerebral infarction in an elderly patient with haemophilia A without inhibitors participating in trial 4307 appears to confirm the inherent thromboembolic risk of treatment with concizumab, also at the amended lower dosing scheme.

The patient did not report any risk factors apart from hypertension, especially no hyperlipidemia, atrial fibrillation etc. and did therefore not present a high risk for thromboembolic events at baseline. Furthermore, the subject did not administer concomitant coagulation factor products, as was reported in the three subjects experiencing 5 thromboembolic events prior to the change in dosing.

Adverse events of special interest

Thromboembolic events

In total, 11 events in 6 of 320 (1.9%) patients were captured by the MedDRA search. These events occurred in trials 4311, 4307 and 4255, as follows:

- Trial 4311: 3 events in 2 patients (Partial and Complete shunt thrombosis [same patient] and Renal infarct)
- Trial 4307: 5 events in 3 patients (Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis [same patient]; Hemiparesis and Acute myocardial infarction)
- Trial 4255: 3 events of Haemorrhoids thrombosed in 1 patient

TEs were reported in 1 patient each with HAwI and HBwI and in 4 patients with HA.

Six (6) of the 11 thromboembolic events captured by the MedDRA search were serious. Seven (7) of 11 events (in 3 patients) captured by the MedDRA search were mild or moderate in severity and 6 events (in 3 patients) were judged by the investigator as unlikely related to trial product.

In the two phase 3 clinical trials (4311 and 4307), 5 non-fatal serious thrombotic events (TE) were reported as AESIs in 3 patients which occurred with the initial concizumab PPX dosing regimen (i.e., prior to the concizumab treatment pause) and led Novo Nordisk to pause treatment with concizumab in trials ongoing at the time (phase 3 trial 4311, 4307 and phase 2 trial 4255). See also section on dose-response.

After the treatment pause, no TEs or events on disseminated intravascular coagulation (DIC) or thrombotic microangiopathy (TMA) were reported in any of the clinical trials.

Evaluation of serious thromboembolic events leading to concizumab treatment pause – trial 4311 and 4310

A total of 5 serious thrombotic events were reported as AESIs in 3 patients in the two phase 3 clinical trials (4311 and 4307), leading Novo Nordisk to pause treatment with concizumab. An in-text narrative for these events is provided in Table 94**:**.

All 5 events were judged as possibly or probably related to concizumab PPX by the investigator and reported as recovered or recovering (94), except one event (Renal infarct) which was reported with outcome 'recovered/resolved with sequalae', as the patient will have ongoing scarring, secondary to the thromboembolic event, despite normal renal function.

The 5 thromboembolic events occurred within 3 months of concizumab treatment initiation. Overall medical assessment of the events revealed multiple risk factors contributing to the development of these events which were a combination of different thromboembolic risk factors and the use of high or frequent doses of breakthrough bleed treatment.

Table 48 Serious thromboembolic events leading to concizumab treatment pause - trials 4311 and 4307.

Age (years) / BMI (kg/m²)/ Haemophilia subtype	Preferred term/ Severity/Outcome/ Onset (study day[a])	Other relevant details (investigator reported)	Thromboembolic risk factors
Trial 4307/ Patient ID subject [redacted] case [redacted] concizumab PPX			
[redacted] HA	Acute myocardial infarction/ Severe/ Recovered/resolved/ 59	The patient developed myocardial infarction after 59 days of treatment with concizumab C 100 mg/mL PDS290. On the evening prior to onset of the event, the patient treated a [redacted] joint bleed with [redacted] 4500 IU (70 IU/kg) and 30 minutes later felt chest and left arm pain and measured increase in blood pressure up to 152/109, for which he took ACE inhibitor ([redacted]), [redacted] (drotaverine), [redacted] (solution of menthol in methyl ether of isovelerianic acid) and Nitroglycerin spray. The patient was hospitalised that night due to persisting pain and started treatment with [redacted] 0500 U i.v. for one day and [redacted] 125 mg and [redacted] 75 mg daily. Coronary angiography confirmed acute myocardial infarction and concizumab treatment was discontinued. Thrombectomy was performed and stent was inserted. During hospitalisation, blood tests showed normal cholesterols, however, LDL levels were 3.15mmol/L (normal range <2.6). The patient was discharged approximately 2 weeks after the procedure and the outcome was reported as 'resolved'. Within the month up to the event (exact dates unknown), the patient experienced two-three episodes of subclinical increases of blood pressure and mild chest pain episodes evaluated as weariness by the patient. No treatment was taken. Approximately 1 month prior to event onset, the patient had received prophylaxis treatment with [redacted] for 3 days due to exacerbation of chronic pulpitis), as well as [redacted] 60.6 IU/kg on multiple occasions (tooth extraction ([redacted] tooth) and removal of sutures approximately one week after surgery). Current conditions: The patient is a smoker, with [redacted] years of smoking history, 7 to 8 cigarettes per day at the time of onset of event, chronic dental pulpitis, joint arthropathy. At the screening visit, the patient displayed an elevated blood pressure (131/98 mmHg) and was referred to a cardiologist, which had not yet taken place. ECG and cholesterols were normal at screening. There was no known diabetes or family history of cardiovascular disease. Investigator-judged causality: 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 5 years • Nitroglycerine ready at home with no report on angina • Treated [redacted] joint bleed FVIII 70IU/kg on day of event
Trial 4307/ Patient ID [redacted] case [redacted] Trial 4307 [M5.3.5.1], Section 14.3.3), concizumab PPX			
[redacted] HA	1. Deep vein thrombosis/Moderate/ Recovering/resolving/86 2. Pulmonary embolism/Moderate/ Recovering/resolving/92 3. Superficial vein thrombosis/Mild/ Recovering/resolving/ 92	The patient experienced a 'deep vein thrombosis [redacted] after 86 days of concizumab C 100 mg/mL PDS290, followed by pulmonary embolism (peripheral type) and superficial thrombosis of vein on day 92. Approximately one month before the event, the patient complained about [redacted] oedema, which was considered due to the patient's BMI and [redacted] by the investigator, as D-dimer was negative and ultrasound did not show any DVT. Blood pressure had gradually increased by visit and was considered due to salty food and increase in weight. The patient complained about difficulties with injection of [redacted] and no reverse blood flow and had ultrasonography performed one month later since TE was not suspected, which found 'Right Peroneal vein (PEV). Thrombosis of fibular veins ([redacted] mb)'. There was oedema of [redacted] mb but no pain. The investigator decided to continue the trial medication and offered the patient to terminate dosing of [redacted] but the patient rejected. Approximately 1 week later (study day 92), the patient had onset of the events "median vein thrombosis [redacted] (localised in the [redacted] region where the patient had attempted repeated intravenous (IV) access without success) and also "pulmonary embolism", which was discovered due to control scan to rule out pulmonary embolism. The patient did not experience respiratory distress nor chest pain. Concizumab treatment was discontinued the same day. Approximately 1 month after discontinuation of concizumab, all 3 events were reported as recovering/resolving, as the "thrombis have shrunk or disappeared but all thrombus had not completely disappeared' and 'D-dimer was stable within normal range and no physical findings such as swelling, erythema and pain'. Current condition [redacted] oedema [redacted] Medical history: chronic hepatitis C. The patient had no history of thrombotic events or recent immobilisation. No family history of thrombophilia nor other identified thromboembolic risk factors and no smoking. With the exception of 3 days, the patient had continued using [redacted] 41 IU/kg) daily during the trial and up until event onset (day 92). Investigator-judged causality: Probable (all 3 events).	• Obesity • [redacted] oedema since 2018 • 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)
Trial 4311/Patient ID [redacted] case [redacted] Trial 4311 [M5.3.5.1], Section 14.3.3), concizumab PPX			
[redacted] HBwI	Renal infarct/Severe/ Recovered/ Resolved with sequelae/21	On study day 18, the patient had a wrist bleed treated with novoseven® (89-130 µg/kg/8hrs). Three days after (21 days after initiating treatment with concizumab PPX), the patient felt pain in the right side of his abdomen and was admitted to hospital the following day. CT scan indicated differential diagnoses of potential infection, scarring or renal infarct at the superior pole of the right kidney and renal nuclear DMSA scan and SPECT imaging showed right kidney upper pole 'scarring'. Echocardiogram and urinanalysis showed no abnormalities and urine culture was negative. Follow-up Nuclear Medicine Kidney Function GFR was normal. After a duration of 205 days, the outcome for the event was 'recovered with sequelae'. Sequelae was reported as the patient will have ongoing scarring secondary to thrombosis event, however, renal function is normal. Current conditions: Haemophilia B, Prader Willi Syndrome, developmental delay, anaphylaxis (to factor IX), obesity, fatty liver, hypercholesterolemia. Medical history: Haematuria in 2013 and 2014, pineal tumour, cholecystectomy, radiosynovectomy of right elbow, Growth Hormone Deficiency, pineal region tumour suboccipital craniotomy, cholelithiasis, multiple removal/replacements of CVAD (due to history of infection or malfunctioning port a cath). Historically, the patient had an annual bleeding rate of >30, which was treated by novoseven® (eptacog alfa (activated)) on demand. Investigator-judged causality: Possible	• Possible/potential renal infarct prior to trial entry was assessed (not confirmed)[b] • Obesity (Prader Willi Syndrome) • NovoSeven for wrist 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"

Notes: aStudy day is calculated based on the treatment start date; bThe Novo Nordisk safety committee requested expert advice from an external radiologist (ICON, Ireland) for adjudication of the reported event of pyelonephritis/infarction/scarring and all relevant imaging was sent from the site to ICON. Initially, based on ICON's review and comparison of historical CT scans to CT scan performed after onset of renal infarct, an indication of an evolving right renal upper pole cortical infarction was observed. However, as confirmation of the date for one of the historical CT scans was not possible, the possible/potential renal infarct prior to trial entry that was assessed was not confirmed. Based on the available information the investigations were finalised as inconclusive. Patient age and BMI are reported at baseline. Abbreviations: ACE: angiotensin-converting enzyme; BMI: body mass index; CVAD: central venous access devices; ECG: electrocardiogram; FVIII: coagulation factor VIII; HA: haemophilia A without inhibitors; HBwI: haemophilia B with inhibitors; LDL: low density lipoprotein; PPX: prophylaxis.

Thromboembolic risk factors were present in approximately 20% of patients across all haemophilia subtypes at baseline with no apparent differences nor clustering of risk factors between haemophilia subtypes. The presence of thromboembolic risk factors in patients not reporting thromboembolic events supports the multi-factorial aetiology of the observed events.

During evaluation, one new event of ischemic cerebral infarction in an elderly patient with haemophilia A without inhibitors participating in trial 4307 was reported as late breaking information. The patient did not report any risk factors apart from hypertension, especially no hyperlipidemia, atrial fibrillation etc. and did therefore not present a high risk for thromboembolic events at baseline. Furthermore, the subject did not administer concomitant coagulation factor products, as was reported in the three subjects experiencing 5 thromboembolic events prior to the change in dosing recommendation. This event substantiates a possible connection between treatment with Alhemo and TEE.

Thromboembolic events with onset outside the on-treatment period (trial 4311)

Approximately 3 months after last dose of concizumab PPX (during the concizumab treatment pause), 1 patient initially allocated to concizumab PPX in trial 4311 experienced a total of 4 severe SAEs within a duration of 20 days (urinary tract obstruction, retinal vascular occlusion, vena cava thrombosis and haematoma).

Hypersensitivity reactions

Hypersensitivity reactions are a class risk for all protein-based medicinal products. Anaphylactic reactions towards therapeutic monoclonal antibodies have been reported in literature but are rare. The risk is expected to be higher with the initial administrations compared to subsequent administrations, and acute generalised hypersensitivity reactions are generally known to occur within the first few hours after administration.

The MedDRA search captured 48 events in 27 (8.4%) patients (0.1 events per PYE). Of note, 15 injection site reactions (Injection site rash [8 events] and Injection site urticaria [7 events]) were captured by the MedDRA search. These events are described under injection site reactions.

Of the 48 captured events, 21 events in 9 (2.8%) patients were assessed as possibly or probably related to concizumab PPX by the investigator. Most of these were injection site reactions (Injection site rash and Injection site urticaria). Apart from injection site reactions, the most frequently captured PT in the total safety pool was Hypersensitivity, for which 8 events were reported in 4 patients: HBwI: 5 events in 3 patients; and HA: 3 events in 1 patient. No events of Hypersensitivity were reported in the HAwI and HB groups.

Two (2) events of Hypersensitivity, reported as possibly or probably related to concizumab PPX by the investigator, led to permanent discontinuation of trial product. The applicant has evaluated that a causal relationship between concizumab and the 2 events is conceivable, as no alterative aetiology was identified. Therefore, PT Hypersensitivity is considered an ADR for concizumab.

- A teenager patient with HBwI treated with concizumab PPX (Trial 4311 PACO) experienced a severe and serious, though not life-threatening, allergic reaction (PT Hypersensitivity') on study day 39, with probable relation to concizumab PPX, including generalised erythema and generalised pruritus with skin rash, persistent dry cough, and abdominal pain, leading to hospitalisation. The patient had a medical history of hypersensitivity towards FIX and had experienced recurrent injection site reactions (urticaria) in the days leading up to the event. Treatment medications included antihistamines, corticosteroids and analgesics. The event was reported as recovered after 6 days. Immunoglobulin E-type ADA status of the

patient was assessed 5 days after onset of the event and the result was negative. However, at a follow-up visit, approximately 240 days after treatment discontinuation, anti-concizumab antibodies were detected (no titre values available). The patient had a medical history of hypersensitivity. Note, this event was counted under 'action taken to trial product: 'drug interrupted'', since the patient initially only temporarily discontinued treatment. However, the patient was later withdrawn from treatment at the discretion of the investigator, as the patient met discontinuation criterion no. 1 as per protocol (PT Hypersensitivity reaction)

- A teenager patient with HBwI treated with concizumab PPX (Trial 4311 PACO experienced a non-serious event of hypersensitivity on study day 18, with possible relation to concizumab PPX. Symptoms included blurred vision, fatigue, and headache. The event led to permanent discontinuation of trial product. Four (4) days prior to onset of 'hypersensitivity', the patient reported a non-serious 'injection site rash'. Both events were of moderate severity and reported as 'recovered' within 10 days.

Two adolescents suffering from HBwI had to stop treatment with concizumab due to hypersensitivity reactions. This proportion represents 10% of subjects between 12 and 17 years with HBwI. Overall, the incidence of hypersensitivity events was highest in HbwI with 17%, which is approximatly 2-3x the rate of the other enrolled haemophilia types.

Injection site reactions

Injection site reactions captured by the pre-defined MedDRA search were reported in an average of 23.8% of patients (range 15.4% [HAwI] to 43.4% [HBwI]) and all but 1 AE (PT Puncture site haemorrhage, judged as unlikely related to concizumab by the investigator) were non-serious and mild or moderate in severity. All but 3 injection site reactions were reported as recovered or recovering. One (1) non-serious AE of Injection site pain of moderate severity led to permanent discontinuation of trial product. One (1) non-serious AE of Injection site rash of moderate severity led to temporary discontinuation of trial product.

Patients with HBwI experienced with 43.4% the highest incidence of injections site reactions, this is two times higher than patients with HA or HB (~20%) and nearly three times higher than patients with HAwI (15.4%).

Three (3) injection site reactions reported as AEs requiring additional data collection were not captured by the MedDRA search. Two (2) of the events were probably related to concizumab PPX as judged by the investigator. All 3 events were non-serious, mild and recovered.

Collectively, the safety profile is considered comparable across haemophilia subtypes. As injection site reactions are expected for any s.c. injectable drug, including concizumab, the different reported PTs related to injection site reactions (excluding Puncture site haemorrhage) have been included in the ADR table under the grouped term 'injection site reactions'. Note these PTs exclude Puncture site haemorrhage, as the only event of Puncture site haemorrhage was reported in connection with blood sampling and judged as unlikely related to concizumab PPX by the investigator.

Medication errors

A total of 12 medication errors were reported in 10 (3.1%) patients in trials 4311, 4310, 4307 and 4159. Apart from 1 AE (Tachycardia) which was co-reported with an event of Accidental overdose (trial 4307), all medication errors with onset during the on-treatment period and reported by the investigator as AEs

requiring additional data collection (or MESI in trial 4159) were captured by the MedDRA search (Trial 4311 56wk). Seven (7) of the 12 medications occurred in patients with HAwI (5 [6.4%] patients [0.1 events per PYE]). No medication errors were reported in patients with HBwI.

Two (2) medication errors were reported in patients with HA (2 [1.6%] patients) and 3 medication errors were reported in patients with HB (3 [4.7%]).

Seven (7) of the medication errors (in 5 patients) concerned overdose (up to 105 increments [approximately 5-fold intended dose]) and the remaining AEs were 2 events in 2 patients of incorrect dose administration; 2 events in 2 patients of underdose and 1 event of accidental overdose.

- All medication errors were of mild (11 of 12 events) or moderate (1 event) severity and resolved
- 10 of 12 events were evaluated as unlikely related to concizumab by the investigator, including mild medication error (Underdose), which led to 'dose increased'.
- 1 event each of 'Overdose' and 'Incorrect dose administered' were reported as possibly and probably, respectively, related to concizumab by the investigator.
- 1 mild AE (Tachycardia) possibly related to concizumab, as judged by the investigator, was co-reported with a moderate event of Accidental overdose (judged as unlikely related to concizumab by the investigator) led to temporary discontinuation of trial product for 1 day. Both events were resolved the same day (Trial 4307).
- Except for the events mentioned above, no action to trial product were taken in relation to the remaining medication errors.

The highest dose administered in error was approximately 500% the intended dose (105 increments instead of 21 increments) and considered due to misinterpretation of the protocol. The medication error was resolved the same day and the patient continued treatment with concizumab PPX (Trial 4311 PACO). One (1) additional patient reported that he injected the drug (at a dose level 0.15 mg/kg) 5 times as there was leakage and thought that no drug was injected into the body. There were no clinical consequences due to the overdose of concizumab and the patient recovered from the event (Trial 4310-ext).

