24 July 2025
EMADOC-1700519818-2287923
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Alhemo

International non-proprietary name: Concizumab

Procedure No. EMA/VR/0000244862

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
ADR	adverse drug reaction
ADS	analysis data set
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrates
AST	aspartate aminotransferase
AUC	area under the concentration−time curve
CACO	confirmatory analyses cut-off
CFR	Code of Federal Regulations
CI	confidence interval
Cmax	maximum concentration
COVID-19	Corona virus disease 2019
CTR	clinical trial report
CV	coefficient of variation
CVAD	central venous access device
DIC	disseminated intravascular coagulation
ECG	electrocardiogram
eGFR	estimated glomerular filtration rate
EHL	extended half-life
ELISA	enzyme-linked immunosorbent assay
EMA	European Medicines Agency
EOP2	end of phase 2
EOT	end of text
FAS	full analysis set
FDA	US Food and Drug Administration
FMQ	FDA medical query
FVIIa	activated coagulation factor VII
FVIII	coagulation factor VIII
FIX	coagulation factor IX

FXa	activated coagulation factor X
GMP	good manufacturing practice
HA	haemophilia A
Haem-A-QoL	haemophilia quality of life questionnaire for adults
HAwI	haemophilia A with inhibitors
HB	haemophilia B
HBwI	haemophilia B with inhibitors
Hemo-TEM	haemophilia treatment experience measure
H-PPQ	haemophilia patient preference questionnaire
HwI	haemophilia with inhibitors
ICE	Intercurrent event
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IDE	investigational device exemption
ISI	Integrated Summary of Immunogenicity
ISTH	International Society for Thrombosis and Haemostasis
ITI	immune tolerance induction
i.v.	intravenous(-ly)
MedDRA	medical dictionary for regulatory activities
MI	multiple imputation
MRD	minimum required dilution
MRI	magnetic resonance imaging
NHF	National Hemophilia Foundation
NOAEL	no-observed-adverse-effects-level
OT	on-treatment
OTexBR	on-treatment without data before restart
OTexIR	on-treatment without data on initial regimen
OTwoATexIR	on-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens
P25/75	25th/75th percentile
PACO	primary analysis cut-off
PD	pharmacodynamic(s)
PEI	Paul-Ehrlich-Institute
PK	pharmacokinetic(s)

PMDA	Pharmaceuticals and Medical Devices Agency, Japan
PPX	prophylaxis
PRO	patient-reported outcome
PT	preferred term
PYE	patient-years of exposure
rFVIIa	recombinant activated coagulation factor VII
SAE	serious adverse event
SAP	statistical analysis plan
SAS	safety analysis set
s.c.	subcutaneous(-ly)
SD	standard deviation
SF-36v2	36-item short form health survey
SMQ	standardised MedDRA query
SOC	system organ class
TF	tissue factor
TFL	tables, figures and listings
TFPI	tissue factor pathway inhibitor
TMA	thrombotic microangiopathy
TMDD	target-mediated drug disposition
ULN	upper limit of normal range
WFH	World Federation of Hemophilia
WHO	World Health Organization

Trial nomenclature

Clinical trials conducted within the concizumab development programme as well as the compassionate use programme are identified by the project name (NN7415) followed by a 4-digit number, e.g., NN7415-4307. In this application the trials are referred to as 'trial xxxx', where 'xxxx' is the 4-digit number (e.g., trial 4307).

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, Novo Nordisk A/S submitted to the European Medicines Agency on 07 January 2025 an application for a variation.

The following changes were proposed:

Variation requested		**Type**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II

Extension of indication to include treatment of haemophilia A without inhibitors and haemophilia B without inhibitors for Alhemo based on final results from study NN7415-4307; this is an interventional study to investigate efficacy and safety of concizumab prophylaxis in patients with haemophilia A or B without inhibitors. As a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.0 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

The requested variation(s) proposed amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0358/2023 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0358/2023 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

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

Scientific advice

The MAH received Scientific Advice from the CHMP in 2019 and 2020 as follows: EMEA/H/SA/2178/3/2019/PA/III, EMEA/H/SA-2178-4-2019-PA-III, EMEA/H/SA-2178-2-FU-1-2016-PA-I, EMEA/H/SA-2178-1-FU-2-2016-PA-III, EMEA/H/SA/2178/FU/3/2020/PA/II and EMEA/H/SA/2178/1/FU/4/2020/PA/II. The Scientific Advice pertained to clinical aspects and in relation to paediatric development of the dossier.

1.2. 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

Timetable	Actual dates
Submission date	7 January 2025
Start of procedure:	26 January 2025
CHMP Rapporteur's preliminary assessment report circulated on:	20 March 2025
PRAC Rapporteur's assessment report circulated on:	25 March 2025
CHMP CoRapporteur's preliminary assessment report circulated on:	31 March 2025
PRAC Rapporteur's updated assessment report circulated on:	3 April 2025
PRAC RMP advice and assessment overview adopted by PRAC:	10 April 2025
CHMP Rapporteur's updated assessment report circulated on:	16 April 2025
Request for supplementary information and extension of timetable adopted by the CHMP on:	25 April 2025
MAH's responses submitted to the CHMP on:	21 May 2025
Re-start of procedure:	26 May 2025
CHMP Rapporteur's preliminary assessment report on the MAH's responses circulated on:	23 June 2025
CHMP Rapporteur's updated assessment report circulated on:	17 July 2025
CHMP opinion:	24 July 2025
The CHMP adopted a report on similarity of Alhemo with Alprolix, Idelvion, Roctavian, Hemgenix and Altuvoct on date	24 July 2025

2. Scientific discussion

2.1. Introduction

Concizumab is a monoclonal antibody that acts as an anti-tissue factor pathway inhibitor (TFPI). It acts independently from coagulation factor VIII (FVIII) and coagulation factor IX (FIX) in patients with haemophilia A with and without inhibitors (HAwI/HA) and haemophilia B with and without inhibitors (HBwI/HB) by enhancing the initiation phase of coagulation through increased activated coagulation factor X (FXa) production, allowing sufficient thrombin generation to prevent bleeds.

Concizumab (Alhemo) of the MAH Novo Nordisk A/S is currently registered in the EU through the centralised procedure EMEA/H/C/005938/0000 since December 2024 for the indications: 'Alhemo is indicated for routine prophylaxis of bleeding in patients 12 years of age or more with haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and haemophilia B (congenital factor IX deficiency) with FIX inhibitors.' With this application, it is proposed to extend the indication to haemophilia A and B without inhibitors.

2.1.1. Problem statement

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.

Claimed therapeutic indication

With this application, it is proposed to extend the indication as follows (new indication in bold):
'Alhemo is indicated for routine prophylaxis of bleeding in patients 12 years of age or more with:

- *haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors.*
- ***severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without FVIII inhibitors.***
- *haemophilia B (congenital factor IX deficiency) with FIX inhibitors.*
- ***moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤2%) without FIX inhibitors.'***

Epidemiology and risk factors, screening tools/prevention

Incidence

Globally, haemophilia A occurs at a rate of approximately 17.1 cases per 100,000 males. 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. According to the US Centers for Disease Control and Prevention (CDC),

approximately 400 boys are born with haemophilia A each year in the US. 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).

Haemophilia B occurs globally at an annual rate of approximately 1 in 30,000 (3.33 per 100,000) male live births and the incidence rate in the US is 5.3 per 100,000 male births. 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 haemophilia A.

Prevalence

The current worldwide population of patients with a diagnosis of haemophilia A, as determined by the World Federation of Haemophilia (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.

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 haemophilia 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). The prevalence (per 100,000 males) is 6.0 cases for severe haemophilia A, and 1.1 cases for severe haemophilia B.

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. 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.

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.

Biologic features, aetiology and pathogenesis

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 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.

Clinical presentation, diagnosis and stage/prognosis

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 2.

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 phenotypes.

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.

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. 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. 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.

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" 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.

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. 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.

Rationale for development

Concizumab is a prophylactic treatment option with a novel mode of action that improves the treatment landscape by providing an alternative convenient, safe and efficacious s.c. PPX treatment option for patients with HA and HB.

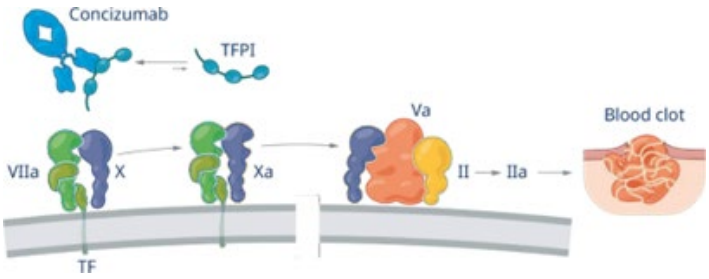
Treatment options, especially with different modes of action, are needed as individual patient pharmacokinetic and efficacy responses to treatment vary, as do patient needs and preferences.

The benefits of the S.C. delivery may include reduced risk of infections, a reduction in pain and anxiety, no collapsed veins, easier self-management, increased treatment ease and convenience as well as lower health care resource utilisation. Furthermore, it has been shown that establishing routines, such as self-administering at the same time every day, can help significantly with treatment adherence.

2.1.2. About the product

Concizumab is an anti-tissue factor pathway inhibitor (anti-TFPI) antibody. TFPI is an inhibitor of factor Xa (FXa). Concizumab binding to TFPI prevents TFPI inhibition of 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.

Figure 1: Mechanism of action



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

Alhemo is presented as a solution for injection in a pre-filled pen.

The agreed indications are (new text in bold): *'Alhemo is indicated for routine prophylaxis of bleeding in patients 12 years of age or more with:*

• *haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors.*

• ***severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without FVIII inhibitors.***

• *haemophilia B (congenital factor IX deficiency) with FIX inhibitors.*

• moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤2%) without FIX inhibitors.'

The agreed posology is:

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. The prophylactic use of factor VIII (FVIII) and factor IX (FIX) products should be discontinued two half-lives before initiating prophylaxis with concizumab. No clinical trial data are available to guide switching patients from non-replacement therapies to concizumab. A wash-out interval of approximately 5 half-lives of the prior therapy, based on the half-life specified in the respective SmPC, could be considered before initiating prophylaxis with concizumab. Haemostatic support with factor products or bypassing agents may be needed during the switch from non-factor-based products.

The recommended dosing regimen is unchanged:

- 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.
- 4 weeks after initiation of treatment: measurement of concizumab pre-dose plasma concentration by concizumab enzyme-linked immunoassay (ELISA).
- When concizumab plasma concentration result is available: individual maintenance dose is set once based on concizumab plasma concentration as indicated in the table below:

Table 2: Individual maintenance dose setting

Concizumab plasma concentration	Once daily dose concizumab
<200 ng/mL	0.25 mg/kg
200–4000 ng/mL	0.20 mg/kg
>4000 ng/mL	0.15 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.

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

2.1.3. The development programme

Overview of the concizumab clinical development programme

Per the application cut-off date of 30 September 2024, the concizumab global clinical trial programme comprises:

- Four clinical pharmacology trials (2 single dose and 2 multiple dose) (trials 33930, 3981, 3986 and 4159).
- Two phase 2 trials (1 in HA and 1 in HwI) (trials 4255 and 4310).
- One phase 3 therapeutic confirmatory trial in HA and HB (confirmatory analyses cut-off [CACO] and 56-week cut-off reached, extension ongoing) (trial 4307).

- One non-interventional study (NIS 4322) providing baseline information on details of haemophilia and physical activity 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 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 ongoing paediatric phase 3 trial including patients mainly ≤12 years with HA, HB, Haemophilia A with Inhibitors (HAwI) or Haemophilia B with Inhibitors (HBwI). Only narratives on serious adverse events (SAEs) and adverse events of special interest (AESIs) (thromboembolic events) from this trial (trial 4616) are included in the current application.

Concizumab has been provided for compassionate use (expanded access) through a compassionate use programme (4807) as well as on an individual patient basis. The compassionate use report has been updated based on an additional interim cut-off compared to the HAwI and HBwI application. A total of 27 patients with HBwI have received concizumab up to the database lock date (28 February 2024) for the interim compassionate use report.

New clinical data in the current application:

Compared to the HAwI and HBwI application, additional clinical results have become available:

- Results from one phase 3 confirmatory trial (trial 4307) in HA and HB patients. This includes results at the confirmatory analysis cut-off (CACO), 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. The results of study 4307 at the CACO were completed and included as supportive data for the authorization of the prophylaxis indication in HwI.
- Long-term results from the 56-week cut-off (trial 4307).
- Results from the latest interim cut-off in the compassionate use programme (trial 4807).

2.1.4. General comments on compliance with GCP

All trials in the clinical development programme were conducted in accordance with ICH Good Clinical Practice.

An external data monitoring committee monitored safety across the phase 3 trials.

2.2. Non-clinical aspects

No new clinical data was submitted in this application, which was considered acceptable by the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

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

- Tabular overview of clinical studies

The main basis for the efficacy/benefit evaluation of concizumab in the new indications "*Routine prophylaxis to prevent or reduce the frequency of bleeding in patients with haemophilia A (congenital factor VIII deficiency) and haemophilia B (congenital factor IX deficiency) ≥ 12 years of age*" is the results from the randomised part of trial 4307 at the CACO (at week 24-32), designed to compare the effect of concizumab PPX to no PPX (intravenous replacement with factor-containing products) in reducing the number of bleeding episodes in adult and adolescent patients with HA or HB.

This trial was conducted with the to-be-marketed dosing regimen within the intended population of HA and HB patients (the dosing regimen is the same as for patients with HAwI and HBwI). The results of study 4307 at the CACO were completed and included as supportive data for the authorization of the prophylaxis indication in HwI. The efficacy evaluation is further supported by descriptive results on bleeding episodes and haemostatic medication from trial 4307 available at the 56-week cut-off.

An overview of the clinical trials contributing to the efficacy evaluation of concizumab in patients with HA and HB is provided in Table 3.

Table 3: 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				
4307	*Efficacy, PK, PD and safety* Randomised, open-label, controlled, multiple-dose Main part: 24 weeks for arm 1 and 32 weeks for arms 2, 3 and 4. Extension part: up to 265 weeks	N = 156[a] 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/kg. Individual maintenance dose set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment	Confirmatory analyses cut-off[b] and 56-week cut-off[c] reached. Extension part ongoing
4311	*Efficacy, PK, PD and safety* Randomised, open-label, controlled, multiple-dose Main part: 24 weeks for arm 1 and 32 weeks for arms 2, 3 and 4. Extension part: up to 265 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	Primary analysis cut-off[d] and 56-week cut-off[c] reached. Extension part ongoing
Non-interventional study				
4322	*Background population* Non-interventional; patients treated according to routine clinical practice[e] ≤115 weeks	N = 231 HA: 75 HB: 72 HAwI: 53 HBwI: 31 (≥12 years)	NA	Completed

Supporting efficacy data are obtained from the studies listed below. These studies were completed and final results were submitted during the centralized procedure EMEA/H/C/005938/0000, that resulted in the MA for the indications of routine prophylaxis of bleeding in patients with haemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and haemophilia B (congenital factor IX deficiency) with FIX inhibitors in December 2024. No new data from these studies were submitted. This comprised of:

- Two phase 2 trials (trial 4255 in HA and trial 4310 in HAwI and HBwI).
- One 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 are included in the current application (trial 4616).

Compassionate use

Concizumab has been provided for compassionate use (expanded access) through a compassionate use programme (4807) as well as on an individual patient basis. The compassionate use report has been updated based on an additional interim cut-off compared to the HAwI and HBwI application. A total of 27 patients with HBwI have received concizumab up to the database lock date (28 February 2024) for the interim compassionate use report.

2.3.2. Pharmacokinetics

With this application, additional data of study 4307 were submitted. In the initial Marketing Authorisation Application (MAA) only data were submitted up until the CACO in trial 4307 as supportive data for the authorisation of the prophylaxis indication in HwI. This trial was conducted with the to-be-marketed dosing regimen within the intended population of HA and HB patients (the dosing regimen is the same as for patients with HAwI and HBwI).

Additional information on pharmacokinetics from trial 4307 are available at the 56-week cut-off. Additionally, the POP-PK analysis submitted in the initial MAA was updated with these data and POP-PK Phase 3 Modelling Report 2 were submitted as part of this application.

Methods

Analytical methods

Concizumab in plasma was quantified using a validated ELISA. Recombinant TFPI was used to capture concizumab and detection was performed by using a horseradish peroxidase-labelled anti human immunoglobulin G4 (IgG4) Fc-specific monoclonal antibody, followed by colorimetric detection of the amount of concizumab present in the calibrators, quality control samples and test samples. The assay measures the total concentration of concizumab, regardless of it being bound or unbound to its target TFPI. The same assay was also used as investigational device intended to quantitate the concentration of concizumab from human citrated plasma, which was used throughout study 4307.

Table 4: Analytical methods used for PK assessments in clinical trials

Method	3813	3981	3986	4159	4310	4255	4311	4807[a]	4307	4616[d]
Concizumab-ELISA investigational device[b]							X	X	X	X
PK assay										

Method	3813	3981	3986	4159	4310	4255	4311	4807[a]	4307	4616[d]
Concizumab-ELISA (plasma concentration)	X	X	X	X	X	X	X	X	X	X

***Notes**: aCompassionate use programme. bUse of the concizumab-ELISA as an investigational device has been implemented only for dose decision visit analyses after re-start of clinical trials 4311, 4616 and 4307. cDilute PT has only been used for analysis of samples from the first cohort of trial 3813. d4616 is an ongoing trial. Accordingly, there are currently no performance data available for the concizumab ELISA for 4616.*

The concizumab-ELISA was originally developed and validated at Novo Nordisk (Study 210390). The assay was soon after further developed and included the afore-mentioned sample pre-treatment step as significant change to the assay procedure. A partial validation was done at Novo Nordisk (Study 210479) to assess the impact of the additional method step. All validation parameters except for sample stability were therefore repeated in Study 210479. Later, the assay was transferred to Celerion Switzerland AG where it was validated again (Study 319097) in accordance with and fulfilled the acceptance criteria of current guidelines.

Table 5: Validation parameters for the concizumab-ELISA

Validation parameter	Novo Nordisk	Celerion
Calibrator	Concizumab in 3.2% citrated plasma	
LLOQ	5.00 ng/mL	
Precision (%CV)	≤20.0	
Accuracy (%RE)	±20.0	
Stability at RT	24h	
Long-term stability	24 months at -20˚C and -80˚C	
Validation study ID	Study 210390 (M5.3.1.4) and Study 210479 (M5.3.1.4)	Study 319097 (M5.3.1.4) and Study 321676 (M5.3.1.4) (Celerion)
Long-term stability study ID	Study 211050 (M5.3.1.4) and Study 211054 (M5.3.1.4) (Novo Nordisk)	Study 321889 (M5.3.1.4) (Celerion)
Applied in trials	3813, 3981, 3986, 4159, 4310, 4255	4311, 4307, 4807, 4616

***Abbreviations:** CV = coefficient of variation; ELISA = enzyme-linked immunosorbent assay; LLOQ = lower limit of quantification; RE = relative error; RT = room temperature.*

Pharmacokinetic data analysis

The area under the concentration-time curve during a dosing interval τ ($AUC_{0-\tau}$) was calculated using the linear trapezoidal method from time 0 to 24 hours, where 0 is time of the concizumab dose. The maximum concizumab plasma concentration (C_{max}) was determined as the highest concentration measured after concizumab administration (from time 0 to 24 hours for trials 4311 and 4307). The pre-dose (trough) concizumab plasma concentration (C_{trough}) was determined as the concentration measured prior to the next concizumab administration.

Evaluation and Qualification of Models

An updated PopPK report was submitted which presents results based on all phase 1 and 2 trials and data obtained up until the 56-week cut-off in phase 3 trials 4311 (in haemophilia A and B patients with inhibitors) and 4307 (in haemophilia A and B patients without inhibitors). The report describes the PK of SC concizumab, assess the impact of intrinsic and extrinsic factors on the pharmacokinetics of concizumab, and to derive predicted individual exposures (eg, AUC, Cmin, or/and Cmax) of concizumab for the exposure-safety and exposure-efficacy analyses.

A total of 367 participants with 7,262 PK samples were included in the population analysis.

Table 6: Demographics of the PK population

Category unit	Group	3813	3981	3986	4159	4255	4307	4310	4311	Total
All N (%) of total		38 (9.4%)	6 (1.5%)	4 (1%)	18 (4.5%)	35 (8.7%)	150 (37.2%)	25 (6.2%)	127 (31.5%)	366 (100%)
Phase	Phase 1	38 (100%)	6 (100%)	4 (100%)	18 (100%)	-	-	-	-	66 (18%)
N (%)	Phase 2	-	-	-	-	35 (100%)	-	25 (100%)	-	60 (16.4%)
	Phase 3	-	-	-	-	-	150 (100%)	-	127 (100%)	240 (65.6%)
Population	Healthy	20 (52.6%)	6 (100%)	4 (100%)	-	-	-	-	-	30 (8.2%)
N (%)	Haemophilia A	15 (39.5%)	-	-	18 (100%)	35 (100%)	87 (58%)	-	-	139 (38%)
	Haemophilia B	3 (7.9%)	-	-	-	-	63 (42%)	-	-	66 (18%)
	Haemophilia A with inhibitors	-	-	-	-	-	-	15 (60%)	76 (59.8%)	78 (21.3%)
	Haemophilia B with inhibitors	-	-	-	-	-	-	10 (40%)	51 (40.2%)	53 (14.5%)
Race	White	27 (71.1%)	-	4 (100%)	14 (77.8%)	23 (65.7%)	100 (66.7%)	19 (76%)	76 (59.8%)	236 (64.5%)
N (%)	Asian	6 (15.8%)	6 (100%)	-	2 (11.1%)	8 (22.9%)	41 (27.3%)	6 (24%)	34 (26.8%)	94 (25.7%)
	Black or African American	4 (10.5%)	-	-	1 (5.6%)	-	4 (2.7%)	-	9 (7.1%)	18 (4.9%)
	Not reported	-	-	-	-	3 (8.6%)	1 (0.7%)	-	5 (3.9%)	8 (2.2%)
	American Indian or Alaska Native	-	-	-	-	-	3 (2%)	-	3 (2.4%)	6 (1.6%)
	Other	1 (2.6%)	-	-	1 (5.6%)	1 (2.9%)	1 (0.7%)	-	-	4 (1.1%)
Ethnicity	Not Hispanic or Latino	36 (94.7%)	6 (100%)	4 (100%)	16 (88.9%)	29 (82.9%)	137 (91.3%)	24 (96%)	116 (91.3%)	335 (91.5%)
N (%)	Hispanic or Latino	2 (5.3%)	-	-	2 (11.1%)	3 (8.6%)	12 (8%)	1 (4%)	7 (5.5%)	24 (6.6%)
	Not reported	-	-	-	-	3 (8.6%)	1 (0.7%)	-	4 (3.1%)	7 (1.9%)
Route	s.c.	15 (39.5%)	6 (100%)	4 (100%)	18 (100%)	35 (100%)	150 (100%)	25 (100%)	127 (100%)	343 (93.7%)
N (% of trial)	i.v.	23 (60.5%)	-	-	-	-	-	-	-	23 (6.3%)
Renal_status	Normal	-	-	-	-	14 (40%)	136 (90.7%)	-	122 (96.1%)	238 (65%)
N (%l)	Renal impairment	-	-	-	-	2 (5.7%)	14 (9.3%)	-	4 (3.1%)	18 (4.9%)
	Not reported	38 (100%)	6 (100%)	4 (100%)	18 (100%)	19 (54.3%)	-	25 (100%)	1 (0.8%)	110 (30.1%)
Hepatic_status	Normal	37 (97.4%)	6 (100%)	4 (100%)	18 (100%)	35 (100%)	146 (97.3%)	24 (96%)	122 (96.1%)	355 (97%)
N (%)	Elevated ALT or AST	-	-	-	-	-	4 (2.7%)	1 (4%)	4 (3.1%)	9 (2.5%)
	Not reported	1 (2.6%)	-	-	-	-	-	-	1 (0.8%)	2 (0.5%)
Body_weight	Mean (SD)	74.8 (11.8)	62.9 (5)	73.8 (8.8)	74.9 (12.7)	76.8 (20.7)	76.9 (20.4)	70.6 (14)	67.4 (20.5)	72.8 (19.6)
kg	Range	[55.7-99.2]	[57.5-70.2]	[65.2-85.5]	[50-98]	[47.1-130]	[38-132.5]	[46.9-99.6]	[27-130.7]	[27-132.5]
BMI	Mean (SD)	24.3 (3.2)	21.8 (2.1)	24 (2.5)	24.3 (3.3)	24.8 (5.1)	25.4 (5.6)	24 (4.2)	23.4 (5.9)	24.4 (5.4)
kg/m²	Range	[17.7-30.3]	[19.7-24.7]	[21.9-27]	[18-29.9]	[16.6-37.2]	[14.5-43.8]	[16.9-32.5]	[12.2-44.2]	[12.2-44.2]
Age	Mean (SD)	34.1 (11.6)	28.3 (7.1)	44 (22)	34.1 (10.4)	36.7 (13)	31.7 (13.8)	35.4 (11.7)	28.1 (13.9)	31.1 (13.5)
years	Range	[18-60]	[21-41]	[23-64]	[19-54]	[19-65]	[12-66]	[18-59]	[12-79]	[12-79]

The total column reflects total unique participants; some participants in trial 4310 and 4255 continued into 4311 and 4307, respectively, and these are therefore counted once. One subject was excluded from trial 4255, one from trial 3813 and one from trial 4307, see Table 10-1.

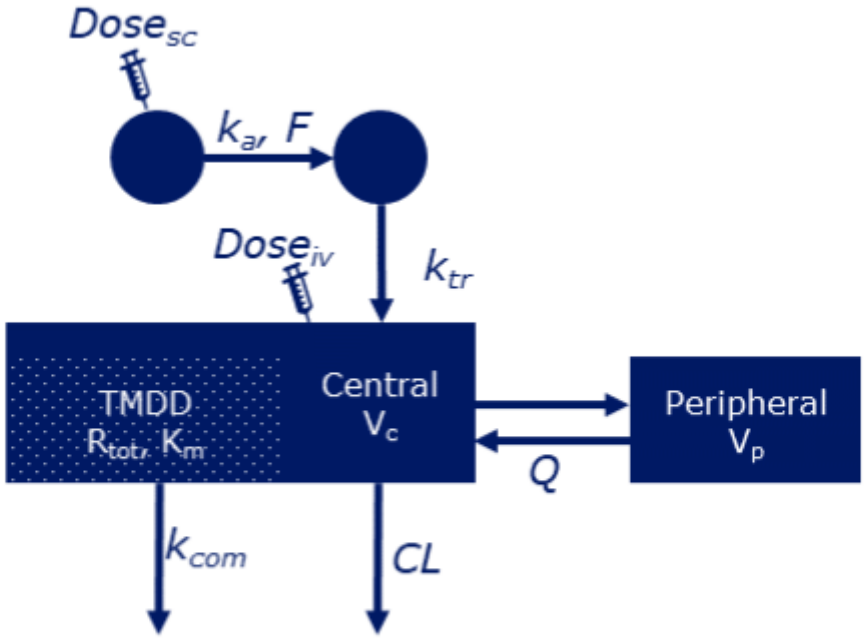
% reflects the percentage for each category within each column, except for the first row, where it reflects the percentage of the total population PK population.
Renal impairment was defined as eGFR <90 mL/min/1.73 m². Elevated liver enzymes was defined as ALT or AST ≥1.5 times the upper limit of normal.

The PK of concizumab in phase 3 was described by a 2-compartment model with combined linear clearance and TMDD based on data from phase 1 and 2 and data obtained up until the 56 week cut-offs in phase 3 trials 4307 (HA and HB patients) and 4311 (HAwI and HBwI patients). Overall, the results and conclusions are the same as those presented in the initial MAA for the HAwI and HBwI indications.

The concizumab PK model was used to evaluate covariate effects on concizumab exposure and the impact of maintenance dose setting on concizumab exposure 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, haemophilia A, adult male ≥ 18 years, body weight 75 kg; 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. The most important covariate for predicting concizumab exposure was body weight, and no other covariates had a significant effect. However, differences in concizumab exposure were not observed between BMI classes in trial 4307. Overall, for patients with low or high exposure, the dose should be adjusted according to the maintenance dose setting, resulting in more similar exposure between patients.

Figure 2: Structural model for the population



CL: linear clearance; k_a: absorption rate constant; k_{tr}: absorption from transit compartment; K_m: concentration at 50% saturation of TMDD; k_{com}: elimination rate constant for concizumab-TFPI complex; F: bioavailability; R_{tot}: total capacity of the TMDD compartment; V_c: central volume of distribution; V_p: peripheral volume of distribution; Q: intercompartmental clearance

PK model

In addition, the base model included body weight scaling on CL, Q, Vc and Vp, using allometric equations:

$$P_i = P_{typ} \cdot \left(\frac{BW_i}{75\ \text{kg}}\right)^{\theta_{BW,P}}$$

where the exponent ($\theta_{BW,P}$) was fixed to 0.75 for CL and Q, and 1.0 for V_c and V_p.

Table 7: Overview of covariates effects

Covariate	Test categories	Reference category	PK parameter included on
Fixed covariate effects in base model			
Baseline body weight		75 kg	CL, Q, V_c and V_p
Pre-defined covariate effects in the full model			
Age group	Adolescents 12 - <18 years	Adults ≥18 years	R_{tot}
Race	Asian, Other or unreported, Black or African American	White	R_{tot}
Ethnicity	Hispanic or Latino	Non-Hispanic or Latino	R_{tot}
Baseline body weight	5th and 95th percentile baseline body weight in PK population	75 kg	R_{tot}
Renal function	Impaired[a]	Normal	R_{tot}
Hepatic function	Impaired hepatic function[b]	Normal	R_{tot}
Haemophilia type	HB, HBwI, HAwI, healthy[c]	HA	R_{tot}
Potential covariates for inclusion in full model[d]			
Trial factors	Phase 3	Not phase 3	-
Baseline free TFPI	5th and 95th percentile of baseline free TFPI in PK population	Median	-

Body weight and baseline free TFPI were evaluated as a continuous covariate, and the remaining covariates were categorical.
a. Renal impairment was defined as eGFR <90 mL/min/1.73 m2.
b. Defined as elevated liver enzymes (ALT or AST ≥ 1.5 times the upper limit of normal)
c. A covariate group for healthy participants was not pre-specified, but considered relevant to include; see Section 5.1.6
d. Covariates to be included in the full model on relevant parameters, if deemed appropriate after exploration of post hoc estimates.

Table 8: Parameter estimates of the base population PK model

Parameter	Label	Units	Estimates	RSE (%)	95% CI	Shrinkage (%)
CL	Clearance	L/h	0.00814	Fixed	Fixed	NA
V2	Volume of distribution	L	2.96	Fixed	Fixed	NA
Q	Inter-compartmental clearance	L/h	0.0603	Fixed	Fixed	NA
KA	Absorption rate	1/h	0.00963	Fixed	Fixed	NA
BA	Bioavailability	fraction	0.777	Fixed	Fixed	NA
BWCLEXP	Body weight covariate on CL and Q	NA	0.750	Fixed	Fixed	NA
BWVEXP	Body weight covariate on V	NA	1.00	Fixed	Fixed	NA
KCOM	Elimination rate for complex at endothelium	1/h	0.188	Fixed	Fixed	NA
KM	Concentration for 50% saturation of TMDD	ng/mL	147	5.63	[131; 163]	NA
KTR	Transit rate constant	1/h	1.97	Fixed	Fixed	NA
RTOT	Total capacity of TMDD	mg	3.32	2.22	[3.18; 3.47]	NA
BASE	Complex in plasma	ng/mL	7.88	Fixed	Fixed	NA
RTOT.IIV	IIV on RTOT (CV%)	%	31.3	4.92	NA	5.27
AddErr	Additive error on log data (SD)	NA	0.825	2.62	NA	2.29

V_p was not estimated, and was instead set to be the same as V_c (V2 in table).

IIV: inter-individual (or between-subject) variability

Table 9: Parameter estimates of the final population PK model

Parameter	Label	Units	Estimates	RSE (%)	95% CI	Shrinkage (%)
CL	Clearance	L/h	0.00814	Fixed	Fixed	NA
V2	Volume of distribution	L	2.96	Fixed	Fixed	NA
Q	Inter-compartmental clearance	L/h	0.0603	Fixed	Fixed	NA
KA	Absorption rate	1/h	0.00963	Fixed	Fixed	NA
BA	Bioavailability	fraction	0.777	Fixed	Fixed	NA
BWCLEXP	Body weight factor on CL and Q	NA	0.750	Fixed	Fixed	NA
BWVEXP	Body weight factor on V	NA	1.00	Fixed	Fixed	NA
KCOM	Elimination rate for complex at endothelium	1/h	0.188	Fixed	Fixed	NA
KM	Concentration for 50% saturation of TMDD	ng/mL	109	6.89	[94.1; 123]	NA
KTR	Transit rate constant	1/h	1.97	Fixed	Fixed	NA
RTOT	Total capacity of TMDD	mg	3.50	2.42	[3.33; 3.66]	NA
BASE	Complex in plasma	ng/mL	7.88	Fixed	Fixed	NA
BWRTOT	Body weight factor on RTOT	NA	0.596	4.04	[0.549; 0.643]	NA
COV_PH3_KM	Phase 3 factor on KM	NA	0.744	22.0	[0.422; 1.06]	NA
RTOT.IIV	IIV on RTOT (CV%)	%	25.8	7.89	NA	7.01
AddErr	Additive error on log data (SD)	NA	0.816	2.58	NA	2.20

V_p was not estimated, and was instead set to be the same as V_c (V2 in table).

IIV: inter-individual (or between-subject) variability

Figure 3: Standard GOF plots for the final population PK model

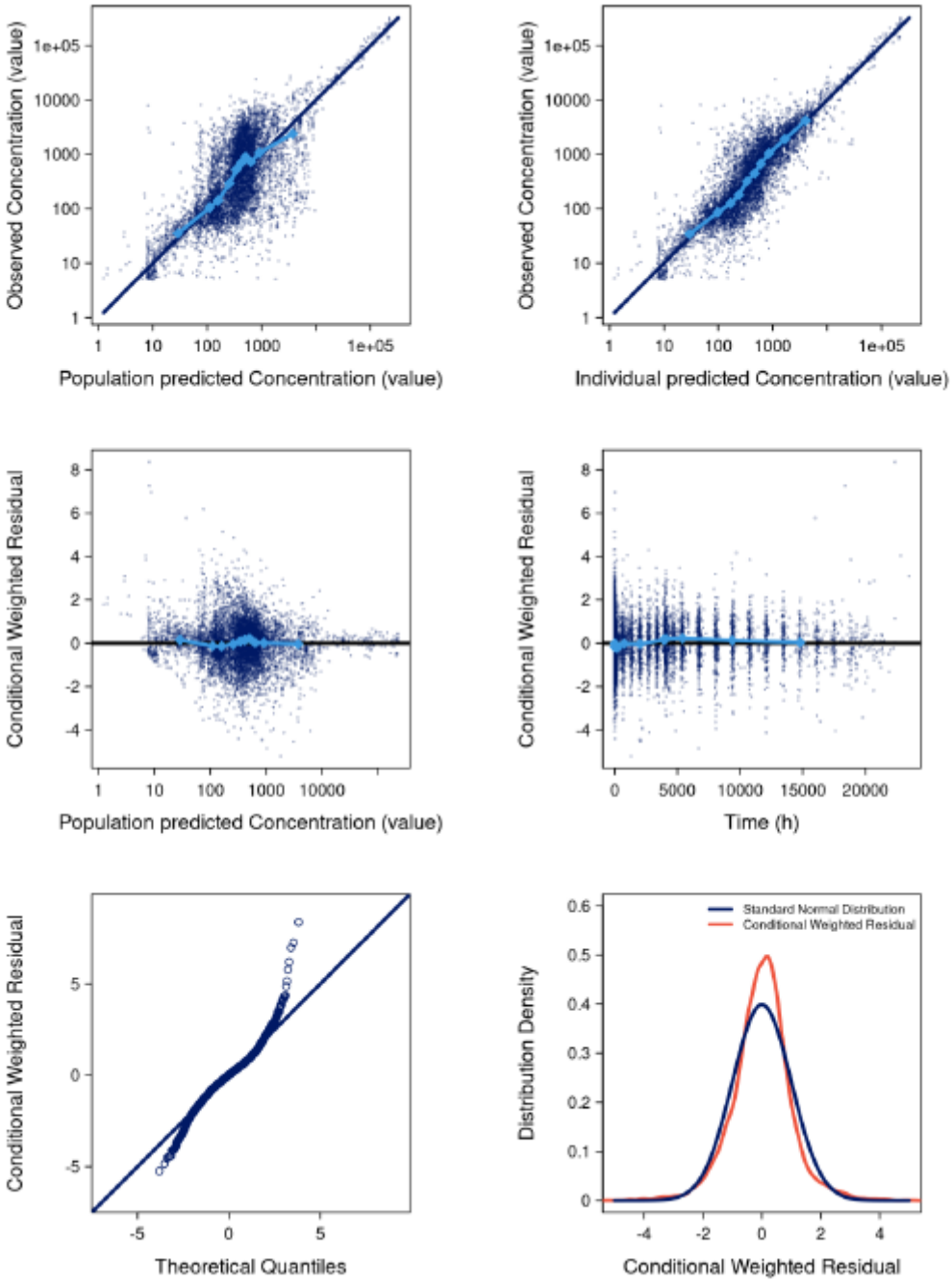


Figure 4: Distribution of ETAs for Rtot for the final population PK model

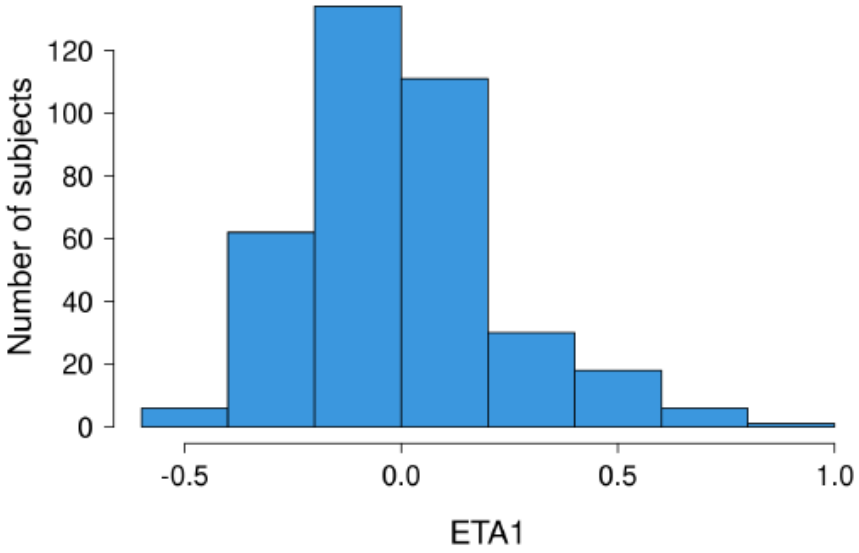


Figure 5: Observed and model-predicted concizumab exposure over time for trial 4307 after restart by covariates

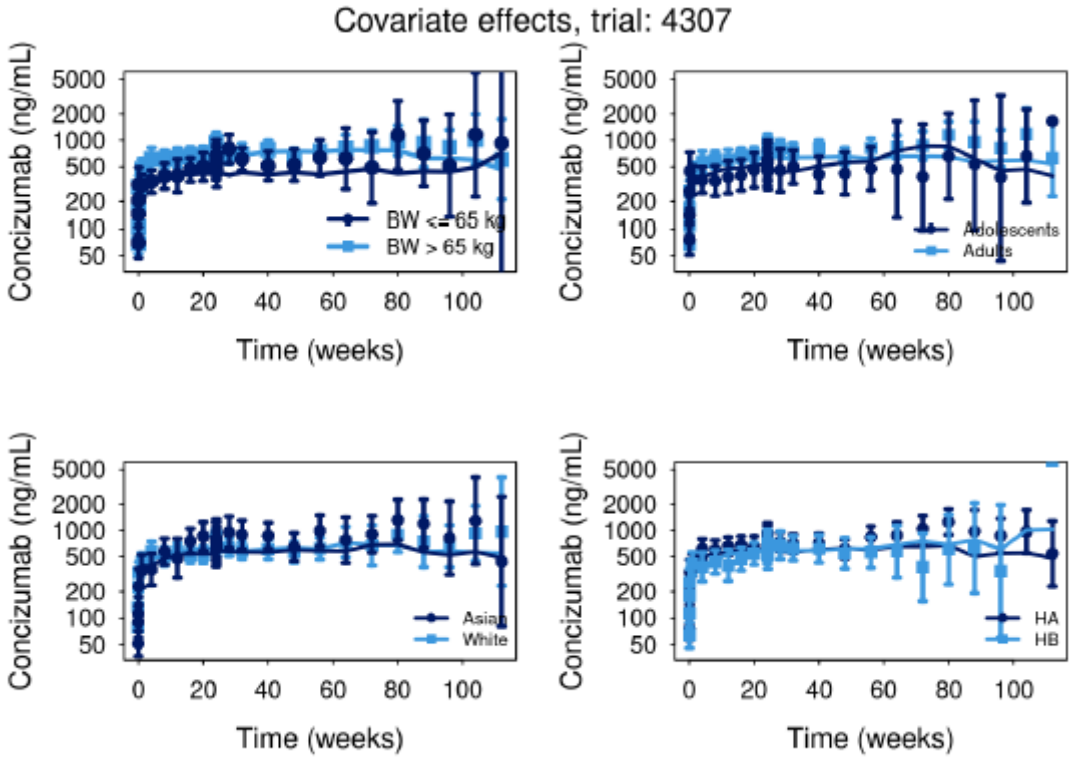
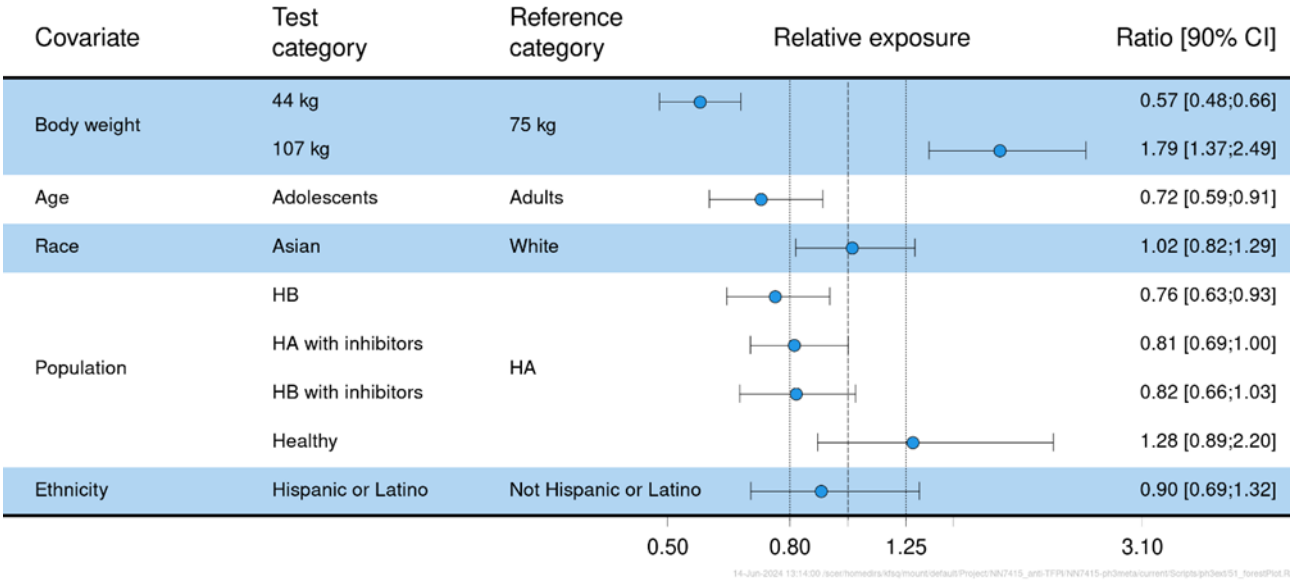


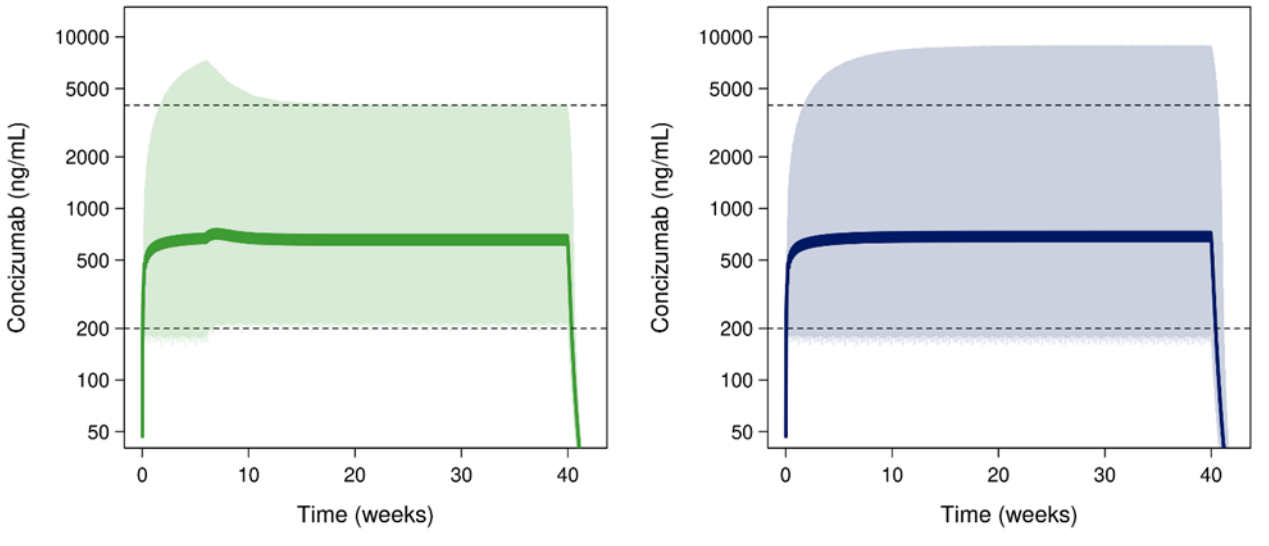
Figure 6: Forest plot of covariate effects on concizumab exposure (0.20 mg/kg)



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. 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.