Overall, AEs related to medication errors in clinical trials with concizumab were rare and did not give rise to clinical consequences. Hence, treatment with concizumab PPX is not likely to represent an increased risk in terms of medication errors.

Increased inflammatory response

TFPI is the natural inhibitor of tissue factor which is the most potent initiator of coagulation. In addition to its role in coagulation, tissue factor is involved in a variety of coagulation-independent processes, including inflammation. In pathophysiological conditions with increased tissue factor expression, such as infection, sepsis, and crush injuries, potentiation of the inflammatory response could potentially pose a risk of adverse reactions. Based on results from animal models as well as in vivo and in vitro nonclinical toxicology studies, the primary risk related to the increased tissue factor expression is thrombosis.

A total of 10 SAEs in 10 (3.1%) patients (0.0 events per PYE) were captured by the search, including 3 serious events of COVID-19. No clustering of PTs was observed, except for the events of COVID-19; all 3 events were judged as unlikely related to concizumab PPX.

- 9 patients recovered and 1 patient died (COVID-19)

- 4 patients temporarily discontinued treatment with concizumab PPX and 1 patient permanently discontinued treatment (due to the fatal event of COVID-19)

Six (6) of 10 SAEs were mild or moderate in severity. Four (4) SAEs were severe (1 event in each haemophilia subtype), of which 1 SAE (Atypical pneumonia) was judged as possibly related to concizumab PPX by the investigator and led to discontinuation of concizumab for 41 days

The proportion of patients with SAEs captured by the NNMQ search and corresponding event rates were similar across haemophilia subtypes.

Overall, there is no indication that concizumab PPX increases the risk of inflammatory response across any of the haemophilia subtypes. Few serious events were captured by the NNMQ search and most (9 of 10 events) were judged as unlikely related to concizumab PPX by the investigator. Based on medical evaluation of the events listed, the applicant does not consider any to have a causal relationship to treatment with concizumab PPX.

Increased bleeding tendency

When the coagulation system is excessively activated, not only thrombosis, but also bleeding could potentially occur due to consumption of coagulation factors. Based on a tendency towards a decrease in fibrinogen observed in the phase 1 trial 4159, albeit mean levels of fibrinogen remained within the normal range throughout the duration of the trial, there has been focus on 'increased bleeding tendency' in clinical trials with concizumab.

No decreases in fibrinogen were observed in the two completed phase 2 trials (4310 and 4255) nor in the phase 3 trials (4311 and 4307).

Trial 4311 – phase 3 – HAwI and HBwI

Fibrinogen levels remained stable and within the reference range throughout the trial up to the 56-week cut-off (after treatment restart), with no apparent correlation with concizumab exposure for the concizumab PPX arms 2−4. The mean (SD) change from baseline to week 56 for concizumab PPX arms 2−4 was -0.54 (0.75) g/L (Trial 4311 56wk).

One event of blood fibrinogen decrease was reported in trial 4311 (Trial 4311 PACO): Patient 214073 (HAwI) experienced a nonserious AE of 'low value of fibrinogen (1.86 g/L)' on study day 195. The AE was mild in severity, evaluated as possibly related to concizumab PPX and the outcome was reported as recovered/resolved after 36 days. No actions to trial product were taken.

Trial 4307 – phase 3 – HA and HB

Fibrinogen levels remained stable and within the reference range throughout the main part of the trial (after treatment restart), with no apparent correlation with concizumab exposure for the concizumab PPX arms 2−4. The mean (SD) change from baseline to week 24 for concizumab PPX arms 2−4 was -0.47 (0.89) g/L for patients with HA and -0.30 (0.94) g/L for patients with HB (Trial 4307).

Trial 4310 – phase 2 – HAwI and HBwI

No tendency of decrease in mean fibrinogen levels was observed in trial 4310. Mean fibrinogen levels remained stable and within the reference range throughout the full trial for patients treated with concizumab PPX. The mean (SD) change from baseline to end-of-treatment (week 76 [visit 16 LOV]) was -0.48 (0.84) g/L, with no apparent correlation with concizumab concentrations (Trial 4310-ext).

Trial 4255 – phase 2 – HA

No tendency of decrease in mean fibrinogen levels was observed in trial 4255. Mean fibrinogen levels remained stable and within the reference range throughout the full trial. The mean (SD) change from baseline to end-of-treatment (week 76 [visit 16 LOV]) was 0.19 (0.51) g/L, with no apparent correlation with concizumab concentrations (Trial 4255-ext).

One event of blood fibrinogen decrease was reported in trial 4255 (Trial 4255-ext). A non-serious AE of low value of fibrinogen was reported on study day 176 (on study day 175 fibrinogen value was 2.27 g/L vs 2.58 g/L at baseline [reference range: 2−4 g/L]). The AE was mild in severity, evaluated as probably related to concizumab PPX and the outcome was reported as recovered/resolved after 33 days. The patient had a medical history of hepatitis B and C infection. No actions to trial product were taken. Of note, the fibrinogen levels for this patient remained within normal reference range (2−4 g/L) throughout the trial.

Trial 4159 – phase 1 – HA

Fibrinogen, which is a substrate for both thrombin and plasmin, decreased approximately 20% compared to baseline levels, yet still within normal range, in both the 0.50 mg/kg and the 0.80 mg/kg dose groups and reached its nadir at the end of the dosing period (Trial).

Notice that all mean values of fibrinogen remained within normal range during the trial, and no tendency to increased bleeding was observed. Mean change from baseline to end-of-treatment (visit 13) in the concizumab PPX dose groups (0.25 mg/kg, 0.5 mg/kg and 0.80 mg/kg) were: -0.06, -0.38 and -0.60 g/L, respectively, vs -0.01 g/L in the placebo group.

Overall, in multiple-dose trials in haemophilia, no clinically significant changes in mean fibrinogen levels were observed over time.

Rare events

Rare events are a safety focus area for all drugs during clinical development to ensure that infrequent potentially drug-induced events are assessed and causality with the investigational product evaluated.

Overall, few events were captured with the search for rare events and no safety concerns were identified. Reported events were mild or moderate in severity with no apparent clustering of events across PTs or haemophilia subtypes (HAwI, HBwI, HA and HB).

Hepatic events

There is no indication that concizumab induces liver toxicity based on the evaluation of biochemical markers of liver function overall. Few AEs related to hepatic disorders were reported in the safety pool, with similar proportions of patients and corresponding event rates reporting AEs across haemophilia subtypes (HAwI, HBwI, HA and HB). Overall, most hepatic events were either unlikely related to concizumab PPX or could be explained by alternative aetiologies.

Given the patient population, many of which presented with a medical history of hepatitis B and C at screening, as also substantiated by abnormal liver parameters at baseline for several patients, fluctuations in liver parameters are expected for this population. Importantly, no clinically significant mean changes in hepatic parameters were observed over time.

Multiple patients had values of ALT and/or AST >3 x ULN or total bilirubin >2 x ULN, however no patients fulfilled the criterion for Hy's law.

Mean observations

Markers of liver function (AST, ALT, ALP and TBL) were assessed in all 5 multiple-dose trials in haemophilia at regular intervals.

No clinically significant changes from baseline were observed for any of the hepatic analytes (ALT, AST, ALP and TBL) assessed in patients with HAwI, HBwI, HA and HB in any treatment group or multiple-dose trial.

Four (4) patients each of the phase 3 trials 4311 (HAwI and HBwI) and 4307 (HA and HB) had elevated liver enzymes (ALT or AST ≥ 1.5 x ULN) at baseline.

Following an initial increase from baseline, mean ALT and AST levels in patients with elevated ALT and AST values (>1.5 x ULN), appeared to approach baseline values at week 56 (trial 4311) and week 24 (trial 4307). No clinically significant changes in mean ALT or AST in patients with normal hepatic function were observed during the trials. There was no indication of an increased risk with concizumab PPX in patients with elevated liver enzymes (ALT or AST ≥ 1.5 x ULN), based on the evaluation of AEs.

Cases of concurrent elevations of ALT or AST >3xULN with TBL >2xULN

No patients met Hy's law criterion for severe hepatotoxicity. As shown, several patients had elevated levels of AST and/or ALT, however, no patients had concurrent elevations of bilirubin >2 x ULN (Trial 4311 56wk).

A 35-year-old male (Japanese) with HBwI and a medical history of fatty liver due to alcohol, had bilirubin levels >2 x ULN (42 µmol/L) at week 48 (study day 344), ALT levels >3 x ULN (160 U/L) at week 64 (study day 456), and AST levels >5 x ULN (360 U/L and 235 U/L) at week 118 (study day 570) and week 126 (study day 624) (Trial 4310-ext). A non-serious AE (fatty liver alcoholic) was reported on study day 344 and judged as unlikely related to concizumab PPX. No action to trial product was taken and after 50 days the outcome was 'recovered'. This case was reported as meeting the Hy's law laboratory criterion in the central laboratory data base, however, did not meet the criterion for reporting of SAE due the alternative aetiology of 'fatty liver due to alcohol'.

Results from MedDRA search

As expected in this patient population, across all trials some patients had abnormal liver parameters at baseline.

Across all haemophilia subtypes, event rates for patients with hepatic events were comparable to those for the total safety pool (range 0.0 to 0.1):

No apparent clustering of events was observed in patients with HAwI, HBwI, HA or HB

In total, 9 AEs in 7 patients were possibly or probably related to concizumab PPX. Note, 4 of these events were 'Blood fibrinogen decreased' (2 AEs) and 'antithrombin III decreased' (2 AEs in the same patient). The remaining 5 possibly related hepatic events were reported in 1 patient with HA and 2 patients with HB:

- Patient (trial 4255) with HA reported 2 AEs (Elevated AST and Elevated bilirubin) on study day 179 (on study day 178 AST was 90 U/L [vs 34 U/L at baseline], and total bilirubin was 22 µmol/L [vs 12 µmol/L at baseline]). Both events were non-serious, mild in severity, judged as possibly related to concizumab PPX by the investigator and reported as resolved after 48 and 222 days, respectively. The patient had previously experienced fluctuations in AST with no AEs reported. No actions to trial product were taken

and the patient continued treatment with concizumab PPX with no additional AEs related to liver parameters reported.

- Patient (trial 4307) with HB reported an AE (AST increased) on study day 7 (visit 3a), where AST levels were 100 U/L (vs 18 U/L at baseline [visit 2a]). For all remaining visits levels of AST ranged from 16−26 U/L and were within normal range (11−36 U/L). At baseline and all subsequent visits, levels of ALT and total bilirubin were within normal range (Trial 4307). The event was reported as 'resolved' after 23 days with no actions to trial product.
- Patient (trial 4307) with HA and a current condition of Hepatitis C and HIV infection reported an AE of 'Hepatic enzyme increased' on study day 421 (week 24), where levels of ALT and AST were 74 U/L (reference range: 6−43 U/L) and 62 U/L (reference range: 11−36 U/L), respectively. The patient had levels of ALT and AST within normal range at baseline (10 U/L and 17 U/L, respectively). The patient recovered with no actions taken to trial product (Trial 4307).

Overall, there is no indication that concizumab induces liver toxicity based on the evaluation of biochemical markers of liver function overall.

Few AEs related to hepatic disorders were reported in the safety pool, with similar proportions of patients and corresponding event rates reporting AEs across haemophilia subtypes (HAwI, HbwI, HA and HB). Overall, most hepatic events were either unlikely related to concizumab PPX or could be explained by alternative aetiologies.

Given the patient population, many of which presented with a medical history of hepatitis B and C at screening, as also substantiated by abnormal liver parameters at baseline for several patients, fluctuations in liver parameters are expected for this population. Importantly, no clinically significant mean changes in hepatic parameters were observed over time.

Multiple patients had values of ALT and/or AST >3 x ULN or TBL >2 x ULN, however no patients fulfilled the criterion for Hy's law.

Like other antibodies, concizumab is cleared via catabolism and not hepatic metabolism and it is therefore unlikely that concizumab increases the risk of hepatic disorders.

Renal events

There was no increased risk of renal disorders with concizumab PPX in any of the haemophilia subtypes (HawI, HBwI, HA and HB) based on the evaluation of renal events. Three (3) of 4 renal events were non-serious, mild or moderate in severity and considered unlikely related to concizumab PPX. One (1) patient experienced a non-fatal event of Renal infarct, which contributed to the concizumab treatment pause.

Suspected transmission of an infectious agent

Overall, no events of suspected transmission of an infectious agent via trial product were reported, hence there is no indication that treatment with concizumab PPX is associated with an increased risk of transmitting infectious agents via trial product.

Adverse drug reactions

Based on cumulative data, Novo Nordisk evaluated the potential causal relationship between all AEs in the safety pool and concizumab. The evaluation of relevant ADRs was based on a thorough medical judgement including frequency of the adverse event, pharmacological plausibility, temporal relationship, confounding factors, and the expected occurrence in the background population.

The identified ADRs are considered consistent across haemophilia subtypes (HAwI, HBwI, HA and HB).

The frequencies below (Table 95**:**) are based on the safety pool. The ADRs are listed by MedDRA SOC and PT, with frequencies having been evaluated according to the following convention: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data). Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

Table 49 Adverse drug reactions in patients with HA, HB, HAwI and HBwI - safety pool (trials 4311, 4310, 4307, 4255 and 4159).

System organ class	Preferred term	Frequency (%)	Frequency grouping
Immune system disorders	Hypersensitivity	1.3%	Common
Investigations	Fibrin D dimer increased	8.8%	Common
	Prothrombin fragment 1.2 increased[a]	7.8%	Common
General disorders and administration site conditions	Injection site reactions[b]	23.8%	Very common
Skin and subcutaneous tissue disorders	Pruritis	1.9%	Common

Notes: aThis also includes the PT 'Prothrombin level increased', for which, the reported terms reflected prothrombin fragment 1.2 increased (excluding 1 of 10 patients [Patient ID:]). For details, refer to footnote 'a' to Table 2-2 (trial 4307) and Table 2-4 (trial 4255). Additionally, 1 patient (Patient ID: NN7415-4255/) who reported both PTs has only been counted once. bInjection site reactions include the preferred terms: 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, Injection site mass and Injection site inflammation. Abbreviations: HA: haemophilia A without inhibitors; HB: haemophilia B without inhibitors; HAwI: haemophilia A with inhibitors; HBwI: haemophilia B with inhibitors.

Safety from ongoing clinical trials and compassionate use

Narratives on deaths, other SAEs and AESIs from the three ongoing extensions of phase 3 trials with concizumab (trial 4311, trial 4307 and trial 4616) were extracted from the ARGUS safety database with a cut-off of 30 August 2022 and are included in this application.

After the lock of the clinical database for the 2 ongoing phase 3 trials 4311 (56-week cut-off date) and 4307 (CACO), updated information concerning SAEs (including new SAEs, i.e., reported after the data cut-off date) are only included in the safety database and not in the clinical database. There were no updates to existing information on deaths, other SAEs or AESIs reported between the safety database cut-off date and the cut-off date for the application.

In pivotal trial 4311, there were no updates to existing information on deaths, other SAEs or AESIs reported between the safety database cut-off date in trial 4311 (56-weeks) and the cut-off date for the application.

Further, no new deaths, or AESIs have been reported between the 56-week cut-off and cut-off date for this application.

A total of 4 SAEs in 4 patients treated with concizumab PPX were reported in trial 4311 after the 56-week cut-off date (PTs: Carpal tunnel syndrome; Laryngeal haematoma; Renal impairment and Haematuria), of which 3 of these SAEs (in 3 patients) had onset after the 56-week safety database cut-off date. The event of Haematuria was severe and remaining events were mild or moderate in severity. All SAEs were judged as unlikely related to concizumab, except for the event of Renal impairment which was judged by the investigator as possibly related to concizumab. The SAE of Laryngeal haematoma was recovering, while the remaining events were reported as 'not recovered'.

Also in trial 4307, no new deaths, or AESIs have been reported between the CACO and the cut-off date for this application.

A total of 4 SAEs in 4 patients treated with concizumab PPX were reported in trial 4307 after the CACO (by PT: 2 SAEs of Renal haematoma; Ligament sprain; and Acute abdomen). The event of Ligament sprain was moderate in severity and the 3 remaining events were severe. All 4 events were judged as unlikely related to concizumab by the investigator. One (1) event of Ligament sprain and the event of Acute abdomen were reported as 'not recovered', whereas the 2 remaining events were reported as 'recovered'.

Trial 4616 is an interventional, multi-national, multi-centre, open-label, non-randomised study with 2 arms. Arm 1 includes concizumab-naïve patients below 12 years of age at the time of consent/assent. Arm 2 includes patients previously treated with concizumab via compassionate use, either on an individual patient basis or through the concizumab compassionate use programme 4807. More information on this trial can be found in the 'efficacy section'. At the application cut-off date (30-Aug-2022), 4 patients in trial 4616 had been exposed to concizumab. No deaths, SAEs or AESIs were reported for patients in trial 4616 until the application cut-off date.

Concizumab has been provided to 14 children and adolescents (aged <18 years) with HBwI for compassionate use both on an individual patient basis and in a compassionate use programme. No deaths, other SAEs or AESIs were reported for patients receiving concizumab until the application cut-off date.

2.6.8.4. Laboratory findings

Haematology

Mean observations

By trial (trials 4311, 4310, 4307, 4255 and 4159)

The haematology parameters evaluated included erythrocytes, haemoglobin, leucocytes, thrombocytes (platelets) and differential leucocytes count (lymphocytes, monocytes, neutrophils, eosinophils and basophiles).

There were no apparent clinically relevant changes in the clinical laboratory haematology parameters in any of the multiple-dose trials in patients with haemophilia. No apparent relationship to dose was observed for the haematology parameters in trials 4310, 4255 or 4159.