PK simulations of the impact of maintenance dose setting on concizumab exposure are presented in Figure 7. 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 between patients.

Figure 7: Simulated concizumab 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 trials 4307 and 4311 (>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.

Statistical methods

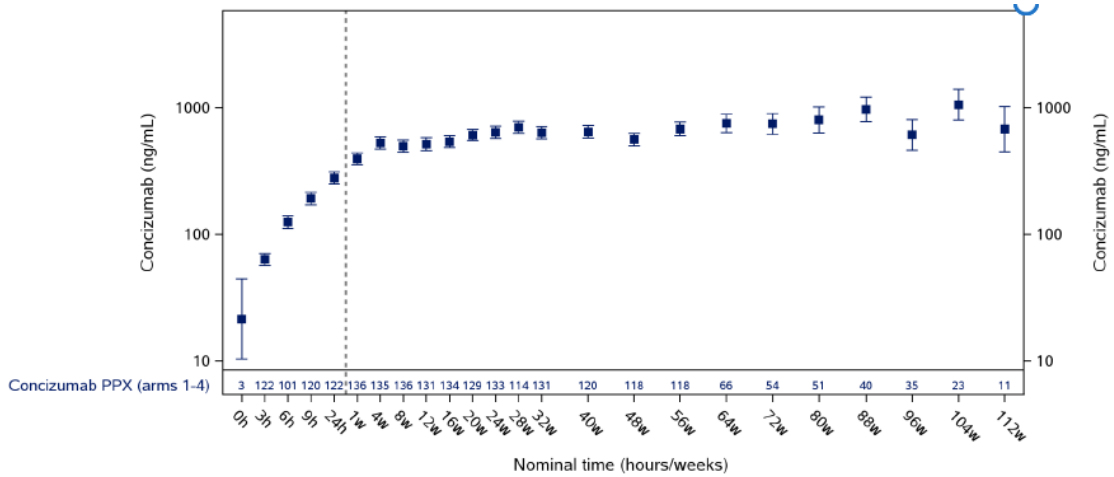
Pharmacokinetic estimates presented in the tables in this module represent geometric mean, and CV%. Figures present the mean ± SD and mean ± 95% CI values.

Results

An updated overview of the results of study 4307 is presented below. For study description see also clinical part of the assessment report. In trial 4307, a total of 80 patients with HA and 64 patients with HB on the dosing regimen after restart (in arms 1−4) 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. Patients in arm 1 were on no PPX for 24 weeks, after which they were to be transferred to concizumab PPX according to trial protocol. Results obtained at the 56-week cut-off are included.

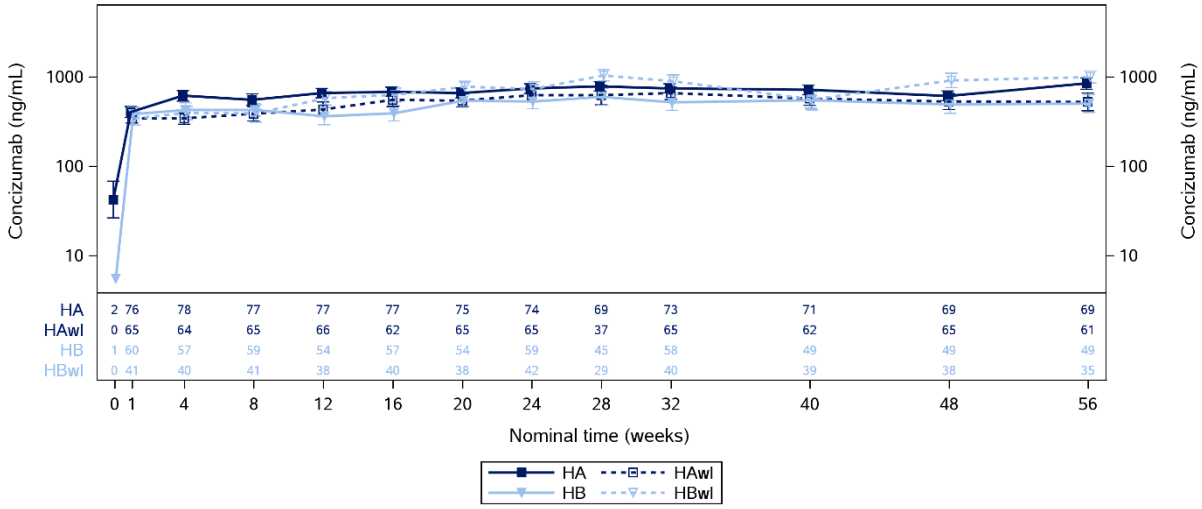
Geometric mean Ctrough levels and 25th and 75th percentiles (P25 and P75) were comparable for HA and HB patients on concizumab PPX at weeks 24, 32 and 56 (Trial 4307 56wk). Geometric mean Cmax and AUC0-τ and mean Cmax/Ctrough ratios were each at comparable levels for HA and HB patients on concizumab PPX at week 24. Concizumab exposure increased rapidly within 24 hours following administration of the concizumab loading dose and was maintained at stable levels over a 24-hour period at week 24 for HA and HB patients on maintenance doses of concizumab. This is supported by PK modelling, where no statistically significant differences were observed between the haemophilia subtypes.

Figure 8: concizumab plasma concentration (ng/mL) - geometric mean plot - HA+HB - OTexBR - safety analysis set - trial 4307 (56-week cut-off)



HA: haemophilia A, HB: haemophilia B, 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. Subjects in arm 1, 2, 3 and 4 on concizumab PPX are included. 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.

Figure 9: Concizumab pre-dose trough plasma concentration (ng/mL) - by haemophilia subtype - HAwI+HBwI+HA+HB - OTexIR+OTexBR - safety analysis set - trial 4311 (56-week cut-off) + trial 4307 (56-week 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 1-4) 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.

Table 10: Pre-dose trough concizumab plasma concentration (ng/mL) - by haemophilia subtype - descriptive statistics - HA and HB - OTexBR - safety analysis set - trial 4307 (56-week cut-off)

	HA Concizumab PPX (arms 1–4)		HB Concizumab PPX (arms 1–4)	
Parameter	**Week 24**	**Week 56**	**Week 24**	**Week 56**
N	74	69	59	49
Geometric mean (CV[%])	743.6 (152.3)	845.7 (173.7)	534.1 (262.7)	504.9 (336.9)
Min ; Max	31.6 ; 6850.0	22.2 ; 4580.0	2.5 ; 6320.0	2.5 ; 5430.0
Median	847.5	1100.0	744.0	803.0
P25 ; P75	331.0 ; 1710.0	418.0 ; 2080.0	255.0 ; 1230.0	147.0 ; 1540.0

Notes: The weeks are relative to the relevant baseline for patients on concizumab PPX (visit 9a for arm 1, visit 2a for arms 2–4). Values below the lower limit of quantification (LLoQ = 5 ng/mL) are set to ½ LLoQ = 2.5 ng/mL.

Abbreviations: CV: geometric coefficient of variation (in percentage), HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, Max: maximum, Min: minimum, OTexBR: On-treatment without data before restart, P25/P75: 25th/75th percentile, PPX: prophylaxis.

Table 11: Pharmacokinetic parameters determined during a 24 hour dosing interval (arms 2–4) by haemophilia subtype baseline and week 24 HA and HB OTexBR safety analysis set trial 4307 (56 week cut off)

	HA Concizumab PPX (arms 2–4)		HB Concizumab PPX (arms 2–4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	70	62	53	41
C_{max} (ng/mL) (geometric mean (CV[%]))	344.9 (195.8)	1028.7 (129.1)	279.7 (224.0)	721.8 (163.7)
$AUC_{0-\tau}$ (ng*hr/mL) (geometric mean (CV[%]))	5119.4 (169.1)	20351.2 (134.3)	4228.8 (199.1)	14220.4 (164.3)
C_{max}/C_{trough} ratio (mean [SD])	-	1.4 (0.4)	-	1.6 (0.6)

Notes: Baseline is defined as visit 2a for concizumab PPX (arms 2–4). Week 24 is relative to the relevant baseline. Profile measurements for 8 patients at week 24 were excluded from endpoint calculations due to either the pre-dose measurement being taken after concizumab dosing or the entire profile being taken a day after dosing (6 patients) or due to profile measurements being taken at another visit than according to trial protocol (2 patients).

Abbreviations: AUCτ: area under the concizumab plasma-concentration-time curve during a dosing interval from 0 to 24 hours, C_{max}: maximum concizumab plasma concentration, C_{trough}: pre-dose trough concizumab plasma concentration, CV: geometric coefficient of variation (in percentage), HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, OTexBR: On-treatment without data before restart, PPX: prophylaxis, SD: standard deviation.

The effect of age group (adolescents and adults) on the PK of concizumab following daily s.c. administration for long-term PPX in HA and HB patients was assessed in trial 4307. Individual concizumab plasma concentrations over time for adolescent and adult patients on concizumab PPX were overlapping. Descriptive statistics indicated slightly lower geometric mean Ctrough levels (at weeks 24, 32 and 56) and geometric mean Cmax and AUC0-τ (at week 24) for adolescents compared to adults on concizumab PPX. In the PK modelling, no statistically significant differences were observed between the age groups. 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.

Table 12: Pre-dose trough concizumab plasma concentration (ng/mL) - by age group - descriptive statistics - HA+HB - OTexBR - safety analysis set - trial 4307 (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	34	28	99	90
Geometric mean (CV[%])	469.0 (231.5)	473.3 (281.4)	715.2 (184.8)	765.1 (222.7)
Min ; Max	29.8 ; 6320.0	39.7 ; 5430.0	2.5 ; 6850.0	2.5 ; 4580.0
Median	560.5	499.0	893.0	1100.0
P25 ; P75	145.0 ; 1110.0	124.0 ; 1680.0	337.0 ; 1710.0	418.0 ; 2050.0

Notes: The weeks are relative to the relevant baseline for patients on concizumab PPX (visit 9a for arm 1, visit 2a for arms 2–4). Values below the lower limit of quantification (LLoQ = 5 ng/mL) are set to ½ LLoQ = 2.5 ng/mL.

Abbreviations: CV: geometric coefficient of variation (in percentage), HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, Max: maximum, Min: minimum, OTexBR: On-treatment without data before restart, P25/P75: 25th/75th percentile, PPX: prophylaxis.

Table 131: Pharmacokinetic parameters determined during a 24 hour dosing interval for patients on concizumab PPX (arms 2–4) by age group baseline and week 24 HA+HB OTexBR safety analysis set trial 4307 (56 week cut off)

	Adolescents Concizumab PPX (arms 2–4)		Adults Concizumab PPX (arms 2–4)	
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**
N	30	25	93	78
C_{max} (ng/mL) (geometric mean (CV[%]))	431.9 (177.5)	591.5 (181.3)	284.6 (214.0)	1019.6 (127.7)
$AUC_{0-\tau}$ (ng*hr/mL) (geometric mean (CV[%]))	6336.9 (153.8)	11707.4 (180.4)	4285.8 (187.8)	20124.4 (132.6)
C_{max}/C_{trough} ratio (mean [SD])	-	1.5 (0.5)	-	1.5 (0.5)

Notes: Baseline is defined as visit 2a for concizumab PPX (arms 2–4). Week 24 is relative to the relevant baseline. Profile measurements for 8 patients at week 24 were excluded from endpoint calculations due to either the pre-dose measurement being taken after concizumab dosing or the entire profile being taken a day after dosing (6 patients) or due to profile measurements being taken at another visit than according to trial protocol (2 patients).

Abbreviations: AUC_T: area under the concizumab plasma-concentration-time curve during a dosing interval from 0 to 24 hours, C_{max}: maximum concizumab plasma concentration, C_{trough}: pre-dose trough concizumab plasma concentration, CV: geometric coefficient of variation (in percentage), HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, OTexBR: On-treatment without data before restart, PPX: prophylaxis, SD: standard deviation.

Missed doses

The expected impact of a proposed guidance for resumed dosing after missed doses was illustrated using simulation based on the final PK modelling.

Simulations of the following scenarios are provided:

- The exposure resulting from missing 1-7 doses and resuming with a single dose is illustrated in Figure 10 (1-7 missed doses).
- The exposure resulting from missing 1-7 doses and resuming with a double dose is illustrated in Figure 11 (1-7 missed doses).
- The exposure resulting from missing 2-7 doses and resuming with a 1 mg/kg loading dose is illustrated in Figure 12 (2-7 missed doses).

Figure 10: Simulation of concizumab plasma concentration (ng/mL) – treatment resumed with a single dose following 1-7 missed dose

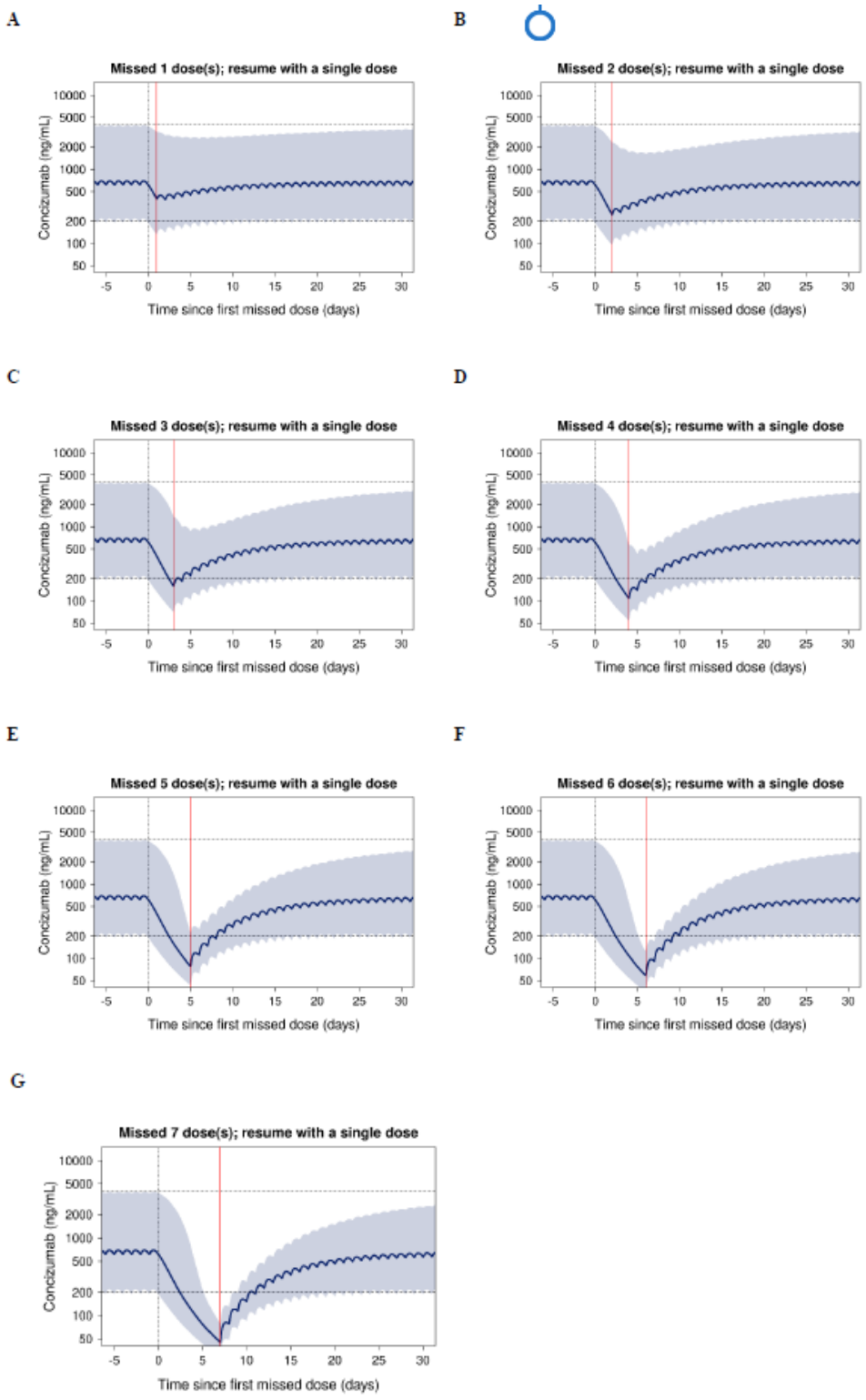


Figure 11: Simulation of concizumab plasma concentration (ng/mL) – treatment resumed with a double dose following 1-7 missed doses

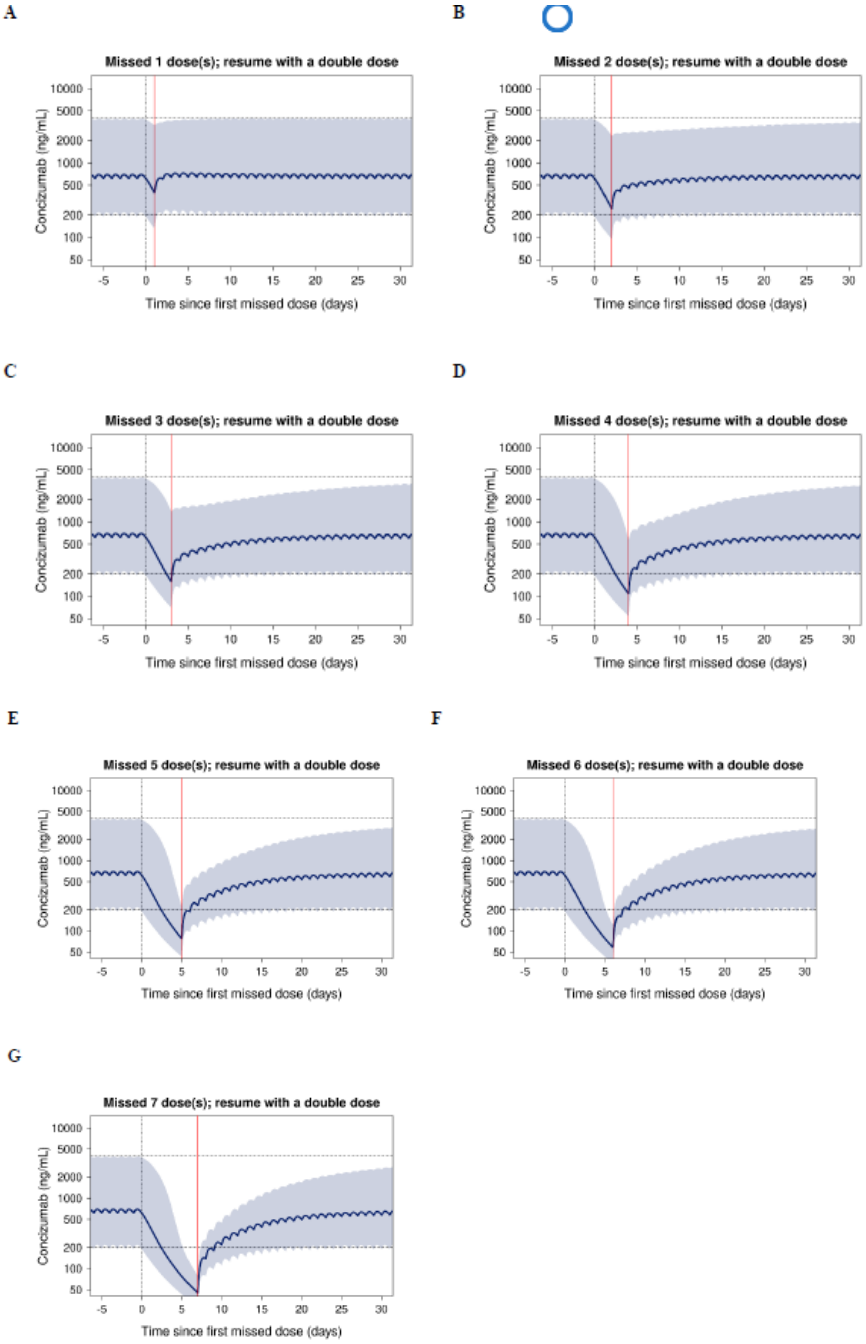
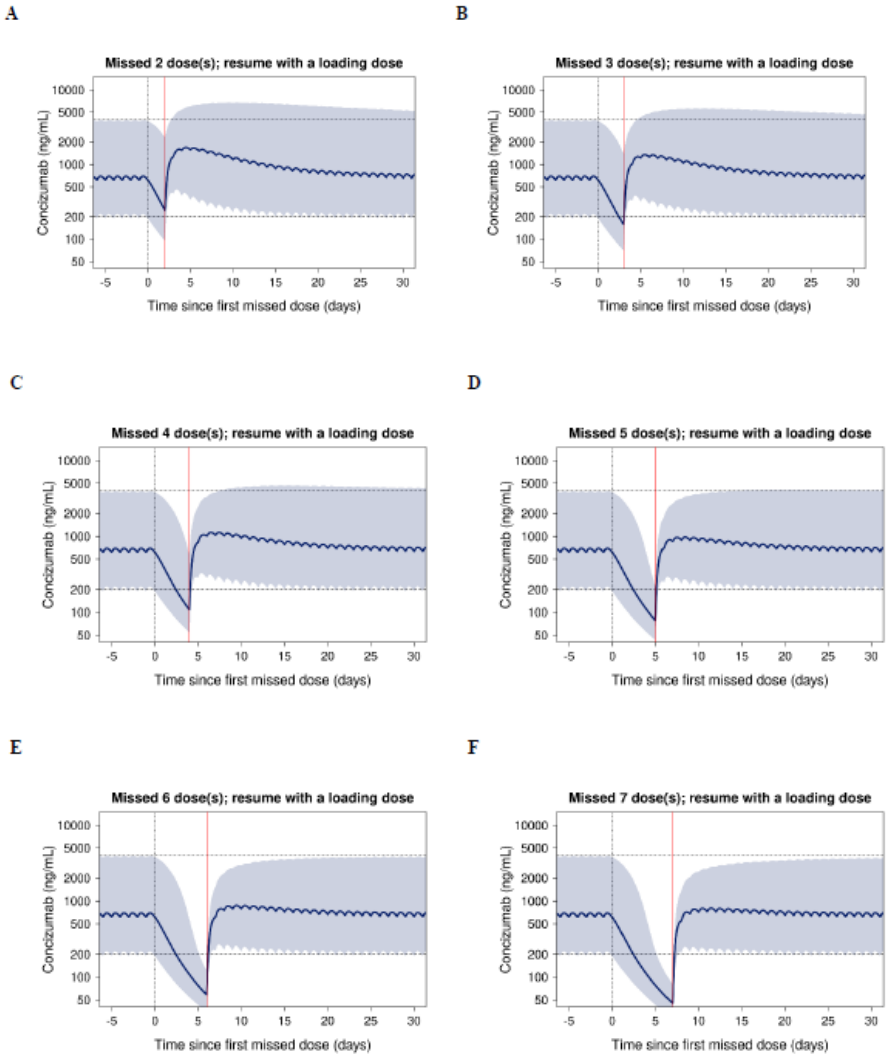


Figure 12: Simulation of concizumab plasma concentration (ng/mL) – treatment resumed with a loading dose of 1 mg/kg following 2-7 missed doses



2.3.3. Pharmacodynamics

No new clinical pharmacology studies were submitted. An overview of primary PD data present in the initial MAA is presented below.

Mechanism of action

Concizumab (Alhemo) is a humanised recombinant monoclonal antibody directed against the tissue-factor pathway inhibitor (TFPI). TFPI is involved in down-regulation of the initiation of coagulation. Concizumab binds specifically to the Kunitz-domain-2 of TFPI and prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa). When the inhibitory activity of TFPI is reduced, the FXa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex will result in sufficient generation of thrombin to achieve haemostasis. The mechanism of action of concizumab is independent of the presence or absence of FVIII or FIX and not influenced by the presence of inhibitory antibodies to FVIII or FIX.

Primary and secondary pharmacology

Primary pharmacology

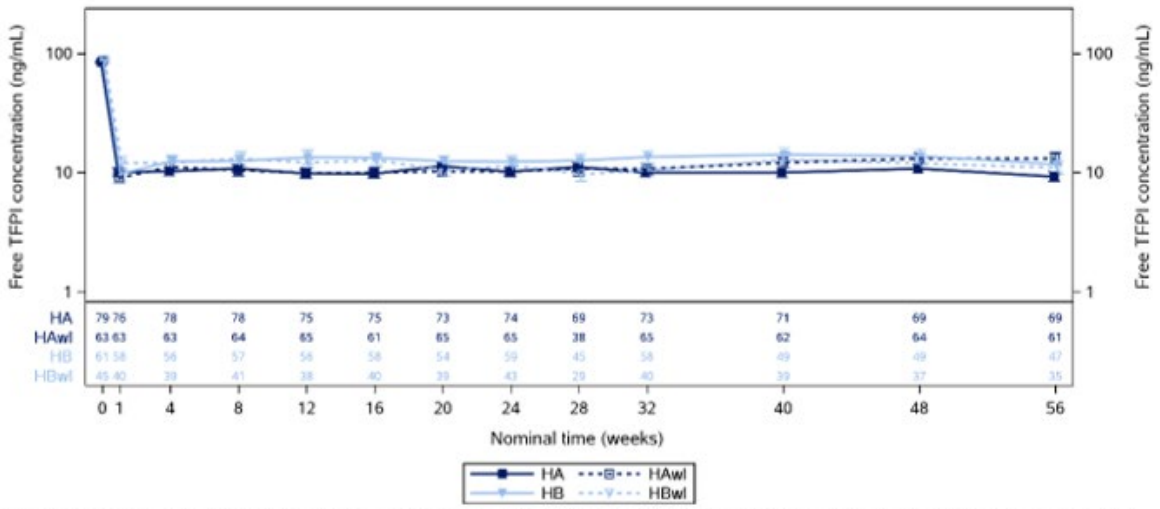
Free TFPI was chosen as the main PD marker following trial 3813, as it exhibited the most consistent exposure-response relationship amongst PD and safety parameters and was considered a good proxy for efficacy and safety. Concizumab administration resulted in a reduction of free TFPI plasma levels, thus confirming the biological mechanism of action of concizumab as an inhibitor of TFPI. 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 effect of concizumab on free TFPI was similar in healthy subjects and haemophilia patients as well as between haemophilia subtypes.

Thrombin generation was affected by concizumab administration for all measured parameters. Thrombin peak levels increased in a dose-dependent manner following concizumab administration. The thrombin generation parameters were brought within the ranges of normal plasma following long-term concizumab PPX.

Overall, the PD results in the present application for HA and HB indications including the 56 week cut offs in trials 4307 (HA and HB) and 4311 (HAwI and HBwI) are in line with those presented in the marketing authorisation application for the HAwI and HBwI indications obtained at the 56 week cut-off in trial 4311 and at the CACO in trial 4307.

In trial 4307, pre-dose *free TFPI plasma levels* decreased from a geometric mean value of 84.2 ng/mL at baseline to 11.1 ng/mL at week 24 for patients on concizumab PPX (arms 1–4), while the geometric mean value was 80.6 ng/mL at week 24 for patients on no PPX (arm 1). After the initial decrease, pre-dose free TFPI levels remained stable over time for patients on concizumab PPX (arms 1–4) (Figure 13).

Figure 13. Pre dose free TFPI concentration (ng/mL) by haemophilia subtype geometric mean plot HAwI+HBwI+HA+HB OTexIR+OTexBR safety analysis set – trial 4311 (56 week cut off) + trial 4307 (56 week 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, TFPI: tissue-factor pathway inhibitor.
The following arms are included: concizumab PPX (arms 1-4) from trial 4311 and concizumab PPX (arms 1-4) 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 free TFPI is 9.6 ng/mL. Numbers shown in the bottom of the figure reflect the number of patients contributing with non-zero values.

Pre dose free TFPI in plasma was maintained at a low level at week 56 with a geometric mean value of 10.2 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). Geometric mean pre-dose free TFPI plasma levels were comparable for HA, HB, HAwI and HBwI patients (arms 1–4 in both trials) at baseline and over time following concizumab PPX.

Table 142: Baseline free TFPI concentration (ng/mL) by haemophilia subtype descriptive statistics HAwI+HBwI+HA+HB safety analysis set trial 4311 (56 week cut off) + trial 4307 (56 week cut off)

	No PPX (arm 1)		Concizumab PPX (arms 1–4)		
Parameter	**Baseline**	**Week 24**	**Baseline**	**Week 24**	**Week 56**
N	20	18	143	133	116
Geometric mean (CV[%])	80.6 (26.3)	80.6 (17.7)	84.2 (18.6)	11.1 (102.4)	10.2 (107.2)
Min ; Max	39.1 ; 133.0	55.9 ; 103.5	42.5 ; 141.4	4.8 ; 85.5	4.8 ; 98.1
Median	83.3	79.5	85.0	11.1	9.8
P25 ; P75	70.0 ; 94.1	74.2 ; 92.2	74.5 ; 96.3	4.8 ; 18.7	4.8 ; 19.1

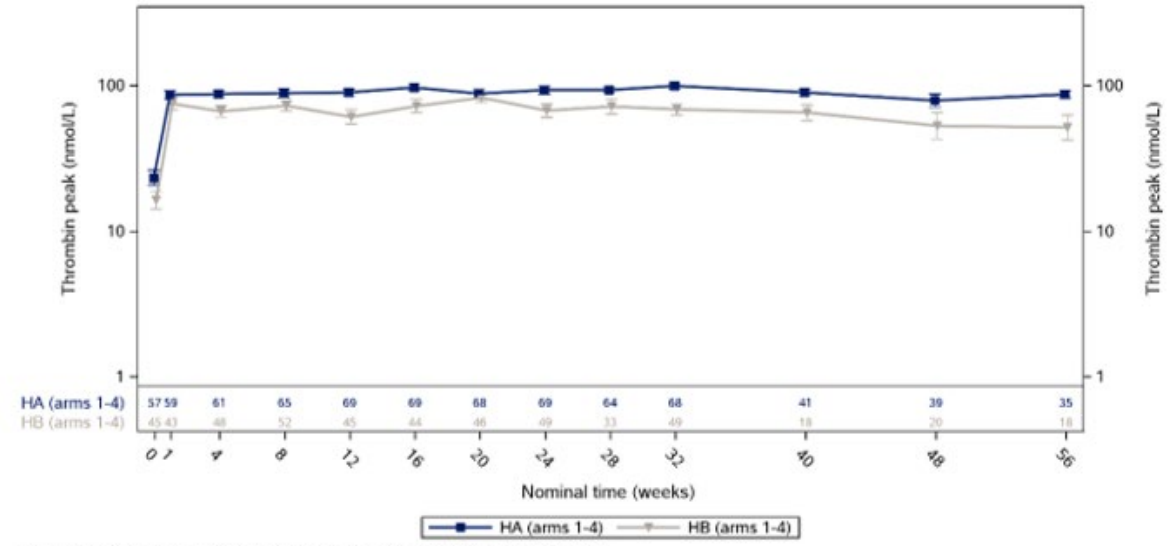
Notes: Baseline is defined as visit 9a for concizumab PPX in arm 1, visit 2a for concizumab PPX in arms 2–4 and visit 2a for no PPX in arm 1. Week numbers are relative to the relevant baseline.
Values below the lower limit of quantification (LLoQ = 9.6 ng/mL) are set to ½ LLoQ = 4.8 ng/mL.

Abbreviations: CV: geometric coefficient of variation (in percentage), HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, Max: maximum, Min: minimum, OTexBR: On-treatment without data before restart, P25/P75: 25th/75th percentile, PPX: prophylaxis, TFPI: tissue factor pathway inhibitor.

Thrombin peak generation

The effect of haemophilia subtype on thrombin peak generation following daily s.c. administration of concizumab for long-term PPX in HA and HB patients was assessed in trial 4307. Pre-dose thrombin peak levels increased to be within the range of normal plasma following concizumab PPX for both haemophilia subtypes with similar relative increases from baseline at weeks 24, 32 and 56 (Figure 14).

Figure 14. Pre dose thrombin peak (nmol/L) by haemophilia subtype geometric mean plot HA and HB OTexBR safety analysis set trial 4307 (56 week cut off)



HA: haemophilia A, HB: haemophilia B, OTexBR: On-treatment without data before restart.
Error bars represent +/- standard error of the geometric mean. The normal range for thrombin peak in the analyses is from 26 to 147 nmol/L. Numbers shown in the bottom of the figure reflect the number of patients contributing with non-zero values. Subjects in arm 1, 2, 3 and 4 on concizumab PPX are included. Week numbers are relative to visit 9a for concizumab PPX arm1 and visit 2a for concizumab PPX (arms 2, 3 and 4).

Descriptive statistics indicated slightly lower geometric mean pre-dose thrombin peak levels at baseline for HB patients on concizumab PPX compared to HA patients on concizumab PPX.

Table 153: Pre dose thrombin peak (nmol/L) by haemophilia subtype descriptive statistics – HA and HB OTexBR safety analysis set trial 4307 (56 week cut off)

	HA Concizumab PPX (arms 1–4)			HB Concizumab PPX (arms 1–4)		
Parameter	**Baseline**	**Week 24**	**Week 56**	**Baseline**	**Week 24**	**Week 56**
N	64	69	35	46	49	18
Geometric mean (CV[%])	25.4 (114.9)	93.0 (55.2)	87.0 (37.6)	16.3 (112.6)	67.3 (84.5)	51.5 (102.9)
Min ; Max	4.0 ; 173.0	12.0 ; 219.0	20.0 ; 146.0	2.0 ; 86.0	5.0 ; 159.0	5.0 ; 148.0
Median	23.0	110.0	90.0	17.5	88.0	70.5
P25 ; P75	12.0 ; 52.5	80.0 ; 125.0	78.0 ; 113.0	10.0 ; 28.0	65.0 ; 102.0	33.0 ; 85.0

Notes: Week numbers are relative to the relevant baseline for concizumab PPX (visit 9a for arm 1, visit 2a for arms 2–4).

Abbreviations: CV: geometric coefficient of variation (in percentage); HA: haemophilia A without inhibitors; HB: haemophilia B without inhibitors; Max: maximum; Min: minimum; OTexBR: on-treatment without data before restart; P25/P75: 25th/75th percentile; PPX: prophylaxis.

2.3.4. Discussion on clinical pharmacology

The population PK model was assessed in the initial MAA, where data from all clinical studies were integrated, including 56-week data from study 4311 (patients with HA and HB with inhibitors) and data from study 4307 (patients with HA and HB without inhibitors) up to the confirmatory analyses cut-off (CACO, defined as the point in time when all patients in arm 1 have completed the 24-week visit or withdrawn and all patients on concizumab PPX (in arms 2 and 4) have completed the 32-week visit or withdrawn). With this submission, the previously developed population PK model was updated to include additional 56-week data from study 4307. The update included a total of 367 participants with 7,262 PK samples.

Compared to the previous phase 3 modelling report, both Rtot and Km were estimated simultaneously, instead of only Rtot. This was a part of the pre-specified analysis but was not possible for the earlier analysis due to model instability. Furthermore, phase 3 was now included as factor on Km. In the previous analysis, a phase 3 factor was implemented on Rtot in the final model without testing the factor on Km.

The impact of covariates on concizumab exposure was assessed using the full model, including all covariates. Only body weight and phase had a statistically significant effect on concizumab exposure. There appeared to be an effect of trial phase (phase 3 versus phase 1 and 2), and phase was therefore included as a covariate on Km in the full model. Although adolescents also showed somewhat lower exposure compared to adults, this is of no concern, as due to the maintenance dose setting after 4 weeks of treatment, patients with low or high exposure should increase or decrease dose, respectively, resulting in more similar exposure across patients.

Simulations of concizumab plasma concentrations following 1-7 missed doses were performed. These mostly confirm the current dosing recommendations in section 4.2 of the SmPC: after 1 missed daily dose, the patient should resume the daily maintenance dose without an additional dose; after 2 to 6 missed consecutive daily doses, the patient should take the daily dose twice, and then continue taking the daily maintenance dose the next day. After 5 or 6 missed doses, resuming

with a loading dose may also be appropriate, according to the simulations. However, even in the case of 7 missed doses, the recommendation in section 4.2 of the SmPC is to resume with a loading dose only after careful consideration. Thus, it is considered more appropriate to resume with a double dose after 5 or 6 missed doses, as currently recommended.

There were 3 patients above 65 years included in study 4307, with no obvious difference in exposure. Hence, section 4.2 and 5.2 of the SmPC were amended to reflect that limited data are available in patients aged 65 and older.

In Section 5.2 of the SmPC, Table 8 shows steady state parameters at week 24 for all haemophilia subtypes investigated (HA/HB/HAwI/HBwI).

2.3.5. Conclusions on clinical pharmacology

Additional 56-week data from study 4307 were the basis of SmPC updates with regards to posology and pharmacokinetics data which are reflected adequately in sections 4.2 and 5.2 of the SmPC.

2.4. Clinical efficacy

2.4.1. Main study

NN7415-4307 (Explorer 8): Efficacy and safety of concizumab prophylaxis in patients with haemophilia A or B without inhibitors (Explorer 8)

Methods

Trial 4307 is the 4-armed multi-national, multi-centre, open-label, confirmatory phase trial in adolescent and adult 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.

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.

Comparators

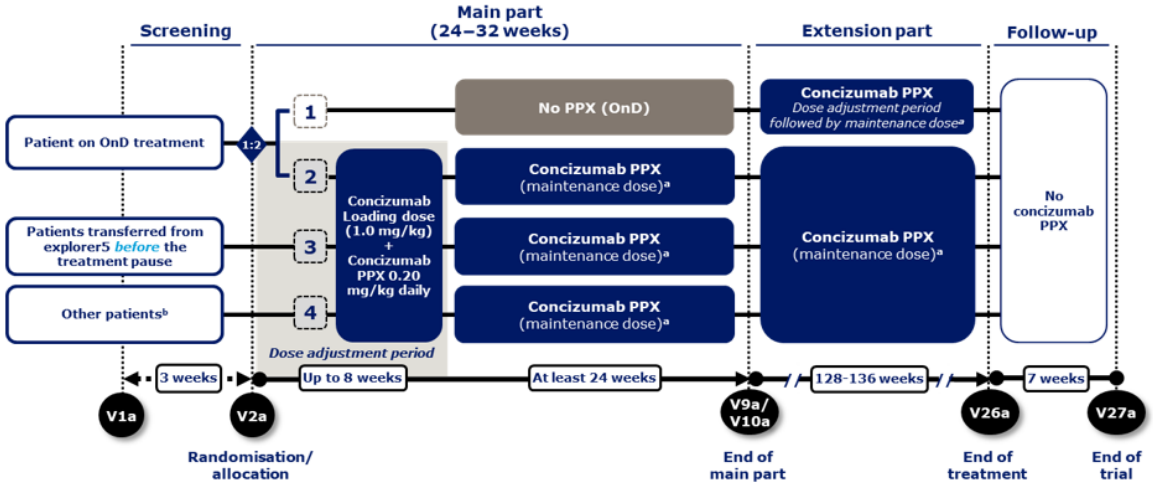
Trial 4307, similar to trial 4311 in patients with HAwI and HBwI, contained a randomised controlled part including comparison of the effect of concizumab PPX (arm 2) to on demand (No PPX) treatment with patients' usual factor-containing products (arm 1).

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.

The trial design is presented schematically in the figure below:

Figure 15: design of trial 4307



Notes: [a]The individual maintenance dose was either 0.15, 0.20 or 0.25 mg/kg concizumab. [b]Additional patients on OnD treatment or patients on PPX with factor replacement, patients from trial 4255 enrolled after the treatment pause and patients randomised to arms 1 or 2 before the treatment pause.

Abbreviations: OnD: on demand, PPX: prophylaxis, V: visit.

Updated trial design after the treatment pause

Below the updated trial design after the concizumab treatment pause and treatment restart.

At the patient level the trial consists of:

- a 3-week screening period
- main part (24-32 weeks treatment period)
- extension part (up to 265 weeks treatment period)
- a 7-week follow-up period

The trial consists of the following 4 arms:

- Arms 1 and 2 consist of patients previously treated on demand, who are randomised to:
  - Arm 1: No PPX (on demand treatment)
  - Arm 2: Concizumab PPX
- Arms 3 and 4 are allocated to receive concizumab PPX treatment and consist of:
  - Arm 3: Patients transferred from trial 4255 prior to the treatment pause
  - Arm 4:
    - Patients on previous PPX, including patients who had been on stable PPX for at least 24 weeks in the non-interventional study 4322 (NIS: non-interventional study)
    - Patients who were randomised to concizumab PPX or no PPX (on demand treatment) prior to the treatment pause
    - Patients who were in trial 4255 at the time of the treatment pause and had subsequently completed trial 4255 (phase II study) when the present trial was restarted
    - Additional on demand patients included after arms 1 and 2 were closed

Main study part (CACO)

The main part of the trial (confirmatory analyses cut-off (CACO)) is considered completed for a patient when the patient has completed at least 24 weeks of participation (screening period not included) for patients on no PPX (arm 1) or 32 weeks of participation (screening period not

included) for patients on concizumab PPX (arms 2, 3 and 4). The longer duration of the main part for arms 2, 3 and 4 is due to the dose adjustment period in these arms.

Extension part

After the main part of the trial, all patients are offered to continue in the extension part of the trial and receive treatment with concizumab for up to an additional 257 weeks (arms 2-4) or 265 weeks (arm 1).

Trial population

It was planned to screen a total of 180 adults and adolescents with haemophilia A or B without inhibitors with the aim to enroll 158 of these patients. Moreover, the aim was to enroll approximately 21 adolescent patients (defined as patients between ≥12 and <18 years at trial start) with HA and approximately 14 adolescent patients with HB.

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:

- Male aged ≥12 years at the time of signing informed consent.
- Body weight >25 kg at screening.
- Congenital severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%).
- Documented treatment with coagulation factor containing product in the last 24 weeks (not applicable for trial 4255 patients enrolled prior to the treatment pause)

Additional inclusion criteria for randomized arm 1 and 2:

- Randomisation criteria:
  On-demand patient transferred from study 4322
- On-demand patient who had ⩾5 documented treated bleeds in the last 24 weeks or ⩾10 treated bleeds during 52 weeks before screening.

The stratification variables:

- Haemophilia subtype (HA, HB)
- Bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ⩾9 bleeding episodes)

Key exclusion criteria:

- Platelets ≤100x109/L at screening.
- Fibrinogen below laboratory lower normal limit at screening.
- Hepatic dysfunction defined as AST and/or ALT >3 times the upper limit combined with total bilirubin >1.5 times the upper limit at screening.
- Renal impairment defined as eGFR ≤30 mL/min/1.73 m2 for serum creatinine measured at screening.

- Known inherited or acquired coagulation disorder other than congenital haemophilia.
- 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. Thromboembolic risk factors could include, but are not limited to, hypercholesterolaemia, diabetes mellitus, hypertension, obesity, smoking, family history of thromboembolic events, arteriosclerosis, other conditions associated with increased risk of thromboembolic events.
- A known systemic inflammatory condition requiring systemic treatment at screening.
- Treatment with emicizumab within 180 days before screening.
- Presence of confirmed inhibitor ⩾0.6 BU at screening.
- Known history of inhibitors ⩾0.6 BU in the last 5 years according to the medical records

Treatments

Concizumab PPX

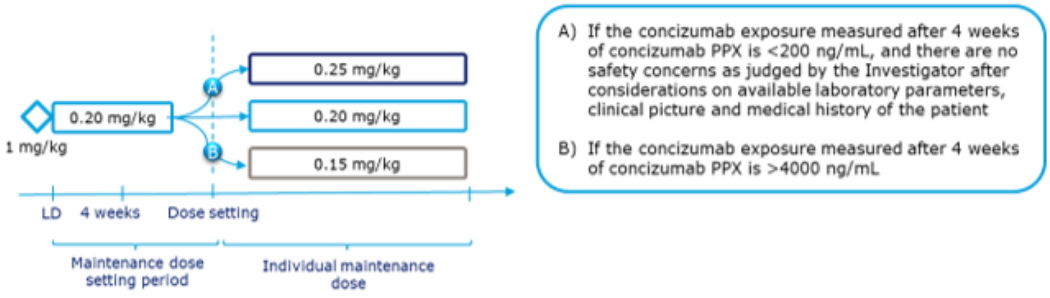
The applied dose regimen of concizumab PPX, and treatment of breakthrough bleeding were similar to study 4311 (Explorer 7) in patients with HawI and HbwI (Figure 16):

Concizumab PPX dosing is initiated with a single s.c. loading dose of 1 mg/kg followed by initial daily s.c. dose of 0.20 mg/kg. Individual maintenance dose (daily, s.c.) is set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment.

Individual maintenance dose setting took place at visit 4a.1 or at visit 9a.3 and was based on the concizumab exposure level measured at the previous visit 4a or 9a.2, as per the below criteria:

- if a patient's with concizumab exposure levels were <200 ng/mL the investigator must increase their individual maintenance dose to 0.25 mg/kg once daily.
- if a patient's with concizumab exposure levels were between 200−4000 ng/mL the investigator must maintain their individual maintenance dose at 0.20 mg/kg once daily.
- if a patient's with concizumab exposure levels were >4000 ng/mL the investigator must decrease their individual maintenance dose to 0.15 mg/kg once daily.

Figure 16. Concizumab dosing regimen upon re initiation of trials 4307 and 4311



Notes: Concizumab exposure level is measured at Visit 4a or visit 9a.2; Individual maintenance dose setting takes place at Visit 4a.1 or visit 9a.3. **Abbreviations**: LD = loading dose; PPX = prophylaxis.

On-demand treatment

Patients in arm 1 were to continue on-demand treatment with their usual replacement therapy until visit 9a (end of the main part for arm 1).

Treatment of breakthrough bleeding episodes

Given the mechanism of action, concizumab is not expected to be effective in acute treatment of a bleeding episode, and breakthrough bleeds would therefore require treatment with a coagulation factor or bypassing agent. The patient was required to contact the site when they have a suspected bleed. The original dosing schedule for prophylactic treatment with concizumab was to continue independent of bleeding episodes and their treatment.

All mild to moderate bleeds occurring during the trial were treated with the patient's usual factor-containing product in line with the guidance provided in the protocol (Table 16). For mild and moderate breakthrough bleeding episodes, use of the lowest locally approved dose of factor product or bypassing agent has been recommended while on concizumab PPX. 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.

Severe and life-threatening bleeding episodes. From a patient safety perspective, specific recommendations for the management of severe and life-threatening bleeding episodes are not considered feasible as such management often poses several complex clinical challenges that need to be addressed case by case by the treating physicians hereby tailoring and securing the optimal treatment, which cases may be high factor replacement doses for extended periods of time.

Table 164: Guidance on management of mild and moderate bleeds during concizumab PPX

	FVIII SHL	FVIII EHL	FIX SHL	FIX EHL	rFVIIa	aPCC	ByClot®
Contact centre (PI)	The patient must 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[a]	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[b]						
Anti-fibrinolytics	Local/topical use is allowed. Use of single systemic doses is allowed after careful benefit-risk evaluation					Not recommended	Not recommended

Notes: [a]Lowest dose in accordance with local labelling. [b]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: aPCC= activated Prothrombin complex concentrate; EHL=extended half-life; rFVII=recombinant factor VII; SHL=standard half-life,

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 are allowed during the trial. During the perioperative period, patients continued daily concizumab prophylaxis. Planned major surgery was not allowed.

Treatment compliance

When patients self-administered trial product at home, compliance with trial product administration was assessed by the investigator and the assessment documented in patient medical records at each dispensing visit, where the information was available. If any suspicion of non-compliance was to arise, apart from occasionally missed doses, the site was to enter into a dialogue with the patient in order to re-emphasize the importance of compliance and uncover barriers to compliance. This dialogue was to be documented.

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 HA 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 HB 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 HA 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 HB without inhibitors
- To investigate the safety of concizumab PPX in adult and adolescent patients with HA or HB without inhibitors

Outcomes/endpoints

Primary endpoints

- number of treated spontaneous and traumatic bleeding episodes in patients with HA without inhibitors
    - For on-demand (arm 1): From randomisation after the pause (week 0) up until start of concizumab treatment (week 24)
    - For concizumab (arm 2): From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)
- number of treated spontaneous and traumatic bleeding episodes in patients with HB without inhibitors

- For on-demand (arm 1): From randomisation after the pause (week 0) up until start of concizumab treatment (week 24)
- For concizumab (arm 2): From start of the new concizumab dosing regimen (week 0) up until the confirmatory analyses cut-off (at least 32 weeks)

Confirmatory secondary efficacy endpoints

- number of treated spontaneous and traumatic bleeding episodes in patients with HA without inhibitors
  - Arm 4 patients who have been on stable PPX at least 24 weeks in non-interventional study NN7415-4322 (NIS) explorer 6, hereafter referred to as study 4322)
    - For previous PPX (study 4322): From the point in time where PPX is stable and up until the end of study
    - For concizumab PPX (trial 4307): From the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off (at least 24 weeks)
- number of treated spontaneous and traumatic bleeding episodes in patients with HB without inhibitors)
  - Arm 4 patients who have been on stable PPX at least 24 weeks in study 4322
    - For previous PPX (study 4322): From the point in time where PPX is stable and up until the end of study
    - For concizumab PPX (trial 4307): From the point in time where the concizumab maintenance dose is confirmed, increased or decreased and up until the confirmatory analyses cut-off (at least 24 weeks)

Supportive secondary endpoints

- Number of treated spontaneous bleeding episodes, number of treated spontaneous and traumatic joint bleeds, number of treated spontaneous and traumatic target joint bleeds (patients with HA without inhibitors)
- Number of treated spontaneous bleeding episodes, number of treated spontaneous and traumatic joint bleeds, number of treated spontaneous and traumatic target joint bleeds in patients with haemophilia B without inhibitors
- 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) in patients with HA or HB without inhibitors

Exploratory endpoints

- Change from baseline to week 24 in patient reported outcomes in patients with HA or HB without inhibitors
- Patient preference assessed by questionnaire at week 24 in patients with HA or HB without inhibitors

Bleeding rate definitions

Bleeding rate is defined as the number of bleeds over the respective observation periods (Table 17, Table 18, Table 19). 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 175: 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 186: 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 197: 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.

Estimands

Estimand for primary objective

The estimand for the primary objective for **patients with HA** is as follows:

The population-level summary measure is the treatment ratio of the ABRs for treated spontaneous or traumatic bleeding episodes up until the confirmatory analysis cut-off between the 2 randomised treatment regimens in the target patient population while patients are adhering to the allocated treatment regimen.

Intercurrent event strategy:

1) Permanent treatment discontinuation: Data from the period after permanent treatment discontinuation are not included.
2) Temporary treatment discontinuation after restart of the trial: The 'treatment policy' strategy is used meaning that the data from this period are included.
3) Use of factor-containing products not related to treatment of a bleed (ancillary therapy): The data during this period are not included.
4) Minor surgery: The 'treatment policy' strategy is used meaning the data from this period are included.

The same applies for the estimand for **patients with HB** where HA in the target patient population is substituted with HB.

Sample size

The sample size calculation was determined based on the estimand for the primary and confirmatory secondary objectives. In the calculations, it was assumed that the treatment duration was 24 weeks for patients in arm 1 and 32 weeks for patients in arm 2. For the comparison of previous PPX to concizumab PPX in arm 4, it was assumed that the treatment duration was 38 weeks (estimated from study 4322) on the previous PPX regimen and 24 weeks on the concizumab maintenance dose. The primary estimands associated with the primary endpoints were addressed using a negative binomial regression analysis. When evaluating the power of this analysis with exposure time as offset and treatment as factor, 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 comparator 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).

The estimands associated with the confirmatory secondary endpoints were also addressed using a negative binomial regression analysis. When evaluating the power of this analysis (with exposure time as offset and treatment as factor and incorporating within-patient repeated measurements using an unstructured covariance matrix) with respect to showing non-inferiority of concizumab PPX versus previous PPX in a within-patient comparison the assumptions were:

- A concizumab ABR of between 3 and 5
- An ABR for previous PPX of 4
- A non-inferiority margin of 2.0 on the relative scale
- A sample size of 30 and a yearly over-dispersion of 13
- A 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%.

Randomisation

Clinical trial 4307 is an open-label trial.

Blinding (masking)

In the main part of the trial, patients were randomised (2:1) to concizumab PPX or on demand treatment (no PPX).

Patients in the randomised arms (arms 1 and 2) of the trial were stratified according to:

- haemophilia type (HA, HB)
- bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ≥9 bleeding episodes) Randomisation and stratification were based on information in the medical records.

Randomisation criteria arm 1 and 2:

- On-demand patient transferred from study 4322
- On-demand patient who had ≥5 documented treated bleeds in the last 24 weeks or ≥10 treated bleeds during 52 weeks before screening.

Statistical methods

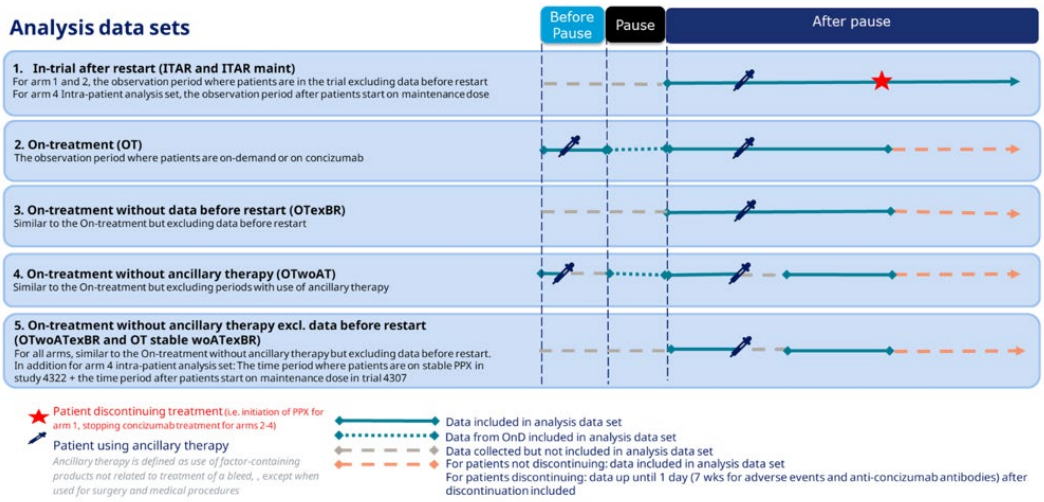
CACO

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 (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.

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.

Figure 17. Defined analysis data sets trial 4307



Main analytical approach

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.

Sensitivity and supplementary analyses for the primary endpoint

A tipping point analysis (sensitivity analysis 1) was implemented for each haemophilia subtype to investigate the missing at random assumption for the patients who permanently discontinued concizumab treatment, whereby patients in arm 2 who permanently discontinued treatment prior to the CACO at week 32 were modelled with a penalty of increasing bleeding rate for the missing period after permanent treatment discontinuation until the conclusion of superiority was changed. Sensitivity analysis 2 investigated the totality of collected data from the randomised arms, where the primary analyses were repeated after including patients from the initial randomisation. In this sensitivity analysis the initial and the new dosing regimens were both included to maximise the amount of data used.

The supplementary analysis 1 investigated impact of handling of the first intercurrent event of "permanent treatment discontinuation" and the third intercurrent event of periods of "use of factor products not related to treatment of a bleed" on the primary analysis by replacing the hypothetical strategy with the treatment policy strategy. The supplementary analysis 2 investigated the dependence on model assumptions of the parametric approach for primary analysis by using a non-parametric Van Elteren test using bleeding frequency (<9 or ≥9 bleeding episodes during the past 24 weeks prior to screening) as stratum comparing the ABRs between arm 1 (no PPX) and arm 2 (concizumab PPX).

Confirmatory secondary efficacy endpoint

The ***IPAS*** and the '***OT stable woATexBR'*** analysis data set were used. The analysis was done using a negative binomial regression model, with the logarithm of the exposure time as offset and treatment as a factor. Within-patient repeated measurements were incorporated using an unstructured covariance matrix. Non-inferiority was confirmed if the upper limit of the 95% CI was below 2.0.

A sensitivity tipping point analysis was implemented for each haemophilia subtype to investigate the missing at random assumption for patients who permanently discontinued concizumab treatment after the dose-adjusting step and before 24 weeks of treatment had been observed. Unlike the analysis model for the primary endpoint analyses with different covariate distribution, the confirmatory secondary endpoint was not analysed twice as the model for this analysis did not use any covariates.

Other endpoints and assessments

The bleed-related endpoints and assessments were calculated in the same way as done for the primary endpoints. The assessment of zero treated spontaneous or traumatic bleeds was analysed between arm 1 (no PPX) and arm 2 (concizumab PPX) using a logistic regression model with

treatment and bleeding frequency (<9 or ≥9 bleeding episodes during the past 24 weeks prior to screening) as fixed effects based on the FAS and the 'OTwoATexBR' analysis data set.

Changes from baseline to weeks 4, 8, 16 and 24 for all exploratory endpoints related to PRO questionnaires, except for those related to the Hemo-TEM, were analysed using a MMRM with treatment and bleeding frequency (<9 or ≥9 bleeding episodes during the past 24 weeks prior to screening) as factors, and the baseline score as a covariate. Endpoints related to the Hemo-TEM were analysed using an ANCOVA.

Analysis at 56-week data cut-off **(Newly submitted data in this submission)**

After 56 weeks of treatment, an additional evaluation was made assessing bleeding episode related endpoints and safety for concizumab. 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). No specific objectives are defined in relation to the 56-week cut-off.

For the analyses related to the 56-week cut-off, no statistical hypotheses are tested. Descriptive statistics were performed. Continuous endpoints/assessments were presented using descriptive statistics which included min, max, mean, SD, median, and quartiles. Event data (including AEs) were summarised including number of patients with an event/episode, percentage of patients with an event/episode, number of events/episodes and rate of events/episodes. Categorical assessments were summarised by number and percent of patients in each category.

Analysis sets. For the assessment of bleeding episodes the FAS using the On-treatment without ancillary therapy excl. data before restart dataset was used. For assessment of safety not relating to events, the SAS using the On-treatment without data before restart dataset was used. For assessment of safety relating to events, the SAS using the On-treatment and On-treatment without data before restart dataset was used.

Bleed-related assessments. The assessments related to bleeding episodes was addressed by use of the FAS and the "On-treatment without ancillary therapy excl. data before restart" analysis dataset. The number of 'treated spontaneous and traumatic bleeding episodes' as event/count data was presented using descriptive statistics.

Results

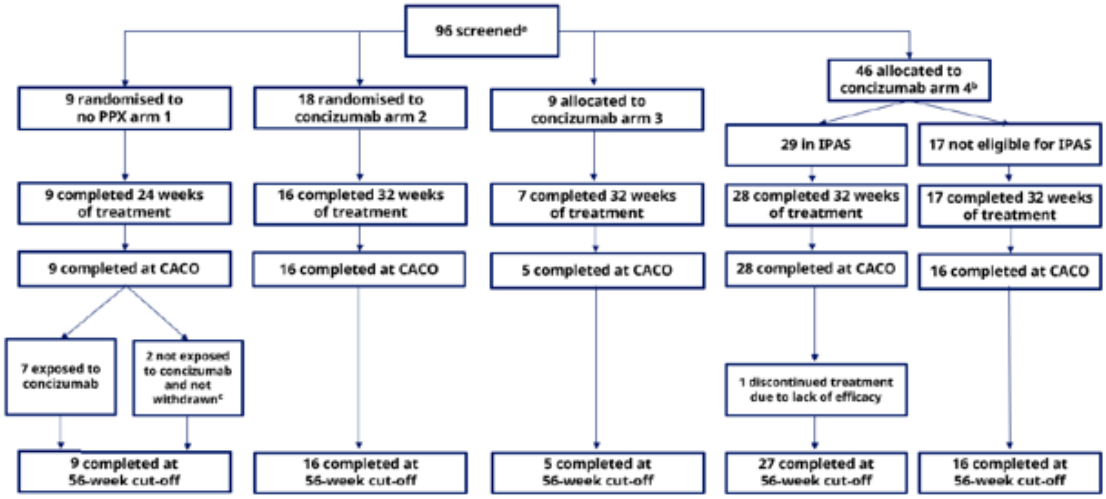
Participant flow

Patients with HA

CACO. Of the 82 patients with HA who were randomised/allocated to treatment after the treatment pause, 8 patients had permanently discontinued concizumab PPX treatment at the CACO (2 patients due to investigator decision, 2 patients due to AEs (PTs: cardiac failure and intra-abdominal haemorrhage), 1 patient due to lack of efficacy and 3 patients due to other reasons).

At 56-week cut-off, 1 patient with HA in arm 4 had discontinued concizumab PPX treatment due to lack of efficacy. At the 56-week cut-off, 71 patients had completed treatment in concizumab PPX arms 1−4 (2 patients from Ukraine were not counted as discontinued from trial or treatment).

Figure 18. Disposition of patients with HA enrolled after the treatment pause at the CACO and 56 week cut off trial 4307



Notes: [a]Before or after the treatment pause. Patients transferred from trial 4255 after the treatment pause were allocated to arm 4. Patients randomised to arms 1 and 2 before the pause were also allocated to arm 4 after restart. 8 patients did not restart treatment after the pause, as shown: [b]Excluding 1 patient who withdrew before the treatment restart.

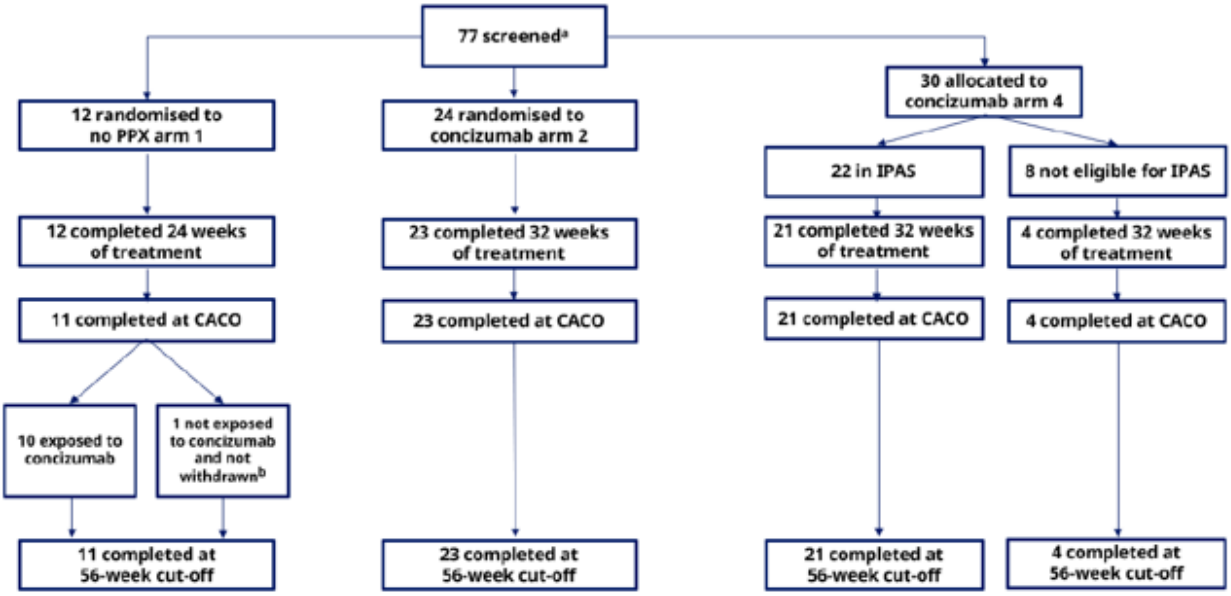
The IPAS was used for a comparison of stable previous PPX regimen in study 4322 to concizumab PPX. **Abbreviations**: CACO: confirmatory analyses cut-off, HA: haemophilia A without inhibitors, IPAS: intra-patient analysis set, PPX: prophylaxis.

Patients with HB

CACO. Of the 66 patients with HB, who were randomised/allocated to treatment after the treatment pause, 6 patients permanently discontinued concizumab PPX treatment (1 patient due to investigator decision, 1 patient due to AE (PT: injection site pain), 1 patient due to a protocol deviation, 3 patients due to other reasons). 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. A total of 59 patients had completed treatment at the CACO: 48 patients from PPX arms 2–4 and 11 patients from no PPX (arm 1).

At the 56 week cut-off, 58 patients had completed treatment in concizumab PPX arms 1−4 (1 patient from India in arm 1 was not switched to concizumab PPX after 24 weeks in on demand treatment as he underwent liver transplant surgery but was not withdrawn).

Figure 19. Disposition of patients with HB enrolled after the treatment pause at the CACO and 56 week cut off trial 4307



Notes: [a]Before or after the treatment pause. Reasons for withdrawal from the trial are shown.
Patients transferred from trial 4255 after the treatment pause were allocated to arm 4. The IPAS was used for a comparison of stable previous PPX regimen in study 4322 to concizumab PPX.

[b]Note that 1 patient was not exposed to concizumab

Abbreviations: CACO = confirmatory analyses cut-off; HB: haemophilia B without inhibitors; IPAS = intra-patient analysis set, PPX = prophylaxis.

Recruitment

The trial was conducted globally, at 76 sites in 31 countries.

Initiation date: 13 November 2019. Data-base Lock: 10 March 2023. Estimated trial completion date: 09 June 2026. The cut-off date for inclusion of data from all completed and ongoing trials in the current application was 30 September 2024.

Conduct of the study

Before and after the treatment pause, a total of 96 patients with HA and 77 patients with HB were screened. Two patients (both with HB) failed screening and 15 patients withdrew before initial randomisation/allocation, and an additional 8 patients did not restart treatment after the pause.

When concizumab treatment was paused, only 12% (i.e., 7 out of 60) of the planned number of randomised patients (arm 1 or 2) in trial 4307 had been enrolled (2 patients in arm 1 (HA n=1; HB n=1) and 5 patients in arm 2 (HA: n=3, and HB: n=2)). It was agreed with health authorities to restart 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. Patients who were allocated to arms 3 and 4 before the pause were to re-enter the arm they were initially allocated to.

Patients enrolled after the treatment pause (relevant for efficacy evaluation)

When concizumab treatment restarted, 148 patients (n=82 with HA, and n=66 with HB) in total were randomised/allocated to treatment (no PPX or concizumab PPX), and were included in the

FAS. Eight (8) patients with HA (of the 156 patients in the SAS who were randomised/allocated to treatment before the treatment pause) did not restart treatment after the pause.

The initial protocol that was in use before treatment pause was version 2.0, dated 6 June 2019. 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. Furthermore, the concizumab clinical development programme was paused (treatment pause) while the thromboembolic events were investigated and consequently, the trial design and statistical considerations were updated to reflect the impact of the sponsor-initiated treatment pause. 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 were categorised as important or non-important. There were 47 trial site level and 277 patient level important protocol deviations (Table 20), of which 3 site level and 28 patient level deviations were due to the COVID-19 pandemic. Many of the protocol deviations (45 trial site level and 211 patient level deviations) were described previously (Trial 4307 CACO). Overall, the protocol deviations were not considered to have an impact on the safety of the patients, the integrity of the trial or interpretability of the trial data.

Table 20: Summary of important protocol deviations at trial site and patient level

Protocol deviation category	Site level (number of deviations)	Patient level (number of deviations)
Informed consent	2	14
Inclusion/exclusion criteria	1	10
Treatment administration	6	67
Trial procedures/assessments	34	106
SAE notification/safety procedures	0	13
Concomitant medication/medical intervention	1	37
Patient visit schedule	0	5
Privacy and data protection	3	12
Patient contact schedule	0	13
Total	**47**	**277**

Abbreviations: SAE: serious adverse event.

Treatment compliance

Treatment non-compliance important protocol deviations concerned missed doses of concizumab for 4 or more consecutive days or 6 or more days within a 14-day period. In total, there were 51 patient level protocol deviations concerning treatment non-compliance in 40 patients. Of the 51 patients, 7 patients missed 4 or more consecutive concizumab doses for various reasons (holiday, lack of IMP at site, non-compliance), including 2 patients who missed consecutive doses on 2 separate occasions. One adolescent had no AEs but did have a severe bleeding episode during the period of non-compliance. Furthermore, 13 patients tested positive for COVID-19 and concizumab treatment was not temporarily paused in error. The majority of the remaining protocol deviations were related to late dose adjustment or incorrect dosing.

Baseline data

Demographics

Demographics and baseline characteristics for all 148 patients in the OTexBR analysis data set, which excluded data from before the treatment pause, who were randomised to arm 1 (no PPX) or treated with the new concizumab PPX dosing regimen are summarised in table 21.

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.

Table 218: Demographics and baseline characteristics - summary - HA+HB - OTexBR - full analysis set.

	No PPX	Concizumab PPX			Total
	(arm 1) N (%)	(arm 2) N (%)	(arm 3) N (%)	(arm 4) N (%)	N (%)
N in FAS and OTexBR ADS	21	42	9	76	148
Age group (years)					
Adolescents (12-17 years)	7 (33.3)	10 (23.8)	0	21 (27.6)	38 (25.7)
Adults (18-64 years)	12 (57.1)	32 (76.2)	7 (77.8)	55 (72.4)	106 (71.6)
Elderly/very elderly (65-84 years)	2 (9.5)	0	2 (22.2)	0	4 (2.7)
Ethnicity					
Hispanic or Latino	2 (9.5)	1 (2.4)	2 (22.2)	7 (9.2)	12 (8.1)
Not Hispanic or Latino	19 (90.5)	41 (97.6)	7 (77.8)	68 (89.5)	135 (91.2)
Not Reported	0	0	0	1 (1.3)	1 (0.7)
Race					
American Indian or Alaska Native	0	0	0	3 (3.9)	3 (2.0)
Asian	7 (33.3)	18 (42.9)	3 (33.3)	14 (18.4)	42 (28.4)
Black or African American	1 (4.8)	2 (4.8)	0	1 (1.3)	4 (2.7)
White	13 (61.9)	21 (50.0)	6 (66.7)	57 (75.0)	97 (65.5)
Not Reported	0	0	0	1 (1.3)	1 (0.7)
Other	0	1 (2.4)	0	0	1 (0.7)
BMI (kg/m^2)					
N	20	42	9	76	147
Mean (SD)	22.4 (4.3)	24.0 (5.8)	25.5 (4.9)	26.5 (5.3)	25.2 (5.5)
Family history of haemophilia					
Yes	10 (47.6)	25 (59.5)	6 (66.7)	40 (52.6)	81 (54.7)
No	5 (23.8)	14 (33.3)	1 (11.1)	25 (32.9)	45 (30.4)
Unknown	6 (28.6)	3 (7.1)	2 (22.2)	11 (14.5)	22 (14.9)
Type of previous treatment, N (%)					
N	21 (100.0)	41 (100.0)	9 (100.0)	69 (100.0)	140 (100.0)
On demand	20 (95.2)	40 (97.6)	2 (22.2)	9 (13.0)	71 (50.7)
Prophylaxis	4 (19.0)	4 (9.8)	8 (88.9)	63 (91.3)	79 (56.4)

Baseline HA/HB disease characteristics

A total of 82 patients (55.4%) had HA and 66 patients (44.6%) had HB. Of the 82 patients with HA, 23 (28.0%) were adolescents and of the 66 patients with HB, 15 (22.7%) were adolescents. Across the treatment arms, 81 patients (54.7%) had a family history of haemophilia, 47/82 (57.3%) of patients with HA and 34/66 (51.5%) patients with HB.

The type of previous treatment regimen patients were on is presented in Table 22. All patients in arms 1 and 2 should have been treated on-demand prior to enrolment. Due to a reporting error, no on-demand treatment was reported in 1 patient in arm 1 and arm 2 each. However, prior on-demand treatment was confirmed in both. The mean (SD) time on the previous treatment regimen was 36.2 (69.2) months for on-demand treatment and 45.7 (42.3) months for PPX. The mean (SD) ABR was 24.0 (30.9) for all patients previously on an on-demand treatment regimen and 31.7 (198.4) for patients previously on PPX.

Prior to enrollment, subjects with HA received on-demand treatment in 32/82 (42.1%) and prophylaxis in 49/82 (64.5%) subjects. The mean (SD) ABR was 19.0 (12.7) for HA patients previously on an on-demand treatment regimen and 5.6 (10.9) for patients previously on PPX.

Subjects with HB received on-demand treatment in 39/66 (60.9%) and prophylaxis in 30/66 (46.9%) subjects. 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.

Table 229: Haemophilia details - summary - HA+HB - OTexBR - full analysis set

	No PPX	Concizumab PPX			Total
	(arm 1) N (%)	(arm 2) N (%)	(arm 3) N (%)	(arm 4) N (%)	N (%)
N in FAS	21	42	9	76	148
N in FAS and ADS	21	42	9	76	148
Classification of haemophilia type					
N	21 (100.0)	42 (100.0)	9 (100.0)	76 (100.0)	148 (100.0)
Haemophilia A	9 (42.9)	18 (42.9)	9 (100.0)	46 (60.5)	82 (55.4)
Haemophilia B	12 (57.1)	24 (57.1)	0 (0.0)	30 (39.5)	66 (44.6)
Factor VIII level at diagnosis					
N	7 (100.0)	12 (100.0)	9 (100.0)	15 (100.0)	43 (100.0)
< 1%	7 (100.0)	11 (91.7)	9 (100.0)	13 (86.7)	40 (93.0)
Factor IX level at diagnosis					
N	8 (100.0)	16 (100.0)	0	3 (100.0)	27 (100.0)
< 1%	5 (62.5)	13 (81.3)	0	2 (66.7)	20 (74.1)
1-2%	1 (12.5)	2 (12.5)	0	1 (33.3)	4 (14.8)
Family history of haemophilia					
N	21 (100.0)	42 (100.0)	9 (100.0)	76 (100.0)	148 (100.0)
Yes	10 (47.6)	25 (59.5)	6 (66.7)	40 (52.6)	81 (54.7)
No	5 (23.8)	14 (33.3)	1 (11.1)	25 (32.9)	45 (30.4)
Unknown	6 (28.6)	3 (7.1)	2 (22.2)	11 (14.5)	22 (14.9)
Family history of prothrombotic disorders					
N	21 (100.0)	42 (100.0)	9 (100.0)	76 (100.0)	148 (100.0)
Yes	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
No	13 (61.9)	27 (64.3)	7 (77.8)	16 (21.1)	63 (42.6)
Unknown	8 (38.1)	15 (35.7)	2 (22.2)	60 (78.9)	85 (57.4)

HA: haemophilia A, HB: haemophilia B, PPX: prophylaxis, OTexBR: On-treatment without data before restart.
N: number of patients, %: percentage of patients, FAS: Full analysis set, ADS: Analysis data set, SD: standard deviation, P25/P75 is the 25th/75th percentile, Min: minimum, Max: maximum.
Baseline is taken at visit 1/1a.
All HA patients reported FVIII activity level <1% at baseline laboratory data, except patient 831083 who already received PPX regimen from Explorer6.
All HB patients reported FIX activity level <=2% at baseline laboratory data.

Numbers analysed

Number of subjects. The FAS was comprised of 148 patients with HA or HB who were randomised/allocated to treatment (no PPX or concizumab PPX) after the treatment pause. There were 82 patients with HA and 66 patients with HB in the FAS.

The IPAS consisted of 51 patients with HA or HB 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. There were 29 patients with HA and 22 patients with HB in the IPAS.

The main basis for the efficacy evaluation at the 56-week cut-off is the results available for the 144 patients exposed to the new concizumab dosing regimen. The 144 patients in total comprised 80 patients with HA (73 patients across concizumab arms 2−4 plus 7 patients in arm 1 who switched to concizumab PPX from on-demand treatment at week 24) and 64 patients with HB (54 patients in arms 2 and 3 plus 10 patients in arm 1 who switched to concizumab PPX at week 24).

Four (4) patients from the FAS (in arm 1) were not included in the evaluation at the 56-week cut-off as they never received concizumab, 2 patients with HA from Ukraine not exposed to concizumab due to the war, and 2 patients with HB, due to withdrawal in one and liver transplantation surgery in one.

Concizumab exposure

CACO. Concizumab exposure in trial 4307 was 79.0 patient years for the patients with HA and 45.2 patient years for the patients with HB. Mean (SD) exposure time in weeks was 51.5 (25.7) weeks for all patients with HA and 36.8 (21.4) weeks for all patients with HB.

56-week data cut off. Concizumab exposure was 111.9 patient years for the patients with HA and 71.1 patient years for the patients with HB; the mean (SD) exposure time was 73.0 (28.3) weeks for all patients with HA and 58.5 (25.1) weeks for all patients with HB.

A total of 60 (76.9%) patients with HA remained on the 0.20 mg/kg daily dose level, 13 (16.7%) had increased their daily dose to 0.25 mg/kg and 5 (6.4%) had decreased their daily dose to 0.15 mg/kg. A total of 33 (55.0%) of patients with HB remained on the 0.20 mg/kg daily dose level, 22 (36.7%) had increased their daily dose to 0.25 mg/kg and 5 (8.3%) had decreased their daily dose to 0.15 mg/kg.

Exposure of haemostatic medication

CACO. A total of 250 bleeds in 50 patients with HA were treated with FVIII, including 234 bleeds in 46 HA patients on concizumab PPX (study arm 2-4). A total of 207 bleeds in 43 patients with HB were treated with FIX, including 192 bleeds in 38 HB patients on concizumab PPX (study arm 2-4).

56-week data cut-off. A total of 355 bleeds in 56 patients with HA were treated with FVIII, and 307 bleeds were treated with FIX in 48 HB patients.

Outcomes and estimation

Bleed-related outcome

Details of treated bleeding episodes until the CACO

Patients with HA

For the randomized comparison, 12 out of 18 patients on concizumab PPX (arm 2) reported 65 treated bleeding episodes up until the CACO. Most of these bleeding episodes (69.2%) were spontaneous, 27.7% were traumatic and 3.1% was surgical. All bleeding episodes (100%) were classified as mild/moderate. Bleeds were most frequently located in joints (80.9%) and muscle (4.4%).

Patients on no PPX (arm 1), 9 patients (100%) reported 122 treated bleeding episodes up until the CACO. Most of these bleeding episodes (69.7%) were spontaneous, 27.9% were traumatic and none were surgical. All bleeding episodes (100%) were classified as mild/moderate. Bleeds were most frequently located in joints (71.7%) and muscle (12.6%).

Patients on concizumab PPX (arms 1−4), 51 patients (63.8%) reported 251 treated bleeding episodes up until the CACO. Most of these bleeding episodes (57.0%) were spontaneous, 41.4% were traumatic and 1.6% were surgical. Most bleeding episodes (96.0%) were classified as mild/moderate, while 4% were classified as severe. Bleeds were most frequently located in joints (68.5%) and muscle (12.7%) (Table 23).

Table 23: 10Bleeding episodes - all treated - summary - HA - OTwoATexBR - full analysis set- CACO

	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 (%) E [%]	
N in FAS	9	7		18		9		46		73		80	
N in FAS and ADS	9(100)	7(100)		18(100)		9(100)		46(100)		73(100)		80(100)	
Zero treated bleeds*	0	3(42.9)		6(33.3)		4(44.4)		15(32.6)		25(34.2)		28(35.0)	
Treated bleeding episodes	9(100)	122[100]	4(57.1)	16[100]	12(66.7)	65[100]	4(44.4)	4[100]	31(67.4)	166[100]	47(64.4)	235[100]	51(63.8)	251[100]
Cause of bleeding episodes														
Spontaneous	9(100)	85[69.7]	4(57.1)	10[62.5]	12(66.7)	45[69.2]	3(33.3)	3[75.0]	26(56.5)	85[51.2]	41(56.2)	133[56.6]	45(56.3)	143[57.0]
Traumatic	5(55.6)	34[27.9]	2(28.6)	5[31.3]	7(38.9)	18[27.7]	1(11.1)	1[25.0]	24(52.2)	80[48.2]	32(43.8)	99[42.1]	34(42.5)	104[41.4]
Surgical	0		1(14.3)	1[6.3]	2(11.1)	2[3.1]	0		1(2.2)	1[0.6]	3(4.1)	3[1.3]	4(5.0)	4[1.6]
Missing	2(22.2)	3[2.5]	0		0		0		0		0		0	
Location of bleeds														
Treated bleeds	9(100)	127[100]	4(57.1)	16[100]	12(66.7)	68[100]	4(44.4)	4[100]	31(67.4)	179[100]	47(64.4)	251[100]	51(63.8)	267[100]
Joint	9(100)	91[71.7]	4(57.1)	11[68.8]	11(61.1)	55[80.9]	2(22.2)	2[50.0]	27(58.7)	115[64.2]	40(54.8)	172[68.5]	44(55.0)	183[68.5]
Target joint	7(77.8)	43[33.9]	3(42.9)	8[50.0]	11(61.1)	38[55.9]	0		2(4.3)	3[1.7]	13(17.8)	41[16.3]	16(20.0)	49[18.4]
Muscular	5(55.6)	16[12.6]	2(28.6)	3[18.8]	2(11.1)	3[4.4]	1(11.1)	1[25.0]	13(28.3)	27[15.1]	16(21.9)	31[12.4]	18(22.5)	34[12.7]
Skin	4(44.4)	7[5.5]	0		1(5.6)	1[1.5]	0		6(13.0)	17[9.5]	7(9.6)	18[7.2]	7(8.8)	18[6.7]
Gastrointestinal or Stomach/gut	0		0		1(5.6)	1[1.5]	0		0		1(1.4)	1[0.4]	1(1.3)	1[0.4]
Mouth, gums or nose	6(66.7)	9[7.1]	1(14.3)	1[6.3]	2(11.1)	2[2.9]	1(11.1)	1[25.0]	4(8.7)	8[4.5]	7(9.6)	11[4.4]	8(10.0)	12[4.5]
Urinary system	0		0		1(5.6)	6[8.8]	0		4(8.7)	4[2.2]	5(6.8)	10[4.0]	5(6.3)	10[3.7]
Central nervous system	0		0		0		0		1(2.2)	1[0.6]	1(1.4)	1[0.4]	1(1.3)	1[0.4]
Other	3(33.3)	4[3.1]	1(14.3)	1[6.3]	0		0		5(10.9)	7[3.9]	5(6.8)	7[2.8]	6(7.5)	8[3.0]
Classification of bleeding episodes														
Mild/moderate	9(100)	122[100]	4(57.1)	16[100]	12(66.7)	65[100]	4(44.4)	4[100]	31(67.4)	156[94.0]	47(64.4)	225[95.7]	51(63.8)	241[96.0]
Severe	0		0		0		0		2(4.3)	10[6.0]	2(2.7)	10[4.3]	2(2.5)	10[4.0]

HA: haemophilia A, PPX: prophylaxis.
N: number of patients, %: percentage of patients, E: number of bleeding episodes, FAS: Full analysis set, ADS: Analysis data set.
* patients that do not complete 24 weeks without permanent treatment discontinuation will be counted as not fulfilling this. Also, all treated bleeds with either of the four causes (spontaneous, traumatic, surgical or missing) will be taken into account.
For location of bleeds the E represents the number of bleeds and [%] is the percentage of bleeds.

Patients with HB

For the randomized comparison, 17 out of 24 patients on concizumab PPX (arm 2) reported 59 treated bleeding episodes up until the CACO. Most of these bleeding episodes (66.1%) were spontaneous, 28.8% were traumatic and 5.1% was surgical. Severe bleeding episodes was reported in 13.6%. Bleeds were most frequently located in joints (79.7%) and muscle (6.8%).

Patients on no PPX (arm 1), 11 patients (91.7%) reported 97 treated bleeding episodes up until the CACO. Most of these bleeding episodes (85.6%) were spontaneous, 14.4% were traumatic and none were surgical. Most bleeding episodes (88.7%) were classified as mild/moderate, while 11.3% were classified as severe. Bleeds were most frequently located in joints (76.6%) and muscle (12.6%).

Patients on concizumab PPX (arms 1−4), 44 patients (68.8%) reported 208 treated bleeding episodes up until CACO. Most of these bleeding episodes (63.0%) were spontaneous, 35.1% were traumatic and 1.9% were surgical. Most bleeding episodes (94.7%) were classified as mild/moderate, while 5.3% were classified as severe. Bleeds were most frequently located in joints (72.9%) and muscle (14.7%) (Table 24).

Table 24: 11Bleeding episodes - all treated - summary - HB - OTwoATexBR - full analysis set-CACO

	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 (%) E [%]
N in FAS	12	10	24	0	30	54	64
N in FAS and ADS	12(100)	10(100)	24(100)	0	30(100)	54(100)	64(100)
Zero treated bleeds*	1(8.3)	4(40.0)	6(25.0)	0	8(26.7)	14(25.9)	18(28.1)
Treated bleeding episodes	11(91.7) 97[100]	6(60.0) 16[100]	17(70.8) 59[100]	0	21(70.0)133[100]	38(70.4)192[100]	44(68.8)208[100]
Cause of bleeding episodes							
Spontaneous	11(91.7) 83[85.6]	6(60.0) 10[62.5]	12(50.0) 39[66.1]	0	16(53.3) 82[61.7]	28(51.9)121[63.0]	34(53.1)131[63.0]
Traumatic	3(25.0) 14[14.4]	3(30.0) 5[31.3]	11(45.8) 17[28.8]	0	12(40.0) 51[38.3]	23(42.6) 68[35.4]	26(40.6) 73[35.1]
Surgical	0	1(10.0) 1[6.3]	3(12.5) 3[5.1]	0	0	3(5.6) 3[1.6]	4(6.3) 4[1.9]
Location of bleeds							
Treated bleeds	11(91.7)111[100]	6(60.0) 17[100]	17(70.8) 59[100]	0	21(70.0)149[100]	38(70.4)208[100]	44(68.8)225[100]
Joint	10(83.3) 85[76.6]	6(60.0) 17[100]	14(58.3) 47[79.7]	0	19(63.3)100[67.1]	33(61.1)147[70.7]	39(60.9)164[72.9]
Target joint	8(66.7) 36[32.4]	1(10.0) 1[5.9]	9(37.5) 28[47.5]	0	7(23.3) 26[17.4]	16(29.6) 54[26.0]	17(26.6) 55[24.4]
Muscular	4(33.3) 14[12.6]	0	2(8.3) 4[6.8]	0	7(23.3) 29[19.5]	9(16.7) 33[15.9]	9(14.1) 33[14.7]
Skin	1(8.3) 6[5.4]	0	2(8.3) 2[3.4]	0	4(13.3) 9[6.0]	6(11.1) 11[5.3]	6(9.4) 11[4.9]
Gastrointestinal or Stomach/gut	0	0	2(8.3) 3[5.1]	0	2(6.7) 2[1.3]	4(7.4) 5[2.4]	4(6.3) 5[2.2]
Mouth, gums or nose	2(16.7) 2[1.8]	0	2(8.3) 2[3.4]	0	2(6.7) 5[3.4]	4(7.4) 7[3.4]	4(6.3) 7[3.1]
Urinary system	4(33.3) 4[3.6]	0	1(4.2) 1[1.7]	0	2(6.7) 2[1.3]	3(5.6) 3[1.4]	3(4.7) 3[1.3]
Central nervous system	0	0	0	0	1(3.3) 1[0.7]	1(1.9) 1[0.5]	1(1.6) 1[0.4]
Other	0	0	0	0	1(3.3) 1[0.7]	1(1.9) 1[0.5]	1(1.6) 1[0.4]
Classification of bleeding episodes							
Mild/moderate	11(91.7) 86[88.7]	6(60.0) 16[100]	14(58.3) 51[86.4]	0	20(66.7)130[97.7]	34(63.0)181[94.3]	40(62.5)197[94.7]
Severe	2(16.7) 11[11.3]	0	4(16.7) 8[13.6]	0	3(10.0) 3[2.3]	7(13.0) 11[5.7]	7(10.9) 11[5.3]

HB: haemophilia B, PPX: prophylaxis.
N: number of patients, %: percentage of patients, E: number of bleeding episodes, FAS: Full analysis set, ADS: Analysis data set.
* patients that do not complete 24 weeks without permanent treatment discontinuation will be counted as not fulfilling this. Also, all treated bleeds with either of the four causes (spontaneous, traumatic, surgical or missing) will be taken into account.

Descriptive summaries of observed ABRs at CACO

HA. ABRs for treated spontaneous and traumatic bleeding episodes in patients with HA are presented as descriptive statistics in Table 25. The overall median ABR for 73 HA patients on concizumab PPX (arms 2−4) was 1.6. 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.

Table 25: 12Bleeding episodes - descriptive statistics - HA - OTwoATexBR - full analysis set-CACO

	No PPX	Concizumab PPX				
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4	Total
N in FAS	9	7	18	9	46	73	80
N in FAS and ADS	9	7	18	9	46	73	80
Person years of exposure in ADS	4.6	2.9	15.3	11.1	49.6	76.1	79.0
Weeks of exposure in ADS							
Median	24.1	16.0	32.9	80.1	54.4	52.7	40.2
P25 ; P75	24.0 ; 28.0	8.9 ; 27.9	32.1 ; 56.4	66.6 ; 86.7	32.3 ; 80.1	32.3 ; 80.1	32.1 ; 80.0
Mean (SD)	26.7 (4.5)	21.3 (16.8)	44.4 (19.7)	64.6 (32.2)	56.3 (23.9)	54.4 (24.6)	51.5 (25.7)
Min ; Max	24.0 ; 36.3	8.1 ; 56.1	21.4 ; 80.4	6.3 ; 88.1	18.3 ; 88.1	6.3 ; 88.1	6.3 ; 88.1
Treated spontaneous and traumatic bleeding episodes							
Number of episodes	122	15	63	4	165	232	247
ABR							
Median	19.6	2.8	2.9	0.0	2.3	1.6	1.6
P25 ; P75	17.3 ; 30.4	0.0 ; 6.4	0.0 ; 5.2	0.0 ; 0.6	0.0 ; 4.9	0.0 ; 4.9	0.0 ; 4.9
Mean (SD)	27.5 (20.1)	4.5 (6.7)	4.5 (7.0)	1.1 (2.7)	4.6 (7.8)	4.2 (7.2)	4.2 (7.1)
Min ; Max	3.3 ; 71.7	0.0 ; 18.7	0.0 ; 29.5	0.0 ; 8.3	0.0 ; 37.1	0.0 ; 37.1	0.0 ; 37.1
Treated spontaneous bleeding episodes							
Number of episodes	85	10	45	3	85	133	143
ABR							
Median	19.3	1.9	1.6	0.0	0.7	0.7	0.7
P25 ; P75	7.2 ; 20.5	0.0 ; 6.4	0.0 ; 4.1	0.0 ; 0.6	0.0 ; 2.6	0.0 ; 2.0	0.0 ; 2.8
Mean (SD)	19.6 (18.0)	3.3 (4.2)	3.3 (5.2)	1.1 (2.7)	2.6 (6.2)	2.6 (5.7)	2.7 (5.5)
Min ; Max	3.3 ; 63.0	0.0 ; 11.2	0.0 ; 20.2	0.0 ; 8.3	0.0 ; 37.1	0.0 ; 37.1	0.0 ; 37.1
Treated spontaneous and traumatic joint bleeding episodes							
Number of episodes	86	11	52	2	109	163	174
ABR							
Median	13.0	1.9	2.9	0.0	1.2	0.7	0.7
P25 ; P75	10.7 ; 28.3	0.0 ; 6.4	0.0 ; 4.9	0.0 ; 0.0	0.0 ; 3.2	0.0 ; 3.2	0.0 ; 3.5
Mean (SD)	19.4 (18.5)	3.5 (4.8)	3.6 (4.3)	0.1 (0.3)	3.2 (6.6)	2.9 (5.7)	3.0 (5.6)
Min ; Max	2.2 ; 60.9	0.0 ; 13.1	0.0 ; 15.5	0.0 ; 0.7	0.0 ; 37.1	0.0 ; 37.1	0.0 ; 37.1
Treated spontaneous and traumatic target joint bleeding episodes							
Number of episodes	40	8	37	0	3	40	48
ABR							
Median	4.3	0.0	1.6	0.0	0.0	0.0	0.0
P25 ; P75	1.6 ; 13.0	0.0 ; 6.4	0.0 ; 3.3	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
Mean (SD)	9.3 (11.8)	2.7 (4.5)	2.7 (3.7)	0.0 (0.0)	0.1 (0.5)	0.7 (2.2)	0.9 (2.5)
Min ; Max	0.0 ; 37.0	0.0 ; 11.2	0.0 ; 14.0	0.0 ; 0.0	0.0 ; 3.2	0.0 ; 14.0	0.0 ; 14.0
All treated and untreated spontaneous and traumatic bleeding episodes							
Number of episodes	131	15	101	6	217	324	339
ABR							
Median	27.9	2.8	3.9	0.6	3.0	2.5	2.6
P25 ; P75	17.3 ; 30.4	0.0 ; 6.4	1.6 ; 9.7	0.0 ; 0.7	0.7 ; 5.8	0.6 ; 5.5	0.6 ; 5.7
Mean (SD)	29.7 (19.6)	4.5 (6.7)	6.3 (7.6)	1.3 (2.7)	5.9 (9.6)	5.4 (8.6)	5.4 (8.5)
Min ; Max	3.3 ; 71.7	0.0 ; 18.7	0.0 ; 29.5	0.0 ; 8.3	0.0 ; 45.1	0.0 ; 45.1	0.0 ; 45.1

HA: haemophilia A, OTwoATexBR: On-treatment without ancillary therapy excluding data before restart, The dose adjustment period in 4307 is included, PPX: prophylaxis.
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, ABR: annualised bleeding rate.
All endpoints other than 'Treated spontaneous bleeding episodes' includes bleeding episodes with missing cause.