Thrombocytes below the lower limit of the normal range were observed in patients treated with concizumab PPX or no PPX with HAwI and HBwI in trials 4311 and 4310 and patients with HA in trials 4307 (only patients on concizumab PPX) and 4255 and HB in trial 4307.

In trial 4311 up until 56-weeks cut-off, 5 patients on concizumab PPX had thrombocytes below the LLN at one (3 patients) or more assessments (2 patients) during the trial. None of these observations were reported as AEs. In trial 4307 until CACO, laboratory values outside the reference range were observed at 1 or more time points during the trial for all haematology parameters, with no apparent treatment differences or patterns observed.

None of these observations were reported as clinically significant (AEs) by the investigator.

Haematology related adverse events

AEs related to standard haematological clinical safety laboratory findings were reported in all 5 multiple-dose trials in haemophilia. No AEs were reported in other clinical pharmacology trials. For concizumab-treated patients in trials 4310, 4255 and 4159, there was no apparent relationship to dose in the reporting of AEs related to haematological clinical safety laboratory findings.

In pivotal trial 4311, 3 patients treated with concizumab PPX reported a total of 4 AEs (Haemoglobin decreased; Iron deficiency, Anaemia and Polycythaemia) on study day 168, 430, 819 and 715, respectively. All 4 events were mild or moderate in severity and judged as unlikely related to concizumab PPX by the investigator, except for the event of Polycythaemia, which was judged as possibly related to concizumab PPX.

The event of haemoglobin decreased was reported (as 'drop of haemoglobin on 2 mmol in 4 weeks') during the treatment pause, approximately 1.5 months after the last dose, and was serious and of moderate severity and evaluated as unlikely related to concizumab. Treatment with ferrous sulphate (oral) was initiated and after 114 days, the outcome was reported as 'recovered/ resolved'.

The event of iron deficiency was non-serious and mild in severity. The outcome was reported as not recovered/not resolved. No actions to trial product were taken.

In trial 4307, 1 patient on concizumab PPX reported an AE (iron deficiency anaemia) on study day 115. The event was non-serious, mild in severity and unlikely related to concizumab. The patient has not recovered. No action to trial product was taken.

Biochemistry

Mean observations

By trial

The biochemistry parameters evaluated included ALT, albumin, alkaline phosphatase, AST, creatinine, bilirubin (total), C-reactive protein and gamma-glutamyl transferase.

There were no apparent clinically relevant changes in the clinical laboratory biochemistry (including urinalysis) parameters in any of the multiple-dose trials in haemophilia. No apparent relationship to dose was observed for the biochemistry parameters in trials 4310, 4255 or 4159.

In trial 4311 and 4307, there were no cases that fulfilled Hy's law criteria for severe hepatotoxicity (ALT or AST >3xULN and total bilirubin >2xULN).

None of these observations were reported as clinically significant (AEs) by the investigator.

Biochemistry-related adverse events

AEs related to standard biochemistry clinical safety laboratory findings were reported in all 5 multiple-dose trials in haemophilia; however, most were related to increases in liver parameters. No AEs were reported for additional biochemical parameters in trial 4310, 4307 or 4159.

For concizumab-treated patients in trials 4310 and 4255, there was no indication of a relationship to dose in the reporting of AEs related to biochemistry clinical safety laboratory findings.

In pivotal trial 4311, 3 patients on concizumab PPX each reported 1 AE related to clinically significant abnormalities in biochemistry tests (C-reactive protein increased [1 event in 2 patients] and Blood creatinine increased). One (1) event of C-reactive protein increased was judged as possibly related to concizumab PPX, whereas the 2 remaining events were judged as unlikely related to concizumab.

All 3 events were non-serious, mild in severity, did not lead to actions to trial product and were resolved.

Coagulation-related parameters

Coagulation-related parameters were assessed in all the clinical trials and included antithrombin, D-dimers, prothrombin fragments 1+2, fibrinogen, activated partial thromboplastin time (aPTT), prothrombin time, international normalised ratio (INR) and total TFPI. Selected coagulation-related parameters (D-dimer and prothrombin fragments 1+2) were also assessed in children and adolescents with HBwI, who received concizumab via the compassionate use programme (4807).

Mean observations

By trial in haemophilia (trials 4311, 4310, 4307, 4255 and 4159)

D-dimer and prothrombin fragment 1+2

D-dimer is a recognised marker for activation of the coagulation and fibrinolysis systems, as well as an indirect marker of individual thrombotic risk. However, elevations in D-dimers are an unspecific diagnostic marker, as elevated D-dimer levels are observed in various conditions, such as thrombosis, obesity, cancer, infections, inflammatory diseases and liver disease, in addition to recent surgical procedures and advanced age.

Changes from baseline in mean D-dimer were overall comparable for patients on concizumab PPX in trials 4311 and 4310 (HAwI and HBwI) and trials 4307 (HA and HB) and 4255 (HA). Elevations in D-dimer were generally more pronounced with concizumab PPX as compared to no PPX (main part of trials 4311, 4310 and 4307) and placebo (trial 4159). However, mean levels above the normal range were observed both at baseline and/or after the treatment period for both concizumab treated patients as well as patients on no PPX (and placebo in trial 4159) in some trials.

For concizumab-treated patients in trials 4311, 4310, 4307 and 4255, increases in mean levels of fibrin D-dimer from baseline were positively correlated with concizumab concentrations, indicating the haemostatic effect of concizumab (Trial 4311 56wk; Trial 4307 and Trial 4255). In trials 4311 and 4307, this was further supported by a positive correlation between levels of D-dimers and prothrombin F1+2 (Trial 4311 56wk and Trial 4307).

For concizumab-treated patients in trials 4311, 4310, 4307 and 4255, increases in mean levels of prothrombin fragment 1+2 from baseline were positively correlated with concizumab concentrations, indicating the haemostatic effect of concizumab.

No clinically significant changes in fibrinogen were observed over time, and for concizumab treated patients in trials 4311, 4310, 4307 and 4255, fibrinogen levels were not correlated with concizumab concentrations.

Remaining coagulation parameters

Following an initial slight increase from baseline, mean levels of total TFPI appeared to reach a plateau. There were no apparent clinically relevant changes in remaining coagulation parameters (prothrombin time, INR, aPTT and antithrombin) parameters, assessed in patients with HAwI and HBwI (trials 4311 and 4310), HA (trials 4307, 4255 and 4159) and HB (trial 4307) in any of the treatment groups or trials.

Trial 4311 – up to 56-weeks cut-off

During the trial until the 56-week cut-off, fluctuations in D-dimer were observed in concizumab PPX arms 2−4. The mean (SD) change in D-dimer from baseline to week 56 for concizumab PPX arms 2−4 was 424 (1184) ng/mL.

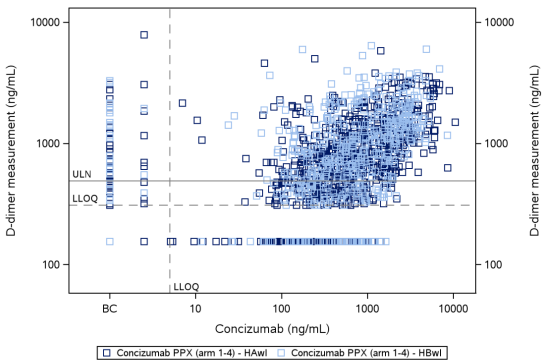
Following an initial increase from a mean (SD) baseline value of 168 (133) pmol/L, prothrombin fragments 1+2 values remained stable over time up to the 56-week cut-off for the concizumab PPX arms 2−4; mean (SD) change from baseline to week 56: 376 (454) pmol/L). Concizumab concentrations were positively correlated with D-dimer and prothrombin fragments 1+2, reflecting the haemostatic effect of concizumab (Table 96a, b).

Following an initial slight increase from baseline, mean levels of total TFPI appeared to reach a plateau up to the 56-week cut-off for the concizumab PPX arms 2−4. The mean (SD) change from baseline to week 56 in total TFPI was 71.5 (84.6) ng/mL for concizumab PPX arms 2−4.

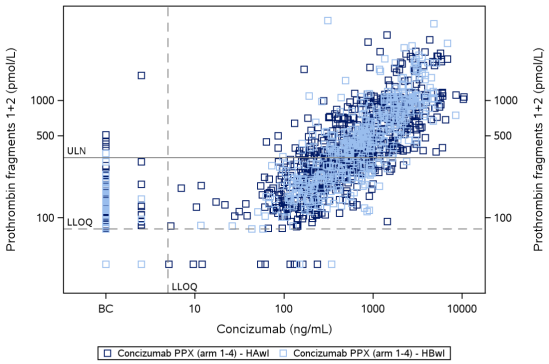
Fibrinogen levels remained stable and within the reference range throughout the trial up to the 56-week cut-off (after treatment restart), with no apparent correlation with concizumab exposure for the concizumab PPX arms 2−4 (Table 96 c).

For most coagulation related parameters, laboratory values outside the reference range were observed across treatment arms at one or more time points during the trial.

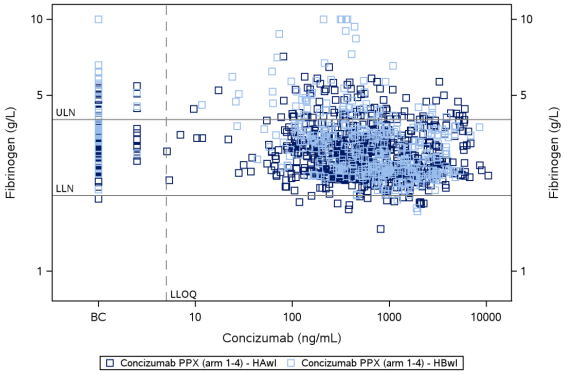
Table 50. Coagulation - D-dimer (a), prothrombin fragments 1 + 2 (b), fibrinogen (c), platelets (d) vs concizumab - scatter plot - Habibie - OTexIR - safety analysis set.



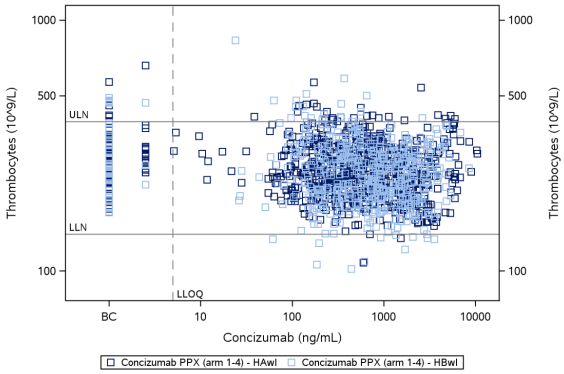
HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen, PPX: Prophylaxis.
BC: baseline measurement for concizumab arm, LLOQ: lower limit of quantification, ULN: upper limit of normal.
Observed data are presented incl measurements at all visits..
nn7415/nn7415-4311-56wks/ctr_20220930_er
11OCT2022:13:50:07 - f-cnzscattersas.sas/f-sctplotcnzddimsas.png



HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen, PPX: Prophylaxis.
BC: baseline measurement for concizumab arm, LLOQ: lower limit of quantification, ULN: upper limit of normal.
Observed data are presented incl measurements at all visits..
nn7415/nn7415-4311-56wks/ctr_20220930_er
11OCT2022:13:50:13 - f-cnzscattersas.sas/f-sctplotcnzptfragsas.png



HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen, PPX: Prophylaxis.
BC: baseline measurement for concizumab arm, LLOQ: lower limit of quantification, ULN: upper limit of normal.
Observed data are presented incl measurements at all visits..
nn7415/nn7415-4311-56wks/ctr_20220930_er
11OCT2022:13:50:16 - f-cnzscattersas.sas/f-sctplotcnzfibsas.png



HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OTexIR: On-treatment without data on initial regimen, PPX: Prophylaxis.
BC: baseline measurement for concizumab arm, LLOQ: lower limit of quantification, ULN: upper limit of normal.
Observed data are presented incl measurements at all visits..
nn7415/nn7415-4311-56wks/ctr_20220930_er
11OCT2022:13:50:18 - f-cnzscattersas.sas/f-sctplotcnzplatesas.png

By haemophilia subtype

For all haemophilia subtypes (HAwI, HBwI, HA and HB) and consistent with the by trial evaluation, concizumab concentrations were positively correlated with D-dimer and prothrombin fragments 1+2, reflecting the haemostatic effect of concizumab.

Coagulation-related parameters related adverse events

AEs related to coagulation parameters were reported in all 5 multiple-dose trials in haemophilia. Most AEs within the SOC of 'Investigations' (primarily concerning Fibrin D-dimer increased and Prothrombin fragments F1.2 increased) were judged as possibly or probably related to concizumab PPX.

In trial 4255, 1 non-serious event of 'aPTT prolonged' was reported. The event was mild in severity, judged as unlikely related to concizumab by the investigator and reported as recovered after 20 days. Additionally, 5 events of 'thrombin-antithrombin III complex increased' in 1 patient and 2 events of 'antithrombin III decreased' in 1 patient were reported in trial 4255. All were nonserious, mild in severity and judged as possibly or probably related to concizumab by the investigator. No action to trial product was taken and all events were reported with outcome 'resolved'.

Study 4311 – up to 56-weeks cut-off

Levels of D-dimer > ULN and prothrombin fragments 1+2 > 3x baseline, were observed across all concizumab PPX treatment arms. Most AEs related to abnormalities in these parameters were non-serious, of mild or moderate severity and did not lead to action to trial product.

Nine (9) patients in concizumab PPX (arms 2−4) had fibrinogen levels <LLN, however, for most patients the changes were evaluated as not clinically significant by the investigator. One patient reported a non-serious AE of low value of fibrinogen (1.86 g/L) on study day 195. The AE was mild in severity, evaluated as possibly related to concizumab PPX and the outcome was reported as recovered/resolved after 36 days. No actions to trial product were taken.

2.6.8.1. Safety in special populations

Intrinsic factors

Safety by age group

The safety pool was divided into subgroups by baseline age in adolescents (12-17 years) and adults (>18 years)

Patients in the adolescent age group were all enrolled in the pivotal trials 4311 (HAwI and HBwI) and 4307 (HA and HB), as no additional trials in the safety pool enrolled adolescents.

Adolescents (12 – 17 years)

A total of 22 adolescents with HAwI and 20 adolescents with HBwI have been exposed to concizumab, with a cumulative exposure of 54.2 PYE. This was evenly distributed across the HAwI and HBwI subgroups. In total, 21 adolescents with HA and 15 adolescents with HB have been exposed to concizumab, corresponding to 18.1 and 11.1 PYE, respectively. Two AEs in 2 patients in the adolescent age group (Hypersensitivity and Injection site pain) led to permanent discontinuation of trial product.

Adults (>18 years)

Total exposure in the adult subgroup ranged from 35.8 (HB) to 144.6 (HA) PYE across haemophilia subtypes.

A total of 6 elderly patients aged 65.0−79.0 years at baseline, have been exposed to concizumab PPX: 1 patient with HBwI and 5 patients with HA. Note, that 1 patient with HA was randomised to no PPX in the main part of trial 4307 and has therefore only been exposed to concizumab PPX in the extension part of the trial.

In the elderly age group, 30 AEs were reported in 5 of 6 patients on concizumab PPX. All were non-serious, mild or moderate in severity and did not lead to actions to trial product. A total of 10 AEs in concizumab-treated patients were reported as 'not recovered'. Six (6) non-serious possibly or probably related AEs were reported in 2 elderly patients (Injection site pruritus and Fibrin D dimer increased [same patient] and Prothrombin fragment 1.2 increased, Fibrin D dimer increased [2 events] and Cognitive disorder [same patient]). All but the event of cognitive disorder was reported as recovered, with no actions to trial product.

Comparison of age groups

Across both age subgroups, common AEs were as observed in the total safety pool. Similar event rates were observed for all commonly reported events. The proportion of adolescents with AEs was lower or comparable to that for adults.

Overall, the proportion of patients and corresponding rates for AEs were slightly lower in the adolescent vs adult age group, though comparable across age groups for severe AEs and SAEs as well as for AEs leading to discontinuation of treatment.

For both the adolescent and adult age group, the proportion of patients with AEs leading to permanent trial product discontinuation was low.

SAEs were reported across all age groups, though most were unlikely related to concizumab, as judged by the investigator and were reported as recovered.

For all age groups, SAEs were reported across several SOCs with no apparent pattern or clustering of PTs. Of note, only 1 SAE (cardiac failure) was reported in concizumab-treated patients in the elderly age group. The

event was unlikely related to concizumab as judged by the investigator, mild in severity and led to permanent discontinuation of concizumab. The patient was reported with outcome 'recovering'.

Of the 5 patients who experienced a SAE with fatal outcome, 1 patient was adolescent. The SAE with fatal outcome was Haemorrhage intracranial and judged as unlikely related to concizumab.

Safety by race

The safety pool was divided into subgroups by race in white, Asian, Black or African-American and other (American Indian, Alaska Native, 'not applicable' or 'not reported').

Overall, there were no notable differences with respect to the distribution of AEs across racial subgroups. The proportion of patients with AEs varied from 63.9% to 85.7% across racial subgroups and the rate of AEs ranged from 2.1 to 3.6 events per PYE.

For 9 of 17 patients in the 'Other' racial subgroup, race was not reported. This includes patients from France where the law prohibits the collection of information about race and ethnic origin.

In the total safety pool, cumulative exposure was highest within the White and Asian racial subgroups (266.7 and 113.2 PYE), where also the highest proportion of patients were observed. A review of the type of AEs reported (SOCs and PTs) showed no unexpected patterns in the distribution of AEs across racial subgroups treated with concizumab. Similar trends were observed as in the total safety pool.

Safety by ethnic origin

The safety pool was divided into subgroups by ethnicity in not Hispanic/Latino, Hispanic/Latino and not reported.