HB. ABRs for treated spontaneous and traumatic bleeding episodes in patients with HB are presented as descriptive statistics in Table 26. The overall median ABR for 54 HB patients on concizumab PPX (arms 2−4) was 1.6. 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.

Table 2613: Bleeding episodes - descriptive statistics - HB - OTwoATexBR - full analysis set

	No PPX	Concizumab PPX				
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4	Total
N in FAS	12	10	24	0	30	54	64
N in FAS and ADS	12	10	24	0	30	54	64
Person years of exposure in ADS	6.0	2.9	18.2	0	24.0	42.3	45.2
Weeks of exposure in ADS							
Median	24.1	11.2	32.3	0.0	32.3	32.3	32.1
P25 ; P75	24.0 ; 25.5	8.1 ; 14.9	32.0 ; 44.4	0.0 ; 0.0	32.0 ; 64.3	32.0 ; 54.1	30.8 ; 51.8
Mean (SD)	26.3 (5.8)	15.3 (14.3)	39.7 (16.8)	0.0 (0.0)	41.8 (22.7)	40.8 (20.1)	36.8 (21.4)
Min ; Max	23.6 ; 44.1	7.7 ; 55.0	2.6 ; 80.3	0.0 ; 0.0	0.6 ; 87.4	0.6 ; 87.4	0.6 ; 87.4
Treated spontaneous and traumatic bleeding episodes							
Number of episodes	97	15	56	0	133	189	204
ABR							
Median	14.9	3.9	1.6	0.0	2.6	1.6	1.7
P25 ; P75	3.3 ; 22.1	0.0 ; 6.5	0.0 ; 4.8	0.0 ; 0.0	0.0 ; 8.0	0.0 ; 6.2	0.0 ; 6.4
Mean (SD)	16.2 (15.4)	4.3 (4.6)	3.2 (4.0)	0.0 (0.0)	10.2 (20.2)	7.1 (15.6)	6.7 (14.4)
Min ; Max	0.0 ; 50.9	0.0 ; 13.2	0.0 ; 11.9	0.0 ; 0.0	0.0 ; 91.3	0.0 ; 91.3	0.0 ; 91.3
Treated spontaneous bleeding episodes							
Number of episodes	83	10	39	0	82	121	131
ABR							
Median	10.8	3.4	0.3	0.0	1.2	0.8	1.0
P25 ; P75	3.3 ; 17.8	0.0 ; 4.4	0.0 ; 2.0	0.0 ; 0.0	0.0 ; 4.1	0.0 ; 3.6	0.0 ; 3.9
Mean (SD)	13.7 (14.0)	2.7 (2.5)	2.2 (3.6)	0.0 (0.0)	8.4 (19.5)	5.6 (14.9)	5.2 (13.8)
Min ; Max	0.0 ; 50.9	0.0 ; 6.5	0.0 ; 11.7	0.0 ; 0.0	0.0 ; 91.3	0.0 ; 91.3	0.0 ; 91.3
Treated spontaneous and traumatic joint bleeding episodes							
Number of episodes	80	15	47	0	95	142	157
ABR							
Median	10.0	3.9	1.3	0.0	0.9	1.0	1.3
P25 ; P75	3.3 ; 18.0	0.0 ; 6.5	0.0 ; 4.0	0.0 ; 0.0	0.0 ; 6.5	0.0 ; 4.7	0.0 ; 5.3
Mean (SD)	13.8 (15.0)	4.3 (4.6)	2.7 (3.9)	0.0 (0.0)	5.7 (11.5)	4.4 (9.0)	4.4 (8.5)
Min ; Max	0.0 ; 50.9	0.0 ; 13.2	0.0 ; 11.9	0.0 ; 0.0	0.0 ; 52.2	0.0 ; 52.2	0.0 ; 52.2
Treated spontaneous and traumatic target joint bleeding episodes							
Number of episodes	34	1	28	0	25	53	54
ABR							
Median	2.2	0.0	0.0	0.0	0.0	0.0	0.0
P25 ; P75	0.0 ; 8.1	0.0 ; 0.0	0.0 ; 1.9	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 1.6	0.0 ; 1.0
Mean (SD)	5.9 (8.2)	0.7 (2.1)	1.6 (3.2)	0.0 (0.0)	2.8 (9.6)	2.3 (7.4)	2.0 (6.9)
Min ; Max	0.0 ; 24.4	0.0 ; 6.5	0.0 ; 11.9	0.0 ; 0.0	0.0 ; 52.2	0.0 ; 52.2	0.0 ; 52.2
All treated and untreated spontaneous and traumatic bleeding episodes							
Number of episodes	128	18	72	0	169	241	259
ABR							
Median	16.5	5.0	3.2	0.0	4.8	3.5	3.9
P25 ; P75	5.4 ; 30.5	0.0 ; 9.8	0.6 ; 5.1	0.0 ; 0.0	1.6 ; 9.7	1.4 ; 8.0	1.3 ; 8.1
Mean (SD)	21.3 (19.9)	6.0 (6.7)	4.1 (4.4)	0.0 (0.0)	12.0 (20.3)	8.5 (15.8)	8.1 (14.7)
Min ; Max	0.0 ; 63.9	0.0 ; 19.6	0.0 ; 13.2	0.0 ; 0.0	0.0 ; 91.3	0.0 ; 91.3	0.0 ; 91.3

HB: haemophilia B, OTwoATexBR: On-treatment without ancillary therapy excluding data before restart, The dose adjustment period in 4307 is included, PPX: prophylaxis.
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, ABR: annualised bleeding rate.
All endpoints other than 'Treated spontaneous bleeding episodes' includes bleeding episodes with missing cause.
The arm 4 patient with an ABR of 91.3 was treated for 4 days only and had 1 bleeding episode.

Primary efficacy endpoint - number of treated spontaneous and traumatic bleeding episodes

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 CACO (at least 32 weeks) for arm 2.

Superiority of concizumab PPX treatment over no PPX (on demand treatment) was confirmed for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes at CACO, for both patients with HA and HB (Table 27).

For patients with HA, the estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.14 [0.07; 0.29]95%CI (p<0.001), corresponding to an 86% reduction in ABR for patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

For patients with HB, the estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.21 [0.10; 0.45]95%CI (p<0.001), corresponding to a 79% reduction in ABR for patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

Table 27: 14Bleeding episodes - statistical analyses – HA, HB and HAwI+HBwI - full analysis set - Trials 4307 CACO (OTwoATexBR) and 4311 at the PACO (OTwoATexIR)

		Estimated mean ABR [95% CI]		ABR ratio [95% CI]	P-value
		No PPX (arm 1)	Concizumab PPX (arm 2)		
Trial 4307 (HA)	N in FAS and ADS	9	18		
	Treated spontaneous and traumatic bleeding episodes	19.3 [11.25; 33.03]	2.7 [1.63; 4.59]	0.14 [0.07; 0.29]	p<0.001
Trial 4307 (HB)	N in FAS and ADS	12	24		
	Treated spontaneous and traumatic bleeding episodes	14.8 [8.14; 26.86]	3.1 [1.91; 5.04]	0.21 [0.10; 0.45]	p<0.001
Trial 4311 (HAwI+HBwI)	N in FAS and ADS	19	33		
	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

Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors, HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis; SD = standard deviation.

Sensitivity Analyses.

(1) When imputing the number of bleeding episodes for the patients in arm 2 who permanently discontinued treatment prior to week 32 and adding a penalty to the imputed number of episodes for these patients, the increase in the number of bleeding episodes required to tip the superiority conclusion of the primary analysis was 55 for HA, and 28 for HB. The magnitude of this penalty was considered implausible, thereby supporting the robustness of the superiority conclusion of the primary analysis.

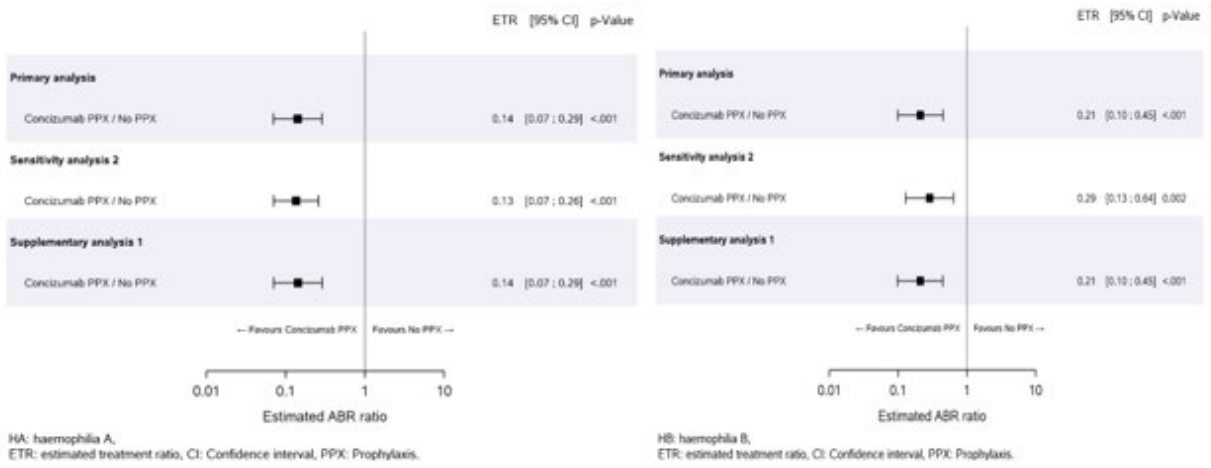
(2) The estimated treatment ratios and associated 95% CIs were similar across the primary analysis and sensitivity analysis 2, that investigated the totality of both randomisations by including the 4 patients with HA and 3 patients with HB from the initial randomisation (before the treatment pause).

Supplemental analyses.

(1) Repeating the primary analysis while handling all intercurrent events by use of the treatment policy strategy including 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), did not impact the conclusion of the primary analysis for HA as well as for HB.

(2) Secondly, Van Elteren non-parametric test comparing ABRs in patients on concizumab PPX (arm 2) and no PPX (arm 1) demonstrated a statistically significant difference in 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 20. Bleeding episodes - treated spontaneous and traumatic - forest plot – primary analysis, sensitivity analysis and supplementary analysis – HA (left) HB (right) - full analysis set



Post-hoc analysis of ABRs based on actual covariate distribution

Mean ABRs presented in Table 28 are marginal estimates, assuming a balanced distribution of covariate of bleeding frequency prior to screening in arms 1 and 2. The marginal estimates of ABRs, based on actual covariate distribution in the study population along with the estimated ABR ratios and corresponding 95% CIs are presented in Table 29.

Table 2815: Bleeding episodes – Statistical analyses (actual covariate distribution)- HA and HB – Trial 4307 CACO – full analysis set (OTwoATexBR)

	Patients with HA			Patients with HB		
	Estimated mean ABR[a] [95% CI]		ABR ratio [95% CI]	Estimated mean ABR[a] [95% CI]		ABR ratio [95% CI]
	No PPX (arm 1)	Concizumab PPX (arm 2)		No PPX (arm 1)	Concizumab PPX (arm 2)	
Primary endpoint Treated spontaneous and traumatic bleeding episodes	24.5 [14.50;41.48]	3.5 [2.18;5.54]	0.14 [0.07; 0.29] p<0.001	15.4 [8.55;27.78]	3.2 [2.00;5.22]	0.21 [0.10; 0.45] p<0.001
Treated spontaneous and traumatic joint bleeding episodes	17.6 [10.19;30.39]	2.8 [1.71;4.56]	0.16 [0.08; 0.33]	13.1 [6.63;26.01]	2.7 [1.58;4.72]	0.21 [0.09; 0.50]
Treated spontaneous and traumatic target joint bleeding episodes[b]	8.8 [4.84;15.91]	2.0 [1.19;3.47]	0.23 [0.11; 0.48]	5.4 [2.22;13.21]	1.9 [0.95;3.67]	0.34 [0.11; 1.06]
All treated and untreated spontaneous and traumatic bleeding episodes	26.8 [15.37;46.72]	6.2 [4.03;9.48]	0.23 [0.11;0.47]	20.2 [11.90;34.17]	4.2 [2.71;6.37]	0.21 [0.10; 0.41]

Notes: p-value is for two-sided tests of no difference from 1.

Bleeding endpoints were 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. [a] The estimated mean ABRs are marginal estimates based on the covariate distribution present in the study population. [b]Treated spontaneous and traumatic target joint bleeding episodes only include patients having target joint(s) at baseline.

Abbreviations: ABR: annualised bleeding rate, CI: Confidence interval, HA: haemophilia A, HB: haemophilia B, N: number of patients, OTwoATexBR: On-treatment without ancillary therapy excluding data before restart. PPX: Prophylaxis.

Confirmatory secondary endpoints

Bleeding episodes – intra-patient comparison

In addition to the evidence of overall effect provided by the primary analyses, confirmatory secondary analyses were performed within a different population. Confirmatory secondary analyses consisted of intra-patient comparison of bleeding-related endpoints in a different population (subgroup 4) on previous PPX compared with concizumab PPX at CACO using the IPAS and the OT

stable woATexBR analysis data set. This reflects the observation period in which patients are considered to be on stable PPX in study 4322 or stable concizumab PPX in trial 4307.

The confirmatory secondary endpoints compared the 'number of treated spontaneous and traumatic bleeding episodes' on stable concizumab PPX (in trial 4307) with the 'number of treated spontaneous and traumatic bleeding episodes' to stable previous PPX (in study 4322) for the patients in the IPAS. The stable regimen for previous PPX treatment was defined as the time after an initial period on PPX treatment of at least 24 weeks in study 4322 and who entered the maintenance period in the present trial.

Number of treated spontaneous and traumatic bleeding episodes

- HA. For patients with HA, the median ABR for treated spontaneous and traumatic bleeding episodes was 2.3 on concizumab PPX (trial 4307) and 2.2 on previous PPX (study 4322).
- HB. For patients with HB, the median ABR was 1.4 on concizumab PPX (trial 4307) and 2.1 on previous PPX (study 4322).
-

Both for patients with HA and HB, the median ABRs for the additional bleed-related assessments in the intra-patient comparison were numerically similar or lower with concizumab PPX (trial 4307) than with previous PPX (study 4322).

Table 29: Treated spontaneous and traumatic bleeding episodes, HA and HB, intra patient analysis set trial 4307 at the CACO and at 56 week cut off (OT stable woATexBR)

	HA			HB		
	Previous PPX (study 4322)	Concizumab PPX at CACO (trial 4307)	Concizumab PPX at 56-week cut-off (trial 4307)	Previous PPX (study 4322)	Concizumab PPX (trial 4307)	Concizumab PPX at 56-week cut-off (trial 4307)
N in IPAS and ADS	29	29	29	22	22	22
Person years of exposure in ADS in study or trial	28.9	31.7	44.6	22.1	15.9	25.9
Mean exposure (SD)	51.9 (26.4)	57.0 (23.8)	80.3 (25.1)	52.5 (33.6)	37.6 (19.4)	61.4 (21.6)
Treated spontaneous and traumatic bleeding episodes						
No. of bleeding episodes	105	105	137	75	91	134
ABR						
Median	2.2	2.3	1.7	2.1	1.4	1.3
Mean (SD)	3.8 (4.0)	5.7 (10.5)	4.8 (9.4)	3.1 (3.0)	5.2 (10.9)	4.7 (10.0)
Min; Max	0.0; 13.5	0.0; 46.7	0.0; 46.7	0.0; 10.6	0.0; 50.6	0.0; 47.3
P25; P75	0.8; 6.2	0.0; 4.7	0.5; 4.8	0.9; 4.2	0.0; 8.1	0.0; 6.4

Notes: P25/P75 is the 25th/75th percentile.

Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set, IPAS = intra-patient analysis set; HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; OT stable woATexBR = On stable treatment without ancillary therapy excluding data before restart; PPX = prophylaxis; SD = standard deviation.

Number of treated spontaneous and traumatic bleeding episodes (previous PPX vs. concizumab PPX comparison)

While the lower limit of the 95% CI was below 1, the upper limit was above the pre-defined non-inferiority margin of 2, hence non-inferiority of concizumab PPX (trial 4307) over previous PPX (study 4322) was not confirmed for both patients with HA and HB.

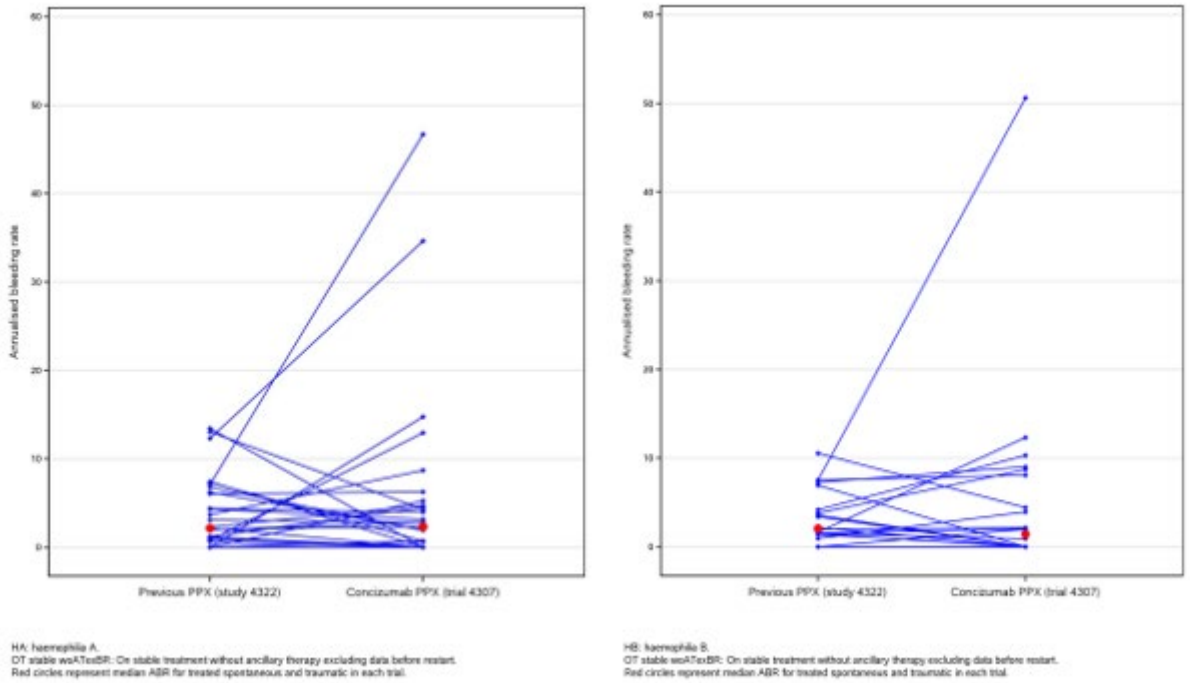
Table 30: Confirmatory secondary endpoints treated spontaneous and traumatic bleeding episodes statistical analysis – HA and HB - intra patient analysis set - trial 4307 at the CACO (OT stable woATexBR)

	Estimated mean ABR [95% CI]		ABR ratio [95% CI]
	Previous PPX (study 4322)	Concizumab PPX (trial 4307)	
Patients with HA (N = 29)	3.7 [2.51; 5.42]	5.1 [2.71; 9.65]	1.39 [0.73; 2.63]
Patients with HB (N = 22)	3.1 [2.07; 4.62]	5.4 [2.27; 12.91]	1.75 [0.81; 3.78]

Abbreviations: ABR = annualised bleeding rate; CI = confidence interval; HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; OT stable woATexBR = On stable treatment without ancillary therapy excluding data before restart; PPX = prophylaxis.

The inferential conclusion above as well as the estimated mean values are seemingly diverging from the median ABRs that showed a similar if not favourable effect of concizumab compared to the effect on previous PPX. For patients with HA, the median ABR for treated spontaneous and traumatic bleeding episodes 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 (study 4322). The difference in observed mean and median ABR for concizumab PPX indicates an inflated variation. Three patients on concizumab PPX (2 patients with HA and 1 patient with HB) had a high bleeding frequency and the variability thereby influenced the estimated mean ABR (Figure 21). A detailed analysis of concizumab pharmacokinetics, pharmacodynamic response and safety along with sports activity assessment was performed for these 3 patients to ascertain an alternative cause of observed high ABRs. Briefly, one patient with HB was a difficult to treat patient with high mean ABRs even on previous replacement factor (FIX product) therapy. The increased ABR in this patient was attributed to inadequate concizumab exposure despite being on highest maintenance dose (0.25 mg/kg), increasing TFPI levels over time and no response in thrombin generation. Additionally, increased physical activity during trial 4307 may have contributed to increased ABR as well. In one patient with HA, the increased ABR was attributed to his worsening target joint/synovitis, which is supported by the absence of bleeding episodes post synovectomy. It was not possible to identify the cause of the high ABR during trial 4307 for the second patient with HA.

Figure 21. Annualised bleeding rate in study 4322 versus trial 4307 - treated spontaneous and traumatic -HA (left) and HB (right)- OT stable woATexBR - intra-patient analysis set-CACO



The mean estimated ABR after at least 24 week concizumab PPX was 5.2 [3.11; 8.82]95%CI. This was similar to the mean ABR of 5.08 [3.40; 6.77] 95%CI observed in patients who received 52-weeks PPX with marstacimab (Hympavzi) — a recently approved anti-TFPI antibody with a mode of action similar to concizumab — after 24 weeks on routine PPX in the BASIS trial. Interestingly, while marstacimab PPX was non-inferior to previous PPX, the mean estimated ABR for HA and HB patients (combined) on previous PPX (7.85 [5.09, 10.61]95%CI) in the BASIS trial was substantially higher than the mean estimated ABRs (3.4, [2.58;4.56]95%CI) for IPAS patients with HA and HB (combined) on previous PPX in study 4322.

The post hoc Hodges-Lehmann estimation showed an estimated median ABR difference (concizumab PPX – previous PPX) of 0.0 [-1.63; 2.60]95% CI for patients with HA and 0.2 [-1.36; 2.45]95% CI for patients with HB, which agreed with the observed medians; the Wilcoxon signed rank test gave a p value of 0.963 for patients with HA and 0.799 for patients with HB. Hence, while the confirmatory analyses did not show non-inferiority at a relative scale, these additional analyses showed more comparable results between the concizumab PPX and previous PPX treatment.

Supportive secondary endpoints

<u>At CACO</u>

For both patients with HA and HB, the estimated mean ABRs from the supportive secondary bleed-related endpoints (number of treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes and treated spontaneous and traumatic target joint bleeding episodes), as well as all treated and untreated spontaneous and traumatic bleeding episodes, were consistently lower for patients on concizumab PPX (arm 2) compared to no PPX (arm 1) at CACO (Table 31, Table 32).

Table 31: 16 Bleeding episodes Statistical analyses (balanced covariate distribution) HA Trial 4307 CACO full analysis set (OTwoATexBR

	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	19.3 [11.25; 33.03]	2.7 [1.63; 4.59]	0.14 [0.07; 0.29] p<0.001
Treated spontaneous bleeding episodes	13.3 [7.44; 23.81]	1.9 [1.04; 3.35]	0.14 [0.06; 0.30]
Treated spontaneous and traumatic joint bleeding episodes	13.9 [7.96; 24.40]	2.2 [1.28; 3.83]	0.16 [0.08; 0.33]
Treated spontaneous and traumatic target joint bleeding episodes[a]	5.8 [2.90; 11.78]	1.4 [0.69; 2.66]	0.23 [0.11; 0.48]
All treated and untreated spontaneous and traumatic bleeding episodes	23.8 [13.26; 42.68]	5.5 [3.52; 8.56]	0.23 [0.11; 0.47]

Note: p-value is for two-sided tests of no difference from 1. 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. [a]Treated spontaneous and traumatic target joint bleeding episodes only include patients having target joint(s) at baseline.
Abbreviations: ABR = annualised bleeding rate; CI = Confidence interval; HA = haemophilia A without inhibitors; OTwoATexBR = on-treatment without ancillary therapy excluding data before restart; PPX = prophylaxis.

Table 32: 17Bleeding episodes - Statistical analyses (balanced covariate distribution) - HB - Trial 4307 CACO - full analysis set (OTwoATexBR)

	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	14.8 [8.14; 26.86]	3.1 [1.91; 5.04]	0.21 [0.10; 0.45] p<0.001
Treated spontaneous bleeding episodes	10.4 [5.66; 19.27]	1.8 [1.02; 3.03]	0.17 [0.08; 0.37]
Treated spontaneous and traumatic joint bleeding episodes	12.5 [6.29; 25.04]	2.6 [1.50; 4.55]	0.21 [0.09; 0.50]
Treated spontaneous and traumatic target joint bleeding episodes[a]	4.8 [1.88; 12.35]	1.7 [0.84; 3.30]	0.34 [0.11; 1.06]
All treated and untreated spontaneous and traumatic bleeding episodes	19.3 [11.31; 32.99]	4.0 [2.58; 6.13]	0.21 [0.10; 0.41]

Notes: p-value is for two-sided tests of no difference from 1. 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. [a]Treated spontaneous and traumatic target joint bleeding episodes only include patients having target joint(s) at baseline.
Abbreviations: ABR = annualised bleeding rate; CI = Confidence interval; HA = haemophilia A without inhibitors; OTwoATexBR = on-treatment without ancillary therapy excluding data before restart; PPX = prophylaxis.

Zero bleeding events CACO

For patients randomized to arm 1 or arm 2, the proportion of patients 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 33.3% on concizumab PPX (arm 2) and 0% on no PPX (arm 1) for patients with HA, and 45.8% on concizumab PPX (arm 2) and 8.3% on no PPX (arm 1) for patients with HB. For patients with HB the estimated odds ratio between concizumab PPX (arm 2) and no PPX (arm 1) was 7.94 [0.87; 72.14]95%CI). As there were no patients with zero treated spontaneous or traumatic bleeding episodes in the HA no PPX group (arm 1), the logistic regression model could not be performed for patients with HA.

In the IPAS, the proportion of patients with zero treated spontaneous and traumatic bleeding episodes during the first 24 weeks after starting stable treatment was 37.9% on concizumab PPX (trial 4307) and 34.5% on previous PPX (study 4322) for patients with HA, and 45.5% on concizumab PPX (trial 4307) and 31.8% on previous PPX (study 4322) for patients with HB.

Haemostatic medication CACO

Up to CACO, 250 bleeds in 50 patients with HA were treated with FVIII, including 234 bleeds in 46 HA patients on concizumab PPX (study arm 2-4). A total of 207 bleeds in 43 patients with HB were treated with FIX, including 192 bleeds in 38 HB patients on concizumab PPX (study arm 2-4).

For patients with HA, the mean consumption of FVIII per injection for patients on concizumab PPX (arms 1–4) was 27.3 IU/kg, which was in line with the updated breakthrough bleed treatment guidance of 20 IU/kg. For patients with HB, the mean consumption of FIX per injection for patients on concizumab PPX (arms 1–4) was 37.6 IU/kg, which was in line with the updated breakthrough bleed treatment guidance of 30 IU/kg.

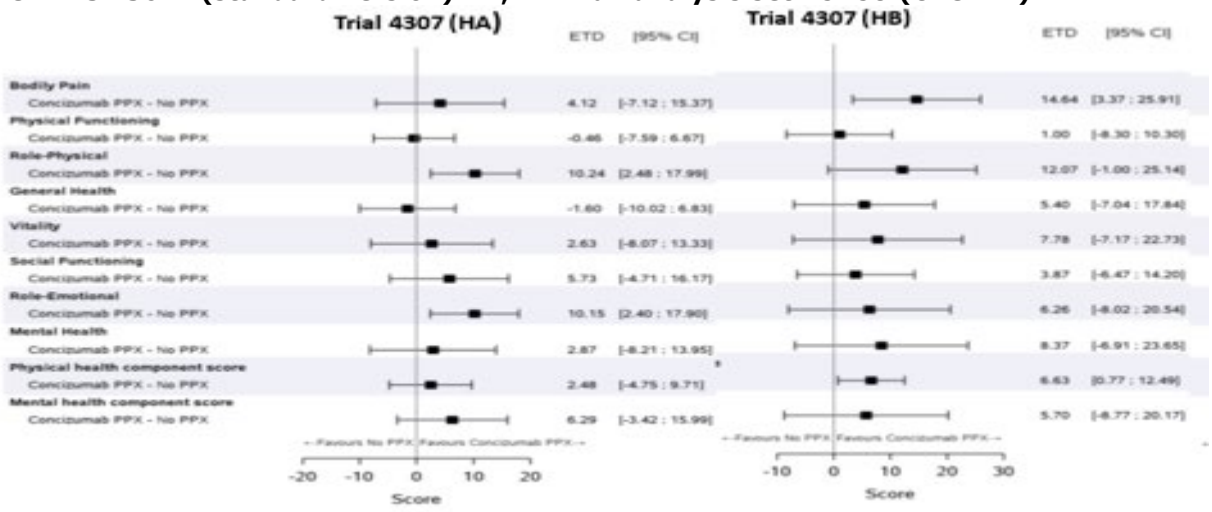
Surgery CACO

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. A variety of minor surgeries was conducted, and the number of surgery-related bleeding episodes was overall low both in patients with HA and HB.

Patient-Reported Outcomes (additional exploratory assessments)

SF-36v2 health scales. For both patients with HA and HB, the estimated change from baseline to week 24 was in favour of concizumab PPX (arm 2) over no PPX (arm 1) for all individual SF-36v2 health scales (except for Physical Functioning and General Health in patients with HA) as well as for the Physical and Mental Health Component Scores. For the health scales Role-Physical and Role-Emotional, the difference estimates at week 24 comparing arms 1 and 2 were statistically significant in patients with HA. For the health scale Bodily Pain and the Physical Health Component Score, the difference estimates at week 24 comparing arms 1 and 2 were statistically significant in patients with HB (Figure 22).

Figure 22. SF 36v2 (standard version) HA, HB full analysis set CACO (OTexBR)

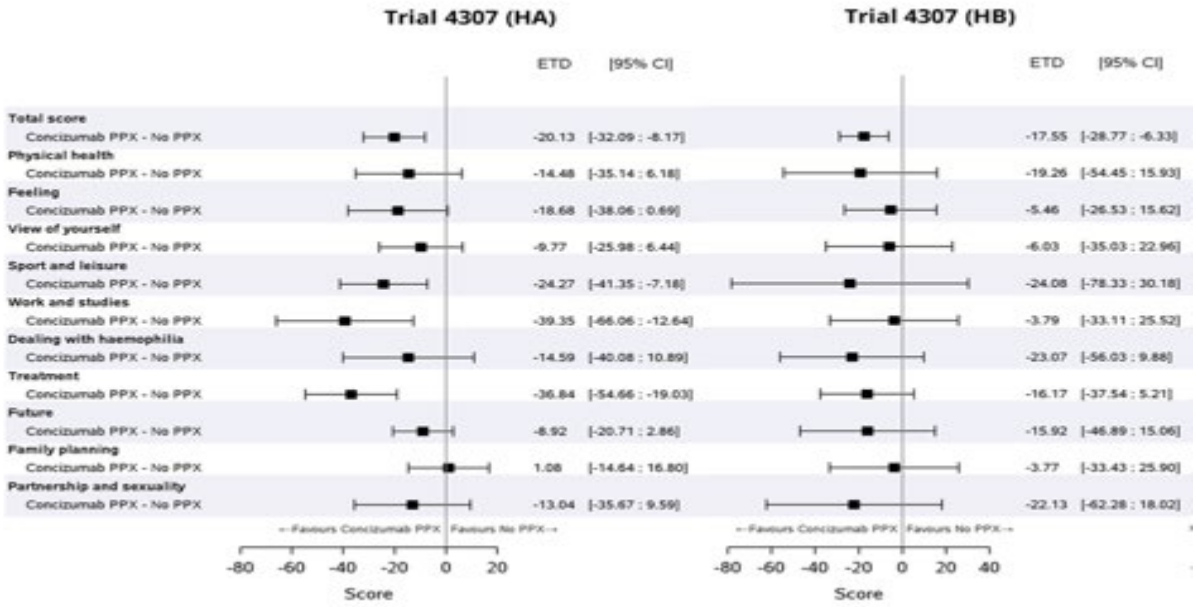


Abbreviations: HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; ETD = estimated treatment difference; OTexBR = on-treatment without data before restart; PPX: prophylaxis.

PROMIS. For both patients with HA and HB, no statistically significant difference in change from baseline to week 24 was observed between patients on concizumab PPX (arm 2) and no PPX (arm 1) in the PROMIS numeric rating scale v. 1.0 pain intensity 1a or the PROMIS short form v2.0 upper extremity 7a.

Haem-A-Qol. For both patients with HA and HB, there was a statistically significant improvement in Haem A QoL Total Score from baseline to week 24 for patients on concizumab PPX (arm 2) compared to no PPX (arm 1) (Figure 23).

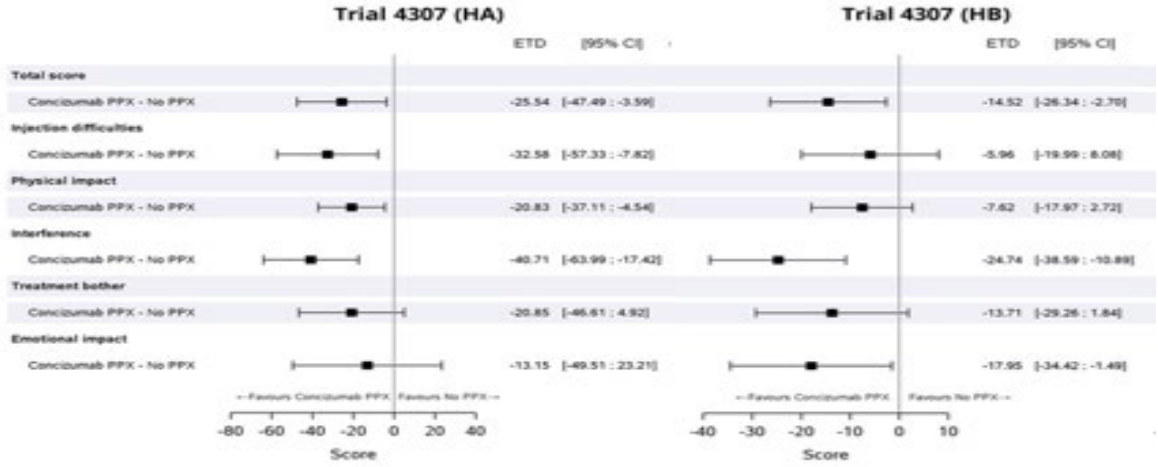
Figure 23. Haemophilia quality of life questionnaire for adults (Haem-A-QoL) - HA, HB full analysis set CACO (OTexBR)



Abbreviations: HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; ETD = estimated treatment difference; OTexBR = on-treatment without data before restart; PPX: prophylaxis.

Hemo-TEM. Both patients with HA and HB on concizumab PPX (arm 2) reported less treatment burden compared to patients on no PPX (arm 1). There was a statistically significant improvement in Hemo-TEM Total Score from baseline to week 24 for patients on concizumab PPX (arm 2) compared to no PPX (arm 1) in both HA and HB (Figure 24).

Figure 24. Haemophilia treatment experience measure (Hemo-TEM) -HA, HB - full analysis set - CACO (OTexBR)



Abbreviations: HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; ETD = estimated treatment difference; OTexBR = on-treatment without data before restart; PPX: prophylaxis.

Treatment preference.

Majority of the patients with HA and HB preferred concizumab to their previous treatment (see below). The two most common reasons cited for preference for concizumab treatment PPX over previous PPX were to "Require less time" and "Fewer bleeds" in patients with HA, and "Require less time" and "Easier to remember to inject" in patients with HB.

Out of the total 73 patients with HA on concizumab PPX (arms 2−4), 62 responded to H PPQ, while 11 did not respond. Of the 62 patients with HA that responded, 53 (85.5%) patients preferred concizumab PPX to their previous treatment, 8 patients had no preference, and 1 patient preferred the previous treatment to concizumab PPX. Out of the total 54 patients with HB on concizumab PPX (arms 2 and 4), 40 responded to H PPQ, while 14 did not respond. Of the 40 patients with HB that responded, 37 (92.5%) patients preferred concizumab PPX to their previous treatment, 2 patients had no preference, and 1 patient preferred the previous treatment to concizumab PPX.

To further investigate the potential benefit of transferring from a stable previous PPX (study 4322) to concizumab PPX (trial 4307), patient preference H-PPQ in the intra-patient analysis set was also performed using the OT stable woATexBR analysis data set. Results were consistent with H-PPQ results in the full HA and HB trial populations described above. For the patients in trial 4307 arm 4, who were on stable PPX for at least 24 weeks in study 4322 and reached the maintenance dose in trial 4307, out of the 27 patients with HA who responded, 23 (85.2%) preferred concizumab PPX to their previous treatment, with the two most common reasons cited being "Require less time" and "Easier to remember to inject". Out of the 17 patients with HB who responded, 14 (82.4%) preferred concizumab PPX to their previous treatment, with the most common reason cited being "Require less time".

56-week cut-off data (new data)

At the 56 week cut-off, the descriptive results for all bleed related endpoints and assessments were consistent with descriptive results seen at the CACO, both for patients with HA and HB.

Details of treated bleeding episodes until the 56 week data cut-off

HA. For patients on concizumab PPX (arms 1−4), 56 patients (70.0%) reported 355 treated bleeding episodes up until the 56-week cut-off (Table 33). Most of these bleeding episodes (53.5%) were spontaneous, 44.8% were traumatic and 1.7% were surgical. Most bleeding episodes (96.9%) were classified as mild/moderate, while 3.1% were classified as severe. Bleeds constituting these bleeding episodes were most frequently located in joints (68.5%) or muscle (12.4%).

Table 3318: Bleeding episodes - all treated - summary - HA - OTwoATexBR - FAS - 56 week data cut-off

	Concizumab PPX											
	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	7		18		9		46		73		80	
N in FAS and ADS	7(100)		18(100)		9(100)		46(100)		73(100)		80(100)	
Zero treated bleeds*	2(28.6)		6(33.3)		4(44.4)		11(23.9)		21(28.8)		23(28.8)	
Treated bleeding episodes	5(71.4)	33[100]	12(66.7)	90[100]	4(44.4)	5[100]	35(76.1)	227[100]	51(69.9)	322[100]	56(70.0)	355[100]
Cause of bleeding episodes												
Spontaneous	4(57.1)	16[48.5]	12(66.7)	60[66.7]	3(33.3)	3[60.0]	28(60.9)	111[48.9]	43(58.9)	174[54.0]	47(58.8)	190[53.5]
Traumatic	3(42.9)	16[48.5]	7(38.9)	27[30.0]	2(22.2)	2[40.0]	29(63.0)	114[50.2]	38(52.1)	143[44.4]	41(51.3)	159[44.8]
Surgical	1(14.3)	1[3.0]	2(11.1)	3[3.3]	0		2(4.3)	2[0.9]	4(5.5)	5[1.6]	5(6.3)	6[1.7]
Location of bleeds												
Treated bleeds	5(71.4)	33[100]	12(66.7)	98[100]	4(44.4)	5[100]	35(76.1)	242[100]	51(69.9)	345[100]	56(70.0)	378[100]
Joint	5(71.4)	26[78.8]	11(61.1)	70[71.4]	3(33.3)	3[60.0]	34(73.9)	160[66.1]	48(65.8)	233[67.5]	53(66.3)	259[68.5]
Target joint	4(57.1)	18[54.5]	11(61.1)	49[50.0]	0		3(6.5)	6[2.5]	14(19.2)	55[15.9]	18(22.5)	73[19.3]
Muscular	2(28.6)	4[12.1]	3(16.7)	9[9.2]	1(11.1)	1[20.0]	15(32.6)	33[13.6]	19(26.0)	43[12.5]	21(26.3)	47[12.4]
Skin	1(14.3)	1[3.0]	1(5.6)	1[1.0]	0		9(19.6)	25[10.3]	10(13.7)	26[7.5]	11(13.8)	27[7.1]
Gastrointestinal or Stomach/gut	0		1(5.6)	1[1.0]	0		0		1(1.4)	1[0.3]	1(1.3)	1[0.3]
Mouth, gums or nose	1(14.3)	1[3.0]	2(11.1)	2[2.0]	1(11.1)	1[20.0]	4(8.7)	8[3.3]	7(9.6)	11[3.2]	8(10.0)	12[3.2]
Urinary system	0		1(5.6)	13[13.3]	0		5(10.9)	5[2.1]	6(8.2)	18[5.2]	6(7.5)	18[4.8]
Central nervous system	0		0		0		1(2.2)	2[0.8]	1(1.4)	2[0.6]	1(1.3)	2[0.5]
Other	1(14.3)	1[3.0]	1(5.6)	2[2.0]	0		6(13.0)	9[3.7]	7(9.6)	11[3.2]	8(10.0)	12[3.2]
Classification of bleeding episodes												
Mild/moderate	5(71.4)	33[100]	12(66.7)	90[100]	4(44.4)	5[100]	35(76.1)	216[95.2]	51(69.9)	311[96.6]	56(70.0)	344[96.9]
Severe	0		0		0		3(6.5)	11[4.8]	3(4.1)	11[3.4]	3(3.8)	11[3.1]

HA: haemophilia A, PPX: prophylaxis.
N: number of patients, %: percentage of patients, E: number of bleeding episodes, FAS: Full analysis set, ADS: Analysis data set.
* patients that do not complete 24 weeks without permanent treatment discontinuation will be counted as not fulfilling this. Also, all treated bleeds with either of the four causes (spontaneous, traumatic, surgical or missing) will be taken into account.
For location of bleeds the E represents the number of bleeds and [%] is the percentage of bleeds.

HB. For patients on concizumab PPX (arms 1−4), 48 patients (75.0%) reported 307 treated bleeding episodes up until the 56-week cut-off (Table 34). Most of these bleeding episodes (63.8%) were spontaneous, 34.5% were traumatic and 1.6% were surgical. Most bleeding episodes (95.8%) were classified as mild/moderate, while 4.2% were classified as severe. Bleeds constituting these bleeding episodes were most frequently located in joints (74.6%) or muscle (13.3%).

Table 3419: Bleeding episodes - all treated - summary - HB - OTwoATexBR - FAS-56 week data cut-off

	Concizumab PPX											
	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	10		24		0		30		54		64	
N in FAS and ADS	10 (100)		24 (100)		0		30 (100)		54 (100)		64 (100)	
Zero treated bleeds*	2 (20.0)		5 (20.8)		0		7 (23.3)		12 (22.2)		14 (21.9)	
Treated bleeding episodes	8 (80.0)	36 [100]	18 (75.0)	92 [100]	0		22 (73.3)	179 [100]	40 (74.1)	271 [100]	48 (75.0)	307 [100]
Cause of bleeding episodes												
Spontaneous	8 (80.0)	22 [61.1]	14 (58.3)	62 [67.4]	0		17 (56.7)	112 [62.6]	31 (57.4)	174 [64.2]	39 (60.9)	196 [63.8]
Traumatic	4 (40.0)	13 [36.1]	12 (50.0)	27 [29.3]	0		13 (43.3)	66 [36.9]	25 (46.3)	93 [34.3]	29 (45.3)	106 [34.5]
Surgical	1 (10.0)	1 [2.8]	3 (12.5)	3 [3.3]	0		1 (3.3)	1 [0.6]	4 (7.4)	4 [1.5]	5 (7.8)	5 [1.6]
Location of bleeds												
Treated bleeds	8 (80.0)	37 [100]	18 (75.0)	93 [100]	0		22 (73.3)	201 [100]	40 (74.1)	294 [100]	48 (75.0)	331 [100]
Joint	8 (80.0)	36 [97.3]	15 (62.5)	77 [82.8]	0		20 (66.7)	134 [66.7]	35 (64.8)	211 [71.8]	43 (67.2)	247 [74.6]
Target joint	3 (30.0)	4 [10.8]	13 (54.2)	44 [47.3]	0		7 (23.3)	41 [20.4]	20 (37.0)	85 [28.9]	23 (35.9)	89 [26.9]
Muscular	1 (10.0)	1 [2.7]	3 (12.5)	5 [5.4]	0		8 (26.7)	38 [18.9]	11 (20.4)	43 [14.6]	12 (18.8)	44 [13.3]
Skin	0		3 (12.5)	3 [3.2]	0		4 (13.3)	11 [5.5]	7 (13.0)	14 [4.8]	7 (10.9)	14 [4.2]
Gastrointestinal or Stomach/gut	0		2 (8.3)	3 [3.2]	0		2 (6.7)	2 [1.0]	4 (7.4)	5 [1.7]	4 (6.3)	5 [1.5]
Mouth, gums or nose	0		3 (12.5)	3 [3.2]	0		3 (10.0)	10 [5.0]	6 (11.1)	13 [4.4]	6 (9.4)	13 [3.9]
Urinary system	0		1 (4.2)	1 [1.1]	0		2 (6.7)	2 [1.0]	3 (5.6)	3 [1.0]	3 (4.7)	3 [0.9]
Central nervous system	0		0		0		1 (3.3)	1 [0.5]	1 (1.9)	1 [0.3]	1 (1.6)	1 [0.3]
Other	0		1 (4.2)	1 [1.1]	0		2 (6.7)	3 [1.5]	3 (5.6)	4 [1.4]	3 (4.7)	4 [1.2]
Classification of bleeding episodes												
Mild/moderate	8 (80.0)	36 [100]	17 (70.8)	82 [89.1]	0		21 (70.0)	176 [98.3]	38 (70.4)	258 [95.2]	46 (71.9)	294 [95.8]
Severe	0		5 (20.8)	10 [10.9]	0		3 (10.0)	3 [1.7]	8 (14.8)	13 [4.8]	8 (12.5)	13 [4.2]

HB: haemophilia B, PPX: prophylaxis.
N: number of patients, %: percentage of patients, E: number of bleeding episodes, FAS: Full analysis set, ADS: Analysis data set.
* patients that do not complete 24 weeks without permanent treatment discontinuation will be counted as not fulfilling this. Also, all treated bleeds with either of the four causes (spontaneous, traumatic, surgical or missing) will be taken into account.
For location of bleeds the E represents the number of bleeds and [%] is the percentage of bleeds.