Overall, there were no notable differences with respect to the distribution of AEs across ethnic subgroups. Ethnicity was not reported for 8 patients in the total safety pool. The data from these patients will not be further described.

A total of 115 AEs in 14 (66.7%) patients were reported in patients of Hispanic or Latino ethnicity vs 1206 AEs in 222 (76.0%) non-Hispanic non-Latino patients.

A review of the type of AEs reported (SOCs and PTs) showed no unexpected patterns in the distribution of AEs across ethnic groups treated with concizumab. Similar trends were observed as in the total safety pool.

Safety in patients with hepatic impairment

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.

Patients were divided into subgroups based on their levels of the liver enzymes alanine aminotransferase (ALT) and aspartate aminotransferase (AST) determined at baseline and were considered to have hepatic impairment if they had elevated levels of ALT or AST (≥1.5 x upper limit of normal [ULN]).

Patients with hepatic dysfunction or severe hepatic disease (defined as ALT >3 x ULN) at screening were excluded from participation in clinical trials with concizumab. Additionally, patients with active hepatitis B and/or hepatitis C infection documented at screening were excluded from participation in trial 4159.

Overall, there were no notable differences with respect to the distribution of AEs across hepatic function group.

Few patients in the concizumab clinical development programme had elevated ALT or AST levels >1.5 x ULN at baseline and 1 patient had missing values.

Safety in patients with renal impairment

The safety pool was divided to subgroups by baseline renal function, in accordance with eGFR calculated by the central laboratory based on the CKD-EPI creatinine equation, as follows:

- Normal renal function (eGFR ≥90 mL/min per 1.73 m2)
- Reduced renal function (eGFR <90 mL/min per 1.73 m2)

As per exclusion criteria, no patients with eGFR <30mL/min per 1.73 m2 were enrolled in the phase 3 (4311 and 4307) and phase 2 (4310 and 4255) clinical trials with concizumab. Few (19 of 302; 6.3%) patients in the concizumab clinical development programme had reduced renal function, thus, results should be interpreted with caution.

There is no indication of a different safety profile of concizumab PPX between patients with reduced -and normal renal function. A review of the type of AEs reported (SOCs and PTs) showed no unexpected patterns in the distribution of AEs across renal function sub-groups treated with concizumab.

Overall, there were no notable differences with respect to the distribution of AEs across renal function groups.

Safety in patients with thromboembolic risk factors

To evaluate the safety profile of concizumab in patients with and without thromboembolic risk factors at baseline, additional MedDRA searches were performed, and selected risk factors were characterised in the trial population based on BMI, medical history and concomitant illness at baseline.

The safety pool and phase 3 (4311 and 4307) and phase 2 (4310 and 4255) trials were divided to subgroups by presence or absence of thromboembolic risk factors at baseline (yes/no).

In the phase 2 and phase 3 trials, there were no notable differences with respect to the distribution of thromboembolic risk factors at screening between the phase 2 and 3 trials in patients with HAwI, HBwI, HA and HB. Across the phase 2 and 3 trials, the proportion of patients with thromboembolic risk factors at baseline was similar in the phase 2 trials (4310 and 4255) as compared to the phase 3 trials (4311 and 4307): 18 (29.0%) patients vs 66 (22.8%) patients, respectively.

For both the phase 2 and phase 3 trials thromboembolic risk factors were spread across multiple SOCs and PTs, with the most frequently reported (≥5%) PT being Hypertension (16.1% and 14.9%, respectively).

A similar pattern was seen in the safety pool, Overall, there were no notable differences with respect to the distribution of AEs in patients with and without thromboembolic risk factors at baseline.

In the safety pool, the most frequently reported thromboembolic risk factor across all haemophilia subtypes was 'Hypertension' (SOC Vascular disorders), followed by 'BMI >35 kg/m2'. Remaining risk factors were spread across multiple SOCs and reported in 1 or 2 patients across haemophilia subtypes. Three (3) patients with thromboembolic risk factors at screening experienced serious thromboembolic events leading to the treatment pause.

However, overall, the safety of concizumab was consistent irrespective of any presence of thromboembolic risk factors at baseline. In the total safety pool, the proportion of patients with AEs and corresponding event rates were comparable between the two subgroups (thromboembolic risk factors vs no thromboembolic risk factors).

AEs were spread across multiple SOCs with similar event rates between subgroups. The pattern of AEs was overall similar between subgroups. With few exceptions, the most common AEs (>5%) were similar across subgroups and reflected the most frequently reported AEs in the total safety pool.

Table 51 Thromboembolic risk factors at screening - based on MedDRA search in medical history - by system organ class and preferred term - by haemophilia subtype - summary - HAwI, HBwI, HA and HB - safety analysis set - trials 4311, 4310, 4307, 4255 and 4159.

	HA N (%)	HB N (%)	HAwI N (%)	HBwI N (%)	HAwI + HBwI N (%)	Total N (%)
N in SAS	134	66	83	55	138	338
Thromboembolic risk factors						
Yes	31 (23.1)	14 (21.2)	17 (20.5)	14 (25.5)	31 (22.5)	76 (22.5)
No	103 (76.9)	52 (78.8)	66 (79.5)	41 (74.5)	107 (77.5)	262 (77.5)
BMI > 35 kg/m^2	5 (3.7)	4 (6.1)	1 (1.2)	6 (10.9)	7 (5.1)	16 (4.7)
Risk factors by SOC and PT						
Vascular disorders	22 (16.4)	8 (12.1)	12 (14.5)	10 (18.2)	22 (15.9)	52 (15.4)
Hypertension	22 (16.4)	7 (10.6)	12 (14.5)	10 (18.2)	22 (15.9)	51 (15.1)
Aortic stenosis	0	1 (1.5)	0	0	0	1 (0.3)
Essential hypertension	0	1 (1.5)	0	0	0	1 (0.3)
Metabolism and nutrition disorders	4 (3.0)	1 (1.5)	2 (2.4)	3 (5.5)	5 (3.6)	10 (3.0)
Type 2 diabetes mellitus	2 (1.5)	1 (1.5)	0	0	0	3 (0.9)
Hypercholesterolaemia	1 (0.7)	0	1 (1.2)	1 (1.8)	2 (1.4)	3 (0.9)
Hyperlipidaemia	1 (0.7)	1 (1.5)	0	1 (1.8)	1 (0.7)	3 (0.9)
Dyslipidaemia	1 (0.7)	0	1 (1.2)	0	1 (0.7)	2 (0.6)
Diabetes mellitus	1 (0.7)	0	0	0	0	1 (0.3)
Hypertriglyceridaemia	0	0	0	1 (1.8)	1 (0.7)	1 (0.3)
Nervous system disorders	0	1 (1.5)	3 (3.6)	0	3 (2.2)	4 (1.2)
Cerebrovascular accident	0	0	2 (2.4)	0	2 (1.4)	2 (0.6)
Haemorrhagic stroke	0	0	1 (1.2)	0	1 (0.7)	1 (0.3)
Hemiparesis	0	0	1 (1.2)	0	1 (0.7)	1 (0.3)
Vascular encephalopathy	0	1 (1.5)	0	0	0	1 (0.3)
Surgical and medical procedures	1 (0.7)	1 (1.5)	0	1 (1.8)	1 (0.7)	3 (0.9)
Central venous catheterisation	1 (0.7)	1 (1.5)	0	1 (1.8)	1 (0.7)	3 (0.9)
Catheterisation venous	0	0	0	1 (1.8)	1 (0.7)	1 (0.3)
Cardiac disorders	1 (0.7)	0	1 (1.2)	0	1 (0.7)	2 (0.6)
Atrial fibrillation	1 (0.7)	0	0	0	0	1 (0.3)
Angina pectoris	0	0	1 (1.2)	0	1 (0.7)	1 (0.3)
Investigations	2 (1.5)	0	0	0	0	2 (0.6)
Blood pressure increased	2 (1.5)	0	0	0	0	2 (0.6)
Congenital, familial and genetic disorders	1 (0.7)	0	0	0	0	1 (0.3)
Factor V Leiden mutation	1 (0.7)	0	0	0	0	1 (0.3)
Gastrointestinal disorders	0	0	0	1 (1.8)	1 (0.7)	1 (0.3)
Gastrointestinal necrosis	0	0	0	1 (1.8)	1 (0.7)	1 (0.3)
Musculoskeletal and connective tissue disorders	0	0	1 (1.2)	0	1 (0.7)	1 (0.3)
Osteonecrosis	0	0	1 (1.2)	0	1 (0.7)	1 (0.3)

Notes: MedDRA 25.0. All arms are included from the trials with multiple arms. Thus, 18 patients on no PPX (trial 4311: 6 patients; trial 4310: 1 patient and trial 4307: 5 patients) or placebo (4159: 6 patients), who were never exposed to concizumab PPX, are also included. BMI >35 kg/m^2 is included as a risk factor along with the terms captured by MedDRA. Table is sorted by system organ class and then by preferred term within system organ class, by descending frequency of number of subjects for Total column. Abbreviations: HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, N: number of subjects, SAS: safety analysis set, BMI: body mass index, %: percentage of subjects.

Extrinsic factors

No specific investigations were performed to assess whether extrinsic factors could influence the safety profile of concizumab.

Use in pregnancy and lactation

Fertility

There is no clinical experience with concizumab use and its potential effects on fertility are unknown. Women of childbearing potential are recommended to use contraception during treatment with concizumab and until 7 weeks after end of treatment.

Pregnancy

There are no available data on concizumab use in pregnant women. Animal reproduction studies have not been conducted with concizumab.

Lactation

It is not known whether concizumab is excreted in human milk. No studies have been conducted to assess the impact of concizumab on milk production or its presence in breast milk. A decision must be made whether to discontinue breast-feeding or to discontinue/abstain from concizumab therapy considering the benefit of breast-feeding for the child and the benefit of therapy for the woman.

Overdose

There is limited experience with overdose of concizumab.

The highest administered dose by error was approximately 500% the intended dose. No clinical consequences were observed based on accidental overdoses in clinical trials with concizumab.

Drug abuse

The available results on the pharmacology, nonclinical and clinical studies do not suggest any potential for drug abuse with concizumab.

Withdrawal and rebound

Based on results from clinical trials, there is no indication that patients cannot safely discontinue concizumab prophylaxis, provided adequate alternative treatment is initiated.

Effects on ability to drive or operate machinery or impairment of mental ability

No studies on the effect on the ability to drive and use machines have been performed.

Technical complaints cartridge and device

Technical complaints were reported in trials 4311, 4310, 4307 and 4255, the majority were related to the cartridge and device. The outcome of most technical complaints was either that a handling fault was verified or that the product was found normal during investigation.

Across all trials, there were 7 AEs (6 events in trial 4311 and 1 event in trial 4310) related to a technical complaint:

- In trial 4311, 6 non-serious AEs of mild severity in 5 patients were associated with technical complaints. Three (3) of these AEs (2 events of 'injection site erythema' reported in 2 patients and 1 event of 'injection site reaction') were considered possibly or probably related to concizumab by the investigator. All 6 AEs were reported as recovered/resolved and did not lead to actions to trial product
- In trial 4310, a non-serious event of 'Overdose' was related to a technical complaint. The event was considered a medication error. No clinical consequences arose from the medication error.

No AEs were reported in relation to the concizumab-ELISA investigational device in trial 4311. In trial 4307, 3 patients each reported an AE in relation to concizumab-ELISA (Injection site erythema; Injection site pain and Fibrin D-dimer increased). The 3 AEs were mild or moderate in severity and judged by the investigator as possibly or probably related to concizumab. Two (2) of the 3 AEs were reported as recovered. The event of injection site erythema was reported as 'recovering'.

2.6.8.2. Immunological events

Anti-concizumab antibodies

As is the case with any therapeutic protein, concizumab may trigger development of ADAs. Assessment for ADAs, including antibodies with *in vitro*-neutralising effects, against concizumab was done as part of the investigational use of concizumab.

Details on antibody evaluation are provided in the Integrated summary of immunogenicity, in accordance with EMA and FDA guidelines on immunogenicity assessment of therapeutic proteins

By trial (trials 4311, 4310, 4307, 4255 and 4159)

An overview of anti-concizumab antibody results by trial for the multiple-dose trials (trials 4311, 4310, 4307, 4255 and 4159) is given in the table below.

Of the 320 patients exposed to concizumab in the 5 multiple-dose trials, a total of 68 patients (21.3%) tested positive for anti-concizumab antibodies at one or more visits after first exposure to concizumab. No patients tested positive for ADAs in phase 1 trial 4159.

A total of 17 patients (5.3%) tested positive for anti-concizumab antibodies with in vitro neutralising effects.

Apart from 1 patient with medium level titres (peak titre 25,600 [with the MRD of 100 factored]) and 1 patient developing high ADA titres (peak titre 204,800 [with the MRD of 100 factored]), all ADA-positive patients had binding anti-concizumab antibody titres ranging from 100 to 6400 (with the MRD of 100 factored) (Integrated summary of immunogenicity, which are considered low titres given the high sensitivity of the binding ADA assay.

Table 52 Overview of ADA-positive patients by trial – HAwI, HBwI, HA and HB – trials 4311, 4310, 4307, 4255 and 4159 - safety analysis set.

	Trial ID					
	4159	**4255**	**4310**	**4311**	**4307**	**Total**
Number of patients exposed to concizumab	18	36	25	127	151	320
Number of ADA-negative patients[a] N (%)	18 (100)	27 (75.0)	19 (76.0)	92 (72.4)	131 (86.8)	252 (78.8)
Number of ADA-positive patients[b] N (%)	0	9 (25.0)	6 (24.0)	35 (27.6)	20 (13.2)	68 (21.3)
Number of *in vitro*-neutralising ADA-positive patients N (%)	0	1 (2.8)	3 (12.0)	8 (6.3)	5 (3.3)	17 (5.3)

Notes: aAll samples after first exposure to concizumab were negative. bOne or more samples after first exposure to concizumab were positive. Note that some patients exposed to concizumab in phase 2 continued treatment in phase 3. Patients exposed in both phases only count once in the "total" column, regardless of when they tested positive for anti-concizumab antibodies. If a patient in phase 3 only tested positive for anti-concizumab antibodies before first concizumab dose in that trial but had been exposed to concizumab already in phase 2, then the patient counts as ADA positive in the phase 3 trial. Abbreviations: ADA = Anti-concizumab antibody; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors.

By haemophilia subtype

An overview of the proportion of patients from each group testing positive for binding and in vitro-neutralising anti-concizumab antibodies is provided in the table below.

Table 53 Overview of ADA-positive patients - by haemophilia type - HAwI, HBwI, HA and HB - trials 4311, 4310, 4307, 4255 and 4159 - safety analysis set.

	Haemophilia type				
	HA	HB	HAwI	HBwI	Total
Number of patients exposed to concizumab	125	64	78	53	320
Number of ADA-negative patients[a] N (%)	103 (82.4)	58 (90.6)	54 (69.2)	37 (69.8)	252 (78.8)
Number of ADA-positive patients[b] N (%)	22 (17.6)	6 (9.4)	24 (30.8)	16 (30.2)	68 (21.3)
Number of *in vitro*-neutralising ADA-positive patients N (%)	4 (3.2)	2 (3.1)	6 (7.7)	5 (9.4)	17 (5.3)

Notes: aAll samples after first exposure to concizumab were negative. bOne or more samples after first exposure to concizumab were positive. Abbreviations: ADA = Anti-concizumab antibody; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors.

Impact of anti-concizumab antibodies on safety

The safety profile in patients testing positive for anti-concizumab antibodies at least once after first concizumab dose vs the profile in anti-concizumab antibody-negative patients was assessed based on NNMQ searches on immunogenicity-related AEs (narrow scope SMQ search 'Hypersensitivity' and NNMQ 'Injection site reactions').

Overall, there was no indication that formation of anti-concizumab antibodies impacts the safety profile of concizumab PPX.

Based on the total safety pool, 68 (21.3%) patients had at least 1 positive anti-concizumab antibody sample after first concizumab dose, and 252 (78.8%) patients were ADA negative at all sampling time points after first concizumab dose.

Based on the NNMQ searches for injection site reactions and hypersensitivity reactions, the following event rates and patient proportions were reported for the groups of anti-concizumab antibody-positive and -negative patients:

- ADA-positive patients: 82 events in 25 (36.8%) patients (0.7 events per PYE)
- ADA-negative patients: 103 events in 59 (23.4%) patients (0.3 events per PYE)

Similar types of events were reported by the groups of anti-concizumab antibody-positive and -negative patients. Furthermore, for the patients positive for anti-concizumab antibodies, there was no clustering or patterns in reporting of injection site reactions and hypersensitivity reactions in relation to when ADAs occurred.

Compassionate use with concizumab

Antibodies against concizumab were detected in 5 patients receiving concizumab via compassionate use (4 patients in the compassionate use programme and 1 patient treated on an individual patient basis). These cases are summarised below.

Of the 7 patients who received concizumab in the compassionate use programme (4807), 4 patients tested positive for anti-concizumab antibodies at 1 or 2 visits after first exposure to concizumab. Antibody titres were low (titre 200 for 3 of the patients and titre 6400 for 1 patient [with the MRD of 100 factored]). Three

(3) of the patients did not experience any immunogenicity-related AEs. The last patient tested negative for anti-concizumab antibodies at the first 3 visits and positive at visit 4 (the patient's last visit before the data cut-off) with low ADA titres (titre 200, with the MRD of 100 factored). This patient reported 6 non-serious injection site reactions from 5.5 months to 1 month prior to the positive ADA test. The AEs were 1 event of Injection site pain and 5 events of Injection site urticaria. All were mild and recovered and probably related to concizumab PPX as judged by the investigator. Of note, 4 of the 6 events were experienced in the same week as the patient tested negative for anti-concizumab antibodies (visit 3). No further AEs were reported for this patient up until the data cut-off for this submission, and the applicant assesses that the 6 reported injection site reactions are unlikely to be caused by anti-concizumab antibodies.

Of the 10 patients who were treated with concizumab on an individual patient basis, 1 patient had a single positive test for in vitro-neutralising anti-concizumab antibodies (taken 576 days after first concizumab dose) during a period where a reduced, though not absent, effect of concizumab was observed (starting from March 2021). The medical practitioner took no action to concizumab treatment, based on clinical judgement, after the positive anti-concizumab antibody test, and no adverse events were reported for this patient to Novo Nordisk's safety database from March 2021 where the bleeding pattern started to worsen. It remains unclear if anti-concizumab antibodies impacted concizumab efficacy in this patient.

2.6.8.3. Safety related to drug-drug interactions and other interactions

No formal drug-drug interaction clinical studies have been performed and no interactions of concizumab with other medicinal products have been reported.

There is no evidence of clinically relevant drug-drug interactions based on *in vitro* and *ex vivo* drug-drug interaction studies performed with rFVIIa, aPCC, recombinant FVIII or recombinant FIX in blood from haemophilia patients on prophylactic treatment with concizumab. Furthermore, no adverse findings were observed after administration of three consecutive doses of up to 1 mg/kg rFVIIa to *Cynomolgus* monkeys treated with concizumab PPX.

No relevant interference of concizumab on standard prothrombin and activated partial thromboplastin time assays nor FVIII or FIX activity measurement, using clot and chromogenic assays, were observed in in vitro studies. Further, no relevant influence on assays for inhibitory antibodies to FVIII or FIX (Bethesda assay) was observed.

2.6.8.4. Discontinuation due to adverse events

By trial (trials 4311, 4310, 4307, 4255 and 4159)

Patients who experienced any of the following events were to permanently discontinue trial product: significant thromboembolic event (AESI), DIC, TMA and severe or serious hypersensitivity reaction related to concizumab.

Patients in trials 4307 and 4311 who tested positive for COVID-19 were to pause treatment with concizumab and were not restarted until the patient tested negative again or had fully recovered from COVID-19, as judged by the investigator.

AEs leading to permanent or temporary treatment discontinuation

A total of 12 AEs in 10 (3.1%) patients led to permanent discontinuation of trial product (see table below), of which 9 AEs in 7 patients were judged by the investigator as possibly or probably related to concizumab.

A total of 48 AEs in 39 (12.2%) patients) led to temporary discontinuation of trial product, of which 12 AEs in 9 patients were judged by the investigator as possibly or probably related to concizumab:

- Trial 4311:
    - 3 possibly or probably related AEs in 3 patients led to permanent discontinuation of concizumab (Congestive cardiomyopathy, Renal infarct and Hypersensitivity)
    - 5 possibly or probably related AEs in 4 patients led to temporary treatment discontinuation (Hypersensitivity [the patient never restarted treatment]; Injection site rash [the patient later permanently discontinued treatment due to the event of Hypersensitivity listed above (first bullet)]; Haematemesis and Melaena [same patient]; and Dizziness).
- Trial 4310:
    - 2 possibly or probably related AEs in 1 patient led to temporary treatment discontinuation (fibrin D-dimer increased and prothrombin level increased [reported term 'Elevated Prothrombin Fragment 1&2'])
- Trial 4307:
    - 6 possibly or probably related AEs in 4 patients led to permanent discontinuation of concizumab: Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis (same patient) and Acute myocardial infarction; Intraabdominal haemorrhage (fatal) and Injection site pain.
    - 2 possibly or probably related AEs in 2 patients led to temporary treatment discontinuation (Tachycardia and Neutropenia)
- Trial 4255:
    - 3 possibly or probably related AEs in 2 patients led to temporary treatment discontinuation (episcleritis; and prothrombin level increased and atypical pneumonia [same patient])

No patients discontinued treatment with concizumab PPX due to AEs in trial 4159.

Of the 21 possibly or probably related events in 15 patients, 5 events (in 4 patients) leading to temporary discontinuation of trial product and 6 events (in 4 patients) leading to permanent discontinuation of trial product were serious and are addressed in Section 'serious adverse events'. All SAEs were recovered or recovering, except for the events of Renal infarct and Craniocerebral injury, which were reported as 'resolved with sequelae.

Table 100: Listing of patients with AEs leading to permanent discontinuation of trial product by trial (trials 4311 and 4307) – on-treatment – safety analysis set

Patient ID	Haem type / Age / BMI	AE no.	Study day[a]/ Duration (days)	SOC / PT	Serious / Severity/ Causality	Outcome
Trial 4311						
		1	501/ 39	Cardiac disorders/ Congestive cardiomyopathy	No/ Moderate/ Possible	Recovering/ Resolving
		2	21/ 205	Renal and urinary disorders/ Renal infarct (AESI: Section 2.2.1)	Yes/ Severe/ Possible	Recovered/ Resolved with Sequelae
		2	18/ 10	Immune system disorders/ Hypersensitivity	No/ Moderate/ Possible	Recovered/ Resolved
		5	553/ 22	Infections and infestations/ COVID-19	Yes/ Severe/ Unlikely	Fatal
4307						
		1	3/48	Gastrointestinal disorders/ Intra-abdominal haemorrhage	Yes/ Severe/ Possible	Recovered/ Resolved
		4	59/15	Cardiac disorders/Acute myocardial infarction (AESI: Section 2.2.1)	Yes/ Severe/ Possible	Recovered/ Resolved
		1	25/48	Injury, poisoning and procedural complications/ Craniocerebral injury	Yes/ Severe/ Unlikely	Recovered/ Resolved with Sequelae
		3	86/63	Vascular disorders/Deep vein thrombosis (AESI: Section 2.2.1)	Yes/ Moderate/ Probable	Recovering/ Resolving
		4	92/57	Respiratory, thoracic and mediastinal disorders/ Pulmonary embolism (AESI: Section 2.2.1)	Yes/ Moderate/ Probable	Recovering/ Resolving
		5	92/57	Vascular disorders/ Superficial vein thrombosis (AESI: Section 2.2.1)	Yes/Mild/ Possible	Recovering/ Resolving
		9	644/26	Cardiac disorders/Cardiac failure	Yes/ Moderate/ Unlikely	Recovering/ Resolving
		1	1/79	General disorders and administration site conditions/ Injection site pain/	No/ Moderate/ Probable	Recovered

Notes: aStudy day is calculated based on the treatment start date. Patient age and BMI are reported at baseline in years and kg/m2, respectively. Abbreviations: AE: adverse event; BMI: body mass index; haem type: haemophilia subtype; HA: haemophilia A without inhibitors; HB: haemophilia B without inhibitors; HAwI: haemophilia A with inhibitors; HBwI: haemophilia B with inhibitors; no.: number; SOC: system organ class; PT: preferred term.

AEs leading to change in concizumab dose

Trial 4311

One (1) patient experienced 3 AEs leading to dose reductions (Fibrin D-dimer increased and Prothrombin fragment 1.2 increased [onset prior to treatment pause] and Vitreous floaters (reported as 'Myodesopsia' [onset after treatment restart]). All 3 AEs were non-serious, of mild or moderate severity and judged as probably or possibly related to concizumab. For the event of Vitreous floaters, the outcome was reported as not recovered/not resolved.

- The 2 AEs of fibrin d-dimer increased and prothrombin fragment 1+2 increased were both reported 27 days after initiation of concizumab PPX treatment (0.25 mg/kg) and led the investigator to reduce the patient's dose from 23 increments (17.25 mg) to 15 increments (11.25 mg). The patient remained on this dose until the treatment pause (approximately 1 month).
- Due to the event of vitreous floaters, the patient did not have his maintenance dose set based on exposure at the scheduled maintenance dose setting visit (visit 4.a.1.) and has since remained on concizumab PPX 0.20 mg/kg (19 increments [14.25 mg]).

An additional 2 patients experienced an AE (Injection site erythema and Synovitis) after treatment restart with action to trial product reported in the AE form as leading to 'dose increased'. However, based on available dosing information, no increases in dose seem to have occurred due to AEs.

All events leading to change in dose in trial 4311 were reported prior to the PACO.

Trial 4307

One (1) patient with HB on concizumab PPX experienced an Injection site reaction which led to a single dose reduction. The event was mild in severity and reported as resolved the same day. The prescribed maintenance dose (0.25 mg/kg) was resumed the next day.

By haemophilia subtype - safety pool

In the total safety pool, 48 (15.0%) patients discontinued treatment due to 60 AEs:

- 10 (3.1%) patients permanently discontinued trial product due to 12 AEs (0.0 AEs per PYE)
- 39 (12.2%) patients temporary discontinued trial product due to 48 AEs (0.1 AEs per PYE).

AEs leading to temporary or permanent discontinuation of trial product were reported across all haemophilia subtypes and multiple SOCs, with no trend.

2.6.8.5. Post marketing experience

Post-marketing data are not available, as concizumab is not marketed.

2.6.9. Discussion on clinical safety

Clinical safety in patients with HAwI and HBwI ≥12 years of age

The **safety database** of concizumab is primarily based on the safety results collected in the 5 multiple-dose trials in patients with haemophilia exposed to concizumab PPX (pivotal phase 3 trial 4311, phase 3 trial 4307, phase 2 trials 4310, 4255 and phase 1 trial 4159). These trials represent the majority of the exposure to concizumab PPX, and therefore this safety database can be considered acceptable.

The phase 3 trial 4311 is the 4-armed pivotal trial for the safety evaluation in the requested indication of treatment of patients with HAwI (n=76) and HBwI (n=51), in which in in arm 1 and 2 concizumab PPX is compared to no PPX, i.e. on-demand treatment. Safety results from trial 4311 are considered up until the 56-week cut-off date, including a primary analysis cut-off (PACO), when all patients had completed visit 24/32-week or withdrawn.

The 4-armed phase 3 trial 4307 concerns a supportive trial providing a safety evaluation in patients with HA (n=90) and HB (n=66) without inhibitors, in which in arm 1 and 2 concizumab PPX is compared to no PPX, i.e. on-demand treatment. Safety results from trial 4307 are considered up until the confirmatory analyses cut-off (CACO), when all patients had completed the 24/32-week visit or withdrawn.

These two trials, with randomised data of 24/32 weeks collected in arm 1 and arm 2, and longer-term data, are presented separately throughout the safety report. Of note, the trials restarted after the treatment pause with a new period of 24/32 weeks with extensions. All safety data before and after the treatment pause is included in this application.

No formal comparisons are made between the concizumab PPX trial data and the placebo or on-demand treatment trial data, due to the inherent difference in the comparators (no PPX, but on-demand treatment in trials 4310, 4311 and 4307 and placebo in trial 4159), as well as to avoid a mixture of within- and between-patient comparison due to patients switching from on-demand treatment (no PPX arm 1) to concizumab treatment (PPX arm 1) after PACO/CACO into the extension part of the trials. Based on these arguments, it can therefore be agreed that, since the comparative arm consisted of patients who were not on concizumab PPX, i.e. no treatment, but on-demand treatment to treat a spontaneous or traumatic bleeding episode, a direct comparison of safety events in this arm versus concizumab PPX is considered not contributing.

The pooled analysis approach (total safety pool), which includes all patients who had taken at least one dose of concizumab, is presented as to supplement the separate study data to increase the likelihood of detecting potential safety signals and to detect potential differences in the safety profile between haemophilia subtype group (HAwI, HBwI, HA, and HB). This approach appears acceptable as supportive safety data source, as this strategy will facilitate the identifcation of safety signals in patients with haemophilia in general by increasing the patient numbers more than twofold.

Impact of COVID-19 pandemic on the collection of data was substantial, since site visits were not possible and protocol-specified assessments were not performed. Instead, study visits have been done via telephone to collect data. Of note, 27 (16 events in trial 4311 and 19 events in trial 4307) COVID-19 infections were reported during the study periods and study treatment was paused. Since this concerns a minority of patients, it can be considered that this had no significant consequences for the available study results on safety.

The new **dosing regimen** used after the treatment pause in both phase 3 trials 4311 and 4307 (the same as included in section 4.2 of the SmPC) was lower with an initial dose of 0.20 mg/kg instead of 0.25 mg from day 2, with the possibility to increase or decrease the dose depending on the concizumab exposure level at

the week 4 visit. The dosing regimens in phase 2 trials 4255 and 4310 used a lower maintenance dosing of concizumab of 0.15 mg/kg (with the possibility to escalate the dose to 0.20 mg/kg and 0.25 mg/kg) as compared to the dose regimen applied in the phase 3 studies. Phase 1 study 4159 used 0.25, 0.50, 0.80 mg/kg every 4th day, with a total of 12 administrations. The total pooled safety data evaluation is, therefore, not entirely based on the same dose regimen applied. However, as also separate phase 3 trial safety data sets are presented, this approach can be considered acceptable.

Regarding pivotal phase 3 trial 4311 in patients with HAwI and HBwI, at PACO, 72/97 patients (74.2%) remained on the 0.20 mg/kg dose level, 24/97 patients (24.7%) increased to 0.25 mg/kg and 1/97 patient (1.0%) decreased to 0.15 mg/kg. Dose level data appeared to be generally similar at the 56 weeks cut-off with no relevant differences on dose level distribution per haemophilia subtype HAwI and HBwI.

The separate dose level data in HA and HB patients without inhibitors in phase 3 trial 4307 at CACO was considered generally similar as observed in trial 4311. Patients with HA, 54/77 (76.1%) remained on the 0.20 mg/kg dose level, 13/77 (18.3%) increased their dose to 0.25 mg/kg and 4/77 (5.6%) decreased their dose to 0.15 mg/kg. For patients with HB, 27/50 (54.0%) remained on the 0.20 mg/kg dose level, 18/50 (36.0%) increased their dose to 0.25 mg/kg and 5/50 (10.0%) decreased their dose to 0.15 mg/kg.

Regarding the **exposure**, a total of 320 patients with HAwI, HBwI, HA and HB have been exposed to at least one dose of concizumab in the clinical trials 4311, 4310, 4307, 4255 and 4159, corresponding to a total of 415 PY.

Across the phase 3 trials 4311 and 4307, 158 with HAwI (n=65), HBwI (n=38), HA (n=39) and HB (n=16) patients were exposed to concizumab for more than 12 months, and 49 patients for more than 24 months. According to the guideline ICH-E1 '*Population Exposure: The Extent of Population Exposure to Assess Clinical Safety*' 100 patients exposed for a minimum of one-year is acceptable to include as part of the safety data base at dosage levels intended for clinical use. Currently, the documented safety exposure consists of 158 patients with HAwI, HBwI, HA and HB on the recommended concizumab dosing regimen for more than 12 months of exposure and does therefore fulfil the requirements of ICH-E1. The exposure data for the populations of the claimed indications are limited to 65 patients with HAwI and 38 patients with HBwI. However, in the context of the rarity of HBwI, i.e. 330 patients world-wide, this number of patients included is reasonable and therefore considered an acceptable number of patients.

Adverse events (AEs). In pivotal phase 3 trial 4311 up until the PACO (24/32 weeks), the percentage of participants with HAwI and HBwI on concizumab PPX who reported AEs was 63% (n=80), compared to 42% (n=8) patients in the patients not in concizumab PPX. The **most frequently reported AEs** (>5%) by preferred term (PT) in the patients on concizumab PPX were arthralgia (n=13 (11.4%) patients), injection site erythema (n=9 (7.9%) patients), upper respiratory tract infection (n=8 (7 %) patients) and prothrombin fragment 1+2 increased (n=7 (6.1%) patients). Most were non-serious and of mild or moderate severity.

The AE rate was at the 56-week cut-off was consistent with that observed up until the PACO with a total of 91 (71.7%) patients who reported 467 AEs. The most frequently reported AEs (> 5%) by PT in the patients were arthralgia (13.4%), COVID-19 (11.8%), pyrexia (7.9%) and upper respiratory tract infection (7.9%).

In phase 3 trial 4307 up until the CACO, the percentage of patients with HA and HB without inhibitors who reported AEs were in the same range with 69% (n=104), as seen in trial 4311. The most frequently reported AEs (>5%) by PT on concizumab PPX were COVID-19 (13%), fibrin D-dimer increased (8%) and upper respiratory tract infection (7%).

In the safety pool, a total of 241 (75.3%) patients reported 1351 AEs. The most frequently reported AEs (>5%) by PT in patients were nasopharyngitis (11.3%), COVID-19 (10.6%), arthralgia (10.0%), headache

(9.1%), fibrin D-dimer increased (8.8%), upper respiratory tract infection (8.4%), pyrexia (7.2%), injection site erythema (5.9%) and prothrombin fragment 1.2 increased (5.3%). Overall, a similar reporting pattern was observed across haemophilia subtypes (HAwI, HBwI, HA and HB).

The **most frequently reported treatment-related AEs** (>5%) by PT in patients in the 56-weeks cut-off data of trial 4311 were injection site erythema (7.1%), prothrombin fragment 1+2 increased (5.5%) and fibrin D-dimer increased (4.7%).

In the 4307-trial data, the most frequently possibly/probably related AEs (>5%) by PT in patients were generally similar as seen in trial 4311 with injection site erythema (4.0%), injection site reaction (4.0%), prothrombin fragment 1+2 increased (6.6%) and fibrin D-dimer increased (5.3%).

The most frequently possibly/probably related AEs (>5%) in the total safety pool were consistent with commonly reported AEs. Also in these data, no relevant differences have been seen across haemophilia subtypes.