Descriptive summaries of observed ABRs at 56-week data cut-off

HA. For the 80 patients with HA on concizumab PPX (arms 1−4), the overall median observed ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 1.7. For the 7 patients with HA in arm 1 (who switched from no PPX to concizumab PPX treatment after at least 24 weeks), the median observed ABR at the 56-week cut-off was 2.6 (Table 35). At the CACO, the median observed ABR for the 9 patients with HA on no PPX (arm 1) was 19.6.

For the 29 patients in the IPAS, the median ABR at the 56-week cut-off was 1.7 for concizumab PPX (trial 4307) and 2.2 for previous PPX (study 4322).

HB. For the 64 patients with HB on concizumab PPX (arms 1−4), the overall median observed ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 2.8. For the 10 patients with HB in arm 1 (who switched from no PPX to concizumab PPX treatment after at least 24 weeks), the median observed ABR at the 56-week cut-off was 3.3 (Table 36). At the CACO, the median observed ABR for the 12 patients with HB on no PPX (arm 1) was 14.9.

For the 22 patients in the IPAS, the median ABR at the 56-week cut-off was 1.3 for concizumab PPX (trial 4307) and 2.1 for previous PPX (study 4322).

Table 20 35: Treated spontaneous and traumatic bleeding episodes descriptive statistics HA and HB FAS 56 week cut off (OtwoATexBR)

	Patients with HA				Patients with HB			
	No PPX	Concizumab PPX			No PPX	Concizumab PPX		
	Arm 1	Arm1	Arm 2	Total	Arm 1	Arm1	Arm 2	Total
N in FAS and ADS	9	7	18	80	12	10	24	64
Person years of exposure in ADS	4.6	6.0	22.5	111.9	6.0	7.2	28.7	71.7
Weeks of exposure in ADS; Mean (SD)	26.7 (4.5)	44.6 (17.7)	65.2 (23.7)	73.0 (28.3)	26.3 (5.8)	37.5 (14.6)	62.4 (18.5)	58.5 (25.1)
Treated spontaneous and traumatic bleeding episodes								
Number of bleeding episodes	122	32	87	349	97	35	89	302
ABR								
Median	19.6	2.6	2.0	1.7	14.9	3.3	2.3	2.8
Mean (SD)	27.5 (20.1)	4.7 (6.9)	4.2 (7.0)	3.9 (6.6)	16.2 (15.4)	4.4 (3.9)	3.1 (3.4)	6.4 (14.2)
Min; Max	3.3; 71.7	0.0; 19.9	0.0; 29.5	0.0; 37.1	0.0; 50.9	0.0; 11.6	0.0; 12.2	0.0; 91.3
P25; P75	17.3; 30.4	0.0; 4.9	0.0; 5.0	0.0; 4.5	3.3; 22.1	1.6; 7.3	0.0; 4.7	0.0; 6.4

Notes: Total = concizumab PPX (arms 1-4); P25/P75 is the 25th/75th percentile. Patients in arm 1 (no PPX) switched to concizumab PPX after 24 weeks in the trial (the extension part)

Abbreviation: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; PPX = prophylaxis; SD = standard deviation.

Table 3621: Bleeding episodes supportive secondary endpoints descriptive statistics HA and HB FAS 56 week cut off (OTwoATexBR)

	Patients with HA				Patients with HB			
	No PPX	Concizumab PPX			No PPX	Concizumab PPX		
	Arm 1	Arm1	Arm 2	Total	Arm 1	Arm1	Arm 2	Total
N in FAS and ADS	9	7	18	80	12	10	24	64
Person years of exposure in ADS	4.6	6.0	22.5	111.9	6.0	7.2	28.7	71.7
Weeks of exposure in ADS; Mean (SD)	26.7 (4.5)	44.6 (17.7)	65.2 (23.7)	73.0 (28.3)	26.3 (5.8)	37.5 (14.6)	62.4 (18.5)	58.5 (25.1)
Treated spontaneous bleeding episodes								
Number of bleeding episodes	85	16	60	190	83	22	62	196
ABR								
Median	19.3	1.3	1.0	0.8	10.8	1.6	1.0	1.3
Mean (SD)	19.6 (18.0)	2.4 (3.4)	3.0 (5.0)	2.4 (5.2)	13.7 (14.0)	2.6 (2.8)	2.1 (3.2)	5.0 (13.7)
Min; Max	3.3; 63.0	0.0; 9.5	0.0; 19.7	0.0; 37.1	0.0; 50.9	0.0; 8.4	0.0; 12.2	0.0; 91.3
P25; P75	7.2; 20.5	0.0; 3.2	0.0; 3.6	0.0; 2.7	3.3; 17.8	1.3; 3.3	0.0; 2.5	0.0; 3.3
Treated spontaneous and traumatic joint bleeding episodes								
Number of bleeding episodes	86	26	65	248	80	34	76	237
ABR								
Median	13.0	2.6	2.0	0.9	10.0	2.5	2.0	1.6
Mean (SD)	19.4 (18.5)	4.0 (5.2)	3.2 (3.9)	2.8 (5.2)	13.8 (15.0)	4.2 (4.0)	2.6 (3.2)	4.1 (8.1)
Min; Max	2.2; 60.9	0.0; 15.1	0.0; 13.4	0.0; 37.1	0.0; 50.9	0.0; 11.6	0.0; 12.2	0.0; 52.2
P25; P75	10.7; 28.3	0.0; 4.9	0.0; 4.0	0.0; 3.6	3.3; 18.0	1.6; 7.3	0.0; 3.7	0.0; 4.6
Treated spontaneous and traumatic target joint bleeding episodes[a]								
Number of bleeding episodes	40	18	47	71	34	4	43	86
ABR								
Median	10.9	1.9	1.9	1.7	2.5	0.0	0.8	0.8
Mean (SD)	11.9 (12.3)	3.4 (4.4)	2.7 (3.3)	2.6 (3.3)	7.0 (8.6)	0.7 (1.2)	1.7 (2.5)	3.1 (8.3)
Min; Max	0.9; 37.0	0.0; 11.4	0.0; 11.6	0.0; 11.6	0.0; 24.4	0.0; 3.4	0.0; 8.9	0.0; 52.2
P25; P75	2.1; 14.9	0.0; 4.9	0.0; 3.3	0.0; 3.7	2.2; 10.0	0.0; 1.6	0.0; 1.6	0.0; 3.0
All treated and untreated spontaneous and traumatic bleeding episodes								
Number of bleeding episodes	131	34	134	459	128	43	106	380
ABR								
Median	27.9	2.6	3.6	2.2	16.5	5.7	2.6	4.4
Mean (SD)	29.7 (19.6)	5.1 (7.1)	5.8 (7.5)	4.9 (7.4)	21.3 (19.9)	5.6 (4.5)	3.7 (3.6)	1.1 ; 7.7
Min; Max	3.3; 71.7	0.0; 20.8	0.0; 29.5	0.0; 37.1	0.0; 63.9	0.0; 12.9	0.0; 13.0	7.6 (14.4)
P25; P75	17.3; 30.4	1.6; 4.9	0.9; 8.4	0.5; 5.1	5.4; 30.5	1.6; 9.8	0.9; 4.9	0.0; 91.3

Notes: Total = concizumab PPX (arms 1-4). P25/P75 is the 25th/75th percentile.

All endpoints other than 'Treated spontaneous bleeding episodes' includes bleeding episodes with missing cause.

[a]'Treated spontaneous and traumatic target joint bleeding episodes' only include patients having target joint(s) at baseline.

Abbreviation: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis; SD = standard deviation.

Intra-patient comparison (IPAS). For patients with HA in the intra-patient comparison at the 56-week cut-off, the median observed ABR for treated spontaneous and traumatic bleeding episodes was 1.7 on concizumab PPX. For patients with HB in the intra-patient comparison at the 56-week cut-off, the median observed was 1.3 on concizumab PPX. For both patients with HA and HB, the

median ABRs for all bleed-related assessments showed a decreasing trend in patients on concizumab PPX in the IPAS with continued treatment up to 56-week cut-off.

Descriptive statistics of Target joints at 56-week data cut-off

Resolution of target joints, defined as a joint in which 3 or more spontaneous bleeding episodes have occurred within a consecutive 6-month period, was evaluated at the 56-week cut-off.

HA. A total of 20 patients on concizumab PPX (arms 1−4) and in the OTexBR analysis data set for at least 12 months had reported 39 target joints at baseline. At the 56-week cut-off, majority of these target joints (34 of 39; 87.2%) were resolved at 12 months or soon thereafter.

HB. A total of 29 patients on concizumab PPX (arms 1−4) and in the OTexBR analysis data set for at least 12 months had reported 41 target joints at baseline. At the 56 week cut-off, majority of these target joints (35 of 41; 85.4%) were resolved at 12 months or soon thereafter.

Descriptive comparison of results in sub-populations up to 56-week cut-off

Efficacy by age on bleeding episodes and haemostatic medication

Age

In trial 4307, the efficacy of concizumab PPX on bleeding episodes and haemostatic medication was evaluated by age group (adolescents (12-17 years of age) and adults (≥18 years of age).

Patients with HA

Out of 21 adolescent patients with HA treated with concizumab PPX (arms 1-4) after treatment pause, 16 patients (76.2%) reported 93 treated bleeding episodes up until the CACO and 17 patients (81.0%) reported 136 treated bleeding episodes up to the 56-week cut-off. Most of these bleeding episodes (53.8%) were spontaneous, while 45.2% were traumatic and 1.1% were surgical up until the CACO; majority of bleeding episodes (53.7%) were traumatic while rest were spontaneous (45.6%) or surgical (0.7%) up to the 56-week cut-off. Up until CACO or 56-week cut-off, bleeding episodes were most frequently located in joints (64.3% and 66.0%) and muscle (17.3% and 16.3%). Up to the CACO and 56-week cut-off, most bleeding episodes (89.2% and 91.9%) were classified as mild/moderate, while the rest (10.8% and 8.1%) were classified as severe. The locations of severe bleeds were joints, muscle or other.

Out of 59 adult patients with HA treated with concizumab PPX (arms 1-4) after treatment pause, 35 patients (59.3%) reported 158 treated bleeding episodes up until the CACO and 39 patients (66.1%) reported 219 bleeding episodes up to the 56-week cut-off. Up to the CACO and 56-week cut-off, most of the bleeding episodes (58.9% and 58.4%) were spontaneous, while the rest were traumatic (39.2% and 39.3%) or surgical (1.9% and 2.3%). Up to the CACO and 56-week cut-off, bleeding episodes were most frequently located in joints (71.0% and 70.0%) and muscle (10.1% for both). All bleeding episodes (100%) were classified as mild/moderate at both the cut-offs.

For the number of treated spontaneous and traumatic bleeding episodes, the observed overall median ABR for patients with HA on concizumab PPX (arms 1-4) at the CACO and the 56-week cut off was 3.2 and 3.7 for adolescents and 0.7 and 1.1 for adults, respectively. For all other bleeding related assessments (treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes, and treated spontaneous and traumatic target joint bleeding episodes) the observed median ABRs at the CACO ranged from 1.6−2.6 for adolescents and 0.6−0.9 for adults. The descriptive results for all the supportive bleed-related endpoints at 56-week cut-off were consistent with those observed at the CACO.

Table 3722: Bleeding episodes - by age group - descriptive statistics - HA - OTwoATexBR - full analysis set - trial 4307 (CACO)

	Concizumab PPX (arms 1-4)	
	Adolescents	Adults
N in FAS	21	59
N in FAS and ADS	21	59
Person years of exposure in ADS	17.2	61.7
Weeks of exposure in ADS		
Median	32.6	56.3
P25 ; P75	32.1 ; 52.7	32.3 ; 80.1
Mean (SD)	42.8 (22.5)	54.6 (26.3)
Min ; Max	18.3 ; 88.1	6.3 ; 88.1
Primary endpoint:		
Treated spontaneous and traumatic bleeding episodes		
Number of episodes	92	155
ABR		
Median	3.2	0.7
P25 ; P75	0.6 ; 9.7	0.0 ; 3.7
Mean (SD)	6.8 (9.2)	3.3 (6.0)
Min ; Max	0.0 ; 37.1	0.0 ; 32.5
Treated spontaneous bleeding episodes		
Number of episodes	50	93
ABR		
Median	1.6	0.6
P25 ; P75	0.0 ; 4.6	0.0 ; 1.9
Mean (SD)	4.1 (8.2)	2.1 (4.2)
Min ; Max	0.0 ; 37.1	0.0 ; 20.8
Treated spontaneous and traumatic joint bleeding episodes		
Number of episodes	59	115
ABR		
Median	1.6	0.6
P25 ; P75	0.0 ; 5.9	0.0 ; 3.2
Mean (SD)	4.9 (8.5)	2.3 (4.1)
Min ; Max	0.0 ; 37.1	0.0 ; 23.4
Treated spontaneous and traumatic target joint bleeding episodes		
Number of episodes	16	32
ABR		
Median	2.6	0.9
P25 ; P75	0.0 ; 7.3	0.0 ; 3.3
Mean (SD)	3.7 (4.1)	2.4 (3.6)
Min ; Max	0.0 ; 11.2	0.0 ; 14.0
All treated and untreated spontaneous and traumatic bleeding episodes		
Number of episodes	135	204
ABR		
Median	3.2	2.0
P25 ; P75	1.6 ; 14.3	0.0 ; 4.9
Mean (SD)	9.3 (12.2)	4.0 (6.2)
Min ; Max	0.0 ; 45.1	0.0 ; 32.5

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, SD: standard deviation, Min: minimum, Max: maximum, ABR: annualised bleeding rate, CACO: Confirmatory analysis cut-off.
P25/P75 is the 25th/75th percentile.
All endpoints other than 'Treated spontaneous bleeding episodes' includes bleeding episodes with missing cause.'Treated spontaneous and traumatic target joint bleeds' do not include patients without target joints at baseline.

Patients with HB

Out of 15 adolescent patients with HB treated with concizumab PPX (arms 1-4) after treatment pause, 12 patients (80.0%) reported 96 treated bleeding episodes up until the CACO and 14 patients (93.3%) reported 132 treated bleeding episodes up to the 56-week cut-off. Most of these bleeding episodes (58.3% and 56.1%) were spontaneous, while the rest were traumatic (40.6% and 42.2%) or surgical (1.0% and 1.5%) up until the CACO and the 56-week cut-off, respectively. Bleeds were most frequently located in joints (58.3% and 59.7) and muscle (25.9% and 22.8%) %) up to the CACO and 56-week cut-off, respectively. Most bleeding episodes (96.9% and 97.0%) up to the CACO and 56-week cut-off, respectively, were classified as mild/moderate, while 3.1% and 3.0% were classified as severe. The location of severe bleeds was gastrointestinal or stomach/gut.

Out of 49 adult patients with HB treated with concizumab PPX (arms 1-4) after treatment pause, 32 patients (65.3%) reported 112 treated bleeding episodes up until the CACO and 34 patients (69.4%%) reported 175 treated bleeding episodes up to the 56-week cut-off. Most bleeding episodes (92.9% and 94.9%) were classified as mild/moderate, while 7.1% and 5.1% were classified as severe, up to the CACO and 56-week cut-off, respectively. Severe bleeds were located in joints, gastrointestinal or stomach/gut, mouth, gums or nose and central nervous system.

For the number of treated spontaneous and traumatic bleeding episodes, the observed overall median ABR for patients with HB on concizumab PPX (arms 1-4) was 4.6 and 3.6 for adolescents and 1.6 and 2.8 for adults, at the CACO and 56-week cut-off, respectively (Table 38). For all other bleeding assessments, the observed median ABRs ranged from 0.0-1.8 for adolescents and 0.0 1.1 for adults at the CACO. The descriptive results for all bleed-related endpoints at 56-week cut-off were consistent with those observed at the CACO.

Table 3823: Bleeding episodes - by age group - descriptive statistics - HB - OTwoATexBR - full analysis set - trial 4307 (CACO)

	Concizumab PPX (arms 1-4)	
	Adolescents	Adults
N in FAS	15	49
N in FAS and ADS	15	49
Person years of exposure in ADS	10.7	34.5
Weeks of exposure in ADS		
Median	32.4	32.1
P25 ; P75	16.0 ; 56.1	31.7 ; 48.3
Mean (SD)	37.2 (22.1)	36.7 (21.4)
Min ; Max	7.7 ; 80.3	0.6 ; 87.4
Primary endpoint:		
Treated spontaneous and traumatic bleeding episodes		
Number of episodes	95	109
ABR		
Median	4.6	1.6
P25 ; P75	0.9 ; 9.8	0.0 ; 5.2
Mean (SD)	8.9 (13.3)	6.0 (14.8)
Min ; Max	0.0 ; 46.3	0.0 ; 91.3
Treated spontaneous bleeding episodes		
Number of episodes	56	75
ABR		
Median	1.8	0.0
P25 ; P75	0.0 ; 6.5	0.0 ; 3.6
Mean (SD)	5.7 (9.6)	5.0 (14.9)
Min ; Max	0.0 ; 33.4	0.0 ; 91.3
Treated spontaneous and traumatic joint bleeding episodes		
Number of episodes	62	95
ABR		
Median	1.6	1.1
P25 ; P75	0.0 ; 7.5	0.0 ; 4.3
Mean (SD)	6.1 (9.6)	3.8 (8.1)
Min ; Max	0.0 ; 29.9	0.0 ; 52.2
Treated spontaneous and traumatic target joint bleeding episodes		
Number of episodes	15	39
ABR		
Median	0.0	0.0
P25 ; P75	0.0 ; 6.5	0.0 ; 3.2
Mean (SD)	2.2 (3.3)	3.5 (9.7)
Min ; Max	0.0 ; 8.7	0.0 ; 52.2
All treated and untreated spontaneous and traumatic bleeding episodes		
Number of episodes	109	150
ABR		
Median	4.8	3.2
P25 ; P75	1.3 ; 11.3	1.3 ; 7.8
Mean (SD)	10.7 (14.9)	7.3 (14.7)
Min ; Max	0.0 ; 51.1	0.0 ; 91.3

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, SD: standard deviation, Min: minimum, Max: maximum, ABR: annualised bleeding rate, CACO: Confirmatory analysis cut-off.
P25/P75 is the 25th/75th percentile.
All endpoints other than 'Treated spontaneous bleeding episodes' includes bleeding episodes with missing cause.'Treated spontaneous and traumatic target joint bleeds' do not include patients without target joints at baseline.

Haemostatic medication

HA. At the CACO, the median (SD) consumption of FVIII per bleed on concizumab PPX (arms 1–4) was 23.0 (151.9) IU/kg for adolescents and 26.0 (34.7) IU/kg for adults to treat mild or moderate bleeding episodes and was 24.0 (170.8) IU/kg for adolescents and 26.0 (34.7) IU/kg for adults for all bleeds.

HB. At the CACO, the median consumption of FIX per bleed for patients with HB on concizumab PPX (arms 1–4) was 59.5 (64.1) IU/kg for adolescents and 30.0 (29.0) IU/kg for adults to treat mild or moderate bleeding episodes and was 59.5 (96.8) IU/kg for adolescents and 30.0 (28.3) IU/kg for adults for all bleeds.

The majority of bleeds were treated with one injection of haemostatic medication for patients irrespective of age.

Efficacy by race

The efficacy of concizumab on bleeding episodes was evaluated by race (Asian, Black or African American, White or Other (including the subcategories 'American Indian or Alaska Native', 'Other' and 'Not Reported')) based on data from trial 4307.

The distributions of cause of bleeds, location, severity of bleeds and location of severe bleeds at CACO were comparable across race. The distributions observed up to 56 week cut-off was consistent with the distributions at CACO, for all races.

HA. At the CACO, the observed overall median (range) ABR for the number of treated spontaneous and traumatic bleeding episodes for patients on concizumab PPX (arms 1-4) was 0.7 (0.0-32.5; n=25) for Asian patients, 14.2 (9.7-18.7; n=2) for Black or African American, 1.9 (0.0-37.1; n=50) for White and 0.0 (0.0-3.2; n=3) for "Other" race patients, respectively. For all other bleeding episodes assessments, as well as results at 56-week cut-off, the observed median ABRs were consistent with results for the number of treated spontaneous and traumatic bleeding episodes for patients.

The 2 Black or African American patients came from study 4322, and despite their higher ABRs compared to the other racial groups, both patients exhibited clinically significant reductions in ABR after starting treatment with concizumab in trial 4307, from 20.0 to 9.7, and from 39.0 to 18.7, respectively.

HB. At the CACO, the observed overall median (range) ABR for number of treated spontaneous and traumatic bleeding episodes for patients with HB on concizumab PPX (arms 1-4) was 1.6 (0.0-13.2; n=16) for Asian patients, 6.4 (0.9-11.9; n=2) for Black or African American, 2.6 (0.0-90.3; n=44) for White and 0.9 (0.0-1.8; n=2) for "Other" race patients, respectively. For all other bleeding episode assessments, the observed median ABRs were consistent with results for number of treated spontaneous and traumatic bleeding episodes.

The two Black or African American patients came from study 4322, and despite their higher ABRs compared to the other racial groups, both patients exhibited clinically significant reductions in ABR after starting treatment with concizumab in trial 4307, from 3.6 to 0.9, and from 39.2 to 11.9, respectively.

There was no indication that the effect of concizumab on ABR in patients with HA or HB was mainly driven by patients of a specific race.

Efficacy by ethnicity

The efficacy of concizumab on bleeding episodes was evaluated by ethnicity (not Hispanic or Latino, Hispanic or Latino, Not reported) based on data from trial 4307.

The distributions of cause of bleeds, location, severity of bleeds and location of severe bleeds at CACO were comparable across ethnicity. The distributions observed up to 56 week cut-off was consistent with the distributions at CACO, for all races.

At the CACO, for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes, the overall median observed ABR for HA and HB patients on concizumab PPX (arms 1-4) was 0.0 (0.0-8.3; n=7) and 1.4 (0.0-1.9; n=5) for patients with the ethnicity "Hispanic or Latino", and 1.9 (0.0-37.1; n=72) and 3.2 (0.0-91.3; n=59) for patients with the ethnicity "Not Hispanic or Latino", respectively.

There was no indication that the effect of concizumab on ABR in patients with HA or HB was mainly driven by patients of a specific ethnicity.

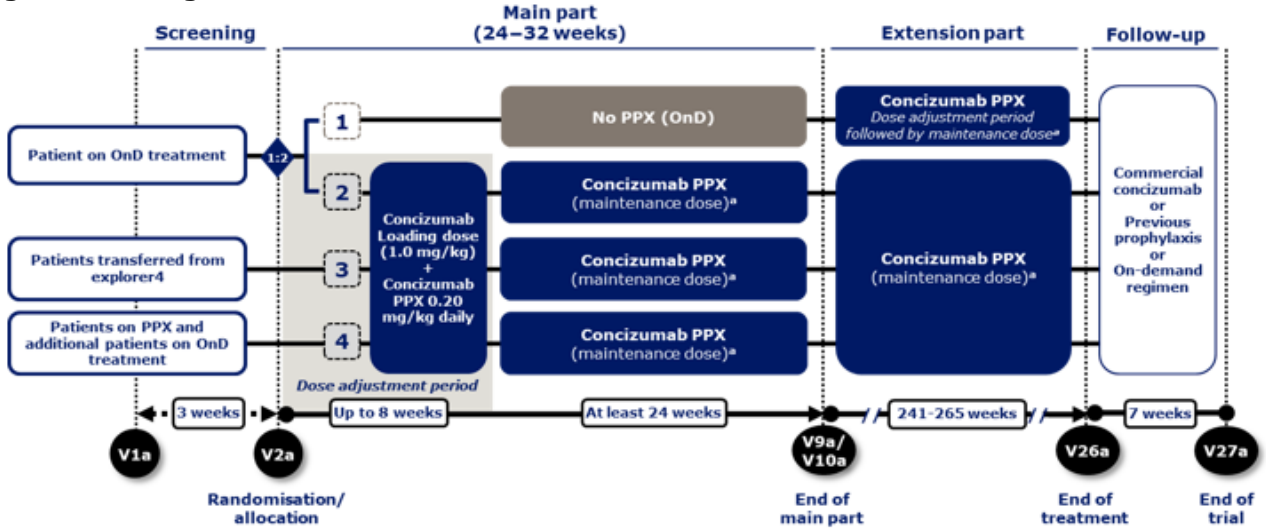
Supportive studies

Study 4311 (Explorer 7)

Methods

Trial 4311 is a phase 3 trial evaluating efficacy, PK, PD and safety of concizumab in adult and adolescent patients with HAwI or HBwI. The trial is an interventional, multi-national, multi-centre, randomised, open-label, confirmatory trial 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 in adult and adolescent patients with HAwI or HbwI, as well as on patient-reported outcomes (PROs). Concizumab dosing regimen was the same as in trial 4307. The study design is depicted in Figure 25.

Figure 25. Design of trial 4311



Notes: [a]The individual maintenance dose will be either 0.15, 0.20 or 0.25 mg/kg concizumab. Explorer4 = trial 4310.
Abbreviations: OnD = on demand; PPX = prophylaxis, V = visit.

Study population. Included were male patients aged >= 12 years with congenital haemophilia A or B of any severity with documented history of inhibitor (≥0.6 BU). The key inclusion and exclusion criteria were similar to study 4307, except for the inhibitor status at baseline.

Study treatments. In trials 4311, concizumab PPX (arm 2) was compared to on demand treatment with patients' usual factor-containing products (arm 1, on demand). The concizumab dosing regimen was similar to the dosing regimen in study 4307. Regarding the treatment of breakthrough bleeding episodes, all mild to moderate bleeds occurring during the trial were treated with the patient's usual factor containing product in line with the guidance provided in the protocol, recommending use of the lowest locally approved dose of factor product or bypassing agent while on concizumab PPX.

Endpoints. The primary, confirmatory secondary and supportive secondary efficacy endpoints corresponding to the primary and secondary efficacy objectives are presented in the Table 39.

Table 3924: Efficacy endpoints in trial 4311

Endpoint	Title	Time frame
Primary endpoint	• The number of treated spontaneous and traumatic bleeding episodes	**On demand (arm 1)** From randomisation (week 0) up until start of concizumab treatment (at least 24 weeks) **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 SF-36v2 bodily pain • Change in SF-36v2 physical functioning	From start of treatment (week 0) until week 24
Supportive secondary endpoints related to efficacy	• Number of treated spontaneous bleeding episodes • Number of treated spontaneous and traumatic joint bleeds • Number of treated spontaneous and traumatic target joint bleeds	**On demand (arm 1)** From randomisation (week 0) up until start of concizumab treatment (at least 24 weeks) **Concizumab (arm 2)** From start of the new concizumab dosing regimen (week 0) up until the primary analysis cut-off (at least 32 weeks)

Abbreviations: SF-36v2 = 36-item short form health survey

No specific objectives or endpoints related to the 56-week cut-off were defined. Descriptive statistics were implemented on all arms.

Sample size. 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).

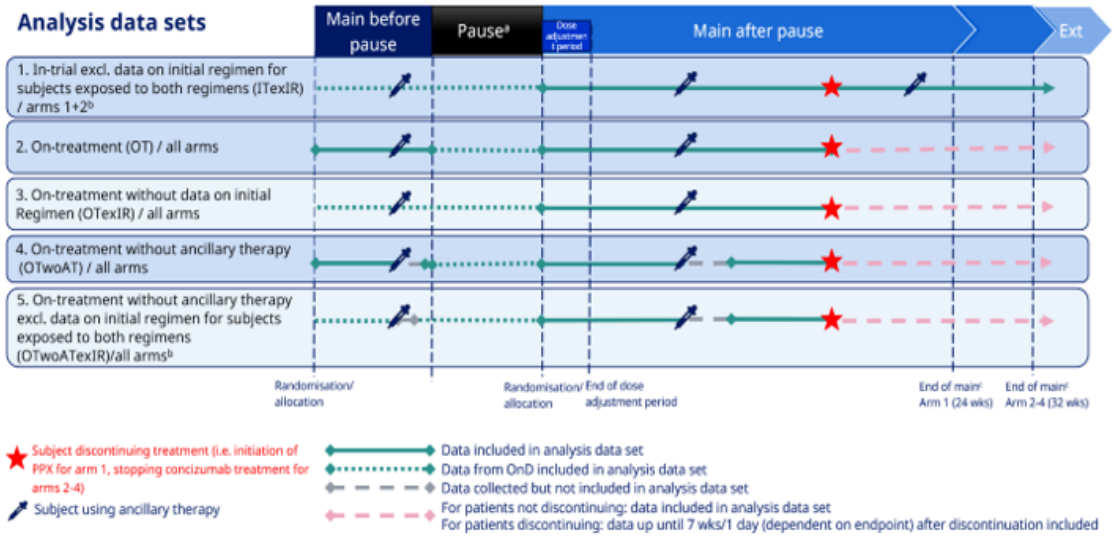
Statistical methodology. For efficacy evaluation, the Full Analysis Set (FAS) consisting of all patients randomised to concizumab PPX or on demand treatment or allocated to arms 3 or 4 was used. Patients from arms 1 and 2 contributed to the evaluation 'as randomised'. A number of observation periods were defined (Figure 26).

- On-treatment (OT). This analysis data set was defined as the observation period where patients were considered to be affected by the on-demand regimen (no PPX) or concizumab PPX.
- On-treatment without data before restart (OTexBR). This analysis data set was defined as the observation period after treatment restarted where patients were considered to be affected by on-demand treatment (no PPX) or treatment with the new concizumab dosing regimen (same as the above bullet but excluding the observation period before treatment restarted).
- On-treatment without ancillary therapy excluding data before restart (OTwoATexBR). This analysis data set was defined as the observation period after treatment restarted where patients were treated by either the new concizumab dosing regimen or were treated by on-demand treatment and additionally had not used ancillary therapy (factor-containing products that were not related to treatment of a bleeding episode except when used in relation to diagnostic procedures, intramuscular injections, or minor surgery). The observation period before treatment restarted was excluded.

In addition, the following analysis data set was relevant for patients in the IPAS:

- On stable treatment without ancillary therapy excluding data before restart (OT stable woATexBR). This analysis data set was defined as the observation period where patients were considered to be affected by stable PPX in study 4322 combined with the observation period after the treatment pause in the present trial where the same patients were on the maintenance concizumab dose and additionally had not used ancillary therapy (see above bullet for definition).

Figure 26. Analysis data sets



Notes: [a]For data sets 2 and 4: concizumab data up until 7 weeks after start of pause was included. [b]In case a patient from arm 2 did not restart concizumab treatment after the pause, the data from before the pause was to be included. [c]End of period was defined as the first of 1) death, 2) withdrawal date, 3) last contact for LTFU patients, 4) start of concizumab (only arm 1, on demand), 5) primary analysis cut-off.

Main analytical approach (primary endpoint). The estimand was addressed comparing the number of treated bleeds between the randomised arms (arms 1 and 2) based on the FAS and the OTwoATexIR analysis. The analytical approach in trial 4311 was essentially the same as in trial 4307, but accounting for the differences in trial design and randomisation between the 2 trials. In trial 4311, haemophilia subtype was an additional factor in the model and therefore the marginal

estimates of ABRs included both the balanced and the actual distribution of this factor along with other covariate of bleeding frequency prior to screening. In addition, the data before pause were included in the model for patients that did not restart after the pause unlike in trial 4307. The treatment pause and the changes implemented to the trial design and their implication for the primary statistical analysis was investigated through 4 sensitivity analyses. Furthermore, 2 supplementary analyses were performed, investigating impact of handling of the intercurrent events of "permanent treatment discontinuation" and of periods of "use of factor products not related to treatment of a bleed" on the primary analysis by replacing the hypothetical strategy with the treatment policy strategy, and investigating the dependence on model assumptions of the parametric approach for primary analysis by using a non-parametric Van Elteren test using type of haemophilia (HAwI or HBwI) and bleeding frequency as stratum comparing the ABRs between arm 1 (no PPX) and arm 2 (concizumab PPX).

The two key secondary endpoints, change in bodily pain and change in physical pain, based on SF 36v2 were analysed using the FAS and the 'OTexIR' analysis data set, using a MMRM (due to the limitation of data collection).

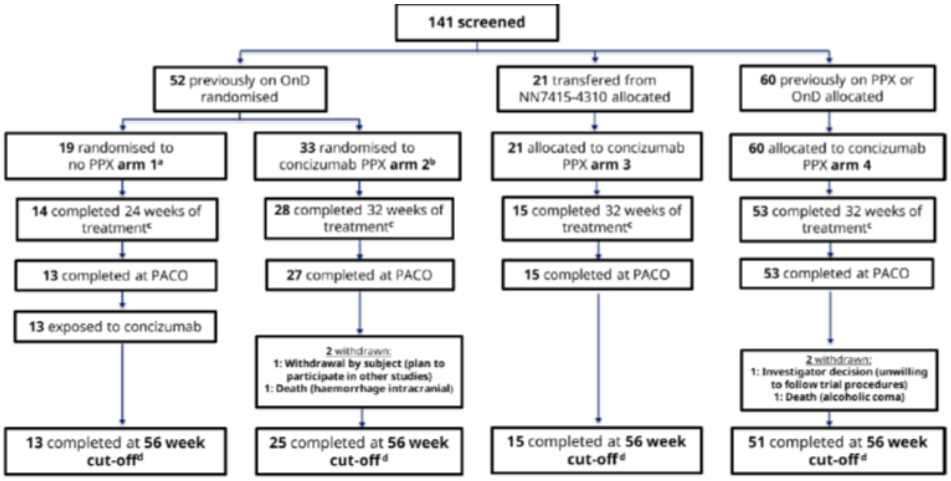
Concizumab treatment pause. Prior to the treatment pause in trial 4311, patients were randomised or allocated into non-randomised treatment arms based on their treatment regimen before the trial. Patients randomised to arm 1 (on-demand treatment) before the treatment pause were instructed to continue their on-demand treatment during the pause and after restart patients used on-demand treatment up to at least 24 weeks (main part). Patients restarting concizumab treatment after the pause entered the same arm as they were initially randomised or allocated to. New patients were randomised to arms 1 or 2, if they fulfilled the randomisation criteria, or allocated to arm 4.

Results

Participant flow

A total of 141 male patients were screened, and 133 patients (100%) were randomised/allocated, with 114 patients exposed to concizumab in the main part of the trial. 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 27.

Figure 27. 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.

Demographics and baseline disease characteristics

For the total group, mean (SD) age, body weight and BMI were 28.1 (13.5) yrs, 67.5 (19.6) kg and 23.5 (5.7) kg/m2, similar across the treatment arms. In randomized arms 1 and 2, 6 (31.6%) and 16 (55.2%) of subjects were adolescents. 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.

Primary efficacy endpoint

Bleeding episodes at PACO

At PACO. Superiority of concizumab PPX treatment over no PPX (on-demand treatment) was confirmed for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes. The four (4) pre-planned sensitivity analyses and two (2) supplementary analysis were in agreement with the primary endpoint results.

The estimated mean ABRs for the supportive secondary bleed-related endpoints and for the assessment of all treated and untreated spontaneous and traumatic bleeding episodes were statistically significantly lower in patients with HAwI and HBwI on concizumab PPX (arm 2) compared to no PPX (arm 1).

Table 40: 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.

Analysis by haemophilia subtype (ancillary analysis).

Using a negative binomial regression model, the 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).

Bleeding-related endpoints at 56-week cut-off.

The descriptive results for all bleed-related endpoints and assessments at the 56-week cut-off were consistent with descriptive results seen at the PACO. For the patients in arm 1 who switched from no PPX to concizumab PPX after completing the main part of the trial, the median ABRs on concizumab PPX was consistently lower than the median ABRs on no PPX.

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. 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 41: Bleeding episodes supportive secondary endpoints HAwI+HBwI full analysis set – trial 4311 56 week cut off (OtwoATexIR)

	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.

Patient-reported outcomes up to CACO

Key secondary endpoints of Bodily Pain and Physical Functioning.

No statistically significant differences were seen between concizumab PPX (arm 2) and no PPX (arm 1) for patients with HAwI and HBwI for the key secondary endpoints of SF 36v2 Bodily Pain and Physical Functioning.

Additional PROs assessed as exploratory endpoints:

- Improvements from baseline to week 24 were observed for all SF 36v2 health scales and component summary scores in patients with HAwI and HBwI on concizumab PPX (arm 2) (Figure 22). For the health scales General Health, Vitality, Role-Emotional and Mental Health, as well as the Mental health Component Score, the estimated difference in change from baseline to week 24 between concizumab PPX (arm 2) and no PPX (arm 1) were statistically significant.
- No statistically significant difference in change from baseline to week 24 in PROMIS Numeric Rating Scale v. 1.0 Pain Intensity 1a or PROMIS Short Form v2.0 -Upper Extremity 7a was observed between patients on concizumab PPX (arm 2) and no PPX (arm 1).

- There was a statistically significant improvement in Haem-A-QoL Total Score from baseline to week 24 in patients with HAwI and HBwI on concizumab PPX (arm 2) compared to no PPX (arm 1)
- Patients with HAwI and HBwI on concizumab PPX (arm 2) reported less treatment burden compared to patients with HAwI and HBwI on no PPX (arm 1).
    - 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.
    - In a post-hoc analysis of this exploratory assessment, there was a statistically significant improvement in Hemo-TEM Total Score from baseline to week 24 for patients on concizumab PPX (arm 2) compared to patients on no PPX (arm 1) (Figure 24).
- Out of the 99 patients with HAwI and HBwI on concizumab PPX (arms 2−4), 83 patients responded to the H-PPQ, while 16 patients did not respond. Of the 83 patients that responded, 77 preferred concizumab PPX to their previous treatment, 5 had no preference and 1 patient preferred previous treatment to concizumab PPX. The two most common reasons cited for preference for concizumab treatment PPX over previous PPX were "Fewer bleeds" and "Require less time".

Study 4322 (Explorer 6 – NIS study)

Methods

Study 4322 is a prospective, multi-national, non-interventional study in haemophilia A and B patients ≥12 years of age with or without inhibitors treated according to routine clinical treatment practice with either on-demand treatment or prophylactic treatment with FVIII/FIX. No patients were exposed to concizumab in this study.

Study 4322 was designed to prospectively collect comprehensive data on bleeding episodes and health-related quality of life in patients with congenital severe HA (FVIII activity <1%) or severe/moderate HB (FIX activity <=2%) or congenital HAwI/HBwI, under routine clinical practice, irrespective of the treatment regimen, during follow-up of at least 24 weeks. While the primary objective of the study was to investigate the number of bleeding episodes in routine clinical treatment practice, the data collected in the study served to allow for intra patient comparison between concizumab PPX (trial 4307) and previous PPX (study 4322) for patients transferred from this study to trial 4307. This is the confirmatory secondary endpoint in trial 4307.

Out of the 231 patients in the study, 84 patients (45 HA and 39 HB) transferred to trial 4307, and 64 patients (39 HAwI and 25 HBwI) transferred to trial 4311. Patients who had been on stable PPX (defined as the time after an initial period on PPX treatment for at least 24 weeks in the study 4322) were eligible to be included in the intra-patient analysis set in the maintenance phase of arm 4 in trial 4307.

Results

A total of 231 patients with HA and HB with and without inhibitors were screened and enrolled in the non-interventional study 4322. Of these, 75 patients had HA, 72 patients had HB, 53 patients had HAwI and 31 patients had HBwI. The observation time for the total 231 patients was 235.1 patient-years during the study.

Baseline demographics. The overall mean age of the study population was 30.2 years (range [min;max] 12 to 78 years). The majority of the patients (151 [65.4%]) were adults (18-64 years), 74 (32.0%) patients were adolescents (12-17 years) and very few patients (6 [2.6%]) were in age group 65-84 years. Baseline disease characteristics are provided in Table 42.

Table 42: Details of haemophilia - summary - haemophilia A and B with and without inhibitors - full analysis set.

	HA + HB		HAwI + HBwI		Total
	OnD	PPX	OnD	PPX	
Number of patients	38	109	49	35	231
Classification of haemophilia type, N (%)					
Haemophilia A	19 (50.0)	56 (51.4)	35 (71.4)	18 (51.4)	128 (55.4)
Haemophilia B	19 (50.0)	53 (48.6)	14 (28.6)	17 (48.6)	103 (44.6)
Inhibitor status, N (%)					
Yes	0	0	49 (100.0)	35 (100.0)	84 (36.4)
No	38 (100.0)	109 (100.0)	0	0	147 (63.6)
Patients with current or previous positive inhibitor test result, N (%)	1 (2.6)	14 (12.8)	49 (100.0)	34 (97.1)	98 (42.4)
Patients with ITI history, N (%)	1 (2.6)	8 (7.3)	3 (6.1)	15 (42.9)	27 (11.7)
ITI treatment outcome for patients with ITI history					
Tolerance	0	8 (7.3)	0	2 (5.7)	10 (4.3)
Partial remission	1 (2.6)	0	0	1 (2.9)	2 (0.9)
Relapse	0	0	1 (2.0)	2 (5.7)	3 (1.3)
Failure	0	0	2 (4.1)	10 (28.6)	12 (5.2)
Severity of haemophilia, N (%)					
Mild	0	0	0	1 (2.9)	1 (0.4)
Moderate	1 (2.6)	3 (2.8)	0	0	4 (1.7)
Severe	37 (97.4)	106 (97.2)	49 (100.0)	34 (97.1)	226 (97.8)
Family history of haemophilia, N (%)					
Yes	18 (47.4)	53 (48.6)	27 (55.1)	19 (54.3)	117 (50.6)
No	15 (39.5)	38 (34.9)	15 (30.6)	14 (40.0)	82 (35.5)
Unknown	5 (13.2)	18 (16.5)	7 (14.3)	2 (5.7)	32 (13.9)
Family history of inhibitors, N (%)					
Yes	2 (5.3)	3 (2.8)	12 (24.5)	4 (11.4)	21 (9.1)
No	27 (71.1)	74 (67.9)	25 (51.0)	23 (65.7)	149 (64.5)
Unknown	9 (23.7)	32 (29.4)	12 (24.5)	8 (22.9)	61 (26.4)

HA: haemophilia A, HB: haemophilia B, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OnD: on-demand patients at end of study, PPX: prophylaxis patients at end of study, N: number of patients, %: percentage of patients, ITI: immune tolerance induction.
Haemophilia is congenital for all patients as per protocol.
One patient developed inhibitor to factor product during the study and is classified as an inhibitor patient in tables, figures and listings.

Primary endpoint was number of treated bleeding episodes from enrolment and up to a maximum of 115 weeks during the study. Of total 231 patients, 182 (78.8%) patients reported 1862 treated bleeding episodes during the observation period. Summary and analysis of ABR for treated bleeding episodes for patients with haemophilia A and B with and without inhibitors, presented by treatment regimen type.

Table 43: Annualised bleeding rates during observation period - treated bleeding episodes - haemophilia A and B without inhibitors - full analysis set

	HA		HB		Total
	OnD	PPX	OnD	PPX	
Number of patients	19	56	19	53	147
Number of treated bleeding episodes	487	209	299	134	1129
Observation time (years)	26.1	53.8	25.8	54.6	160.4
ABR					
Mean (SD)	21.5 (17.7)	4.7 (5.9)	10.5 (8.6)	2.2 (3.0)	6.7 (10.2)
Median	16.7	2.2	10.5	0.9	3.3
Min; Max	1.8; 58.1	0.0; 33.2	0.0; 39.2	0.0; 12.6	0.0; 58.1
ABR estimate (95%CI)	21.4 (13.5; 33.9)	4.2 (3.1; 5.7)	10.7 (6.6; 17.3)	2.3 (1.6; 3.2)	-

HA: haemophilia A, HB: haemophilia B, OnD: on-demand patients at end of study, PPX: prophylaxis patients at end of study, N: number of patients, SD: standard deviation, Min: minimum, Max: maximum, ABR: annualised bleeding rate, CI: confidence interval.

Bleeding episodes related to surgery are not included in summaries or analyses.

Table 4425: Annualised bleeding rates during observation period - treated bleeding episodes - haemophilia A and B with inhibitors - full analysis set

	HAwI		HBwI		Total
	OnD	PPX	OnD	PPX	
Number of patients	35	18	14	17	84
Number of treated bleeding episodes	372	166	59	136	733
Observation time (years)	33.7	17.7	5.6	10.4	67.4
ABR					
Mean (SD)	15.2 (14.8)	10.3 (8.5)	9.3 (13.3)	12.4 (14.1)	12.6 (13.3)
Median	10.1	8.3	4.1	5.5	7.9
Min; Max	0.0; 60.2	0.0; 32.5	0.0; 49.4	0.0; 50.5	0.0; 60.2
ABR estimate (95%CI)	14.3 (10.6; 19.3)	10.0 (6.6; 15.1)	9.8 (5.2; 18.3)	12.7 (7.5; 21.8)	-

HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors, OnD: on-demand patients at end of study, PPX: prophylaxis patients at end of study, N: number of patients, SD: standard deviation, Min: minimum, Max: maximum, ABR: annualised bleeding rate, CI: confidence interval.

Bleeding episodes related to surgery are not included in summaries or analyses.

The *supportive secondary endpoint* was number of all bleeding episodes from enrolment and up to a maximum of 115 weeks. Of total 231 patients enrolled in the trial 188 patients experienced 2289 (1999 treated bleeding episodes, 290 non-treated bleeding episodes) treated and non-treated bleeding episodes. Mean (SD) ABR for all bleeding episodes during the study was 10.4 (13.7).

Phase 2 4310 (Explorer 4) and studies 4255 (Explorer 5)

Study 4310 (explorer 4) was the first clinical proof-of-concept study. This 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. Concizumab dose regimen consisted of a loading dose of 0.5 mg/kg, and an initial maintenance dose of 0.15 mg/kg, with dose-escalation to 0.20 mg/kg and 0.25 mg/kg, if a patient experienced ≥ 3 spontaneous bleeding episodes.

The estimated ABR on last dose level was 4.5 (95% CI 3.2-6.4) on concizumab PPX and 20.4 (95% CI 14.4-29.1) on eptacog alfa (rFVIIa) on-demand treatment. The ABR ratio was 0.22 (95% CI 0.13-0.36) and the primary Clinical Proof-of-Concept criterion was met.

The secondary clinical Proof-of-Concept, evaluating bleeding episodes during the entire treatment period, was also met, with an ABR ratio of 0.26 (95% CI 0.15-0.44).

Study 4255 (Explorer 5) was the second clinical proof-of-concept study. This was a phase 2 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 if a patient experienced ≥3 spontaneous bleeding episodes) administered daily s.c. in 36 patients with severe haemophilia A without inhibitors. The main rationale of this trial was 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.

An ABR of 12 was chosen as threshold for prophylactic efficacy, reflecting a ~50% reduction of ABR as compared to ABR during on-demand treatment. In this study, the estimated ABR on each

patient's last dose level was 7.0 (95% CI 4.6-10.7), and therefore the primary clinical proof of concept was met. The secondary proof-of-concept, evaluating ABR on all doses during the main part of the study lasting for 24 weeks, was not met since the estimated ABR was 13.9 (95% CI 9.5-20.3).

Patients from trial 4255 prior to treatment pause were enrolled in arm 3 of study 4307.

Studies in paediatric patients

Compassionate use programme

Concizumab has been provided on a compassionate use basis in children, adolescents and adults with congenital haemophilia, who have the highest unmet need for prophylactic treatment of bleeding episodes. Concizumab has been provided for compassionate use both on an individual patient basis and in a compassionate use programme (CUP) based on a specific protocol (NN7415-4807).

The primary objective of the CUP was to provide expanded access to concizumab to patients with congenital haemophilia who could not be treated satisfactorily with authorised and marketed medicines, and who were not able to enrol in clinical trials designed to support the development and registration of concizumab. The secondary objective was to monitor patient safety and clinical benefit by collecting relevant safety and bleed data. The dosing regimen for the CUP was identical to that applied in the phase 3 clinical trials for concizumab in adults and adolescents (trials 4307 and 4311) as well as the dosing regimen for the ongoing phase 3 trial 4616, which includes children below 12 years of age.

The third interim report on compassionate use for concizumab describes the cumulative results for patients who received concizumab on an individual patient basis until the interim database lock (DBL) date (28-Feb-2024) and the cumulative results for patients who received concizumab in the CUP (4807) up to the date of the last visit occurring on or before the data cut-off date (28-Feb-2024).

A total of 19 patients (including 4 patients aged 12 to < 18 years, and 1 adult), all with HbwI, have received concizumab as compassionate use on individual patient basis for a duration of 1 month to 4 years, 2 months.

A total of 11 patients (including 3 patients aged 12 to < 18 years and 1 adult), all with HbwI, have received concizumab in the CUP (4807) for a duration of 3 months to 2 years, 2 months. In general, the number of bleeding episodes and corresponding calculated ABRs were lower than or comparable to those observed on previous on-demand or PPX treatment. One patient had an ABR of 17.39 after 1 year of concizumab treatment but the patient had substantially higher ABR (49.9) on previous PPX. Two (2) other patients had ABR of 13.60 and 11.96 after 6 months and 1 year, 5 months of concizumab treatment, respectively, which were comparable to ABRs observed on their previous treatment regimens, 9.4 and 8.43, respectively.

Study 4616

Study 4616 is an ongoing interventional study to investigate the efficacy, safety and PK in at least 80 of age) concizumab-naive paediatric patients aged 1-12 yrs, with HA, HB, HAwI or HBwI (arm 1)), and patients (regardless previously treated with concizumab via compassionate use (arm 2). This study is ongoing and expected to be completed by June 2026. So far, no outcome data are available.

Summary of main studies

The following tables summarise the efficacy results from main study 4307 and supportive study 4311 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 4526: Summary of efficacy for study 4307 (Explorer 8)

Title: Explorer 8: phase 3a, prospective, multi-national, multi-centre, randomised, controlled, open label, study 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 HA or HB.		
Study identifier	Study NN7415-4307 (short title: Explorer 8), EudraCT: 2018-004891-36	
Design	Randomised (arms 1 and 2), controlled, open-label, parallel group, multicentre, global. In addition, in arm 4 a within-patient comparison for concizumab PPX vs prophylactic treatment according to routine clinical care was investigated in subjects enrolled from study 4322.	
	Dose-setting phase Main phase Extension phase 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	For the randomised comparison, superiority of concizumab PPX over no PPX (on-demand bleeding treatment with factor-containing products) For the within-patient comparison, non-inferiority of concizumab PPX vs prophylactic treatment according to routine clinical care.	
Treatments groups	**Concizumab PPX (arm 2)**	Males aged >= 12 years with congenital severe HA (FVIII<1%) or moderate/severe HB (FIX<=2%). 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 factor-containing product (see below). Duration: 24 weeks at confirmatory analysis cut-off (CACO) (extension phase 56 weeks-cut off) Number randomized:42(18 HA, 24 HB)
	On-demand (arm 1)	Males aged >= 12 years with congenital severe HA (FVIII<1%) or moderate/severe HB (FIX<=2%). Treatment: On-demand breakthrough bleeding treatment with factor-containing product (see below).

			Duration: 24 weeks at confirmatory analysis cut-off (CACO) (extension phase 56 weeks-cut off) Number randomized:21 (9 HA, 12 HB)
	<u>For both groups: Breakthrough bleeding treatment with factor-containing product:</u> • FVIII (1st and 2nd dose 20 IU/kg) or FIX (1st dose 30 iu/kg, 2nd dose at investigator discretion) • rFVIIa (dose 90 mcg/kg) • aPCC (FEIBA), single dose <= 50 U/kg, daily dose <= 100 U/kg) • By ByClot (Plasma-derived factors VIIa and X mixtures), single dose <= 60 µg/kg, daily dose <=90 µg/kg		
Endpoints and definitions *Note:* *All endpoints are analysed for HA and HB separately*	**Primary endpoints**	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 CACO (at least 32 weeks). • For on-demand (arm 1): from randomisation (week 0) up until start of concizumab treatment (at least 24 weeks).
	Confirmatory secondary endpoints	ABR (estimated annual bleeding rate)	The number of treated spontaneous and traumatic bleeding episodes • Within patient comparison in Arm 4 patients enrolled from study NN7415-4322 (explorer 6) who were on stable routine clinical care PPX for at least 24 weeks in study 4322. Duration: • for previous routine clinical care PPX (during study 4322): from the point in time where PPX is stable and up until the end of study • for concizumab PPX (during trial 4307): from confirmation of maintenance dose up until CACO (at least 24 weeks)
	Supportive secondary endpoints	ABR (estimated annual bleeding rate)	• Number of treated spontaneous bleeding episodes, • number of treated spontaneous and traumatic joint bleeds, • number of treated spontaneous and traumatic target joint bleeds
	Exploratory endpoints		Change from baseline to week 24 in patient reported outcomes
Database lock	30 September 2023		
<u>Results and Analysis</u>			
Analysis description	**Primary Analysis**		
Analysis population and time point description	<u>Full analysis set</u> (FAS, all patients randomised to concizumab PPX or no PPX after the treatment pause)		

	Intra-patient analysis set (IPAS): 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 of study 4307 Time point: CACO, Confirmatory analysis-cut-off • For endpoints related to bleeding episodes, the Analysis Data Set On-treatment without ancillary therapy excluding data before restart (OTwoATexBR) was used, reflecting the observation period in which patients are exposed to either on-demand treatment or the new concizumab dosing regimen without using ancillary therapy. • For the key secondary endpoint the On stable treatment without ancillary therapy excluding data before restart (OT stable woATexBR) was used, defined as the observation period where patients were considered to be affected by stable PPX in study 4322 combined with the observation period after the treatment pause in the present trial where the same patients were on the maintenance concizumab dose • Statistical test: negative binomial regression model			
Effect estimate per comparison (mean (95%CI))				
Primary endpoint	Treatment group	On-demand (no PPX, arm 1)	Concizumab PPX (arm 2)	Estimated ABR ratio (concizumab PPX / on-demand)
HA	Number of subjects randomized	9	18	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes	19.3 (11.25, 33.03)	2.7 (1.63, 4.59)	0.14 (0.07, 0.29) (p<0.001)
HB	Number of subjects randomized	12	24	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes	14.8 (8.14, 26.86)	3.1 (1.91, 5.04)	0.21 (0.10, 0.45) (p<0.001)
Confirmatory secondary endpoint Of note: within-patient comparison	Treatment phase	Routine clinical care PPX in study 4322	Concizumab PPX (arm 4)	Estimated ABR ratio (concizumab PPX / routine clinical care
HA	Number of subjects	----------29----------		
	Estimated ABR for treated spontaneous and traumatic bleeding episodes	3.7 (2.51, 5.42)	5.1 (2.71, 9.65)	1.39 (0.73, 2.63) Non-inferiority not demonstrated (IM 2.0)
HB	Number of subjects	----------22----------		
	Estimated ABR for treated spontaneous and traumatic bleeding episodes	3.1 (2.07, 4.62)	5.4 (2.27, 12.91)	1.75 (0.81, 3.78) Non-inferiority not demonstrated (IM 2.0)
Explorative secondary endpoints **Bleeding episodes (estimated ABR)**	Treatment group	On-demand (no PPX, arm 1)	Concizumab PPX (arm 2)	Estimated ABR ratio (concizumab PPX / on-demand)
HA	Treated spontaneous bleeding episodes	13.3 (7.44, 23.81)	1.9 (1.04, 3.35)	0.14 (0.06, 0.30) (p<0.001)
	Treated spontaneous and traumatic joint bleeding episodes	13.9 (7.96, 24.40)	2.2 (1.28, 3.83)	0.16 (0.08, 0.33) (p<0.001)

	Treated spontaneous and traumatic target joint bleeding episodes	4.4 (2.04, 9.34)	1.1 (0.54, 2.33)	0.26 (0.11, 0.60) (p<0.001)
	All treated and untreated spontaneous and traumatic bleeding episodes	23.8 (13.26, 42.68)	5.5 (3.52, 8.56)	0.23 (0.11, 0.47) (p<0.001)
HB	Treated spontaneous bleeding episodes	10.4 (5.66, 19.27)	1.8 (1.02, 3.03)	0.17 (0.08, 0.37) (p<0.001)
	Treated spontaneous and traumatic joint bleeding episodes	12.5 (6.29, 25.04)	2.6 (1.50, 4.55)	0.21 (0.09, 0.50) (p<0.001)
	Treated spontaneous and traumatic target joint bleeding episodes	3.9 (1.52, 10.05)	1.4 (0.70, 2.92)	0.37 (0.12, 1.16) (p<0.001)
	All treated and untreated spontaneous and traumatic bleeding episodes	19.3 (11.31, 32.99)	4.0 (2.58, 6.13)	0.21 (0.10, 0.41) (p<0.001)
Bleeding episodes at 56-week cut-off Off note: Single-arm extension phase, **observed** ABRs (median, IQR)				
HA	Observed ABR for treated spontaneous bleeding episodes	1.7 (0.0;4.5)		
HB	Observed ABR for treated spontaneous bleeding episodes	2.8 (0.0;6.4)		
a: 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. b: adapted post-hoc analysis using MMRM-model, due to high proportion of missing values.				

Table 4627: 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.	
	Dose-setting phase Main phase Extension phase 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)	
Treatments 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 break through 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	30 September 2023			
Results and Analysis				
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			
Effect estimate per comparison (mean (95%CI)) **Primary endpoint**	Treatment group	On-demand (no PPX)	Concizumab PPX	Estimated ABR ratio (concizumab PPX / on-demand)
	Number of subjects	19	33	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes	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)	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)	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)
Explorative secondary endpoints	Estimated ABR for treated spontaneous bleeding episodes	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	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	1.1 (0.25, 5.20)	0.1 (0.02, 0.85)	0.12 (0.02, 0.84)
	Estimated ABR for 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)
Sub-group analysis (post-hoc)				
HAwI	number	9	17[b]	
	Estimated ABR for treated spontaneous and traumatic bleeding episodes	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	7.2 (2.61, 20.06)	2.2 (0.76, 6.52)	0.31 (0.07, 1.36) P=0.12[c]
Bleeding episodes at 56-week cut-off Off note: Single-arm extension phase, **observed** ABRs (median, IQR)				
HawI and HBwI	*Observed* ABR for treated spontaneous and traumatic bleeding episodes	0.8 (0;3.2)		
All results are reported as mean (95%CI). [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.				

Analysis performed across trials (pooled analyses and meta-analysis)

Bleeding episodes

Primary efficacy endpoints

The primary endpoint of trials 4307 and 4311 was number of treated spontaneous and traumatic bleeding episodes from randomisation after the pause (week 0) up until start of concizumab treatment (week 24) for arm 1, and from start of the new concizumab dosing regimen (week 0) up until the CACO (4307) or PACO (4311) (at least 32 weeks) for arm 2.

The descriptive results for treated spontaneous and traumatic bleeding episodes in trial 4307 at the CACO and in trial 4311 at the PACO are summarized in Table .

Table 4728: Primary endpoint - bleeding episodes - descriptive statistics – HA, HB, HAwI+HBwI - full analysis set - trials 4307 at the CACO (OTwoATexBR) and 4311 at the PACO (OTwoATexIR

	Trial 4307						Trial 4311		
	HA			HB			HAwI + HBwI		
	No PPX	Concizumab PPX		No PPX	Concizumab PPX		No PPX	Concizumab PPX	
	Arm 1	Arm 2	Total	Arm 1	Arm 2	Total	Arm 1	Arm 2	Total
N in FAS and ADS	9	18	80	12	24	64	19	33	127
Person years of exposure in ADS	4.6	15.3	79.0	6.0	18.2	45.2	11.6	24.2	92.8
Weeks of exposure in ADS; Mean (SD)	26.7 (4.5)	44.4 (19.7)	51.5 (25.7)	26.3 (5.8)	39.7 (16.8)	36.8 (21.4)	31.9 (18.3)	38.3 (15.6)	38.1 (16.7)
Treated spontaneous and traumatic bleeding episodes									
Number of bleeding episodes	122	63	247	97	56	204	166	59	280
ABR									
Median	19.6	2.9	1.6	14.9	1.6	1.7	9.8	0.0	0.0
Mean (SD)	27.5 (20.1)	4.5 (7.0)	4.2 (7.1)	16.2 (15.4)	3.2 (4.0)	6.7 (14.4)	18.4 (24.7)	3.8 (11.7)	3.1 (8.1)
Min; Max	3.3; 71.7	0.0; 29.5	0.0; 37.1	0.0; 50.9	0.0; 11.9	0.0; 91.3	0; 94.7	0; 66.4	0; 66.4
P25; P75	17.3; 30.4	0.0; 5.2	0.0; 4.9	3.3; 22.1	0.0; 4.8	0.0; 6.4	6.5; 20.2	0; 3.3	0; 3.6

Notes: Total = concizumab PPX (arms 1-4); P25/P75 is the 25th/75th percentile. Patients in arm 1 (no PPX) switched to concizumab PPX after 24 weeks in the trial (the extension part)
Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors, HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis; SD = standard deviation.

Superiority of concizumab PPX over no PPX was confirmed for the primary endpoints in both trials 4307 and 4311 at the CACO and PACO, respectively. The effect of concizumab PPX compared to no PPX in reducing the ABR (79-86%) in patients with HA and HB from trial 4307 is consistent with the reduction (86%) observed for patients with HAwI and HBwI in trial 4311 (Table 48).

Table 4829: Bleeding episodes - statistical analyses - full analysis set - Trials 4307 at CACO (OTwoATexBR) and 4311 at the PACO (OtwoATexIR)– HA, HB and HAwI+HBwI

		Estimated mean ABR [95% CI]		ABR ratio [95% CI]	P-value
		No PPX (arm 1)	Concizumab PPX (arm 2)		
Trial 4307 (HA)	N in FAS and ADS	9	18		
	Treated spontaneous and traumatic bleeding episodes	19.3 [11.25; 33.03]	2.7 [1.63; 4.59]	0.14 [0.07; 0.29]	p<0.001
Trial 4307 (HB)	N in FAS and ADS	12	24		
	Treated spontaneous and traumatic bleeding episodes	14.8 [8.14; 26.86]	3.1 [1.91; 5.04]	0.21 [0.10; 0.45]	p<0.001
Trial 4311 (HAwI+HBwI)	N in FAS and ADS	19	33		
	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

Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors, HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis; SD = standard deviation.

In both trials 4307 and 4311, results from the pre-planned sensitivity analyses as well as the pre-planned supplementary analyses for the primary endpoint supported the conclusion of superiority for the primary analysis.

Key secondary endpoint

In study 4307, the confirmatory secondary endpoints were addressed through analysis of the non-inferiority of concizumab PPX versus previous PPX. Non-inferiority of concizumab PPX (trial 4307) over previous PPX (study 4322) was not confirmed for both patients with HA and HB.

Although, the confirmatory analyses did not show non-inferiority of concizumab PPX over previous PPX, the estimated mean ABR for patients with HA and HB after switching from a previous PPX to concizumab PPX was comparable to that observed for patients after switching from a routine previous PPX to marstacimab (Hympavzi), a recently approved TFPI antagonist based on indirect comparisons.

Additional bleed-related endpoints and assessments

In both trials 4307 and 4311, the results of the supportive secondary bleed-related endpoints (number of treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes and treated spontaneous and traumatic target joint bleeding episodes) as well as for the assessment of all treated and untreated spontaneous and traumatic bleeding episodes were consistent with results for the primary endpoint, further supporting the efficacy of concizumab PPX in reducing ABR in patients with HA, HB, HAwI and HBwI. Results for the supportive secondary bleed-related endpoints, as well as the assessment of all treated and untreated spontaneous and traumatic bleeding episodes, are presented for trial 4307 at the CACO and trial 4311 at the PACO as descriptive results in Table .

Table 4930: Bleeding episodes - supportive secondary endpoints - descriptive statistics – HA, HB and HAwI+HBwI - full analysis set - trials 4307 at the CACO (OTwoATexBR) and 4311 at the PACO (OTwoATexIR)

	Trial 4307						Trial 4311		
	HA			HB			HAwI + HBwI		
	No PPX	Concizumab PPX		No PPX	Concizumab PPX		No PPX	Concizumab PPX	
	Arm 1	Arm 2	Total	Arm 1	Arm 2	Total	Arm 1	Arm 2	Total
N in FAS and ADS	9	18	80	12	24	64	19	33	127
Person years of exposure in ADS	4.6	15.3	79.0	6.0	18.2	45.2	11.6	24.2	92.8
Treated spontaneous bleeding episodes									
Number of bleeding episodes	85	45	143	83	39	131	123	40	181
ABR									
Median	19.3	1.6	0.7	10.8	0.3	1.0	8.4	0.0	0.0
Mean (SD)	19.6 (18.0)	3.3 (5.2)	2.7 (5.5)	13.7 (14.0)	2.2 (3.6)	5.2 (13.8)	13.3 (16.3)	3.2 (11.7)	2.2 (7.4)
Min; Max	3.3; 63.0	0.0; 20.2	0.0; 37.1	0.0; 50.9	0.0; 11.7	0.0; 91.3	0.0; 58.2	0.0; 66.4	0.0; 66.4
P25; P75	7.2; 20.5	0.0; 4.1	0.0; 2.8	3.3; 17.8	0.0; 2.0	0.0; 3.9	3.9; 14.3	0.0; 1.3	0.0; 1.6
Treated spontaneous and traumatic joint bleeding episodes									
Number of bleeding episodes	86	52	174	80	47	157	124	47	204
ABR									
Median	13.0	2.9	0.7	10.0	1.3	1.3	6.5	0.0	0.0
Mean (SD)	19.4 (18.5)	3.6 (4.3)	3.0 (5.6)	13.8 (15.0)	2.7 (3.9)	4.4 (8.5)	14.9 (22.5)	3.4 (11.6)	2.3 (7.3)
Min; Max	2.2; 60.9	0.0; 15.5	0.0; 37.1	0.0; 50.9	0.0; 11.9	0.0; 52.2	0.0; 81.2	0.0; 66.4	0.0; 66.4
P25; P75	10.7; 28.3	0.0; 4.9	0.0; 3.5	3.3; 18.0	0.0; 4.0	0.0; 5.3	3.2; 13.1	0.0; 2.6	0.0; 2.5
Treated spontaneous and traumatic target joint[a] bleeding episodes									
Number of bleeding episodes	40	37	48	34	28	54	28	12	76
ABR									
Median	10.9	1.8	1.6	2.9	0.0	0.0	1.9	0.0	0.0
Mean (SD)	12.0 (12.2)	3.0 (3.8)	2.7 (3.7)	7.0 (8.5)	1.9 (3.3)	3.1 (8.4)	7.1 (15.8)	3.9 (12.7)	2.0 (6.9)
Min; Max	1.6; 37.0	0.0; 14.0	0.0; 14.0	0.0; 24.4	0.0; 11.9	0.0; 52.2	0.0; 51.7	0.0; 49.8	0.0; 49.8
P25; P75	2.1; 14.9	0.0; 3.5	0.0; 3.3	2.2 ; 10.0	0.0; 2.1	0.0; 3.2	0.0; 4.8	0.0; 1.3	0.0; 1.1
All treated and untreated spontaneous and traumatic bleeding episodes									
Number of bleeding episodes	131	101	339	128	72	259	181	136	426
ABR									
Median	27.9	3.9	2.6	16.5	3.2	3.9	10.9	2.6	2.2
Mean (SD)	29.7 (19.6)	6.3 (7.6)	5.4 (8.5)	21.3 (19.9)	4.1 (4.4)	8.1 (14.7)	19.4 (24.6)	7.0 (16.2)	4.6 (10.1)
Min; Max	3.3; 71.7	0.0; 29.5	0.0; 45.1	0.0; 63.9	0.0; 13.2	0.0; 91.3	0.0; 94.7	0.0; 83.0	0.0; 83.0
P25; P75	17.3; 30.4	1.6; 9.7	0.6; 5.7	5.4; 30.5	0.6; 5.1	1.3; 8.1	6.5; 20.2	0.0; 5.5	0.0; 5.0

Notes: Total = concizumab PPX (arms 1-4). P25/P75 is the 25th/75th percentile.

[a]'Treated spontaneous and traumatic target joint bleeds' only include patients having target joint(s) at baseline.

Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors, HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis; SD = standard deviation.

In both trials 4307 and 4311, the estimated mean ABRs from the supportive secondary bleed-related endpoints (number of treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes and treated spontaneous and traumatic target joint bleeding episodes) at the CACO and PACO, respectively, were consistently lower for patients on concizumab PPX (arm 2) compared to no PPX (arm 1) (Table 50), which is in line with the superiority conclusion from the primary endpoint analyses. In addition, the estimated mean ABRs from the assessment of all treated and untreated spontaneous and traumatic bleeding episodes were lower for patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

Table 50: Supportive secondary endpoints - bleeding episodes – statistical analyses - HA, HB and HAwI+HBwI - full analysis set - trials 4307 at the CACO (OTwoATexBR) and 4311 at the PACO

		No PPX (arm 1) Estimated mean ABR [95% CI]	Concizumab PPX (arm 2) Estimated mean ABR [95% CI]	ABR ratio [95% CI]
Trial 4307 (HA)	Treated spontaneous bleeding episodes	13.3 [7.44; 23.81]	1.9 [1.04; 3.35]	0.14 [0.06; 0.30]
	Treated spontaneous and traumatic joint bleeding episodes	13.9 [7.96; 24.40]	2.2 [1.28; 3.83]	0.16 [0.08; 0.33]
	Treated spontaneous and traumatic target joint bleeding episodes[a]	5.8 [2.90;11.78]	1.4 [0.69;2.66]	0.23 [0.11; 0.48]
	All treated and untreated spontaneous and traumatic bleeding episodes	23.8 [13.26; 42.68]	5.5 [3.52; 8.56]	0.23 [0.11; 0.47]
Trial 4307 (HB)	Treated spontaneous bleeding episodes	10.4 [5.66; 19.27]	1.8 [1.02; 3.03]	0.17 [0.08; 0.37]
	Treated spontaneous and traumatic joint bleeding episodes	12.5 [6.29; 25.04]	2.6 [1.50;4.55]	0.21 [0.09; 0.50]
	Treated spontaneous and traumatic target joint bleeding episodes[a]	4.8 [1.88;12.35]	1.7 [0.84;3.30]	0.34 [0.11;1.06]
	All treated and untreated spontaneous and traumatic bleeding episodes	19.3 [11.31; 32.99]	4.0 [2.58; 6.13]	0.21 [0.10;0.41]
Trial 4311 (HAwI+HBwI))	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[a]	2.5 [0.54; 11.91]	0.5 [0.07; 3.76]	0.21 [0.04; 1.17]
	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; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors, HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis;

In both trial 4307 and 4311, the results of the supportive secondary bleed-related endpoints (number of treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes and treated spontaneous and traumatic target joint bleeding episodes) as well as for the assessment of all treated and untreated spontaneous and traumatic bleeding episodes were consistent with results at CACO and PACO, respectively.

Patients with zero treated bleeding episodes

In both trials 4307 and 4311, the proportion of patients with zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment was higher in patients on concizumab PPX compared to no PPX. Similarly, the proportion of patients with zero bleeding episodes within 24 first weeks of treatment was higher in patients on concizumab PPX compared to no PPX for all supportive secondary bleed-related endpoints and all treated and untreated bleeds in both trials.

Table 51: Bleeding episodes zero treated spontaneous and traumatic bleeding episodes during the first 24 weeks of treatment summary – HA, HB and HAwI+HBwI full analysis set trials 4307 at the CACO (OTwoATexBR) and 4311 at the PACO (OtwoATexIR)

	Trial 4307						Trial 4311		
	HA			HB			HAwI + HBwI		
	No PPX	Concizumab PPX		No PPX	Concizumab PPX		No PPX	Concizumab PPX	
	Arm 1 N (%)	Arm 2 N (%)	Arms 2-4 N (%)	Arm 1 N (%)	Arm 2 N (%)	Arms 2-4 N (%)	Arm 1 N (%)	Arm 2 N (%)	Arms 2-4 N (%)
N in FAS	9	18	73	12	24	54	19	33	114
N in FAS and ADS	9 (100)	18 (100)	73 (100)	12 (100)	24 (100)	54 (100)	19 (100)	33 (100)	114 (100)
Zero Treated spontaneous and traumatic bleeds									
Yes	0	6 (33.3)	32 (43.8)	1 (8.3)	11 (45.8)	20 (37.0)	2 (10.5)	21 (63.6)	68 (59.6)
Yes, and completed 24 weeks	0	6 (33.3)	31 (42.5)	1 (8.3)	10 (41.7)	18 (33.3)	1 (5.3)	17 (51.5)	54 (47.4)
Yes, but discontinued before week 24	0	0	1 (1.4)	0	1 (4.2)	2 (3.7)	1 (5.3)	4 (12.1)	14 (12.3)
No	9 (100)	12 (66.7)	41 (56.2)	11 (91.7)	13 (54.2)	34 (63.0)	17 (89.5)	12 (36.4)	46 (40.4)

Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors, HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; OTwoATexIR = On-treatment without ancillary therapy excl. data on initial regimen for patients exposed to both regimens; PPX = prophylaxis.

56-week data cut-off

Primary endpoint. The descriptive results for treated spontaneous and traumatic bleeding episodes in trials 4307 and 4311 at the 56-week cut-off were consistent with descriptive results at the CACO and PACO, respectively (Table 52 and Table 53).

Table 52: Bleeding episodes Treated spontaneous and traumatic descriptive statistics – HA and HB full analysis set trial 4307 56 week cut off (OTwoATexBR)

	Patients with HA				Patients with HB			
	No PPX	Concizumab PPX			No PPX	Concizumab PPX		
	Arm 1	Arm1	Arm 2	Total	Arm 1	Arm1	Arm 2	Total
N in FAS and ADS	9	7	18	80	12	10	24	64
Person years of exposure in ADS	4.6	6.0	22.5	111.9	6.0	7.2	28.7	71.7
Weeks of exposure in ADS; Mean (SD)	26.7 (4.5)	44.6 (17.7)	65.2 (23.7)	73.0 (28.3)	26.3 (5.8)	37.5 (14.6)	62.4 (18.5)	58.5 (25.1)
Treated spontaneous and traumatic bleeding episodes								
Number of bleeding episodes	122	32	87	349	97	35	89	302
ABR								
Median	19.6	2.6	2.0	1.7	14.9	3.3	2.3	2.8
Mean (SD)	27.5 (20.1)	4.7 (6.9)	4.2 (7.0)	3.9 (6.6)	16.2 (15.4)	4.4 (3.9)	3.1 (3.4)	6.4 (14.2)
Min; Max	3.3; 71.7	0.0; 19.9	0.0; 29.5	0.0; 37.1	0.0; 50.9	0.0; 11.6	0.0; 12.2	0.0; 91.3
P25; P75	17.3; 30.4	0.0; 4.9	0.0; 5.0	0.0; 4.5	3.3; 22.1	1.6; 7.3	0.0; 4.7	0.0; 6.4

Notes: Total = concizumab PPX (arms 1-4); P25/P75 is the 25th/75th percentile. Patients in arm 1 (no PPX) switched to concizumab PPX after 24 weeks in the trial (the extension part)
Abbreviation: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; HA = haemophilia A without inhibitors; HB = haemophilia B without inhibitors; N = number of patients; OTwoATexBR = On-treatment without ancillary therapy excluding data before restart; PPX = prophylaxis; SD = standard deviation.

Table 5331: Bleeding episodes Treated spontaneous and traumatic descriptive statistics HAwI+HBwI full analysis set trial 4311 56 week cut off (OTwoATexIR)

	No PPX	Concizumab PPX		
	Arm 1	Arm1	Arm 2	Total
N in FAS and ADS	19	13	33	127
Person years of exposure in ADS	11.6	14.9	36.3	140.6
Weeks of exposure in ADS; Mean (SD)	31.9 (18.3)	59.7 (22.5)	57.3 (23.5)	57.8 (23.5)
Treated spontaneous and traumatic bleeding episodes				
Number of bleeding episodes	166	24	89	403
ABR				
Median	9.8	1.3	0.9	0.8
Mean (SD)	18.4 (24.7)	1.4 (1.4)	3.9 (11.7)	3.0 (8.0)
Min; Max	0.0; 94.7	0.0; 4.3	0; 66.4	0; 66.4
P25; P75	6.5; 20.2	0.0; 2.0	0; 2.8	0; 3.2

Notes: Total = concizumab PPX (arms 1-4); P25/P75 is the 25th/75th percentile. Patients in arm 1 (no PPX) switched to concizumab PPX after 24 weeks in the trial (the extension part)
Abbreviations: ABR = annualised bleeding rate; ADS = analysis data set; FAS = full analysis set; 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 patients exposed to both regimens; PPX = prophylaxis; SD = standard deviation.

Secondary bleed-related endpoint. For both trial 4307 as well as 4311 at the 56-week cut-off, the descriptive results for the supportive secondary bleed-related endpoints, as well as for the assessment of all treated and untreated spontaneous and traumatic bleeding episodes, were consistent with descriptive results at the CACO/PACO.

Target joints. In trial 4307, a total of 20 patients with HA and 29 patients with HB on concizumab PPX (arms 1−4) and in the OTexBR analysis data set for at least 12 months had reported 39 and 41 target joints, respectively, at baseline. At the 56-week cut-off, majority of these target joints (34 of 39 (87.2%) and 35 of 41 (85.4%), respectively) were resolved at 12 months or soon thereafter.

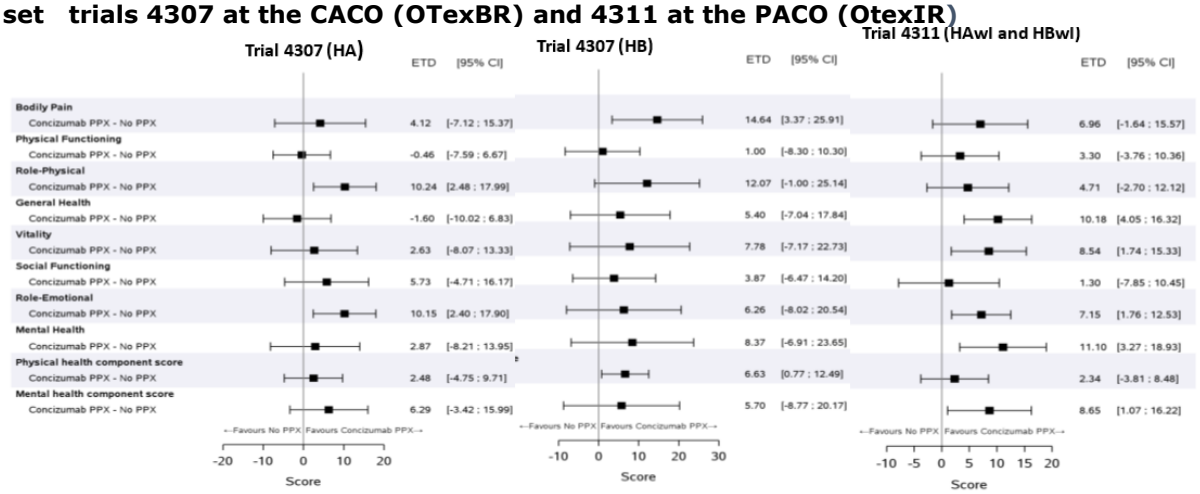
The proportion of patients with resolution of target joints in trial 4307 was largely consistent with the proportion observed in trial 4311, where 78 out of 85 (91.8%) target joints evaluated at the 56 week cut-off were resolved at 12 months or soon thereafter for patients on concizumab PPX (arms 1-4).

Patient-reported outcome

The PRO assessments in both studies in general were extrapolatory in nature and performed to provide an overall assessment of health-related quality of life, treatment burden and patient preference for treatment.

In **study 4311** in patients with HwI, no statistically significant differences were seen between concizumab PPX (arm 2) and no PPX (arm 1) for patients with HAwI and HBwI for the key secondary endpoints of SF 36v2 Bodily Pain and Physical Functioning. However, improvements from baseline to week 24 were observed for all SF 36v2 health scales and component summary scores in patients with HAwI and HBwI on concizumab PPX (arm 2) (Figure 28).

Figure 28. SF 36v2 (standard version) week 24 HA, HB and HAwI+HBwI full analysis set trials 4307 at the CACO (OTexBR) and 4311 at the PACO (OtexIR)

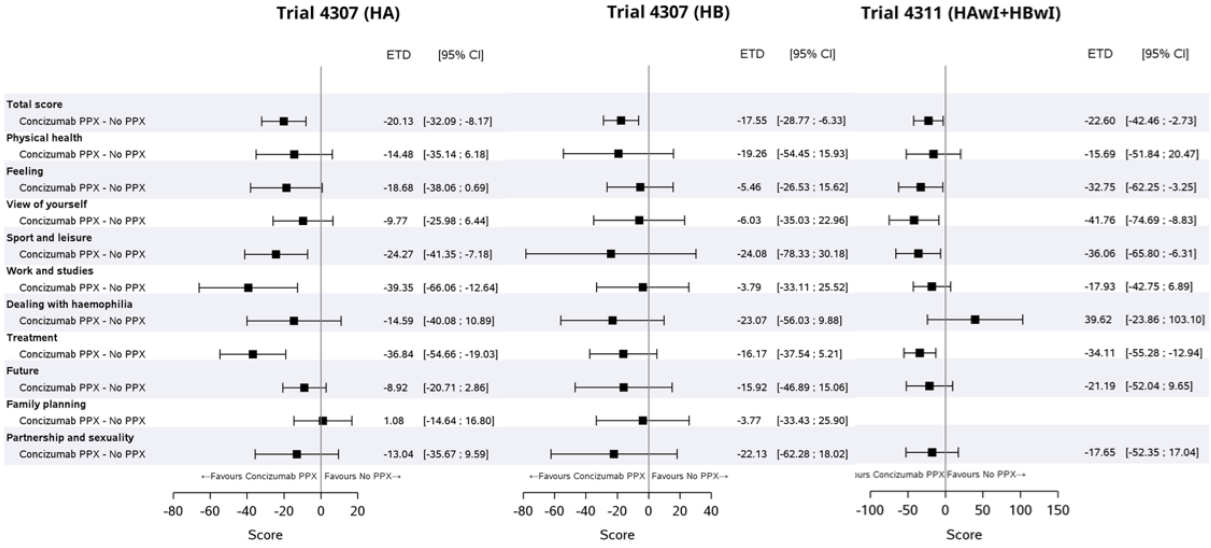


Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; ETD = estimated treatment difference; OTexIR = on-treatment without data on initial regimen; OTexBR = on-treatment without data before restart; PPX = prophylaxis.

In study 4311, no statistically significant difference in change from baseline to week 24 in PROMIS Numeric Rating Scale v. 1.0 Pain Intensity 1a or PROMIS Short Form v2.0 -Upper Extremity 7a was observed between patients on concizumab PPX (arm 2) and no PPX (arm 1).

There was a statistically significant improvement in Haem-A-QoL (Figure 29).

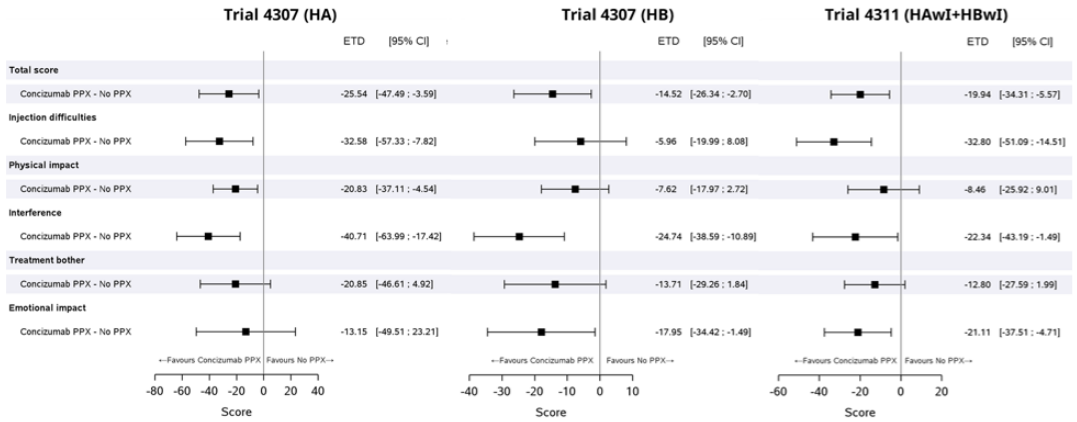
Figure 29. Haemophilia quality of life questionnaire for adults (Haem-A-QoL) - week 24 - HA, HB and HAwI+HBwI - full analysis set - trials 4307 at the CACO (OTexBR) and 4311 at the PACO (OtexIR)



Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; ETD = estimated treatment difference; OTexIR = on-treatment without data on initial regimen; OTexBR = on-treatment without data before restart; PPX: prophylaxis.

In study 4311, patients with HAwI and HBwI on concizumab PPX (arm 2) reported less treatment burden compared to patients with HAwI and HBwI on no PPX (arm 1) (Figure 30).

Figure 30. Haemophilia treatment experience measure (Hemo-TEM) – week 24 -HA, HB and HAwI+HBwI - full analysis set - trials 4307 at the CACO (OTexBR) and 4311 at the PACO (OtexIR)



Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB = haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; ETD = estimated treatment difference; OTexIR = on-treatment without data on initial regimen; OTexBR = on-treatment without data before restart; PPX = prophylaxis.

In study 4311, of the 83 patients that responded to the H-PPQ, 77 preferred concizumab PPX to their previous treatment, 5 had no preference and 1 patient preferred previous treatment to concizumab PPX.

Persistence of efficacy / immunogenicity

Persistence of efficacy

The persistent efficacy of concizumab in trial 4307 is evidenced by the consistently low median ABRs observed for all bleeding endpoints at the 56-week cut-off. Given that only 1 patient was withdrawn from the trial between the CACO and the 56-week cut-off, the consistency of prophylactic effect observed at the CACO and at the 56-week cut-off further supports the long-term efficacy of concizumab in both patients with HA and HB. The observed efficacy of concizumab at the 56-week cut-off in trial 4311 further illustrates the persistence of the prophylactic effect of concizumab in the long-term.

Tolerance - development of antibodies

Formation of anti-concizumab antibodies (hereafter referred to as ADAs) may result in altered drug exposure, leading to indirect reduction in concizumab efficacy. ADAs may also directly affect efficacy by preventing concizumab from binding TFPI (drug neutralising effects). Formation of binding ADAs as well as ADAs with in vitro-neutralising effects was monitored throughout the course of the clinical development programme.

Impact of ADAs

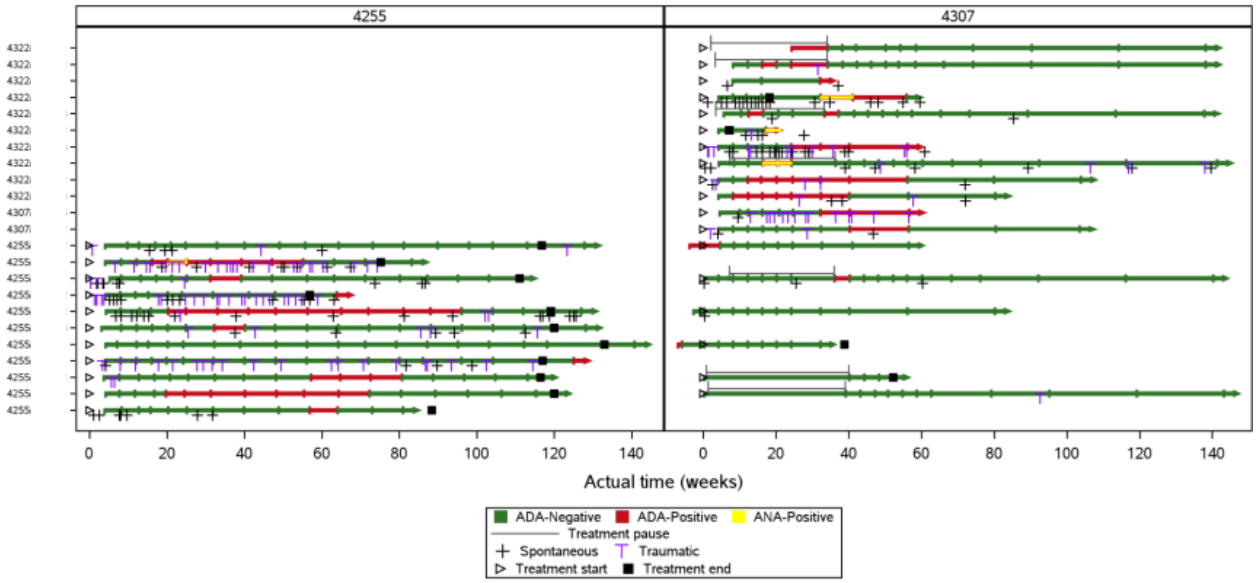
Concizumab exposure. In both phase 2 and phase 3 trials, concizumab exposure over time after first dose was similar between patients positive and negative for ADAs. The results from phase 3 trials 4311 and 4307 also show that the geometric mean Ctrough values were similar between ADA-positive and ADA-negative samples, regardless of the ADAs being binding or in vitro-neutralising.

Pharmacodynamics. In both phase 2 and phase 3 trials, free TFPI plasma concentration profiles were similar between patients positive and negative for ADAs. Individual plots for pre-dose free TFPI plasma concentration do not show a general change in bleeding episodes in patients who

tested positive for ADAs with in vitro-neutralising effects in trials 4307 and 4311. Seroconversion did not appear to cause a general change in free TPFI plasma levels in any but 2 of the ADA-positive patients (see case narratives below).

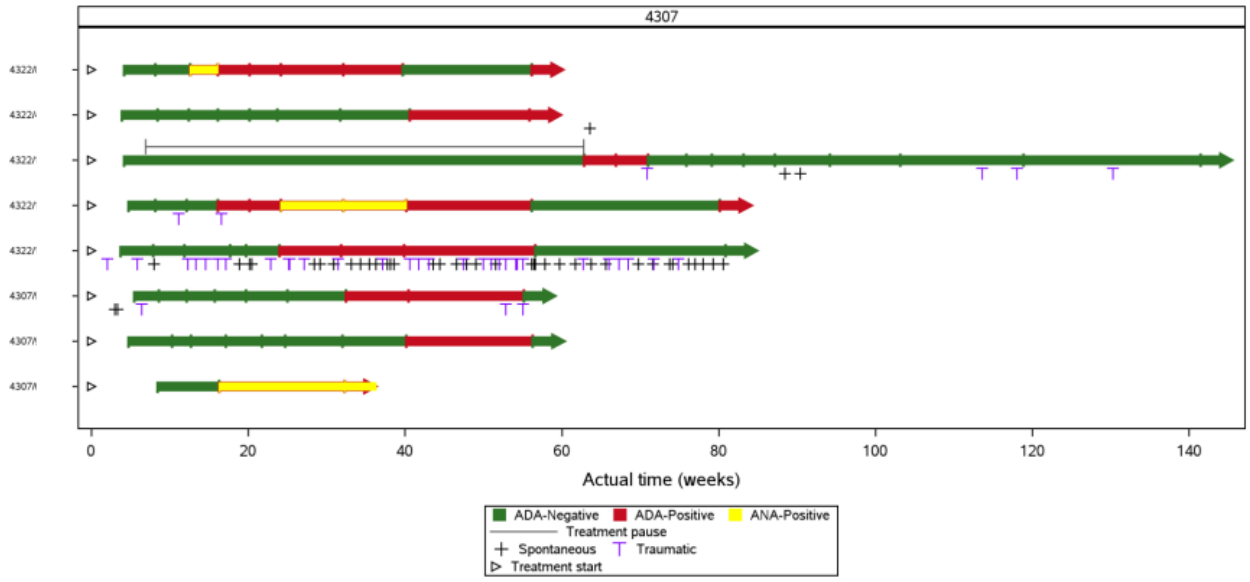
Efficacy. The pattern of treated spontaneous and traumatic bleeding episodes for each patient was generally not different between times of presence or absence of ADAs and/or ADAs with in vitro-neutralising effects. Results of studies 4255 and 4307 in HA and HB are provided in Figure 31 and Figure 32.