In total, 8 **deaths** have been reported, 7 patients were reported in pivotal trial 4311 (n=5 up until the PACO, n=2 new since PACO) and 1 patient (n=1 up until CACO) in the 4307 trial. Additionally, 1 patient had died at screening for study 4311. From the 7 patients, who died in pivotal trial 4311, one patient was not on concizumab PPX and two patients had not been on concizumab for the past 3 and 6 months prior to the event, respectively. Further, three patients died due to other factors, since one suffered from an alcoholic coma with a conforming medical history, one died due to COVID-19 with a high BMI and did not have any symptoms related to the study drug and one died due to multiple injuries due to a motor vehicle accident and underwent major surgery for which concizumab was expected to be stopped. The applicant judged these 6 fatal cases, therefore, as not related to the use of concizumab, which is agreed upon. The last case concerned a young old male with an intracranial haemorrhage. Since the patient has no family or personal history of an intracerebral haemorrhage and/or aneurysms, the conclusion of the applicant of no relation to study drug cannot be agreed as due to absence of background data a causal relationship with the use of concizumab cannot be ruled out. Further, in trial 4307, an adult patient with HA from Europe died, according to autopsy, due to a diffuse intraabdominal bleeding, after 9 months use of concizumab. Although the event could be related to the underlying disease, it is agreed with the applicant that a causal relationship with the use of concizumab is considered possible.

Regarding the **serious adverse events (SAEs)**, the incidence of subjects with SAEs was relatively low in the patients on concizumab PPX up until the PACO in pivotal phase 3 trial 4311. A total of 14 (12.3%) patients treated with concizumab PPX reported SAEs. In 5 of these patients, the SAEs were **possibly or probably related** to the study drug, and concerned a renal infarct, a hypersensitivity, a melaena and a haematemesis (both PTs were reported in the same patient), dizziness, and fibrin d-dimer increased and prothrombin fragment 1+2 increased (both PTs were reported in the same patient). No clear trend can be found from these data, as all reported SAEs were isolated cases, except for COVID-19, which was reported twice.

Results up until 56-week cut-off showed the same pattern of SAEs. The overall incidence of SAEs was also low with a total of 22 (17.3%) patients treated on concizumab PPX.

Results from study 4307 up until CACO were comparable, since 14 (9.3%) patients exposed to concizumab PPX reported SAEs.

As expected, the data from the safety pool demonstrated a similar safety profile, as seen in the separate phase 3 studies. In total, 45 (14.1%) patients reported SAEs. The SAEs in 10 (3.1%) patients in the safety pool were judged as possibly or probably related to concizumab PPX by the investigator. Both the proportion

of patients with possibly/probably related SAEs and SAE rates were similar across haemophilia subtypes. Most were isolated cases.

Spontaneous atraumatic retroperitoneal haematoma was reported in one young adult patient with HAwI in trial 4311 and one teenager patient with HA in trial 4307. Taken together with the three instances of intraabdominal bleeding and the fatal intracranial haemorrhage in a teenager boy, a high frequency of severe bleedings has been observed. However, several confounding factors influence the causality assessment of the above-mentioned serious bleeding events, thus they cannot be attributed to treatment with concizumab with reasonable certainty.

Regarding an **update of the data from the ongoing trials**, four new SAEs in ongoing extensions of phase 3 studies 4311 and 4307 have been reported until the application cut-off date, ie. carpal tunnel syndrome, renal impairment, haematuria and laryngeal haematoma treated with eptacog alfa, which resolved. All were agreed to be unlikely related to the use of concizumab, except for the event of renal impairment which was judged by the investigator as possibly related to concizumab. Furthermore, as a late breaking information, one event of ischemic cerebral infarction in an elderly patient with haemophilia A without inhibitors participating in trial 4307 was reported. Based on updated information on the patient the event is now assessed as "unlikely related" by the investigator and the DMC due to longstanding hypertension and subsequent occlusion of pontine perforating arteries, which is accepted.

An in-depth evaluation of the following **areas of medical focus/special interest** was performed:

- As observed for other pro-coagulant compounds, there is a potential risk of thrombosis with concizumab due to exaggerated pharmacology. In total, 11 events in 6 of 320 (1.9%) patients were reported as **thromboembolic events** (TEs). All these cases occurred before the treatment pause. In 6 of the events a causal relationship with the use of concizumab PPX was considered unlikely.
  A total of 5 non-fatal serious TEs in 3 patients in the two phase 3 clinical trials (renal infarction in HBwI patient in trial 4311 and myocardial infarction (MI) and deep vein thrombosis (DVT) followed by a pulmonary embolism (PE) and superficial thrombosis in two HA patients in trial 4307), have led to the concizumab treatment pause.
  Based on the case narratives, it was noted that 2 of the 3 cases concerned arterial TEs (renal infarction in trial 4311 and MI in trial 4307) and the third case concerned venous TEs (DVT in trial 4307). In all 3 cases, concomitant coagulant treatment was used. In 2 cases this concerned on-demand treatment for a breakthrough bleeding and in 1 case this concerned continuous concomitant treatment with FVIII since trial initiation (MI in HA patient in trial 4307). Concomitant coagulant treatment may have contributed to the occurrence of the TEs, as it may be that treatment of bleeding episodes in patients receiving concizumab PPX requires less procoagulant compound, as compared to patients not receiving concizumab PPX. Further, all 3 patients had several risk factors for arterial or venous TEs. Although, the patients were on concomitant coagulant treatment and the patients had several risk factors, it can be agreed with the applicant, that based on the MoA with respect to the event, a relationship with concizumab in both cases of arterial TEs (renal infarction in HBwI patient in trial 4311 and (MI) in HA patient in trial 4307) is possible and the relationship with concizumab in the venous TEs is probable (DVT in HA patient in trial 4307), the latter since concizumab directly interferes with the venous coagulation system.
  Consequently, the treatment pause was initiated during which the applicant had revised the dose regimen with more restrictive dosing with regards to the use of breakthrough bleed treatments, i.e. recommending doses in the lower range of that advised in the WFH dosing recommendations. Further, training of investigators and patients had been implemented.

During evaluation, one new event of ischemic cerebral infarction in an elderly patient with haemophilia A without inhibitors participating in trial 4307 was observed. The patient did not report any risk factors apart from hypertension, especially no hyperlipidemia, atrial fibrillation etc. and did therefore not present a high risk for thromboembolic events at baseline. Furthermore, the subject did not administer concomitant coagulation factor products, as was reported in the three subjects experiencing 5 thromboembolic events prior to the change in dosing recommendation.
Therefore, based on the available evidence from clinical trials, especially on the 3 cases who have led to the treatment pause and the new event of ischaemic cerebral infarction, a causal relationship between concizumab PPX treatment and TEs in patients with haemophilia is considered possible. Although risk mitigation measures had been implemented and trial protocols had been updated, and although no new TEs has been reported up till data lock point, a warning in section 4.4 of the SmPC has been added on Thromboembolic events. 'Thromboembolic events' has been added in section 4.8 of the SmPC with the frequency uncommon. Furthermore, 'thromboembolic events' has been included as an important identified risk in the safety specification of the risk management plan (RMP) with an additional pharmacovigilance activities in the form of a registry-based cohort study (please see RMP).
Further, it is noted that the following exclusion criteria were employed in the phase 3 trials: 1) History of thromboembolic disease. 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. 2) 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. 3) 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.

- **Hypersensitivity reactions** are a class risk for all protein-based medicinal products and reported in 27 (8.4%) patients. In 9 (2.8%) cases were assessed as possibly or probably related to concizumab PPX by the investigator. Most concerned injection site reactions. In 2 cases, the patients were withdrawn from concizumab treatment. Hypersensitivity reactions is included as a warning in section 4.4 of the SmPC and hypersensitivity is included as an ADR in section 4.8 of the SmPC of concizumab.
- As with other drugs for injection, the s.c. administration of concizumab can lead to **injection site reactions.** These events were frequently reported in an average of 23.8% of patients using concizumab. Event rates were similar across HAwI, HBwI, HA and HB patient groups. Injection site reactions has been included as a warning in section 4.4 of the SmPC and as an ADR in section 4.8 of the SmPC.
- AEs related to **medication errors** in clinical trials with concizumab were rarely reported in 10 (3.1%) patients and did not give rise to clinical consequences. Hence, treatment with concizumab PPX is considered not likely to represent an increased risk in terms of medication errors. It can be agreed that medication errors are not considered as an ADR.
- Tissue factor is involved in a variety of coagulation-independent processes, including inflammation. A total of 10 (3.1%) patients with infections were identified, including 3 SAEs of COVID-19. Except for the COVID-19 events, the cases did not lead to a clear trend or pattern. SAEs have been presented only. The data of the non-serious AEs show the same safety profile as for the SAEs showing that there is no indication that concizumab PPX increases the risk of **inflammatory response** across any of the haemophilia subtypes. The following statement has been included in Section 4.4 of the SmPC: 'In conditions in which tissue factor is overexpressed (e.g., advanced atherosclerotic disease, crush injury,

cancer or septicaemia), there may be a risk of thromboembolic events or disseminated intravascular coagulation (DIC). In these situations, the potential benefit of treatment with concizumab should be weighed against the risk of these complications.'

- When the coagulation system is excessively activated, not only thrombosis, but also bleeding could potentially occur due to consumption of coagulation factors. No clinically significant changes in mean fibrinogen levels were observed over time in the trials. Fibrinogen levels remained within the normal range and no dose-response relationship was observed with the use of concizumab. Furthermore, the incidence of AEs concerning changes in fibrinogen were low and similar between the different haemophilia subtypes. Therefore, from these data a causal relationship of **increased bleeding tendency** with the use of concizumab could not be observed.
- Rare events are a safety focus area for all drugs during clinical development to ensure that infrequent potentially drug-induced events are assessed and causality with the investigational product evaluated. No trends or patterns could have been identified from the data search. No safety concerns were identified with respect to the evaluation of **rare events**.
- Like other antibodies, concizumab is cleared via catabolism and not hepatic metabolism and it is unlikely that concizumab increases the risk of hepatic disorders. Given the patient population, many of which presented with a medical history of hepatitis B and C at screening, with abnormal liver parameters at baseline for several patients, fluctuations in liver parameters are expected for this population. Based on the data provided on **hepatic events**, a low number of 15 (4.7%) patients reported AEs on hepatic disorders, and rates were generally similar across haemophilia subtypes. No SAEs were reported, and there were no cases reported that fulfilled Hy's law criteria for severe hepatotoxicity. In 3 patients the hepatic events were considered related to the use of concizumab by the applicant. Elevated AST and bilirubin levels in a patient with history fluctuations in AST could have played in the role in the current occurrence of the events. The second patient had only increased AST levels at one visit one week after start of study medication. The third patient suffering from hepatitis C and HIV had elevated hepatic enzymes at one visit but recovered. No significant risk on hepatic safety could be revealed by the use of concizumab, Overall, most hepatic events were either unlikely related to concizumab PPX or could be explained by alternative aetiologies.
- Like hepatic disorders, a low number of cases on **renal disorders** have been reported within the 5 studies. Three cases were non-serious AEs and concerned isolated cases of pyelonephritis, increased creatinine and renal hamartoma in different haemophilia subtypes (HAwI and HA). They were considered not related to the study drug and no specific pattern or trend could be revealed from these data.
- In accordance with current practice for the applicant a search on event related to **suspected transmission of an infectious agent via trial product** was done. No events were reported. Therefore, there is no evidence that treatment with concizumab PPX is associated with this risk.

Laboratory findings. Regarding **haematology**, no apparent clinically relevant changes in the clinical laboratory haematology parameters have been observed. Further, the number of AEs related to haematology were low and were all isolated cases.

Further, no safety signals in the abnormalities of **biochemistry** were identified.

Regarding **coagulation-related parameters**, D-dimer and prothrombin fragments 1+2 increase with the use of concizumab, which is expected, since D-dimer is a recognised marker for activation of the coagulation systems. It is, however, also an indirect marker of individual thrombotic risk. In trial 4311 data up to 56-weeks cut-off, 96% of the patients had a D-dimer >ULN with the use of concizumab, which was higher as

compared to the patients not on concizumab, i.e. 74% of patients with a D-dimer >ULN. The effect of concizumab on prothrombin fragments 1+2 was larger with 86% 3x>baseline in patients on concizumab versus 11% in patients not on concizumab. In conclusion, concizumab concentrations were positively correlated with D-dimer and prothrombin fragments 1+2, reflecting the haemostatic effect of concizumab. Fibrinogen levels remained within the normal range. This is in line with the earlier PD data on coagulation-related parameters observed in the phase 1 and 2 studies (explorer 1-5) and the data of the main parts of the phase 3 studies. Across trials, no differences in coagulation-related parameters between haemophilia subtypes could be observed. The following statement has been included in section 4.4 of the SmPC: 'Effects of concizumab on coagulation tests: Concizumab therapy does not produce clinically meaningful changes in standard measures of coagulation including activated Partial Thromboplastin Time (aPTT) and Prothrombin Time (PT).'

Regarding the **vital signs** no clinically meaningful changes have been observed in the blood pressure and pulse measurements over the duration of treatment. Regarding the physical examination no clinically meaningful changes have been observed over the duration of treatment.

Based on the non-clinical and phase 1 study findings, no **QT prolongation** was detected. Therefore, no QT prolongation potential was to be expected during the clinical phase 2 and 3 studies in a target population generally not at increased risk for arrhythmias. As expected, no abnormal findings have been reported at screening in the clinical phase 2 and 3 studies.

No trends or patterns have been observed in **special populations**. Subgroup analyses were performed for the intrinsic factors of age, race, ethnicity, hepatic and renal function groups, with and without thromboembolic risk factors. Data on these special populations are in general currently sufficiently covered in the SmPC. However, the age distribution of subjects included into the pivotal trial 4311 is skewed towards a younger population, with a median of 27 years in Arm 1, 17 years in arm 2 and 25 years overall.

No relevant information has been identified from the 5 cases of **overdose**. The potential acute symptoms and signs based on all available information, and further expected monitoring are clearly described and appropriately addressed in section 4.9 of the SmPC. Also, the the cases on technical complaints with the cartridge and device have not led to new significant patterns or trends in safety.

Regarding the **immunology events**, a total of 68/320 (21.3%) patients exposed to concizumab (total safety pool) tested positive for **anti-concizumab antibodies (ADAs)** at one or more visits after first exposure to concizumab. Of these 320 patients, a considerable number of 17 (5.3%) tested positive for ADAs with in-vitro neutralising effects, of whom 15 had low titres ranging from 100 to 6400. The applicant implied that in these 17 patients, there was no indication that formation of ADAs impacted the safety profile of concizumab PPX. Two of the 17 patients reported AEs 'contact dermatitis from tape' and 'traumatic swelling of the lower lip', which are considered unlikely related to the study drug. The following warning has been included in section 4.4 of the SmPC: 'Immunogenicity: Development of neutralising anti-concizumab antibodies, observed in some patients, has not led to loss of efficacy (see section 5.1). However, patients with clinical signs of loss of efficacy (e.g. increase in breakthrough bleeding events) should be evaluated to assess the etiology and other therapeutic options should be considered if neutralising anti-concizumab antibodies are suspected.'

When categorised by haemophilia subtype, there were more ADA-positive HAwI and HBwI patients (24/78 [30.8%] and 16/53 [30.2%], resp.) versus HA and HB patients (22/125 [17.6%] and 6/64 [9.4%0, resp.). There were also numerically more in-vitro neutralising ADA-positive HAwI and HBwI patients (n=6 [7.7%] and n=5 [9.4%], resp.) vs HA and HB patients (n=4 [3.2%] and n=2 [3.1%], resp.).

The AEs injection site reactions and hypersensitivity reactions were more reported in ADA-positive patients (25 (36.8%) patients versus in ADA-negative patients 59 (23.4%). The applicant currently appropriately addressed the findings on ADAs, the impact thereof on safety (and efficacy) in section 5.1 of the the SmPC.

The incidence of **AEs leading to discontinuations**, in the total safety pool, was low with a total of 3.1% (n=10 patients) who permanently discontinued trial product due to AEs, and 12.2% (n=39 patients) who temporary discontinued trial product due to AEs.

In trial 4311, the patients with reported AEs possibly/probably related to permanent discontinuations had congestive cardiomyopathy, renal infarct and hypersensitivity.

In trial 4307, the patients with AEs related to permanent discontinuations had DVT, MI, and intra-abdominal haemorrhage (fatal) and injection site pain. No pattern with respect to type of AE leading to permanent discontinuation of study drug could be observed. AEs leading to temporary or permanent discontinuation of trial product were reported across all haemophilia subtypes and multiple SOCs, with no trend.

2.6.10. Conclusions on the clinical safety

HAwI and HBwI patients ≥ 12 years of age

Based on the currently available data in HAwI and HBwI patients ≥ 12 years of age, concizumab appears to be generally well tolerated with only 10 (3.1%) patients, who permanently discontinued trial product due to AEs and 39 (12.2%) patients, who temporary discontinued trial product due to AEs in the safety pool during the treatment period. The most common treatment-related AEs in trial 4311 were hypersensitivity reactions including injection site erythema (7.1%), prothrombin fragment 1+2 increased (5.5%) and fibrin D-dimer increased and were of mild or moderate nature. These findings were supported by findings in trial 4307 and in the total safety pool with generally similar outcomes across the haemophilia subtypes. However, in these patients two main clinically relevant safety risks are present: the potential for thromboembolic events and the incidence of severe and sometimes fatal, bleeding events. Severe bleeding events have been reported, and 10% of all reported bleeding episodes were classified as severe. The risk of thromboembolic events and risk of serious bleeds have been appropriately reflected in the SmPC.

Children with HBwI <12 years of age

Despite taking into consideration the extreme rarity of the indication and high unmet medical need in children with HBwI <12 years of age, the available quantity and quality of paediatric safety data for concizumab are not sufficient to allow an assessment of the benefit / risk balance in this age cohort and consequently the applicant has withdrawn the intended label claim for this population.

2.7. Risk Management Plan

2.7.1. Safety concerns

Table 101: Summary of the safety specifications

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

2.7.2. Pharmacovigilance plan

Table 102: 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.

2.7.3. Risk minimisation measures

Table 103: 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 Section 4.4 of the SmPC that cases of non-fatal arterial and venous thromboembolic events have been reported in the concizumab clinical trials. These cases occurred in patients with multiple risk factors including high or frequent doses of breakthrough bleed treatment. Section 4.4 also includes a statement highlighting that caution should be exercised when the patient is at high risk of developing thromboembolic events. PL Section 2 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 Section 4.4, 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)

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

2.7.4. Conclusion

The CHMP considers that the risk management plan version 0.4 is acceptable.