Figure 31. Bleeding episodes over time in relation to ADA status - ADA-positive patients - HA - trials 4255 and 4307 (56-week cut-off) - safety



ADA: Anti-concizumab antibody, ANA: Anti-Concizumab Neutralising Antibody, HA: haemophilia A without inhibitors.
The plot includes all patients who were positive for ADAs at one or more timepoints after first concizumab dose. Patients were exposed to concizumab from treatment start to treatment end except during the treatment pause for patients receiving first concizumab dose in trial before the pause.
Only treated bleeding episodes are marked under the ADA status line of each patient.

Figure 32. Bleeding episodes over time in relation to ADA status - ADA-positive patients - HB - trial 4307 (56-week cut-off) - safety analysis set



ADA: Anti-concizumab antibody, ANA: Anti-Concizumab Neutralising Antibody, HB: haemophilia B without inhibitors.
The plot includes all patients who were positive for ADAs at one or more timepoints after first concizumab dose. Patients were exposed to concizumab from treatment start to treatment end except during the treatment pause for patients receiving first concizumab dose in trial before the pause.
Only treated bleeding episodes are marked under the ADA status line of each patient.

- One (1) unusual case from phase 2 trial 4310 for which high ADA titres and positive samples for in vitro-neutralising ADAs co-occurred with restoration of free TFPI to baseline levels, yet the impact of the ADAs on concizumab exposure and efficacy remained inconclusive.
- One (1) case from phase 3 trial 4307 for which low ADA titres and positive samples for in vitro-neutralising ADAs co-occurred with reduction in concizumab plasma levels and restoration of free TFPI. However, the observed changes in PK and PD were unlikely to be attributed to the ADA-positive status, as the decrease in the concizumab exposure and the restoration of free TFPI continued even after the titre values decreased and the patient tested negative for in vitro-neutralising ADAs. The patient missed 5 consecutive doses of concizumab. The decrease in concizumab exposure or increase in free TFPI was not accompanied by any significant worsening in bleeding patterns or occurrence of immunogenicity-related AEs in the patient.

2.4.1. Discussion on clinical efficacy

With this application, the MAH applies for an extension of indication, to also include routine prophylaxis of bleeding in patients with:

- *severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without FVIII inhibitors and of 12 years of age or more.*
- *moderate/severe haemophilia B (congenital factor IX deficiency, FIX ⩽2%) without FIX inhibitors and of 12 years of age or more.*

The main basis for the efficacy/benefit evaluation of concizumab in the proposed indication are the results from the randomised part of trial 4307 at the CACO (at week 24-32), designed to compare the effect of concizumab PPX to no PPX (on demand with intravenous replacement with factor-containing products) in reducing the number of bleeding episodes in patients with HA or HB aged 12 years and older.

These randomized results (CACO) of study 4307 were already completed and included as supportive data in the initial MAA for the indication in *patients with HA and HB with inhibitors*, and therefore already assessed in the initial MAA. The efficacy is further supported by newly submitted data consisting of descriptive results available up to the 56-week cut-off from the OLE of trial 4307. Further, additional supportive summarized data of pivotal phase 3 study 4311 (Explorer 7) in patients with HA and HB with inhibitors are also presented in the Summary of efficacy and Overview documents, which data formed the main basis for initial MAA for the indication of treatment of patients with HAwI and HBwI aged 12 years and older.

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 subject to scientific advice and found acceptable in SA EMEA/H/SA/2178/1/FU/3/2020/PA/II, and during centralized procedure EMEA/H/C/005938/0000.

When concizumab treatment was paused, only 12% (i.e. 7 out of 60) of the planned number of randomised patients (arm 1 or 2) in trial 4307 had been enrolled. Randomisation was restarted 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. Therefore, all randomized patients in arms 1 and 2 were new and treated according to the new dosing regimen.

Concizumab dosing regimen after the treatment pause. During concizumab treatment pause, the initial loading dose of 1 mg/kg SC remained unaltered. The initial daily maintenance dose of 0.25 mg/kg sc was adapted for all phase 3 studies, to an initial daily dose of 0.20 mg/kg, with a dose setting step at 4 to 6 weeks 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. This dosing regimen has been approved for the current HAwI and HBwI indications in adolescents and adults. Due to the mode of action of concizumab being the same regardless of the presence of inhibitors, the same dosing regimen is recommended for PPX in patients with HA and HB. In addition, a more restrictive dosing regimen with regards to the treatment of **breakthrough bleedings** was included, i.e. recommending doses in the lower range of that advised in the WFH dosing recommendations. For severe bleeds, the treatment remained at the discretion of the treating physician.

Design and conduct of the clinical studies

Pivotal study 4307 (Explorer 8) is a 4-armed multi-national, multi-centre, open-label, confirmatory trial in patients aged 12 years and older 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 (CACO), and an ongoing uncontrolled extension phase (OLE) of 128-136 weeks. Arm 3 and arm 4 consist of patients allocated to concizumab PPX treatment only, that enabled within-patient comparison of concizumab with previous factor-containing PPX treatment, and also 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), i.e. a total of 265 weeks.

In the randomized part (**arm 1 + 2**), patients in arm 1 (no PPX) continued on-demand treatment with their usual factor replacement therapy, and patients in arm 2 received concizumab PPX.

In (non-randomised) **arm 3**, patients were enrolled who already completed trial 4255 prior to treatment pause

In (non-randomised) **arm 4**, patients who completed study 4255 after the treatment pause were enrolled as well as from the non-interventional study (NIS) study 4322 (enabling a within-patient comparison with historical ABR previously obtained with factor-containing prophylaxis).

As **comparator**, on-demand therapy has been selected. A comparison of prophylaxis treatment against on-demand treatment was considered acceptable in haemophilia patients with inhibitors. However, in HA/HB without inhibitors, a comparison to on-demand treatment does not reflect the standard of care in many EU countries, where treatment for HA and HB consists of prophylactic iv factor replacement therapy (HA/HB) or Hemlibra (HA). Therefore, a sole comparison against on-demand treatment was not considered acceptable in SA EMEA/H/SA/2178/3/2019/PA/III. However, the confirmatory secondary endpoint was to demonstrate non-inferiority of concizumab

PPX vs previous PPX treatment with FVIII/FIX, via a within-patient comparison on concizumab PPX (IPAS in study 4307) with the historical ABR on FVIII/FIX product PPX, for those patients coming from the NIS study 4322, thus providing relevant active comparison data.

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 emicizumab studies.

In the main part of the trial, patients were **randomised** (2:1) to concizumab PPX or on demand treatment (no PPX). Patients in the randomised arms (arms 1 and 2) of the trial were stratified according to haemophilia type (HA, HB); and bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ⩾9 bleeding episodes). Randomisation and stratification were based on information in the medical records.

Study Participants. Patients aged ⩾12 years with congenital severe HA (FVIII <1%) or moderate to severe HB (FIX ⩽2%) without inhibitors, were included, in line with the proposed target population in the SmPC. Additional inclusion criteria for randomized arm 1 and 2 were either on-demand patients transferred from study 4322, or on-demand patients 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). Excluded were patients who were treated within 180 days with eculizumab (Hemlibra) and who had presence of inhibitor at screening or known history of ⩾0.6 BU in the last 5 years according to the medical records. Additional inclusion and exclusion criteria for arm 1 and 2 are in line with study 4311, and acceptable.

Efficacy endpoints. The **primary efficacy analysis** for both HA and HB was to demonstrate superiority of concizumab PPX in Arm 2 vs. no PPX in Arm 1 on the primary efficacy endpoint of the number of treated spontaneous and traumatic bleeding episodes. Efficacy in HA and HB patients was planned to be analysed separately, which was endorsed since these conditions are less rare as compared with HawI and particularly HBwI. The confirmatory secondary analysis was to demonstrate non-inferiority of concizumab PPX vs. standard coagulation factor PPX, on the number of treated spontaneous and traumatic bleeding episodes using historical ABRs from NIS-trial 4322. Thereby, an intra-patient comparison of prophylaxis with concizumab versus prophylaxis with the previous FVIII or FIX product was performed, providing relevant active-comparative data for Europe.

The **sample size** calculation was determined based on the estimand for the primary and confirmatory secondary objectives. For the primary estimand, 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. These assumptions are considered reasonable and given these assumptions, the sample size calculations can be followed. For the confirmatory secondary endpoint, the NI margin of 2 has not been justified based on clinical relevance, like impact of bleedings on (target) joints, or quality-of-life. However, since the NI margin was not met, the issue was not further pursued. It was planned to screen a total of 180 adults and adolescents with haemophilia A or B without inhibitors with the aim to enroll 158 of these patients, including approximately 35 adolescent patients with HA or HB. For the within-patient comparison for the secondary confirmative endpoint (IPAS subset in arm 4), it was planned to enroll 30 subjects with HA and 30 subjects with HB.

In trial 4307, the following **analysis data sets** were defined for the efficacy evaluation both at the CACO and at the 56-week cut-off:

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, defined as the time after an initial period on PPX treatment of at least 24 weeks in study 4322 and who entered the maintenance period in the present trial.

The **primary estimands** were addressed using the FAS and the 'OTwoATexBR' analysis data set reflecting 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 regimen. The estimands associated with the confirmative secondary endpoint are addressed by applying statistical inference on the IPAS and the OT stable woATexBR analysis data set. This reflects the observation period in which patients are considered to be on stable PPX in study 4322 or stable concizumab PPX in trial 4307. The statistical analysis of the primary endpoint uses a negative binomial model, including stratification factors (randomised treatment regimen and bleeding frequency (<9 or ⩾9 bleeding episodes during the past 24 weeks prior to screening) and using the log of observation time as offset. Supportive and sensitivity analyses were performed, taking into account the changes in the study design due to the treatment pause, and using alternative population/observation period definitions and different handling of intercurrent events. This is considered standard for count endpoints and is acceptable.

Efficacy data and additional analyses

Results Confirmatory analysis (CACO)

At data cut-off date 30 September 2024, results were available of the completed main part of study 4307 (CACO, data-base lock 2023), that was already assessed at initial MAA, and new data consisting of the 56 week cut-off data of the single arm extension phase, that is planned to last for 128 to 136 weeks.

Participant flow. In (1:2) randomized arms 1 (on-demand treatment) and 2 (concizumab PPX), a total of 9 vs 18 subjects with HA (including 4 vs 4 adolescents) and 12 vs 24 subjects with HB (including 3 vs 6 adolescents) were enrolled. In arm 4, 29 subjects with HA (including 7 adolescents) and 22 subjects with HB (including 4 adolescents) were enrolled in the IPAS. The sample size that was planned for the IPAS of 30 subjects each with HA and HB was not met. Therefore, only a limited amount of comparative data vs previous routine prophylaxis are available, which is particularly the case for adolescents.

A total of 8 out of 82 patients with HA permanently discontinued concizumab PPX treatment at the CACO (2 patients due to investigator decision, 2 patients due to AEs (PTs: cardiac failure and intra-abdominal haemorrhage), 1 patient due to lack of efficacy and 3 patients due to other reasons. A total of 6 out of 66 patients with HB permanently discontinued concizumab PPX treatment (1 patient due to investigator decision, 1 patient due to AE (injection site pain), 1 patient due to a protocol deviation, 3 patients due to other reasons).

Baseline demographic and disease characteristics. All included subjects were male. Only 3 patients aged >= 65 years were included, and only 2 were exposed to concizumab (in arm 3), therefore data on treatment in elderly are limited. A sufficient number of patients from Europe was included in this global study. Generally, the recruited patients reflect a population of subjects with

congenital severe HA (FVIII <1%) or moderate/severe HB (FIX ⩽2%), with a sufficient number of subjects with both haemophilia types included.

Previous haemophilia treatment and bleed history. For the randomized groups 1 and 2, prior to enrolment, 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. These ABRs are in line with the intention to include patients with a bleeding frequency of at least 5 bleeds per 24 weeks.

The intra-patient analysis set (IPAS) consisted of a different population (subgroup of study-arm 4) on previous factor-containing PPX compared with concizumab PPX. A total of 51 subjects were enrolled, 29 with HA and 22 with HB. They received prophylactic treatment in NIS-study 4322, prior to study 4307, for a mean (SD) of 52.9 (26.4) weeks for HA and 52.5 (33.6) weeks for HB. Different types of factor products according to standard-of-care, either FVIII or FIX, were used during the prophylaxis treatment period before allocation to arm 4 of study 4307. Mean (SD) duration of exposure to concizumab PPX in study 4307 was 57.0 (23.8) weeks for HA and 37.6 (19.4) weeks for HB. No subject was treated with emicizumab.

Numbers analysed. 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). With regard to concizumab **exposure** time, 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. Mean (SD) patient years exposure was 1.0 (0.5) years.

Bleeding-related outcomes at CACO

Primary endpoint - mean annual bleeding rate (ABR) at 24/32 weeks in patients with HA or HB

Superiority of concizumab PPX treatment over no PPX (on-demand treatment) was confirmed for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes, both for patients with HA and HB:

For **HA**, the estimated mean ABR of treated spontaneous and traumatic bleeding episodes was 19.3 (95% CI 11.25-33.03) on on-demand treatment (arm 1) and 2.7 (95% CI 1.63-4.59) on concizumab PPX (am 2), with an estimated ABR ratio of 0.14 (95% CI 0.07-0.29). This corresponds to a 86% reduction of ABR for patients on concizumab PPX as compared with on-demand treatment.

For **HB**, the estimated mean ABR of treated spontaneous and traumatic bleeding episodes was 14.8 (95% CI 8.14-26.86) on on-demand treatment (arm 1) and 3.1 (95% CI 1.91-5.04) on concizumab PPX (am 2), with an estimated ABR ratio of 0.21 (95% CI 0.10-0.45). This corresponds to a 79% reduction of ABR for patients on concizumab PPX as compared with on-demand treatment.

Superiority was demonstrated on the primary efficacy endpoint of number of treated spontaneous and traumatic bleeding episodes for concizumab PPX vs on-demand treatment for both HA and HB, reflecting a clinically relevant 86% and 79% reduction of bleeding events, respectively.

Sensitivity analyses intended to investigate the impact of potential bias introduced by the treatment pause, and supplementary analysis using the treatment policy strategy consistently support the robustness of the primary analysis, for both patients with HA and HB. In addition, consistent results were seen in a post-hoc analysis based on covariate distribution using the characteristics as given in the study arms at baseline on bleeding frequency.

Key secondary endpoint – intra-patient comparison

For HA, the median (IQR) *observed* ABR of treated spontaneous and traumatic bleeding events was 2.1 (0.9-4.2) on previous PPX vs 2.3 (0.0-8.1) on concizumab PPX. The estimated ABR was 3.7 (95% CI 2.51-5.42) for patients on previous PPX (study 4322) and 5.1 (95% CI 2.71-9.65) for patients on concizumab PPX (study 4307). The estimated ABR ratio was 1.39 (95% CI 0.73-2.63).

For HB, the median (IQR) *observed* ABR of treated spontaneous and traumatic bleeding events was 2.2 (0.8-6.2) on previous PPX vs 1.4 (0.0-4.7) on concizumab PPX. The estimated ABR was 3.1 (95% CI 2.07-4.62) for patients on previous PPX (study 4322) and 5.4 (2.27-12.91) for patients on concizumab PPX (study 4307). The estimated ABR ratio was 1.75 (95% CI 0.81-3.78).

Therefore, non-inferiority of concizumab PPX (trial 4307) over previous PPX (study 4322) was not confirmed for both patients with HA and HB.

The non-inferiority margin for the comparison of previous routine prophylaxis and concizumab prophylaxis was defined as 2 on the relative scale (doubling of ABR). The margin derivation seems to have been conducted based on FDA guidance and based on statistical consideration, an acceptable margin justification from a clinical perspective is missing. This issue was however not further pursued since concizumab non-inferiority compared to standard of care factor prophylaxis was not met.

Though concizumab non-inferiority was not demonstrated, the ABR CIs for both HA and HB included 1 and mean point-estimates of the estimated ABR for bleeding events of 1.39 and 1.75 is not suggestive of a substantially higher ABRs on concizumab prophylaxis, which may be counterbalanced by favourable trends in QoL and treatment preferences, as well as limiting the risk of developing inhibitors to FVIII/FIX containing products.

From the data provided, high HA ABR results were triggered by 2 patients with particularly high ABR increases during concizumab prophylaxis (ABRs >30 and ABR >40). One of these patients had 3 target joints (left ankle, right ankle, right elbow) at the beginning of run-in study 4322, with an aggravation of target joints following increased physical activity after covid lockdown and amelioration of target joint related AEs after synovectomy. For the other patient, reason for high ABR during study 4307 was unclear, as adequate PK and PD parameter response to concizumab treatment and no lifestyle changes as well as low/no risk from sport activity were reported. Regarding the HB population, 1 patient was identified with substantially increased ABR (>50) during concizumab treatment compared to prior routine prophylaxis, which seems to have been caused due to reported lifestyle changes during concizumab treatment including increased sportsmanship.

Also, it is noted that the observed median ABRs showed results more in favour of concizumab prophylaxis. In patients with HA, median ABR (treated spontaneous and traumatic bleedings) was 2.2 on previous routine prophylaxis compared to 2.3 on concizumab prophylaxis. In patients with

HB, median ABR was 2.1 on previous routine prophylaxis compared to 1.4 on concizumab prophylaxis.

Supportive secondary endpoints

For both patients with HA and HB, the estimated mean ABRs from the supportive secondary bleed-related endpoints (number of treated spontaneous bleeding episodes, treated spontaneous and traumatic joint bleeding episodes and treated spontaneous and traumatic target joint bleeding episodes), as well as all treated and untreated spontaneous and traumatic bleeding episodes, were consistently lower for patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

Ancillary analyses

The proportion of patients with zero treated spontaneous and traumatic bleeding episodes within the first 24 weeks of treatment (and who did not discontinue before week 24) was 33.3% (6/18 subjects) and 41.7% (10/24 subjects) in the concizumab group (arm 2) for HA and HB, respectively. In the on-demand group (arm 1), there was no HA patient and 1 HB patient with zero bleeds.

Patient-reported outcome

In study 4307, patient-related outcome was analysed as exploratory endpoints, using the on-treatment data after the treatment pause. The analysis included 8 PRO questionnaires, including the general SF-36v2 health survey and the haemophilia-specific Haem-A-QoL and Hemo-TEM, that measures treatment burden. The number of patients participating in this analysis was limited, with a substantial number of missing values. Though these missing values might be related to logistical issues, selective non-response for PRO from patients in relation to perceived efficacy or safety issues cannot be excluded. In general, the results demonstrated a tendency for a more favourable judgment by the patient on concizumab of the reported outcome. The results are in line with the findings in study 4311 and can be considered in favour of concizumab PPX in subjects with HA and HB, though estimation of clinical relevance of these findings is limited due to the small sample size, and potential bias related to the open label design.

Descriptive efficacy results over 56-weeks

A total of 74 patients with HA and 59 patients with HB completed treatment at the CACO and were enroled in the OLE of study 4307. At 56-week cut-off, 1 patient with HA in arm 4 had discontinued concizumab PPX treatment due to lack of efficacy, and 1 patient with HB was not switched to concizumab as he underwent liver transplantation.

At the 56-week cut-off, the descriptive results for all bleed related endpoints and assessments were consistent with descriptive results seen at the CACO, both for patients with HA and HB. For the patients in arm 1, who switched from no PPX to concizumab PPX after completing 24 weeks in the main part, the median ABR on concizumab PPX (arm 1 at 56-week cut-off) was consistently lower than the median ABR on no PPX (arm 1 at the CACO).

For the 80 patients with HA on concizumab PPX (arms 1−4), the overall median ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 1.7. For the 7 patients with HA in arm 1 (who switched from no PPX to concizumab PPX treatment after at least 24 weeks), the median ABR at the 56-week cut-off was 2.6. At the CACO, the median ABR for the 9 patients with HA on no PPX (arm 1) was 19.6.

For the 64 patients with HB on concizumab PPX (arms 1−4), the overall median ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 2.8. For the 10 patients with HB in arm 1 (who switched from no PPX to concizumab PPX treatment after at least 24

weeks), the median ABR at the 56-week cut-off was 3.3. At the CACO, the median ABR for the 12 patients with HB on no PPX (arm 1) was 14.9.

These results are supportive of maintenance of treatment effect of concizumab PPX on ABR during longer-term treatment up to 56 weeks.

At 56-weeks, target-joints, defined as three or more spontaneous bleeds into a single joint within a consecutive 6-month period, were evaluated for the first time, to assess frequency of resolution. For patients on concizumab PPX (arms 1-4) reporting pre-existing target joints at baseline, the majority (~85% for both HA and HB) of these target joints were resolved.

Immunogenicity and tolerance. A total of 58 out of 278 (20.9%) exposed to concizumab in studies 4307 and 4311, developed concizumab, with in-vitro neutralizing effects in 14/278 (5%) of patients (see further section 'discussion on clinical safety'). In 1 patient with ADAs with in vitro effects, impact on PD (one case of restoration of free TFPI back to baseline after treatment for 40 weeks), and in 2 cases increased bleeding tendency was seen that was however more likely caused by other factors than ADA's (in one case bleeding frequency remained high though ADA's were not detected anymore, and in one case treatment non-compliance was implicated).

Analysis across age. In studies 4307 and 4311, patients aged >= 12 years were included, in line with the proposed indicated target population. The median observed ABR for treated spontaneous and traumatic bleeding episodes in adolescents was slightly higher compared to adults on concizumab PPX, for HA 3.2 (0.0;37.1) vs 0.7 (0.0;32.5), and for HB 4.9 (0.0;46.3) vs 1.6 (0.0-91.3). Additionally, a higher number of severe bleeding episodes were reported from adolescents across study arms 1-4 (adolescents: 10 severe bleeding episodes in 2 patients vs 0 in adults). This is not in line with findings in study 4311 in HwI, where the observed mean ABR for treated spontaneous and traumatic bleeding episodes numerically was slightly lower in adolescents compared to adults on concizumab PPX (arms 1−4), 1.5 (SD 2.1) vs 3.8 (SD 9.7), mainly driven by a few adult patients with high ABRs (>20) due to target joints. In study 4307, similar to study 4311, a substantial variation in ABRs is seen for both HA and HB, that may be a reflection of disease characteristics like the existence of target joints or lifestyle factors like physical activities. Due to the small sample size of adolescent patients, interpretability of data on bleeding events is limited. Comparably high ABRs reported from the adolescent subpopulation in the intra-patient analysis set (n=11) seem to have been mostly triggered by two adolescent patients with particularly high ABRs reported from one patient with HA and one patient with HB (ABRs of 46.7 and 50.6, respectively). From the provided data on treatment compliance, non-compliance could be ruled out to be responsible for the reported increased ABRs in adolescents. Overall, in the majority of adolescent patients without inhibitors concizumab prophylaxis provided adequate prophylactic treatment.

Across all study arms, 25.4% of patients were eligible for dose escalation to 0.25 mg/kg maintenance therapy, based on concizumab exposure level. An imbalance between haemophilia types was evident, as HB patients underwent dose escalation to 0.25 mg/kg maintenance at a substantially higher frequency compared to HA patients (HA: 13/80, 16.7%; HB: 22/64, 36.7%). According to study protocol, dose-escalation was based on concizumab exposure level at the dose-setting step at 4 weeks after initiation of concizumab. Background information summaries for patients with dose escalation to 0.25 mg/kg maintenance dosing were provided. Some differences in subgroup composition between disease types were noted. More HB patients requiring dose escalation were adolescents compared to the HA sample (45.5% vs 15.4%), and most notably, significantly more HB patients had at least one target joint at baseline (63.6%) compared to patients with HA (30.8%). Interpretability of the observed differences between disease types was limited due to the low available numbers in the sample of patients requiring dose increase. No

concerns arose from the provided data regarding the maintenance dose recommendations in HB patients.

Supportive study 4311 in patients with HAwI and HBwI

A summary of efficacy results of study 4311 was presented as supportive data. Study 3411 of similar design was the main study to support the MAA for the HAwI and HBwI indications for concizumab, therefore, design, conduct and results at the CACO as well as at 56 weeks data cut-off have been assessed and discussed before in the initial MAA. In this study, adult and adolescent patients aged ⩾12 years with a diagnosis of congenital haemophilia A or B of any severity and documented history of high-titre inhibitor (i.e. ⩾5 BU) were included. Instead of using the initial severity scale at the moment of diagnosis based on endogenous FVIII or FIX activity, patients were included based on their need of treatment of breakthrough bleeds with bypassing agents prior to inclusion, which reflects clinical severity of their bleeding disorder. In study 4311, HawI and HbwI were analyzed together, since based on the MoA of concizumab a similar effect in these patients was expected and for feasibility due to the rarity of especially HBwI. The concizumab dose regimen is similar for haemophilia A and B patients either without or with inhibitors.

For the randomized comparison of arm 1 (on-demand treatment) vs arm 2 (concizumab PPX) using the OTexIR data set (based on on-treatment without ancillary therapy and excluding data on initial regimen for subjects exposed to both regimens), 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.

Superiority for the primary endpoint, a reduction of the number of treated spontaneous and traumatic bleeding episodes was demonstrated:

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 1.01-2.87) 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 clinically relevant reduction of 86% in ABR for patients on concizumab PPX (arm 2) compared to on-demand treatment (arm 1).

Sensitivity analyses aimed at investigating potential bias due to the treatment pause, and supplementary analysis using a treatment policy strategy all were consistent with the primary analysis and thus supported the robustness of the primary analysis.

Given the rarity of HBwI, a separate superiority analysis for patients with HBwI alone was not considered feasible and the study was not powered to detect a statistical significant effect on bleeding events for haemophilia subgroups separately. An ancillary analysis of treated spontaneous and traumatic bleeding episodes on concizumab PPX vs on-demand treatment revealed an ABR ratio of 0.09 (95% CI 0.04-0.18; p<0.001), for HAwI, and 0.31 (95% CI 0.07- 1.36; p=0.12), for HBwI. Though not reaching statistical significance, these data do not indicate that the effect on bleeding events was driven solely by one haemophilia subtype.

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 **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, were all consistent with the results obtained for the primary endpoint.

The **56-week extension data** indicated that the treatment effect of concizumab PPX on ABR is maintained during longer-term treatment up to 56 weeks.

Compassionate use programme

The third interim compassionate use report with data cut-off date 07-Nov-2024 was included at submission. In the compassionate use programme, patients with HbwI are included in either the individual base group, or in the protocolized-CUP study. Most patients (21 out of 27) are < 12 years of age, and only 2 adults are included. For most patients, a reduction of ABR was seen on concizumab PPX. The observative design and the characteristics of the included patients, all with HbwI and only a few patients at the age of 12 years of older, limit further conclusions. However, these results are in support of a beneficial effect of concizumab in reducing bleeding frequency in haemophilia.

2.4.2. Conclusions on the clinical efficacy

Based on the current available data, consisting of an efficacy data set up to 56 weeks from the pivotal study 4307, a statistical significant and clinically relevant reduction of bleeding frequency of 86% in HA and 79% in HB as compared to on-demand treatment with factor VIII/IX-containing products has been demonstrated in adult and adolescent patients with severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%). This beneficial effect on bleeding frequency is maintained during longer-term treatment up to 56 weeks of the ongoing OLE of study 4307. Though, based on an in-patient comparison (comparison with historical ABR previously obtained with factor-containing prophylaxis), non-inferiority was not demonstrated as compared with previous standard-of-care prophylaxis with factor VIII /IX-containing products, the results were not suggestive of a large difference in treatment effect. In general, other secondary and explorative endpoints on bleed-related outcomes were supportive of the primary endpoint, while patient reported outcomes suggested improvement in aspects of health-related QoL and treatment burden.

The efficacy results are supportive for the indication of prophylactic treatment of patients older than 12 years of age with severe HA (FVIII<1%) or moderate/severe HB (FIX ≤2%) without inhibitors.

2.5. Clinical safety

Introduction

Safety profile observed in the existing indication: HAwI and HBwI patients ≥ 12 years of age

Based on the available data in HAwI and HBwI patients ≥ 12 years of age at initial MAA, concizumab appeared 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 in patients with HA and HB without inhibitors 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 safety of concizumab was previously evaluated in the initial MAA for the HAwI and HBwI indications based on results from a safety pool of five phase 1 to 3 multiple-dose trials conducted in patients with HAwI, HBwI, HA and HB (trials 4159, 4310, 4255, 4311 and 4307, with results obtained at the 56-week cut-off in trial 4311 and at the confirmatory analyses cut-off [CACO] in trial 4307), with cut-off date 30 August 2022.

Compared to the initial HAwI and HBwI application, additional clinical results have become available:

- Results from one phase 3 confirmatory trial (trial 4307) in HA and HB patients, which includes results at the confirmatory analysis cut-off (CACO) (already included in the initial MAA), supplemented with long-term results from the 56-week cut-off.
- Results from the latest interim cut-off in the compassionate use programme (trial 4807)

Basis for the safety evaluation – The (updated) safety pool

In the present application with cut-off date 30-Sep-2024, safety results from an updated safety pool of the five multiple-dose trials, with results included up until the 56-week cut-off in trial 4307, were provided to support the safety evaluation of concizumab in HA and HB patients.

Rationale for safety pool (also applied in the initial MAA)

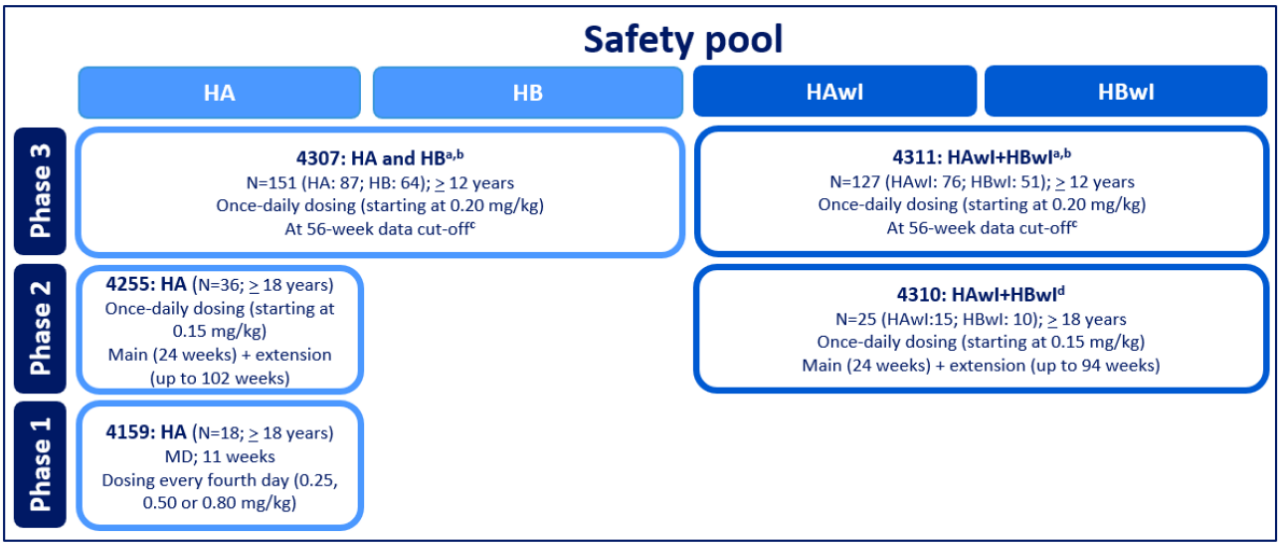
The concizumab mechanism of action is the same across haemophilia subtypes and because there are no noteworthy differences in pharmacokinetic (PK) and pharmacodynamic (PD) properties of concizumab between haemophilia patients with and without inhibitors. Evaluation of the safety pool ensures a comprehensive and aggregated evaluation of the safety of concizumab PPX and increases the likelihood of detecting potential safety signals.

The five multiple-dose trials comprising the safety pool are:

- Completed phase 1 trial 4159 (HA patients)
- Completed phase 2 trials 4255 (HA) and 4310 (HAwI and HBwI)
- Ongoing phase 3 trials 4307 (HA and HB) and 4311 (HAwI and HBwI). Results are included up until the respective 56-week cut-offs.

Included in the safety pool are all patients from the five multiple-dose trials exposed to at least 1 dose of concizumab (in phase 3 trials: before and/or after the treatment pause). An overview of trials contributing to the pooled safety evaluation is provided in Figure 33 below:

Figure 33: Overview of trials contributing to pooled safety evaluation.



Notes: [a]16 patients with HA from trial 4255 were transferred to trial 4307 (cross-reference: ADSL.sas7bdat [Trial 4307]) and 21 patients from trial 4310 were transferred to trial 4311 (Trial 4311 PACO [M5.3.5.1], Table 10-1 [arm 3]). [b]Patients randomised to on demand treatment who were exposed to at least one dose of concizumab following the main part of the trial, contributed to the pooled safety evaluation. [c]The 56-week cut-off was defined as when all patients in arms 2, 3 and 4 had completed visit 13a (or permanently discontinued treatment). [d]Patients randomised to on-demand treatment in the main part, who have been exposed to at least one dose of concizumab in the extension part of the trial, contribute to the pooled safety evaluation. Further details on exposure to concizumab are available in Section 1.2. Abbreviations: HA: haemophilia A without inhibitors; HB: haemophilia B without inhibitors; HAwI: haemophilia A with inhibitors; HBwI: haemophilia B with inhibitors; MD: multiple-dose; N: number of patients exposed to at least one dose of concizumab

The following safety pool and relevant groupings within the safety pool were defined:

- The safety pool, comprising all multiple-dose trials (4307, 4255, 4311, 4310 and 4159) in patients with haemophilia exposed to at least one dose of concizumab (in phase 3 trials: before and/or after the treatment pause): 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 (HA, HB, HAwI and HBwI): to assess consistency in the safety profile across haemophilia subtypes.
- Safety data were also evaluated for several subgroups, based on Intrinsic factors age, race, ethnicity, baseline hepatic function and renal function, and baseline thromboembolic risk.

Safety in ongoing trials and compassionate use

In addition to locked trial results and results from compassionate use of concizumab obtained up until 28-Feb-2024, the summary also includes information on 'safety in ongoing trials' to further support the safety evaluation for concizumab. Ongoing safety results from trials 4307, 4311 and 4616 and compassionate use and individual patient basis data are included until the application cut-off of 30-Sep-2024.

Analysis sets

The safety analysis set (SAS)

The safety analysis set was based on the 5 multiple-dose phase 1-3 trials.

All safety evaluations are based on the SAS.

For safety evaluations based on data from pivotal phase 3 trial 4307 and phase 3 trial 4311, 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 OTexIR/OTexBR analysis data sets representing the OT period after concizumab treatment restart
    - The **on-treatment excluding data before restart (OTexBR**) analysis data set (trial 4307).
    - The **on-treatment excluding data on initial dose regimen (OTexIR)** analysis data set (trial 4311)

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.

Patient exposure

Dosing regimens

In patients with haemophilia, concizumab PPX was administered s.c. either daily in trials 4311, 4310, 4307 and 4255 or every 4 days in trial 4159. For all trials, dosing by body weight was used.

In phase 3 trial 4307 in HA and HB and phase 3 trial 4311 in HAwI and HBwI, patients received an initial single loading dose of 1.0 mg/kg (4311 and 4307) on the first day followed by an initial daily dose of 0.20 mg/kg, respectively, concizumab from treatment day 2. 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 trial 4310, a loading dose of 0.5 mg/kg concizumab was given, followed by daily doses of 0.15 mg/kg, with the possibility to escalate the dose to 0.20 mg/kg and 0.25 mg/kg.

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 phase 3 trial 4307, patients randomised to arm 1 were to continue on-demand treatment with their usual replacement therapy.

In the main part of trials 4310 and 4311, patients randomised to on-demand treatment (arm 1) received i.v. eptacog alfa (rFVIIa) or on-demand treatment with their usual bypassing product, respectively, and treated according to local treatment practice.

Dosing in Trial 4307 in patients with HA or HB without inhibitors after the treatment pause:

At 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 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.

At 56-week cut-off:

Up until the 56-week cut-off, 64 patients with HB were exposed to concizumab across arms 1−4, including 54 patients who were randomised/allocated to arms 2 and 4 after the treatment restarted and 10 patients in arm 1 (no PPX) who continued in the extension part of the trial who switched to concizumab PPX at week 24. Four (4) patients withdrew from the trial and did not have a maintenance dose reported. Of the remaining 60 patients, 33 (55.0%) remained on the 0.20 mg/kg daily dose level, 22 (36.7%) increased their daily dose to 0.25 mg/kg and 5 (8.3%) decreased their daily dose to 0.15 mg/kg.

Implications of COVID-19

The outbreak of Coronavirus Disease 2019 (COVID-19) was declared a global pandemic by the WHO on 11-Mar-2020. Novo Nordisk has followed the guidance provided by FDA and EMA on how to handle changes to trials related to COVID-19. Overall, no safety concerns were observed for concizumab treatment in trials 4307, 4255 and 4311 in relation to the COVID-19 pandemic. For the remaining multiple-dose trials in haemophilia (trial 4310 and 4159), database lock (DBL) had already occurred at the time of the pandemic.

Patient disposition total (updated) safety pool

A total of 320 patients with HA, HB, HAwI and HBwI have been exposed to concizumab in the multiple-dose clinical trials 4307, 4255, 4311, 4310 and 4159, corresponding to a total of 474.7 patient years of exposure (PYE). The five multiple-dose trials represent the majority of patient exposure to concizumab during the development programme. The pivotal phase 3 trials in patients with HA and HB (4307) and in patients with HAwI and HBwI (4311) up until the respective 56-week cut-offs contributed with most of the total exposure (193.6 PYE and 160.0 PYE, respectively), whereas mean exposure time was higher in the phase 2 trials (4255 and 4310), where also extension part data are included.

<u>By haemophilia subtype – total (updated) safety pool</u>

The total duration of exposure to concizumab in the safety pool by haemophilia subtype:

- Total exposure for patients with HA and HB was 195.8 PYE and 73.5 PYE, respectively,
- Total exposure for patients with HAwI and HBwI was 121.3 PYE and 84.0 PYE, respectively.

Of the 320 HA, HB, HAwI and HBwI patients exposed to concizumab in the multiple-dose trials, 275 (86%) patients were exposed for at least 6 months, roughly corresponding to the duration of the main part in trials 4307, 4255, 4311 and 4310. Of the 275 patients, 249 (78%) patients were exposed for more than 12 months, and 63 (20%) patients were exposed for more than 24 months.

Patient disposition by trial (trials 4307, 4255, 4311, 4310 and 4159)

A by-trial overview of patients with haemophilia exposed to concizumab PPX in the five multiple dose trials as well as the number of patients completing treatment at the cut-off date for the most recent CTR for each of the trials is presented in the figure below. Note that 16 patients continued from the phase 2 trial 4255 into the phase 3 trial 4307 and 21 patients continued from the phase 2 trial 4310 into the phase 3 trial 4311. Overall, the proportion of patients completing treatment was high, though the fraction of randomised/allocated patients who completed treatment at the latest cut-off (56-week for phase 3) was lower in the phase 3 trials than in phase 1 trial 4159 and the two phase 2 trials. Most of the withdrawals in the phase 3 trials occurred during the treatment pause. Overall, there were few discontinuations due to AEs in the five trials.

Table 5432: Overview of patient disposition by trial – patients on concizumab PPX - Trials 4307 (56-week cut-off), 4255, 4311 (56-week cut-off), 4310 and 4159.

Trial ID	4307 (HA and HB)	4255 (HA)	4311 (HAwI and HBwI)	4310 (HAwI and HBwI)	4159 (HA)[f]
Treatment	Concizumab (arms 1–4)	Concizumab	Concizumab (arms 1–4)	Concizumab	Concizumab
Exposed patients	151[a]	36	127[a]	25	18
Patients completing treatment	129 (82.7)[b]	30 (83.3%)[c]	104 (78.2%)[d]	22 (88.0%)[e]	18 (100%)

Notes: Detailed information on patient disposition in the 5 trials, including information for the periods before and/or after the treatment pause in trials 4307 and 4311, are found in Summary 2.7.4, Section 1.1.5.2 and in the individual trial reports. [a]Number of patients exposed to concizumab PPX in trial before and/or after the treatment pause. [b]Patients completing treatment at the 56-week cut-off: Randomised/allocated patients in concizumab PPX arms 1–4 (including 17 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-week 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 (156 patients). [c]Patients completing treatment in the main and extension part of the trial. [d]Patients completing treatment at the 56-week cut-off: 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-week 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). [e]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). fFor trial 4159, end-of-trial corresponds to visit 18 (week 11) (see Table 9-3 [flowchart] in the clinical trial report).
Abbreviations: HA = haemophilia A without inhibitors; HAwI = haemophilia A with inhibitors; HB; haemophilia B without inhibitors; HBwI = haemophilia B with inhibitors; PPX = prophylaxis.

Patient disposition Trial 4307 – phase 3 – HA and HB

The main basis for the safety evaluation at the 56-week cut-off

For trial 4307 (HA and HB), the SAS consists of 156 (100%) patients randomised or allocated to treatment before and/or after the treatment pause, of which 90 were patients with HA and 66 were patients with HB. Of the 156 HA and HB patients, 135 patients were randomised or allocated to treatment in concizumab PPX arms 2–4 and 21 patients to no PPX arm 1. A total of 134 (of 135)

patients in concizumab PPX arms 2−4 were exposed to concizumab PPX during the main part of the trial and 17 of 21 patients on no PPX were exposed to concizumab PPX (arm 1) during the extension part of the trial. Hence up until the 56-week cut-off, a total of 151 patients were exposed to concizumab PPX (arms 1−4), of which 87 were patients with HA and 64 were patients with HB. Five (5) patients from No PPX arm 1 were not included in the evaluation at the 56-week cut-off as they never received concizumab. The 151 patients exposed to concizumab PPX up until the 56-week cut-off constitute the main basis for the safety evaluation at this cut-off in trial 4307. Of these, 115 HA and HB patients had completed 56 weeks of concizumab treatment. Patient disposition is presented in Table 55 below:

Table 5533: Patient disposition study 3407 - summary - HA+HB - all patients

	Previous OnD treatment		Concizumab Non-naive	Miscellaneous		
	No PPX (arm 1) N (%)	Concizumab PPX (arm 2) N (%)	Concizumab PPX (arm 3) N (%)	Concizumab PPX (arm 4) IPAS N (%)	Concizumab PPX (arm 4) Others N (%)	Total N (%)
Screened						173
Screening failures						2
Withdrawn before initial randomisation/allocation						15
Patients restarting old arms [a]			9	14	1	
Moved from old arm 1+2 [b]					1+4	
Not restarting [c]			1		7	
Allocated after restart				37	19	
Randomised/allocated	21 (100.0)	42 (100.0)	10 (100.0)	51 (100.0)	32 (100.0)	156 (100.0)
Exposed to Concizumab		42 (100.0)	10 (100.0)	51 (100.0)	31 (96.9)	134 (85.9)
Completed 56 weeks of concizumab treatment on new regimen		39 (92.9)	7 (70.0)	49 (96.1)	20 (64.5)	115 (85.8)
Completed treatment at 56 weeks cut-off [d]		39 (92.9)	5 (50.0)	48 (94.1)	20 (64.5)	112 (83.6)
Discontinued treatment		3 (7.1)	5 (50.0)	3 (5.9)	11 (35.5)	22 (16.4)
Adverse Event		0	1 (10.0)	0	5 (16.1)	6 (4.5)
Protocol deviation		1 (2.4)	0	0	0	1 (0.7)
Lack of efficacy		0	0	2 (3.9)	0	2 (1.5)
Lost to follow-up		0	0	0	0	0
Technical problems		0	0	0	0	0
Discretion of Investigator		1 (2.4)	1 (10.0)	0	1 (3.2)	3 (2.2)
Other		1 (2.4)	3 (30.0)	1 (2.0)	5 (16.1)	10 (7.5)
Withdrawn from trial	1 (4.8)	2 (4.8)	4 (40.0)	1 (2.0)	12 (37.5)	20 (12.8)
Withdrawal of consent [e]	0	2 (4.8)	2 (20.0)	1 (2.0)	9 (28.1)	14 (9.0)
Lost to follow-up	0	0	0	0	0	0
Investigator decision	1 (4.8)	0	2 (20.0)	0	2 (6.3)	5 (3.2)
Death	0	0	0	0	1 (3.1)	1 (0.6)
Full analysis set [f]	21 (100.0)	42 (100.0)	9 (90.0)	51 (100.0)	25 (78.1)	148 (94.9)
Safety analysis set	21 (100.0)	42 (100.0)	10 (100.0)	51 (100.0)	32 (100.0)	156 (100.0)

HA: haemophilia A, HB: haemophilia B, PPX: prophylaxis, N: number of patients, %: Percentage of randomised/allocated patients, OnD: on-demand, IPAS: Arm 4 patients who have been on stable PPX for at least 24 weeks in study NN7415-4322 and who entered the maintenance period in NN7415-4307. The patients who are moved from arm 1 and 2 to arm 4 after restart are included in arm 4 counts. [a]: The count is only for the patients that are not allocated to a new arm after restart. [b]: The count is only for the patients that are allocated to a new arm (arm 4) after restart. [c]: Patients that were in arm 1+2 before the restart and did not restart are counted in arm 4 (two patients in total). [d]: Randomised/ allocated patients who did not discontinue concizumab treatment prior to the 56 weeks cut-off. [e]: Withdrawal of consent by patient, patient's parent or patient's legally acceptable representative (LAR). [f]: Full analysis set does not include the patients in arm 1 who are only treated with on-demand before the restart and patients in arm 2-4 who are only treated with the old concizumab regimen.

The main basis for the efficacy evaluation at the 56-week cut-off is the results available for the 144 patients across arms 1−4 who were exposed to the new concizumab dosing regimen: 127 patients who were randomised/allocated when treatment restarted plus 17 patients in arm 1 (out of the 21 initially randomised to no PPX) who continued in the extension part of the trial and were thus exposed to concizumab. Of the 144 exposed patients, 80 were patients with HA and 64 were patients with HB. Four (4) patients from the FAS (in arm 1) were not included in the evaluation at the 56-week cut-off as they never received concizumab.

Adverse events

The safety evaluation is based on standard assessments (e.g., serious and non-serious adverse event (AEs and SAEs), 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 below.