2.8. Pharmacovigilance

2.8.1. Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

2.8.2. Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did request alignment of the PSUR cycle with the international birth date (IBD). The IBD is 10 March 2023. The new EURD list entry will therefore use the IBD to determine the forthcoming Data Lock Points i.e. 31 March.

2.9. Product information

2.9.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.9.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Alhemo (concizumab) is included in the additional monitoring list as it is a news active substance which, on 1 January 2011, was not contained in any medicinal product authorised in the EU.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-risk balance

3.1. Therapeutic Context

3.1.1. Disease or condition

The agreed indication: Alhemo is indicated for routine prophylaxis of bleeding in patients with:

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and of 12 years of age or more.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors and of 12 years of age or more.

3.1.2. Available therapies and unmet medical need

The current standard of care for haemophilia A and B is replacement of the missing coagulation factor via exogenous factor VIII and IX products. Factor prophylaxis has to be administered via intravenous infusion up to 3 times weekly. Newer extended half-life products have reduced infusion frequency but still require IV access. For haemophilia A, Hemlibra is an option for prophylactic treatment by a subcutaneous route of administration. In addition, for the control of spontaneous or traumatic bleeding events, on demand infusion of FVIII or FIX products are frequently necessary despite baseline prophylaxis. Recently, gene therapy treatments have been approved for both haemophilia A (Roctavian) and Haemophilia B (Hemgenix) in patients without inhibitors against factors VIII or X respectively. Marstacimab has received a positive CHMP opinion in September 2024 for routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with; severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors, or; severe haemophilia B (congenital factor IX deficiency, FIX < 1%) without factor IX inhibitors, however overall the options remain limited for patients with inhibitors.

3.1.3. Main clinical studies

Dose finding was performed in two phase 2 studies (**proof-of-concept dose-response study 4310** and **dose-response study 4255**). The initial dose regimen used in the pivotal phase 3 study 4311 in subjects with HAwI or HBwI and in the study 4307 in subjects with HA or HB was a loading dose of 1 mg/kg, followed by a daily maintenance dose of 0.25 mg/kg. This dose was based on integrated analyses of PK, PD, effect and safety data from the completed main parts of the phase 2 trials 4310 (explorer 4) and 4255 (explorer 5) and PK modelling. The clinical program was put on hold due to the occurrence of 5 thromboembolic events in 3 subjects (n=1 study 4311, n=2 study 4307).

During the treatment pause, a **new dosing regimen**, consisting of a loading dose of 1 mg/kg, followed by a lower initial daily maintenance dose of 0.20 mg/kg was developed. The new regimen was based on a re-evaluation of efficacy, safety, and PD data, and new PK/PD modelling data. As concizumab is subject to target mediated PK, with a large variation between subjects in concizumab exposure seen at a similar dose level, a dose setting step was introduced at 4 week after initiation, with an upward or downward dose titration to 0.25 or 0.15 mg/kg/day if the concizumab level was <200 or >4000 ng/ml, in order to maintain an optimal efficacy level and to prevent reaching constant high exposure levels. In addition, for treatment of mild and moderate **breakthrough bleeding episodes** that occur during concizumab treatment, new

guidance for the use of the lowest dose of factor product or bypassing agent is advised in line with the WFH guidelines.

Two phase 3 trials have been submitted within the dossier: a **pivotal study (4311, Explorer 7)** in patients with HAwI or HBwI >12 years of age, and a supportive **study 4307 (Explorer 8**) in patients with HA or HB without inhibitors >12 years of age.

Study 4311 is a 4-armed, open-label, pivotal phase 3 trial, which includes a comparison of on-demand treatment with bypassing agents (no PPX) with concizumab PPX in adult and adolescent patients with HAwI or HBwI in randomized arms 1 and 2. The main part of the study has a duration of 24-32 weeks, followed by a 128-136 week open-label, non-controlled extension treatment period, for which data have been provided at 56-week cut-off. In the randomized part, 52 subjects with HAwI or HBwI were randomized (1:2) to arm 1 on-demand treatment (n=9 for HAwI, n=10 for HBwI) or to arm 2 concizumab PPX (n=17 for HAwI, n=12 for HBwI) for a period of 24-32 weeks. In addition, 81 subjects were allocated to uncontrolled arm 3 and 4, all receiving concizumab PPX. Key inclusion criteria were patients aged ≥12 years with a diagnosis of congenital HA or HB of any severity and documented history of high-titre inhibitor (i.e. ≥5 BU), and are prescribed, or in need of, treatment with bypassing agents in the last 24 weeks prior to screening (for patients not previously enrolled in phase 2 study 4310 (Explorer 4)). Additional inclusion criteria for randomized arm 1 and 2 were participants from study 4322, or subjects previously treated on demand, with at screening ≥ 6 documented treated bleeds in the last 24 weeks or ≥ 12 treated bleeds in the last 52 weeks. Key exclusion criteria were a history of (arterial or venous) thromboembolism (TE) or considered to be at increased risk for TE, and ongoing or planned Immune Tolerance Induction treatment. The **primary efficacy endpoint** analysis consisted of demonstration of superiority of concizumab PPX over no PPX (on-demand treatment) in reduction of the number of treated spontaneous and traumatic bleeding episodes based on **annualised bleeding rate** (ABR). Sensitivity analyses to assess the impact of changes of study design during the treatment pause were performed. The **2 key secondary endpoints** evaluated the Change in SF36v2-bodily pain and SF36v2-physical functioning. **Supportive endpoints** consisted of bleeding episodes differentiated for cause, location or indication for treatment, and number of patients with zero bleeds. **Explorative endpoints** consisted of patient-related outcome (PRO) scores (SF36v2, Haem-A-Qol, Hemo-TEM) and data on physical activity (ActiGraph physical activity tracker).

Further, supportive phase 3 **study 4307**, a 4-armed, open-label study with an almost similar design was performed in subjects ≥12 years of age with congenital severe HA (FVIII <1%) and moderate/severe HB (FIX ≤2%) without inhibitors. This study includes separate randomized comparison of on-demand treatment with bypassing agents (no PPX) with concizumab PPX in adult and adolescent patients with HA and HB without inhibitors in arms 1 and 2. The concizumab dose regimen and eligibility criteria were similar as with study 4311 except for the requirement of having developed inhibitors. The **primary endpoint** analysis consisted of demonstration of superiority of concizumab PPX over no PPX (on-demand treatment) reduction of the number of treated spontaneous and traumatic bleeding episodes in patients with HA or HB on concizumab PPX (arm 2) versus no PPX (arm 1). Patients with HA and HB were analyzed separately. Sensitivity analyses to assess the impact of changes of study design during the treatment pause were performed. The **2 confirmatory secondary endpoints** for HA and HB patients were to demonstrate non-inferiority in reduction of the number of treated spontaneous and traumatic bleeding episodes of concizumab PPX versus historical ABRs obtained with standard prophylactic treatment using factor containing products from trial 4322 (NIS; explorer 6) (within-patient comparison). This **study 4322** was a non-interventional study in HA and HB patients with or without inhibitors treated according to routine clinical practice, designed to collect data on bleeding episodes over a period of at least 24 weeks for this comparison.

3.2. Favourable effects

In the pivotal **study 4311** in subjects with HAwI or HBwI, superiority for the **primary efficacy endpoint** in reduction in number of treated spontaneous and traumatic bleeding episodes of concizumab PPX over on-demand treatment over 24/32 weeks has been demonstrated:

- The estimated mean **ABR** was 1.7 (95% CI 1.0-2.87) for patients on concizumab PPX versus 11.8 (95% CI 7.03-19.86) for patients receiving on-demand treatment only.
- The estimated **ABR ratio** between patients on concizumab PPX and on-demand treatment was 0.14 (95% CI 0.07-0.29; p<0.001), corresponding to an 86% statistically significant reduction in ABR.
- The **observed reduction in ABR** relative to on-demand treatment of 86% is indicative of a clinically relevant improvement.
- The outcomes of the **sensitivity analyses** were all consistent with the primary endpoint.

Dose regimen Prior to the treatment pause the sample size was not yet reached, but after the treatment pause (lasting several months) the majority of these patients were treated with a different dose regimen and have restarted in the trial by entering a new 24/32 weeks randomized period. The high threshold level of 4000 mg/kg in relation to the 200 mg/kg minimum level has been adequately substantiated.

The treatment pause and the 2 different dose regimens have introduced uncertainties, but the positive outcome of the sensitivity analyses and supplement analyses testing the impact of the treatment pause are reassuring that the obtained data can be considered sufficiently robust.

The **supportive secondary outcomes** related to number of treated bleeding episodes, differentiated for cause (either spontaneous or traumatic), location (joints and target joints) and whether treatment was provided, were all consistent with the results obtained for the primary endpoint.

Assessed as an **additional analysis**, the proportion of subjects with zero bleeding episodes for subjects on concizumab PPX as compared with on-demand treatment was 63.6% versus 10.56%, further supporting the efficacy of concizumab in prevention of bleeding events.

Regarding **haemostatic medication for breakthrough bleeding events**, most frequently used was rFVIIa, in 15/33 subjects on concizumab PPX and 13/19 subjects on on-demand treatment. For rFVIIa, the number of injections to treat the bleed was comparable for the concizumab PPX group (arm 2) and the on demand group (arm 1), with 45.8 vs 50.9% of bleeds requiring 1 injection, 6.8 vs 12.3% requiring 2 injections, and 47.5 vs 36.8% requiring at least 3 injections. Mean consumption of rFVII to treat a bleed was 305.3 (459.2) IU/kg for subjects on concizumab PPX (arm 2) vs 336.5 (902.2) IU/kg for subjects on on-demand treatment (arm 1). These data suggest that a similar amount of rFVII is required to treat bleeding events, regardless of the use of concizumab. However, considering the limited number of patients the variety in type of bleeding, no reliable conclusion can be drawn.

The ABR on concizumab PPX observed at 24 weeks was similar when arms 2, 3 and 4 were combined. The noted reduction in ABR was maintained during uncontrolled **long-term treatment** with concizumab PPX up to 56 weeks-cut-off. Further, in 91.8% of subjects on concizumab PPX pre-existing target joints were resolved.

For **study 4307**, the **primary endpoint** in subjects with HA and HB without inhibitors, the results were in line with the abovementioned results in study 4311. Superiority for the **primary efficacy endpoint** in reduction in number of treated spontaneous and traumatic bleeding episodes of concizumab PPX over on-

demand treatment over 24 weeks has been demonstrated, and outcome of the **sensitivity analyses** were consistent with the primary endpoint. The outcome was of similar magnitude as noted in study 4311 in patients with HAwI and HBwI, indicating that efficacy is independent of haemophilia subtype and the precent or absence of inhibitors.

Long-term data At baseline, 55 participants (49.1%) of the analysis data set reported 85 target joints. Until the 56-week cut-off, 91.8% of these target joints were resolved, compared to four patients who reported 5 newly developed target joints.

The data collected in **paediatric population with HBwI** through compassionate use programme and individual patient basis are limited, but suggested a meaningful clinical improvement in ABR in most of these subjects with high unmet medical need. In the **compassionate use programme in paediatric patients** with HbwI, the condition was rated "much improved" in 5/10 cases treated on individual base. Out of 7 subjects in study 4807 receiving concizumab PPX based on protocolized compassionate use, a reduction in ABR as compared to ABR prior to concizumab PPX was seen in 4 cases, and a similar ABR was seen in 2 cases with treatment burden of daily subcutaneous injection of PPX vs daily or alternate-daily iv administration of factor-containing products.

3.3. Uncertainties and limitations about favourable effects

Key secondary endpoints. No superiority for the key secondary endpoints of change in SF-36 v2 for the items bodily pain or physical functioning was demonstrated. However, for both items a numerical greater increase was noted in favour of concizumab, as well as greater proportions of responders at week 24. The reliability of these results is limited due to a high rate of missing values, the fact that patients were not concurrently treated, different baseline situations in arm 2 (naïve and non-naïve to the IP due to the treatment pause), and the open label design of the study.

Comparing HawI and HbwI, the estimated ABR ratio for bleeding events on concizumab PPX vs on-demand treatment, was numerically more pronounced for HAwI (0.09; 95% CI 0.0- 0.18) as compared with HBwI (0.31; 0.07- 1.36). However, the ABR on concizumab PPX is similar for HawI and HBwI, 1.6 (95% CI 0.89-2.83) and 2.2 (95% CI 0.76-6.52). The difference in ABR ratio is mainly due to a lower ABR for HBwi in the on-demand group. The study was not powered to determine the effect of concizumab in both haemophilia subgroups separately. In Study 4307 in patients with HA and HB inhibitors, no difference was noted in ABR ratio.

Advice on actions to be taken regarding monitoring or dose interruption during surgery or other intercurrent conditions in which tissue factor is overexpressed (like septicaemia) or ITI provided is based on limited data. This is reflected in the SmPC in which Section 4.2 states that as there is limited clinical experience in using Alhemo concizumab during major surgeries, it is generally recommended to pause concizumab at least 4 days prior to a elective major surgery. Concizumab therapy can be resumed 10-14 days after surgery on the same maintenance dose without a new loading dose, considering the overall clinical picture of the patient.

Due to the low number of severe bleeding episodes, no statistical analysis related to severity of bleeding events has been conducted. Numerically, the reduction in ABR is seen for all grades of severity of bleeding episodes, though it seems to be more pronounced for mild/moderate severity than for severe bleeding events. On concizumab PPX 14/59 (23.7%) of treated bleeding events in 7 out of 33 (21.2%) subjects were classified as severe, versus 14/167 (8.4%) severe bleeding events in 5 out of 19 (26.3%) subjects on on-demand treatment.

There are no PD markers readily suitable for treatment monitoring in clinical practice.

A total of 13/278 (4.7%) patients in the phase 3 trials, was tested positive for **anti-concizumab antibodies** (ADAs) with in-vitro neutralising effects at one or more visits after first exposure to concizumab. In 2 patients with ADAs with in vitro effects, impact on PD (restoration of free TFPI back to baseline after treatment for 40 weeks) and efficacy (increased frequency of bleeding events) is considered likely. This potential effect is reported in section 4.4 and 5.1 of the SmPC.

3.4. Unfavourable effects

In general, the **exposure** to concizumab in haemophilia patients in the safety database is considered sufficient. A total of 158 patients with HAwI, HBwI, HA and HB were exposed according to the dosing recommendations in the SmPC for more than a year, across the phase 3 trials 4311 and 4307.

In the pivotal phase 3 trial 4311 up until the PACO (32 weeks), the percentage of patients with HAwI and HBwI on concizumab PPX who reported **adverse events (AEs)** was 63% (n=80) in the patients on concizumab, compared to 42% (n=8) patients not on concizumab PPX. The **most frequently reported AEs (>5%)** by preferred term (PT) in patients on concizumab PPX were arthralgia (n=13 (11.4%) patients), injection site erythema (n=9 (7.9%) patients), upper respiratory tract infection (n=8 (7%) patients) and prothrombin fragment 1+2 increased (n=7 (6.1%) patients). Most were non-serious and of mild or moderate severity. The safety profile at the 56-week cut-off was consistent with that observed up until the PACO.
In trial 4307 up until the CACO, the percentage of patients with HA and HB without inhibitors who reported AEs was in the same range with 69% (n=104) and with similar PTs, as reported in trial 4311.
In the total safety pool, a total of 241 (75.3%) patients reported 1351 AEs. The **most frequently reported AEs (>5%**) were nasopharyngitis (11.3%), COVID-19 (10.6%), arthralgia (10.0%), headache (9.1%), fibrin D-dimer increased (8.8%), upper respiratory tract infection (8.4%), pyrexia (7.2%), injection site erythema (5.9%) and prothrombin fragment 1.2 increased (5.3%). Overall, a similar reporting pattern was observed across haemophilia subtypes.

The **most frequently reported treatment-related AEs** (>5%) in patients in the 56-weeks cut-off data of trial 4311 were injection site erythema (7.1%), prothrombin fragment 1+2 increased (5.5%) and fibrin D-dimer increased (4.7%).
In the 4307 trial and in the total safety pool data were consistent with trial 4311. Also in these data, no relevant differences have been seen across haemophilia subtypes.

In total, 8 **deaths** have been reported in the safety database, 7 patients were reported in trial 4311 (n=5 up until the PACO, n=2 new since PACO) and 1 patient (n=1 up until CACO) in trial 4307. Additionally, 1 patient had died at screening before entering study 4311.
One patient was not on concizumab PPX, two patients had not been on concizumab for the past 3 and 6 months prior to the event, respectively, and three patients had major confounding factors (alcoholic coma with a conforming medical history, COVID-19 infection with a BMI of 43, a motor vehicle accident). These 6 fatal cases were assessed as not likely related to the use of concizumab.
In 1 case, concerning a teenager HBwI male with an intracranial haemorrhage, with no family or personal history of such events, a causal relationship with the use of concizumab cannot be ruled out. A further case concerning an adult patient with HA died, according to autopsy, due to a diffuse intraabdominal bleeding, after 9 months use of concizumab is assessed as possibly related with the use of concizumab.

Regarding the **serious adverse events (SAEs)**, the incidence of subjects with SAEs was relatively low in the patients on concizumab PPX up until the PACO in trial 4311. A total of 14 (12.3%) patients reported SAEs. In 5 of these patients, the SAEs were **possibly or probably related** to the study drug, and concerned a renal infarct, a hypersensitivity, a melaena and a haematemesis (reported in same patient), dizziness, and fibrin d-dimer increased and prothrombin fragment 1+2 increased (reported in same patient). No clear pattern or further trend can be found from these data, as all reported SAEs were isolated cases, except for COVID-19, which was reported twice. Results up until 56-week cut-off showed the same pattern.
Generally, a comparable SAE profile was seen in trial 4307.
In the total safety pool, a similar pattern was shown as seen in the separate phase 3 studies. In total, 45 (14.1%) patients reported SAEs. The SAEs in 10 (3.1%) patients in the safety pool were judged as possibly or probably related to concizumab PPX by the investigator. The SAE rates were similar across haemophilia subtypes.

AE of special interest or areas of medical focus.

- In total, 11 events in 6 of 320 (1.9%) patients were reported as **thromboembolic events (TEs)**, which all had occurred before the treatment pause. A total of 5 non-fatal serious TEs in 3 patients in the two phase 3 clinical trials (renal infarction in HBwI patient in trial 4311 and myocardial infarction (MI) and deep vein thrombosis (DVT) followed by a pulmonary embolism (PE) and superficial thrombosis in two HA patients in trial 4307), have led to the concizumab treatment pause.
  Based on the case narratives, it was noted that 2 of the 3 cases concerned arterial events and the third suffered from venous thrombotic events. In all 3 cases, concomitant coagulant treatment was used. In 2 cases, this concerned on-demand treatment for a breakthrough bleeding and in 1 case the patient used continuous concomitant treatment with FVIII since trial initiation. Concomitant coagulant treatment may have contributed to the occurrence of the TEs, as it may be that treatment of bleeding episodes in patients receiving concizumab PPX requires less procoagulant compound, as compared to patients not receiving concizumab PPX. Further, all 3 patients had several risk factors for arterial or venous TEs. Although, the patients were on concomitant coagulant treatment, the patients had several risk factors, it can be agreed with the applicant, that based on the MoA with respect to the event, a relationship with concizumab in both cases of arterial TEs is possible and in the venous TEs is probable, the latter since concizumab directly interferes with the venous coagulation system.

  Late breaking information of one event of ischemic cerebral infarction in an elderly patient with haemophilia A without inhibitors participating in trial 4307 became available. The case was assessed as unlikely related to the use of concizumab as the patient suffered from longstanding hypertension and subsequent occlusion of pontine perforating arteries.

  Based on this, warnings and precautions on thromboembolic events are included in section 4.4 of the SmPC. 'Thromboembolic events' has been added in section 4.8 of the SmPC with the frequency uncommon. Furthermore, thromboembolic events has been included as an important identified risk in the safety specification of the risk management plan (RMP) with an additional pharmacovigilance activities in the form of a registry-based cohort study.

  After the treatment pause, the applicant had revised the dose regimen, and recommended a more restrictive dosing with regards to the use of breakthrough bleed treatment, with implementing a training of investigators and patients. Furthemorer, TEs are included as an ADR in section 4.8 of the SmPC and as an important identified risk in the safety specification of the risk management plan (RMP). Additional pharmacovigilance activities in the form of a registry-based cohort study are proposed.

- **Hypersensitivity reaction events** were reported in 27 (8.4%) patients. In 9 (2.8%) patients these were assessed as possibly or probably related to concizumab PPX. Most of these were injection site reactions. In 2 cases, the patients were withdrawn from concizumab treatment. Based on the class risk and the 2 drug-related hypersensitivity cases, hypersensitivity reactions was added as a warning in section 4.4 of the SmPC and it is also included as an ADR in section 4.8 of the SmPC of concizumab.
- **Injection site reactions** were frequently reported in 23.8% of patients using concizumab. Event rates were similar across haemophilia subtypes. Injection site reactions are expected for any s.c. injectable drug, including concizumab, and frequently reported within this population. Hypersensitivity reactions is included as a warning in section 4.4 of the SmPC and hypersensitivity is included as an ADR in section 4.8 of the SmPC of concizumab. Of note, the population of patients with HBwI showed the highest incidence of hypersensitivity reactions, injection site reactions, anti-drug antibodies and neutralising antibodies. 10% of adolescents had to stop treatment with concizumab due to hypersensitivity reactions.
- AEs related to **medication errors** in clinical trials with concizumab were rarely reported in 10 (3.1%) patients and did not give rise to clinical consequences.
- Also no safety concerns were identified with respect to evaluation of the SAEs of **rare events**.
- No clinically significant changes in mean **fibrinogen levels** were observed over time. Fibrinogen levels remained within the normal range and no dose relationship was observed with the use of concizumab. Further, the incidence of AEs concerning changes in fibrinogen were low and similar between the different haemophilia subtypes. Therefore, from these data a causal relationship of **increased bleeding tendency** with the use of concizumab was not observed.
- Based on the data provided on **hepatic events**, there is no indication that concizumab induces liver toxicity based on the evaluation of biochemical markers of liver function overall. A low number of 15 (4.7%) patients reported AEs on hepatic disorders, all non-serious, and rates were generally similar across haemophilia subtypes. No trend or pattern have been observed with these data. No significant effect on the risk of hepatic safety could be revealed using concizumab, and a causal relationship could therefore not be found.
- A low number of cases on **renal disorders** have been reported within the safety database. Three cases were non-serious AEs and concerned isolated cases. They were considered not related to the study drug and no specific pattern or trend could be revealed from these data.
- No events of **suspected transmission of an infectious agent** via trial product were reported. Therefore, there is no evidence that treatment with concizumab PPX is associated with this risk.

Spontaneous atraumatic retroperitoneal haematoma was reported in one young adult patient with HAwI in trial 4311 and one teenager patient with HA in trial 4307. Taken together with the three instances of intraabdominal bleeding and the fatal intracranial haemorrhage in a teenager boy, a high frequency of severe bleedings has been observed. In consequence, this has been reflected in section 4.8 of the SmPC.

Regarding the **immunology events**, 17 of 320 (5.3%) patients on concizumab were tested positive for **anti-concizumab antibodies (ADAs)** with *in-vitro* neutralising effects in the safety pool. Safety (and efficacy) information on ADAs has currently been appropriately presented in section 4.4 and 5.1 of the SmPC. The overall incidence of **AEs leading to discontinuations** in the total safety pool remained overall low with a total of 10 (3.1%) patients, who permanently discontinued trial product due to AEs and 39 (12.2%) patients, who temporary discontinued trial product due to AEs.

No trends or patterns have been observed in **special populations**, i.e. age, race, ethnicity, hepatic and renal function groups, with and without thromboembolic risk factors.

3.5. Uncertainties and limitations about unfavourable effects

Insufficient information on the presence of potential genotoxic impurities is available as the risk evaluation concerning the presence of nitrosamines impurities is incomplete.

The long-term safety profile is not yet established, since the mean (median) duration of exposure was 1.6 (1.4) years for patients with inhibitors. Additional long term safety data will be provided in the registry-based cohort study (please see RMP).

3.6. Effects table

Table 104: Effects Table for concizumab PPX for the treatment of bleeding in patients with HAwI >12 years of age and HbwI >12 years of age (data cut-off: August 2022).

Effect	Short Description	Unit	Concizumab PPX	On-demand treatment	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
Primary endpoint Baseline to week 32 (Annual Bleeding Rate)	Estimated ABR In **HAwI and HBwI**	Mean (95% CI)	1.7 (1.01, 2.87)	11.8 (7.03, 19.86)	**SoE:** • Consistent across studies [8] • Consistent in 4 sensitivity analyses • Consistent for all types of bleeding • Maintenance of effect over >56 weeks **Unc:** • Combined analysis of HAwI and HBwI patients • Only subjects ≥ 12 years of age included	[7]
		ABR ratio Mean (95%CI, p-value)	0.14 (0.06, 0.30, p<0.001)			
Key secondary endpoints Baseline to week 24	Estimated Change in SF-36v2 bodily pain score	Mean change in score (95%CI)	9.2 (5.06,13.25)	2.2 (-5.14, 9.52)	**SoE:** • Explorative endpoints SF-36v2 items, Haem-A-Qol and Hemo-TEM have shown a positive trend for concizumab PPX **Unc:** • Both key 2nd endpoints not statistically significant • High numbers of missing values • Open-label study design	[7]
		Difference at week 24 (95%CI, p-value)	6.96 (-1.64, 15.57, p=0.109)			
	Change in SF-36v2 physical functioning	Mean change in score (95%CI)	4.5 (0.77, 8.19)	1.2 (-4.76, 7.10)		
		Difference at week 24 (95%CI, p-value)	3.3 (-3.8; 10.4, p=0.347			
Primary endpoint Baseline to week 32	Estimated ABR in **HA** without inhibitors	Mean (95% CI)	2.7 (1.63-4.59)	19.3 (11.25-33.03)	**SoE:** • Consistent with [7] • Consistent in 4 sensitivity analyses • Consistent for all types of bleeding episodes • Maintenance of effect over >56 weeks **Unc:** • Only subjects >= 12 years of age included •	~~[8]~~
		Estimated ABR ratio Mean (95%CI, p-value)	0.14 (0.0- 0.29; p<0.001)			
	Estimated ABR in **HB** without inhibitors	Mean (95%CI)	3.1 (1.91-5.04)	14.8 (8.14-26.86)		
		ABR ratio Mean (95%CI, p-value)	0.21 (0.10- 0.45; p<0.001)			
Confirmative secondary endpoint	ABR vs. historical ABRs	Within-patient comparison	Concizumab PPX	PPX with Factor VIII/IX product		
	Estimated ABR for **HA**	Mean (95% CI)	5.1 (2.71, 9.65)	3.7 (2.51, 5.42)	**SoE:**	[8]

24 week prior to baseline-week 24		Estimated ABR ratio Mean (95% CI, p-value)	1.39 (0.73, 2.63)		• Within-patient comparison with PPX **Unc:** • Non-inferiority not demonstrated, sample size too small	
	Estimated ABR for **HB**	Mean (95% CI)	5.4 (2.27; 12.91)	3.1 (2.07, 4.62)	**SoE:** • Within-patient comparison with PPX **Unc:** • Non-inferiority not demonstrated, sample size too small	[8]
		Estimated ABR ratio Mean (95% CI, p-value)	1.75 (0.81, 3.78)			
Unfavourable Effects						
Thromboembolic events (TEs)	Frequency of TE AEs after treatment pause	N (%)	0 (0%)	-	**SoE:** • Similar findings in [8] • Lower as compared to TE cases before treatment pause (6/320 (1.9%)) **Unc:** • Low numbers • Maintenance of effect over >56 weeks	[9]
Anti-concizumab antibodies (ADAs)	Frequency of AEs	N of N (%)	17 of 320 (5.3%)		**Unc:** • Low numbers • Maintenance of effect over >56 weeks	TSP

Abbreviations: ABR: annualised bleeding ratio for treated spontaneous and traumatic bleeding episodes; PPX: prophylactic treatment; SOC: standard-of-care; TSP: Total safety pool; [7] Study 4311 (Explorer 7) [8] Study 4307 (Explorer 8) [9] Study 4311

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Patients aged ≥12 years of age with HAwI or HBwI

Currently, the standard of care for patients with haemophilia A or B without inhibitors is replacement therapy with FVIII or FIX products, which necessitates treatment with regular intravenous infusions every 2 to 3 days. For newer extended half-life products, IV infusion intervals every week or even every 14 days can be sufficient, and for patients with haemophilia A, a subcutaneous prophylaxis option exists with Hemlibra. Concizumab is a monoclonal humanised IgG4 anti-tissue factor pathway inhibitor (anti-TFPI) antibody. The binding of concizumab to TFPI prevents that TFPI inhibits Fxa. The increased Fxa activity prolongs the initiation phase of coagulation and allows sufficient thrombin generation for effective haemostasis. Concizumab acts independently from FVIII and FIX and the effect of concizumab is not influenced by the presence of inhibitory antibodies to FVIII or FIX. This is expected to result in a reduction of the frequency of bleeding episodes in line with its proposed mechanism of action.

The agreed indication of concizumab is as follows: Alhemo is indicated for routine prophylaxis of bleeding in patients with:

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and of 12 years of age or more.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors and of 12 years of age or more.

The application is mainly based on the results of one pivotal study 4311 in male patients aged ≥12 years, with congenital HAwI or HBwI of any severity with documented history of inhibitor (⩾0.6 BU), and at screening ≥ 6 documented treated bleeds in the last 24 weeks. Patients with a history of or considered at high risk of TEs, and patients with ongoing or planned Immuno Tolerance Induction treatment were excluded.

This patient population is representative for the target population of patients aged ≥12 years with HAwI and HBwI.

The studies were, in general, well-conducted. The investigated endpoints related to bleeding episodes are robust (please see section 5.1 of the SmPC) and PROs on health-related QoL and treatment burden although exploratory are relevant to subjects with HAwI and HBwI. The duration of the main (at least 24 weeks) and extension (56 weeks) part is considered acceptable. As the prophylactic options in HBwI are limited, and those for HAwI are not available in all countries, on-demand treatment was used as comparator, which is considered acceptable.

The phase 3 studies were put on hold due to 5 thromboembolic events in 3 subjects (1 case in study 4311 and 2 cases in study 4307), of which 2 were on treatment of a breakthrough bleeding episode and one on continuous combined use with FVIII. A warning has been added in section 4.4 of the SmPC, 'thromboembolic events' has been added in section 4.8 of the SmPC with the frequency uncommon. Furthermore, 'thromboembolic events' has been included as an important identified risk in the safety specification of the risk management plan (RMP) with an additional pharmacovigilance activity in the form of a registry-based cohort study (please see RMP).

The dosing regimen of concizumab was revised and restricted and training of investigators and patients was implemented, after which the studies were restarted with a new 24-week period followed by long-term extensions.

Results of study 4311 show a significant and clinically relevant reduction in annual bleeding rate (ABR) to 1.7 (1.01, 2.87) compared to 11.8 (7.03, 19.86) in patients with no PPX, with an estimated ABR ratio of 0.14 (95%CI 0.06, 0.30), reflecting an 86% reduction in ABR in patients receiving concizumab, compared to the ABR in patient on no PPX (on-demand treatment). The study was not powered to perform a separate analysis for HAwI and HBwI. However, the results on this primary efficacy endpoint, obtained in study 4307, reported comparable reductions in frequency of bleeding events on concizumab PPX versus on-demand treatment, with estimated ABR ratios of 0.14 (95% CI 0.07, 0.29) in subjects with HA and 0.21 (95% CI 0.10, 0.45) in subjects with HB, reflecting a reduction in annualised bleeding frequency of 86% and 79%, respectively. These results are considered robust evidence that the effect on ABR that efficacy is similar across haemophilia subtype.

There is good concordance among supportive secondary efficacy endpoints of bleeding episodes differentiated for cause (spontaneous or traumatic), location (general, joint or target joint) and indication for breakthrough bleeding treatment. Furthermore, the effect on bleeding episodes was sustained over time through 56 weeks of use with the study drug. Therefore, it can be agreed that the reduction of annualised bleeding rate for subjects with HAwI or HBwI on concizumab PPX relative to on-demand treatment, is clinically relevant in the target population ≥12 years of age, especially for patients with HBwI for which PPX options are very limited. For the key secondary endpoints of change in SF-36v2 bodily pain score and SF-36v2 physical functioning score, results showed a trend in favour of concizumab PPX, though no statistically significant effect was demonstrated. In line with the key secondary endpoints, similar positive trends were noted for exploratory endpoints on various PROs.

The clinical safety database is, in general, sufficient, as the duration of exposure for the safety evaluation was more than a year in 158 patients with HAwI, HBwI, HA and HB. The posology section of the SmPC provides adequate recommendations. Concizumab is well-tolerated, since most of the adverse events are mild to moderate in severity, without relevant differences between the haemophilia subtypes, and the discontinuations due to drug-related adverse events are low (3.1%).

3.7.2. Balance of benefits and risks

In terms of benefit, concizumab when given as prophylaxis provides a significant and clinically meaningful benefit over no prophylaxis (on demand treatment) in reduction of spontaneous and traumatic bleeding episodes in patients aged ≥12 years with HBwI and HAwI, as measured by reductions in ABR during a treatment period of at least 24 weeks. The reduction in frequency of bleeding episodes was accompanied by some suggestion of improvement in exploratory PROs on health-related and haemophilia-specific QoL. The use of concizumab appeared to be generally well tolerated with an acceptable safety profile. The main safety signals, a potential for thromboembolic events and high incidence of severe and sometimes fatal bleeds is reflected in the SmPC and pharmacovigilance activities, in the form of a registry-based cohort study (please see Section 2.7.3 and RMP).

3.7.3. Additional considerations on the benefit-risk balance

Not Applicable.

3.8. Conclusions

The overall benefit/risk balance of Alhemo is positive.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Alhemo is not similar to Alprolix, Idelvion, Roctavian, Hemgenix and Altuvoct within the meaning of Article 3 of Commission Regulation (EC) No. 847/2000. See Appendix on Similarity.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Alhemo is favourable in the following indications:

Alhemo is indicated for routine prophylaxis of bleeding in patients with:

- haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and of 12 years of age or more.
- haemophilia B (congenital factor IX deficiency) with FIX inhibitors and of 12 years of age or more.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The educational material for healthcare professionals shall include:

- The Summary of Product Characteristics.
- Guide for healthcare professionals with the following key elements:
  - Brief introduction to concizumab and the risk of thromboembolic events.
  - Guidance on the use of concizumab incl. the following information:
    - o Physicians should discuss with the patient and/or the caregiver about the dose and schedule of bypassing agents, if required while receiving concizumab prophylaxis.
    - o Caution should be exercised when the patient is at high risk of developing thromboembolic events.
    - o Patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events.
    - o In case of suspicion of thromboembolic events, 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 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 thromboembolic events.
  - Description of signs and symptoms of thromboembolic events.
  - 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 adverse events 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 thromboembolic events.
  - Contact details of the patient's concizumab prescriber.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that Concizumab is to be qualified as a new active substance in itself as it is not a constituent of a medicinal product previously authorised within the European Union.

Refer to Appendix on new active substance (NAS).

Paediatric Data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0371/2021 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.