Table 5634: 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
Injection site reactions	MedDRA search performed on AE data
Medication errors	MedDRA search performed on AE data
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

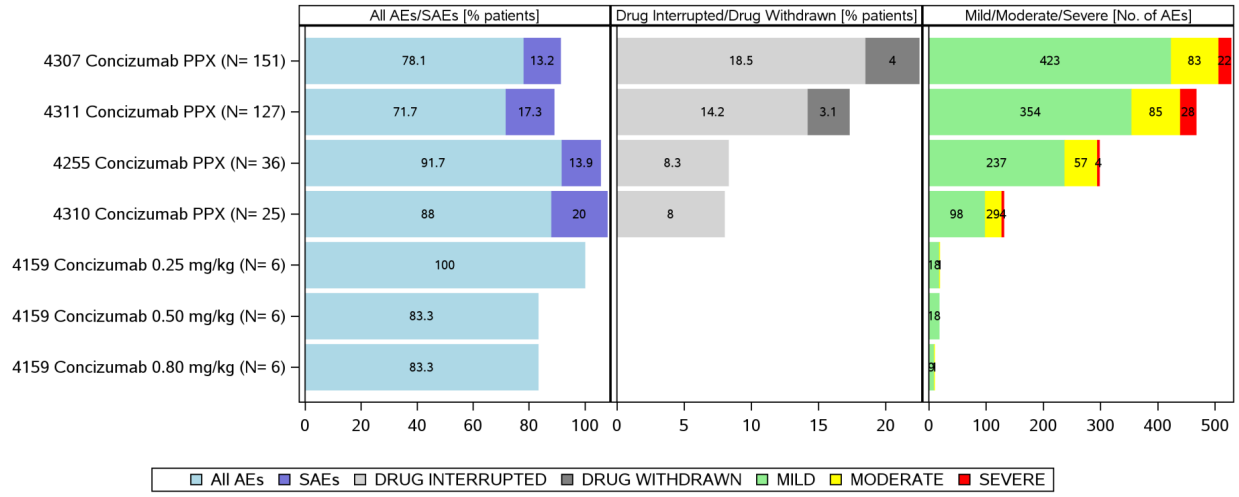
By trial (trials 4307, 4255, 4311, 4310 and 4159)

Patients on concizumab PPX

Proportion of patients with AEs and AE rate

An overview of the proportion of patients with AEs and corresponding event rates in the five multiple-dose trials is provided in the Figures below, respectively. Data in these figures 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 respective 56-week cut-offs (trials 4307 and 4311) including the on-treatment period. Note that the total percentage can exceed 100%, as some patients reported multiple AEs (Figure 34), and that only the overall AE rate is available from 4159 (Figure 35).

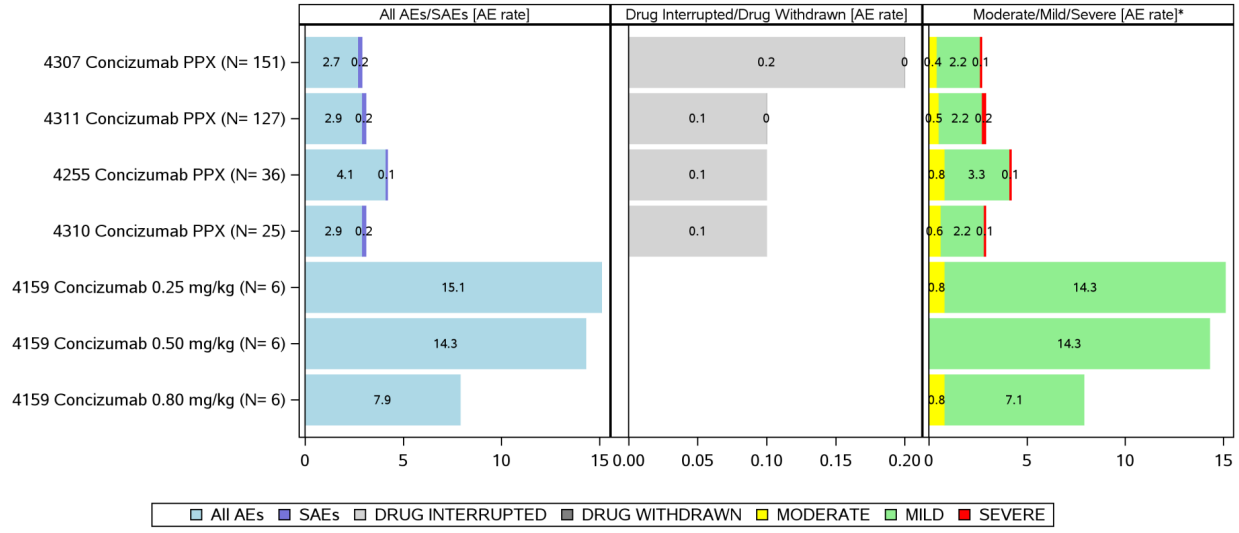
Figure 34: Overview of AEs - percentage of patients - by trial for patients exposed to concizumab PPX - trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off) - on treatment - SAS.



AE: adverse event. SAE: serious adverse event. PPX: prophylaxis.
% patients: percentage of patients with adverse event.
Patients exposed to concizumab are included. This means that placebo data from 4159, Eptacog alfa 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.
In the 4159 trial there are very few AEs compared to the other trials and the numbers are thus hard to read in the figure. Instead they are given here:
In 0.25 mg/kg group, 18 mild AEs and 1 moderate AE; in 0.50 mg/kg group, only 18 mild AEs; in 0.80 mg/kg group, 9 mild AEs and 1 moderate AE reported.
Note that the total percentages of patients can exceed 100% as categories depicted are not mutually exclusive.

nn7415/nn7415-summary/safety_hahb_ema_20241111_er
21NOV2024:06:40:37 - f-ae-overview-ppx-trial.sas/f-ae-overview-pct-ppx-trial.png

Figure 35: Overview of AEs - AE rate - by trial for patients exposed to concizumab PPX trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off) - on treatment - SAS.



AE: adverse event. SAE: serious adverse event. PPX: prophylaxis.
AE rate: rate calculated as number of adverse events per patient years of exposure.
Patients exposed to concizumab are included. This means that placebo data from 4159, Eptacog alfa 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.
* For visualization purposes the order of the AE categories are shown as Moderate/Mild/Severe in this plot.

nn7415/nn7415-summary/safety_hahb_ema_20241111_er
21NOV2024:06:40:46 - f-ae-overview-ppx-trial.sas/f-ae-overview-rate-ppx-trial.png

Safety pool

The proportion of patients with AEs were comparable across the two phase 3 trials (trials 4307 [HA and HB] and 4311 [HAwI and HBwI]) and higher in the phase 2 (trials 4255 [HA] and 4310 [HAwI and HBwI]) and 1 (trial 4159 [HA]) trials. Across phase 2 and 3, similar AE rates were observed in trials 4307, 4311 and 4310, 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.

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 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 of the reported events (54 of 56 AEs in 18 patients) were mild in severity. Note, event rates per AE severity classification were not reported in trial 4159.

Common AEs (≥5%) by SOC and PT

The most frequently reported AEs (events reported in >5% of patients within any haemophilia subtype) across haemophilia subtypes (in descending order by 'total' safety pool) were:

- events common to the general population, represented by the SOCs of:
    - 'Infections and infestations' (mainly concerning PTs: COVID-19, Nasopharyngitis and Upper respiratory tract infection)
    - 'General disorders and administration site conditions' (mainly concerning PT: Pyrexia)
- events most likely to be the consequence of haemophilia, represented by the SOC:
    - 'Musculoskeletal and connective tissue disorders' (mainly concerning PT: Arthralgia)
- events related to injection of concizumab, represented by the SOC 'General disorders and administration site conditions' (mainly concerning PT: Injection site erythema)

Most frequently reported AEs by preferred term (PT)

In the total safety pool, the most frequently reported AEs by preferred term (PT) were COVID-19 (14.7%), Nasopharyngitis (12.5%), Arthralgia (10.9%), Headache and Upper respiratory tract infection (both 9.4%), Fibrin D-dimer increased (9.1%), Pyrexia (7.2%), Injection site erythema (5.9%) and Prothrombin fragment 1+2 increased (5.6%).

Most common (≥5%) AEs possibly or probably related to concizumab PPX

In the total safety pool, 320 AEs reported in 115 (35.9%) patients (0.7 events per PYE) were evaluated as possibly or probably related to concizumab by the investigator. Of these, 14 AEs in 10 patients were serious, including 1 fatal event. Nine (9) possibly or probably related AEs in 7 patients led to permanent discontinuation of trial product and 12 AEs in 9 patients led to temporary discontinuation of trial product. Most (104 of 115) patients with possibly or probably related AEs had recovered or were recovering as of the data cut-off.

The most frequently reported possibly/probably related AEs (>5%) in the total safety pool were events under the SOCs of '*General disorders and administration site conditions' (PT Injection site erythema)* and '*Investigations' (PTs Fibrin D-dimer increased and Prothrombin fragment 1+2 increased)*. These results are in line with the established knowledge on the concizumab drug product: Injection site reactions are expected for drugs administered subcutaneously. Increased levels of D-dimers and prothrombin fragment 1+2 in plasma indicate the haemostatic effect of concizumab, and events of D-dimer increased were often reported together with events of Prothrombin fragment 1+2 increased.

Possibly or probably related AEs reported by <5% of patients

Most were one to a few events reported in 1 or 2 patients with exceptions including PTs: 'Migraine' (20 AEs) and 'Migraine with Aura' (4 AEs) (all events with these PTs were reported in the same patient) and 'Headache' (7 AEs in 4 patients) within the SOC of 'Nervous system disorders'; 'Hypersensitivity' (5 AEs in 3 patients within the SOC 'Immune system disorders'; and 'Pruritus' (3 AEs in 2 patients) and 'Pruritus allergic' (2 AEs in 1 patient) within the SOC of 'Skin and subcutaneous tissue disorders'.

All possibly/probably related events of Migraine (20 AEs) and Migraine with aura (4 AEs) were reported by a single patient with HAwI with a medical history of 'Myopia'. All of these events were non-serious, most were mild or moderate in severity and resolved after 1 day. The patient had previously reported multiple events of PT Headache and PT Visual field defect (reported term: Scotoma in the eyes) in relation to SAEs of PTs D-dimer increased and Prothrombin fragment 1+2 increased before the trial treatment pause. Magnetic resonance imaging (MRI) showed no signs of focal and space-occupying lesions in the brain.

All 7 possibly/probably related events of PT Headache were non-serious, mild in severity, lasted for 1-2 days and did not lead to any action taken to trial product. Onset day of the reported headaches varied from day 1 to day 138 of treatment. Three (3) of 7 events of Headache were reported in 1 patient within 1 week. The patient also reported an event of PT Upper respiratory tract infection with onset the same day as the last event of headache. Headaches lasting 1-2 days are commonly seen in the general population and with no pattern in time to onset the causal relation to concizumab is assessed unlikely.

All 3 reported possibly/probably related events of Pruritus (reported by 2 patients) were nonserious, mild in severity and resolved with no action taken to trial product: 1 patient with a concomitant illness of 'Iron deficiency anaemia' reported itching in the face and upper limbs on study day 1 and 2, respectively, which resolved after 1 day; 1 patient in treatment for concomitant illness of HIV reported itching and erythema on right side of abdomen on treatment day 29, which resolved after 29 days.

The 2 events of Pruritus allergic were reported as pruritus due to contact allergen on treatment day 19 and 107 in a patient with concomitant illness of 'Vitamin D deficiency' and 'Inflammatory bowel disease' which can lead to malnutrition and thereby pruritus. The events were non-serious and mild and resolved after 36 and 6 days, respectively, with no action taken to trial product. Following thorough medical assessment of these events, a causal relationship to concizumab was assessed unlikely by Novo Nordisk. An exception was some of the events with the PTs 'Hypersensitivity' (see Section 2.2.2) and 'Pruritus'.

Adverse events by haemophilia subtype - total safety pool

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, i.e. 4 (3.2%) in HA and 6 (3.1%) in Hb group. All reported deaths were previously presented in the initial MAA for the HAwI and HBwI indications. An overview is presented in Table 57 below.

Table 5735: Adverse events on concizumab - overview - by haemophilia subtype - summary - HA, HB, HAwI and HBwI - safety analysis set – trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off).

	HA			HB			HAwI			HBwI			Total		
	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]	N	(%)	E [R]
N	125			64			78			53			320		
PYE	195.8			73.5			121.3			84.0			474.7		
Total events	109	(87.2)	648 [3.3]	47	(73.4)	225 [3.1]	59	(75.6)	326 [2.7]	40	(75.5)	272 [3.2]	255	(79.7)	1471 [3.1]
Serious															
Yes	17	(13.6)	23 [0.1]	8	(12.5)	12 [0.2]	9	(11.5)	12 [0.1]	17	(32.1)	24 [0.3]	51	(15.9)	71 [0.1]
No	108	(86.4)	625 [3.2]	43	(67.2)	213 [2.9]	57	(73.1)	314 [2.6]	38	(71.7)	248 [3.0]	246	(76.9)	1400 [2.9]
Severity															
Severe	14	(11.2)	16 [0.1]	6	(9.4)	10 [0.1]	7	(9.0)	14 [0.1]	14	(26.4)	18 [0.2]	41	(12.8)	58 [0.1]
Moderate	43	(34.4)	107 [0.5]	23	(35.9)	35 [0.5]	20	(25.6)	68 [0.6]	19	(35.8)	46 [0.5]	105	(32.8)	256 [0.5]
Mild	99	(79.2)	525 [2.7]	40	(62.5)	180 [2.4]	56	(71.8)	244 [2.0]	35	(66.0)	208 [2.5]	230	(71.9)	1157 [2.4]
Relationship to trial product															
Probable	36	(28.8)	87 [0.4]	13	(20.3)	36 [0.5]	14	(17.9)	39 [0.3]	14	(26.4)	37 [0.4]	77	(24.1)	197 [0.4]
Possible	33	(26.4)	55 [0.3]	8	(12.5)	9 [0.1]	12	(15.4)	49 [0.4]	9	(17.0)	10 [0.1]	62	(19.4)	123 [0.3]
Unlikely	104	(83.2)	503 [2.6]	44	(68.8)	180 [2.4]	55	(70.5)	235 [1.9]	37	(69.8)	216 [2.6]	240	(75.0)	1134 [2.4]
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]	9	(2.8)	17 [0.0]
Outcome															
Fatal	1	(0.8)	1 [0.0]	0			0			4	(7.5)	6 [0.1]	5	(1.6)	7 [0.0]
Not Recovered	42	(33.6)	74 [0.4]	22	(34.4)	42 [0.6]	20	(25.6)	47 [0.4]	17	(32.1)	36 [0.4]	101	(31.6)	199 [0.4]
Recovered with sequelae	4	(3.2)	4 [0.0]	0			1	(1.3)	1 [0.0]	1	(1.9)	1 [0.0]	6	(1.9)	6 [0.0]
Recovering	3	(2.4)	6 [0.0]	0			7	(9.0)	7 [0.1]	5	(9.4)	7 [0.1]	15	(4.7)	20 [0.0]
Recovered	106	(84.8)	563 [2.9]	46	(71.9)	183 [2.5]	58	(74.4)	271 [2.2]	38	(71.7)	222 [2.6]	248	(77.5)	1239 [2.6]
Unknown	0			0			0			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]	10	(3.1)	12 [0.0]
Drug interrupted	21	(16.8)	27 [0.1]	10	(15.6)	10 [0.1]	12	(15.4)	16 [0.1]	8	(15.1)	9 [0.1]	51	(15.9)	62 [0.1]
Dose reduced	2	(1.6)	2 [0.0]	1	(1.6)	1 [0.0]	1	(1.3)	3 [0.0]	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]	3	(0.9)	3 [0.0]
Dose not changed	101	(80.8)	557 [2.8]	42	(65.6)	202 [2.7]	48	(61.5)	279 [2.3]	36	(67.9)	228 [2.7]	227	(70.9)	1266 [2.7]
Unknown	0			0			0			0			0		
N/A	28	(22.4)	53 [0.3]	6	(9.4)	7 [0.1]	13	(16.7)	23 [0.2]	14	(26.4)	22 [0.3]	61	(19.1)	105 [0.2]
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]	9	(2.8)	17 [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 patients, %: percentage of patients 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. Patients exposed to concizumab are included. This means that placebo data from 4159, Eptacog alfa 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 by haemophilia subtype

The observed 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. The distribution of AEs by SOC in the total safety pool reflected the most commonly reported PTs.

Differences in event rates were observed among haemophilia subtypes for the SOC of 'General disorders and administration site conditions', for which HA and HB patients showed lower event rates and patient proportions compared to patients with HBwI (mainly due to more patients with HBwI reporting non-serious injection site reactions), and the SOC of 'Nervous system disorders', where patients with HA, HB and HBwI showed event rates lower than patients with HAwI. The higher event rate in the HAwI group was primarily attributed to a single patient in this group

reporting 30 of the 46 events under this SOC. All 30 events were non-serious and included a number of Migraine and Migraine with aura events which are presented below under 'Most common (≥5%) AEs possibly or probably related to concizumab PPX'.

Possibly or probably related AEs

Across haemophilia subtypes, despite varying patient proportions, event rates for possibly or probably related AEs were comparable (range 0.6−0.7 AEs per PYE). A similar pattern of AEs with possible or probable relation to concizumab PPX was observed between the individual haemophilia subtypes.

Trial 4307 – phase 3 – HA and HB

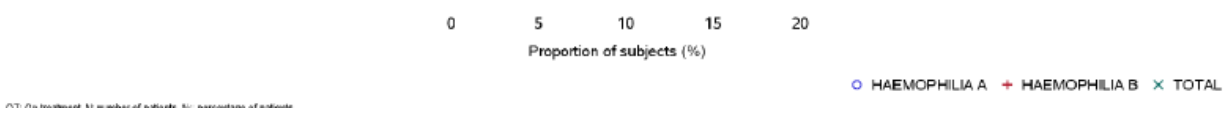
Patients on concizumab PPX – up until the CACO

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, see Table below.

Table 5836: Adverse events - by preferred term - most frequent (>=5%) in concizumab PPX (arms 1−4) - summary plot - HA+HB - OT - safety analysis set – trial 4307.

Preferred term	HAEMOPHILIA A N	%	R	HAEMOPHILIA B N	%	R	TOTAL N	%	R
COVID-19	12	(13.8)	0.14	7	(10.9)	0.15	19	(12.6)	0.14
Fibrin D dimer increased	8	(9.2)	0.10	4	(6.3)	0.09	12	(7.9)	0.10
Upper respiratory tract infection	7	(8.0)	0.09	3	(4.7)	0.09	10	(6.6)	0.09
Nasopharyngitis	8	(9.2)	0.10	1	(1.6)	0.02	9	(6.0)	0.07
Prothrombin fragment 1.2 increased	8	(9.2)	0.11	1	(1.6)	0.02	9	(6.0)	0.08
Arthralgia	5	(5.7)	0.06	3	(4.7)	0.06	8	(5.3)	0.06
Headache	3	(3.4)	0.05	5	(7.8)	0.15	8	(5.3)	0.08
Influenza	3	(3.4)	0.03	4	(6.3)	0.11	7	(4.6)	0.06
Pyrexia	5	(5.7)	0.08	2	(3.1)	0.06	7	(4.6)	0.07
Injection site reaction	2	(2.3)	0.02	4	(6.3)	0.13	6	(4.0)	0.06



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 were in SOC general disorders, injection site disorders with PT injection site erythema/reaction (n=12, 8%), and investigations with PT fibrin D dimer increased (n=10, 6.6%) and prothrombin fragment 1.2 increased (n=8, 5.3%) in trial 4307 are provided in Table 59 below. Of note, causality was judged only for patients on concizumab PPX in this trial.

Table 5937: 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		
	N (%)	E [R]		N (%)	E [R]	
N in SAS	87			64		
N in SAS and ADS	87 (100)			64 (100)		
PYE	87.0			47.0		
Total events	29 (33.3)	53 [0.6]		18 (28.1)	38 [0.8]	
General disorders and administration site conditions	11 (12.6)	12 [0.1]		13 (20.3)	27 [0.6]	
Injection site erythema	3 (3.4)	4 [0.0]		3 (4.7)	9 [0.2]	
Injection site reaction	2 (2.3)	2 [0.0]		4 (6.3)	6 [0.1]	
Investigations	12 (13.8)	23 [0.3]		5 (7.8)	6 [0.1]	
Fibrin D dimer increased	8 (9.2)	9 [0.1]		2 (3.1)	2 [0.0]	
Prothrombin fragment 1.2 increased	7 (8.0)	9 [0.1]		1 (1.6)	1 [0.0]	

	Total		
	N (%)	E [R]	
N in SAS	151		
N in SAS and ADS	151 (100)		
PYE	133.9		
Total events	47 (31.1)	91 [0.7]	
General disorders and administration site conditions	24 (15.9)	39 [0.3]	
Injection site erythema	6 (4.0)	13 [0.1]	
Injection site reaction	6 (4.0)	8 [0.1]	
Investigations	17 (11.3)	29 [0.2]	
Fibrin D dimer increased	10 (6.6)	11 [0.1]	
Prothrombin fragment 1.2 increased	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%.

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 CACO 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 and there were no new deaths. No hypersensitivity type reactions were reported up until the 56-week cut-off and all injection site reactions reported since the CACO were non-serious and mild in severity.

Up until the 56-week cut-off, a total of 118 of 151 (78.1%) patients reported 528 AEs (2.7 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 resolved. A total of 96 events in 54 patients had not resolved as of the cut-off date. All unresolved events were nonserious except for 2 events in 2 patients: Haemophilic arthropathy and Hemiparesis.

The most frequently reported AEs by PT (>5% of patients with either haemophilia subtype in concizumab PPX arms 1−4) included (in descending order) COVID-19, Fibrin D dimer increased, Nasopharyngitis and Upper respiratory tract infection.

The most frequently reported possibly or probably related AEs (reported in ⩾5% patients in concizumab PPX arms 1−4 [total]), as judged by the investigator, in trial 4307 were in SOC investigations: Fibrin D dimer increased (n=13, 18.6%), and Prothrombin fragment 1.2 increased (n=9, 6%). Of note, causality was judged only for patients on concizumab PPX. In general, the adverse event pattern up to 56 weeks of treatment noted in the HA and HB patients in study 3407 appears comparable with that observed in HAwI and HBwI patients in study 3411.

Serious adverse event/deaths/other significant events

Deaths

All deaths reported in the clinical trials up until the application cut-off were previously presented in the marketing authorisation application for the HAwI and HBwI indication.

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 Table 60.

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 but 1 death (Intra-abdominal haemorrhage) were unlikely related to concizumab, as judged by the investigator.

Table 60: Listing of deaths – trials 4311 and 4307.

Trial/Period	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	Day 540/21	Unlikely
		Femur fracture	Day 540/21	Unlikely
		Humerus fracture	Day 540/21	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)	/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 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.

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 (see table above):

- 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).

No additional deaths were reported between the 56-week cut-off and the application cut-off.

Serious adverse events

Safety pool

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. Across the five multiple-dose trials, a total of 51 (15.9%) patients reported 71 SAEs (0.1 events per PYE):

- The majority of these (57 SAEs in 41 [12.8%] patients) were unlikely related to concizumab, as evaluated by the investigator.
- 19 SAEs in 16 (5.0%) patients led to temporary discontinuation of trial product.
- 7 (2.2%) patients permanently discontinued trial product due to 9 SAEs, including 1 fatal event of COVID-19 (Section 5.8) and 5 AESIs (thromboembolic events)

For all haemophilia subtypes, most SAEs were recorded as single events in 1 or 2 patients with no clustering of events across SOCs. Event rates and patient proportions for SAEs were comparable across haemophilia subtypes (HA, HB, HAwI and HBwI), though lower proportions of patients with HA, HB and HAwI compared to patients with HBwI reported SAEs. This was primarily due to more patients with HBwI reporting SAEs, judged as unlikely related to concizumab PPX by the investigator, under the SOCs of 'Musculoskeletal and connective tissue disorders' (5 SAEs in 5 [9.4%] patients) 'Injury, poisoning and procedural complications' (7 SAEs in 4 [7.5%] patients) and 'Nervous system disorders' (3 SAEs in 3 [5.7%] patients).

Possibly or probably related SAEs

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. SAEs judged as possibly or probably related to concizumab by the investigator are listed by trial and haemophilia subtype summarised below and presented in the table below:

- 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 4 AESIs (Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis (same patient) and Acute myocardial infarction).
    - 2 patients with HA permanently discontinued treatment with concizumab PPX per protocol due to possibly or probably related SAEs (AESIs, i.e. thromboembolic events).
    - Except for the fatal event, remaining patients with HA with possibly or probably related SAEs had recovered or were recovering at the data cut-off.
- In patients with **HB**, 1 SAE in 1 (1.6%) patient was judged as possibly related to concizumab: Intra-abdominal haemorrhage (2 alternative aetiologies were reported: 'suspected malignity' and 'underlying haemophilia'). The event was severe and led to permanent discontinuation of trial product. The patient was reported as recovered from the event.
- In patients with HAwI, 5 SAEs in 3 (3.8%) patients were judged as possibly or probably related to concizumab: Haematemesis and Melaena (same patient), Dizziness, and Fibrin D-dimer increased and Prothrombin F1+2 increased (same patient).
    - No possibly or probably related SAEs in patients with HAwI led to permanent discontinuation of trial product.
    - All patients with HAwI with possibly or probably related SAEs had recovered.
- In patients with **HBwI**, 2 SAEs in 2 (3.8%) patients were judged as possibly or probably related to concizumab: Renal infarct and Hypersensitivity.
    - Both events led to permanent treatment discontinuation as per protocol discontinuation criteria.
    - Except for the SAE of Renal infarct, which was reported as 'resolved with sequelae', all patients with HBwI with possibly or probably related SAEs had recovered.

Table 61: Listing of SAEs possibly or probably related to concizumab PPX – by haemophilia subtype and trial - safety analysis set - trials 4307 (56-week cut-off), 4255 and 4311 (56-week cut-off)

Haemophilia type/ Age/ BMI	AE no.	Study day/ Duration (Days)	SOC / PT	Action / outcome
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
HB	2	21/205	Renal and urinary disorders/ Renal infarct	Drug Withdrawn/ Recovered/Resolved With Sequelae
HB	8	39/8	Immune system disorders/ Hypersensitivity	Drug Interrupted/ Recovered/Resolved
HA	1	8/78	Nervous system disorders/ Dizziness	Drug Interrupted/ Recovered/Resolved
HA	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
HA	1	368/11	Gastrointestinal disorders/ Haematemesis	Drug Interrupted/ Recovered/Resolved
	2	367/12	Gastrointestinal disorders/ Melaena	Drug Interrupted/ Recovered/Resolved

Notes: Patient age and BMI are reported at baseline. Abbreviations: AE: Adverse event; BMI: body mass index; HA:
haemophilia A without inhibitors; HAwI: haemophilia A with inhibitors, HB: haemophilia B; HBwI: haemophilia B with inhibitors; SOC: system organ class; PT: preferred term

Trial 3407

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).

Of the 30 reported SAEs, 22 SAEs in 14 patients were reported previously in trial 4307. 8 SAEs were reported by 8 patients after the cut-off date for the trial 4307 CACO. 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

Six (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, see above). 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.

Patients on concizumab PPX – up until 56-week cut-off

Overall, the number of SAEs was low, and the SAEs were distributed across multiple SOCs and PTs, with the majority reported as single PTs. No apparent clustering across SOCs and PTs was observed. No SAEs (by PT) were reported in ≥5% patients with HA or HB treated with concizumab PPX (arms 1–4).

In total, 30 SAEs (0.2 events per PYE) were reported in 20 (13.2%) 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 (24 SAEs in 16 [10.6%] patients) and resolved (22 SAEs in 16 [10.6%] patients)

Possibly or probably related SAEs

No new possibly or probably related SAEs have been reported after the CACO.

Compassionate use (compassionate use programme [4807] and individual patient

A total of 24 SAEs were reported in 11 patients with HBwI receiving concizumab via compassionate use up until data lock point 28-Feb-2024. Fourteen (14) SAEs were reported as part of 6 cases for patients treated on an individual patient basis:

- 1 case concerned 2 SAEs of post-traumatic haemarthrosis, 1 of elbow and 1 of knee due to fall. Both events resolved, with no change in concizumab treatment and considered unlikely related to concizumab treatment by the medical practitioner.
- 1 case concerned 2 SAEs of Influenza and Muscle haematoma. Outcomes were not reported. The events did not lead to change in concizumab treatment and were considered unlikely related to concizumab PPX by the medical practitioner.
- 1 case concerned 2 SAEs of Injection site haematoma and Injection site swelling. Both SAEs resolved and did not lead to change in concizumab treatment. Causality was not reported for the 2 events.

- 1 case concerned 1 SAE of Haemarthrosis of elbow. Outcome of the event was not reported. The SAE was considered unlikely related to concizumab treatment by the medical practitioner, and it did not lead to a change in concizumab treatment.
- 1 case concerned 1 SAE of Abdominal pain, which resolved and was considered unlikely related to concizumab treatment by the medical practitioner. The event did not lead to a change in concizumab treatment.
- 1 case concerned 6 SAEs of Human rhinovirus test positive, Haematoma, Muscle haemorrhage, Fall, Lip swelling and Lip haemorrhage. No symptoms, signs, outcome and causality were reported for the event of Human rhinovirus test positive. The events of Muscle haemorrhage and Haematoma resolved and were considered probably related to concizumab PPX by the medical practitioner. The MAH assesses the patient's HBwI as alternative aetiology for these events. The events of Fall, Lip swelling and Lip haemorrhage were resolving at the data cut-off and no causality was reported by the medical practitioner.

Four (4) of 19 patients in the compassionate use programme reported a total of 10 SAEs:

- 1 patient reported 3 SAEs: Limb injury, Haemarthrosis and Muscle haematoma.
- 1 patient reported 2 SAEs: Pharyngitis streptococcal and Hematemesis
- 1 patient reported 3 SAEs: Intra-abdominal haematoma, Toothache and Fall.
- 1 patient reported 2 SAEs: COVID-19 and Staphylococcal bacteraemia.

All events were unlikely related to concizumab as judged by the investigator and all were reported resolved. Three (3) events in 2 patients (PTs: Pharyngitis streptococcal, Hematemesis and Toothache) led to temporary discontinuation of concizumab PPX. The SAE of Intra-abdominal haematoma was reported for a teenager with HBwI after having been on concizumab PPX for about 3 months. No trauma was known to have occurred prior to onset of the haematoma symptoms. The patient had a medical history of 'platelet delta storage pool disorder' which could have contributed to the event, since a known complication is bleeding due to platelets not functioning normally.

Adverse events of special interest (AESIs)

Thromboembolic events – safety pool

As observed for other procoagulant compounds, there is a potential risk of thrombosis associated with concizumab treatment due to exaggerated pharmacology.

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.

In the safety pool (up until the 56-week cut-offs for the phase 3 trials), a total of 11 AESIs were captured by a broad, pre-specified MedDRA search for '*embolic and thrombotic events'* in 6 of 320 (1.9%) patients treated with concizumab PPX:

- Trial 4307: 5 events in 3 patients with PTs Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis (same patient); Hemiparesis (following a head injury due to fall from stairs; No thromboembolic events were reported for this patient); Acute myocardial infarction.

- Trial 4311: 3 events in 2 patients with PTs Partial and Complete shunt thrombosis (following a non-serious event of haematoma infection; event onset 2 weeks after concizumab had been paused due to the trial treatment pause); Renal infarct.
- Trial 4255: 3 events of PT Haemorrhoids thrombosed in 1 patient.

The thromboembolic events were reported in 1 patient each with HAwI and HBwI and in 4 patients with HA. No thromboembolic events were reported in patients with HB.

Serious AESIs before the treatment pause:

Six (6) of the 11 AESI events captured by the MedDRA search were serious, of which 5 SAEs in 3 patients were also reported as AESIs (4 events in 2 patients in trial 4307 and 1 event in trial 4311). All these cases occurred before the treatment pause.

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. All 5 events were judged as possibly or probably related to concizumab PPX by the investigator and reported as recovered or recovering, 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 break-through bleed treatment. These cases have been thoroughly evaluated in the initial MAA.

Other serious AESIs (before and after treatment pause)

The other 7 SAE events in 3 patients captured by the MedDRA search were mild or moderate in severity and judged by the investigator as unlikely related to trial product (6 events in 3 patients). Of these unlikely related AEs:

- 1 SAE concerned the previously mentioned 'Hemiparesis' in trial 4307 (reported prior to the treatment pause), which was co-reported with a serious event of Craniocerebral injury after the patient had fallen on stairs. Tomogram performed the same day showed intracranial subdural haematoma of right frontoparietal lobe, skull cap fracture and skull base fracture with separation of sagittal and coronal suture. No thromboembolic events were reported for this patient.
- 3 AEs in 1 patient in trial 4255 concerned 'Haemorrhoids thrombosed'.
- 2 AEs of moderate (partial) and severe (complete) shunt thrombosis in 1 patient in 4311 were co-reported in relation to an AE reported as 'infected haematoma after shunt puncture' (AE number 2; [trial 4311]) and had onset 2 weeks after concizumab had been paused due to the trial treatment pause.

No thromboembolic events were reported after the treatment pause up until the 56-week cut-offs for trials 4307 and 4311, and all the events captured by the MedDRA search were previously included in the marketing authorisation application for the HAwI and HBwI indications.

No thromboembolic events were reported in trial 4616 up until the application cut-off.

AESI of TE reported after the 56-week cut-off study 4307:

Two (2) non-fatal serious thromboembolic events were reported from trial 4307 after the 56-week cut-off. Two (2) of the SAEs (1 event of PT Ischaemic stroke and 1 event of Cerebral infarction) were reported as AESIs:

- A non-fatal SAE of PT ischaemic stroke was reported as an AESI in a patient with HA, who was treated with a daily concizumab dose of 0.20 mg/kg for almost 2.5 years before event onset, and received the last dose of concizumab one day after event onset. The patient presented with dizziness, speech disorders and drooping of the corner of his mouth. A cranial CT scan confirmed an ischaemic stroke. The patient was treated with low-molecular-weight heparin (enoxaparin) 1x40 mg s.c. and recovered. The patient's last bleeding episode was in January 2024, where he received 3 doses of FVIII 22 IU/kg. The patient had a previous stroke (December 2018/ January 2019) confirmed by an MRI scan and also has ongoing hypertension since December 2018. The patient's blood pressure has not been well controlled during the trial and has fluctuated between 131/93 mmHg and 200/115 mmHg. Two (2) AEs (non-serious) of worsening of hypertension were reported, from which the patient has still not recovered. The investigator judged the Ischaemic stroke as possibly related to concizumab PPX. Although a potential causal relationship between concizumab administration and the ischaemic stroke cannot be ruled out, the case has relevant alternative aetiologies such as underlying disease, fluctuating hypertension and previous stroke.
- A non-fatal SAE of PT Cerebral infarction was reported as an AESI in a patient with HA, who was previously enrolled in phase 2 trial 4255 and had more than 5 years of concizumab exposure up until onset of the SAE, including exposure before and after the treatment pause in trial 4307. The patient presented with visual disturbance, facial weakness, ataxia and slurred speech. The patient was hospitalised and treated for ischaemic stroke. The outcome of the SAE was reported as 'resolved'. The patient had a medical history of hypertension since 2013 and was treated with anti-hypertensive medication. MRI images of the patient's brain as well as the CT scans taken after event onset were shared with a specialist (neuro-radiologist) who judged the specific lesions (perforating arteries) found on the scans are most seen in patients with a medical history of hypertension. The investigator judged the causality of the event as 'unlikely related' to concizumab PPX. In addition to hypertension being a risk factor for ischemic as well as haemorrhagic stroke, the patient's advanced age is also considered a risk factor12. The patient discontinued concizumab treatment permanently as per protocol discontinuation criterion. Four (4) months after onset of the Cerebral infarction, a mild SAE of Amnesia, judged as unlikely related to concizumab PPX, was reported for the patient as he attended the emergency department after experiencing 30 minutes of neurological deficit/ absence/ memory loss. Brain scans were performed, and there were no signs of recent infarction. The patient was discharged the same day, and the event was reported as resolved.

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.

Patients with known or suspected hypersensitivity to any constituent of the trial product or related products were excluded from clinical trials with concizumab.

A pre-defined MedDRA search captured 51 events in 29 (9.1%) patients (0.1 events per PYE).

Event rates and patient proportions were overall comparable across haemophilia subtypes (HA, HB, HAwI and HBwI), though lower proportions of patients with HA, HB and HAwI reported hypersensitivity events compared to patients with HBwI, for whom most reported hypersensitivity cases were events judged as unlikely related to trial product, and no action was taken to trial product for these events. Across haemophilia subtypes, most events captured were reported in a few patients across multiple PTs. Of note, the majority of the cases were injection site reactions (Injection site rash and Injection site urticaria) which are addressed under injection site reactions.

Twenty-three (23) events in 10 (3.1%) patients were considered possibly or probably related to concizumab PPX by the investigator. All events, except 1, were reported with outcome 'resolved'. Two (2) events led to permanent treatment discontinuation and are described below. No anaphylactic reactions were reported.

Note that these 2 events were previously presented in the MAA for the HAwI and HBwI indications: One HBwI patient experienced recurrent non-serious injection site reactions (Urticaria) in the days leading up to a severe and serious event of Hypersensitivity. Another HBwI patient experienced a non-serious event of Injection site rash prior to a non-serious event of moderate Hypersensitivity. The MAH has evaluated that a causal relationship between concizumab and the 2 events is conceivable, as no alternative aetiology was identified. The MAH assessed the remaining events identified, except the injection site reactions, as explained by alternative aetiologies and/or without establishment of a temporal relationship.

Apart from injection site reactions, the most frequently captured PTs in the total safety pool were Hypersensitivity, for which 8 events were reported in 4 (1.3%) patients: 3 events in 1 patient with HA and 5 events in 3 patients with HBwI. No events of Hypersensitivity were reported in the HB or HAwI group.

Injection site reactions

As with other drugs for injection, the s.c. administration of concizumab can lead to injection site reactions.

In the safety pool, a total of 159 injection site reactions were captured in 79 (24.7%) patients (0.3 events per PYE) based on a pre-defined MedDRA search. All events, except 1 (a Puncture site haemorrhage, described below), were non-serious and of mild (151 out of 159 events) or moderate (7 out of 159 events) severity. All events, except 3, were reported with outcome 'resolved' or 'resolving'. There was no apparent trend in the timing of onset of events.

The proportions of patients reporting injection site reactions were comparable between HA (24.8%), HB (20.3%) and HAwI (15.4%) patients and lower than the proportion of HBwI patients reporting injection site reactions (43.4%).

For the total safety pool, a single PT - Injection site erythema - was frequently reported, i.e., reported in ≥5% of the patients. Across haemophilia subtypes, this PT had comparable event rates (range: 0.0-0.1 events per PYE).

One (1) severe SAE of Puncture site haemorrhage in relation to blood sampling was captured, but however, not related to injection of concizumab and therefore not considered an injection site reaction. The case was previously presented in the marketing authorisation application for the HAwI and HBwI indications.

One (1) patient with HB reported a non-serious event of Injection site pain of moderate severity which led to permanent treatment discontinuation. Apart from this case, 1 patient with HBwI temporarily discontinued treatment due to an event of injection site rash and permanently discontinued trial product due to a hypersensitivity reaction few days after onset of the injection site rash. The patient recovered from both events.

Medication errors – safety pool

A total of 12 medication errors were reported as AEs in 10 (3.1%) patients in trials 4307, 4255, 4311, 4310, and 4159, and consisted of:

- Seven (7) of the medication errors reported as AEs in 5 patients concerned Overdose (approximately 5-fold intended dose in 2 of the events in 2 patients) and the remaining were 2 events in 2 patients of Incorrect dose administration; 2 events in 2 patients of Underdose and 1 event of Accidental overdose.
- Ten (10) of 12 events were evaluated as unlikely related to concizumab by the investigator, including 1 event of Underdose, which led to 'dose increased'.
- One (1) event each of 'Overdose' and 'Incorrect dose administered' were reported as possibly and probably, respectively, related to concizumab by the investigator.
- One (1) event (PT Tachycardia), possibly related to concizumab as judged by the investigator, was co-reported with an event of Accidental overdose (judged as unlikely related to concizumab by the investigator) and led to temporary discontinuation of trial product for 1 day. Both events were resolved the same day.

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 56wk). 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 extension part).

In summary, AEs related to medication errors were rare in the clinical trials 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, therefore no additional guidance, apart from usual treatment guidance, is included in the concizumab product information.

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 considered to be thrombosis.

Note, patients with any known systemic inflammatory condition requiring systemic treatment at screening are excluded from participation in clinical trials with concizumab.

A total of 12 SAEs in 12 (3.8%) patients were captured by the search, including 3 SAEs 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. For the 12 patients reporting SAEs related to an inflammatory response:

- 11 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)

Seven (7) of 12 SAEs were mild or moderate in severity. Five (5) SAEs were severe (1 event in each of the haemophilia subtypes HA, HAwI and HBwI and 2 events in the HB group, 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 remaining 11 SAEs were judged as unlikely related to concizumab PPX by the investigator.

The proportion of patients (range: 2.6 to 4.7%) with SAEs was similar across haemophilia subtypes.

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. Patients with fibrinogen levels below the laboratory lower limit of normal at screening were excluded from participation in clinical trials with concizumab.

No decreases in fibrinogen levels were observed in the two completed phase 2 trials (4255 and 4310) nor in the phase 3 trials (4307 and 4311).

Trial 4307 – phase 3 – HA and HB

Fibrinogen levels remained stable and within the reference range 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 of fibrinogen levels from baseline to week 56 for concizumab PPX arms 2−4 was -0.43 (0.91) g/L for patients with HA and -0.18 (0.90) g/L for patients with HB.

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 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.

One event of blood fibrinogen decrease was reported in trial 4255. The patient reported a non-serious AE of low value of fibrinogen 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 reported as resolved after 33 days. The patient had a medical history of hepatitis B and C infection. No actions were taken to trial product.

Of note, the fibrinogen levels for this patient remained within normal reference range (2−4 g/L) throughout the trial.

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: Patient (HAwI) experienced 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 reported as resolved after 36 days.

No actions were taken to trial product.

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.

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 safety concerns were identified in the search of rare events. No safety concerns were identified in the search of rare events.

A total of 26 AEs in 24 (7.5%) patients were captured. Rare events were reported across multiple SOCs, with no apparent pattern or clustering. Rare events were reported across multiple SOCs, with no apparent pattern or clustering. All events were of mild or moderate severity and most (25 of 26) events were non-serious. The one SAE (PT: Loss of consciousness) was judged as unlikely related to concizumab. The patient had been drinking alcohol the day before event onset. The event was reported as resolved on the day of event onset (Trial 4310 extension part).

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

Hepatic disorders were not a pre-specified safety area of interest in the clinical development programme for concizumab, based on its mechanism of action and mechanism of clearance (similar to other antibodies, concizumab is cleared via catabolism and not hepatic metabolism) and the pathophysiology of haemophilia.

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.

Results from liver tests

Markers of liver function (AST, ALT, ALP and TBL) were assessed in all five multiple-dose phase 1-3 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 HA, HB, HAwI and HBwI in any treatment group or multiple-dose trial.

No clinically significant changes in mean ALT or AST were observed over time from treatment restart up until the 56-week cut-offs in trials 4307 and 4311 in patients with normal hepatic function or in patients with elevated ALT and AST values at baseline. There was no indication of an increased risk of concizumab PPX treatment in patients with elevated liver enzymes (ALT or AST ≥ 1.5 x ULN), based on the evaluation of AEs. No patients met Hy's law criterion for severe hepatotoxicity. Several patients had elevated levels of AST and/or ALT, however, no patients had concurrent elevations of bilirubin >2 x ULN.

Four (4) patients in each of the phase 3 trials 4307 (HA and HB) and 4311 (HAwI and HBwI) had elevated liver enzymes (ALT or AST ≥ 1.5 x ULN) at baseline. ALT or AST values ≥ 1.5 x ULN at baseline was considered states of hepatic impairment. 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.

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 patient 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 AEs were 'Blood fibrinogen decreased'(2 AEs) and 'antithrombin III decreased' (2 AEs in the same patient). 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, where AST levels were 100 U/L (vs 18 U/L at baseline). 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, ALT and total bilirubin were within normal range. The event was '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.

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.

Renal events

Like other antibodies, concizumab is cleared via catabolism and not renal excretion. It is therefore unlikely that concizumab increases the risk of acute renal failure. Thus, based on the mechanism of action and clearance of concizumab and on the pathophysiology of haemophilia, renal disorders were not a pre-specified safety area of interest in the clinical development programme.

Patients with renal dysfunction (trial 4159), severe (trials 4307, 4255, 4311 and 4310) or moderate (trials 4255 and 4310) renal impairment, defined as eGFR $\leqslant$ 30 mL/min/1.73 m2 and eGFR $\leqslant$60 mL/min/1.73m2, respectively, for serum creatinine, or evidence of renal damage at screening were excluded from participation in clinical trials with concizumab.

There was no increased risk of renal disorders with concizumab PPX in any of the haemophilia subtypes (HA, HB, HBwI and HAwI) based on the evaluation of renal events. Four (4) of 6 reported renal events were non-serious, mild or moderate in severity and considered unlikely related to concizumab PPX. One (1) serious and severe event of Renal haematoma was reported in a patient with HB, who had ongoing bilateral congenital urethra-hydronephrosis. The investigator judged the event as unlikely related to concizumab PPX, and trauma was a suspected reason for the event. No action was taken to trial product, and the patient recovered from the event. One (1) patient with HBwI experienced a non-fatal serious event of Renal infarct, which contributed to the concizumab treatment pause.

Suspected transmission of an infectious agent

No events of suspected transmission of an infectious agent via trial product were captured by the NNMQ search across trials 4311, 4310, 4307, 4255 and 4159.

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

No new data have been provided.

Laboratory findings

Haematology, biochemistry and coagulation-related parameters

Mean observations

Haematology and biochemistry (including urinalysis)

No apparent clinically relevant changes for clinical laboratory haematology parameters (including platelets) or biochemistry parameters (including urinalysis) were observed in the multiple-dose trials (4307, 4255, 4311, 4310 and 4159).

Coagulation-related parameters

Comparable results were obtained across the five multiple-dose trials for D-dimers and prothrombin fragment 1+2 in terms of changes from baseline over time with concizumab PPX or no PPX, correlation between changes in the 2 coagulation parameters and correlations of each individual parameter with plasma concizumab concentration. Of note, similar results were observed for the two phase 3 trials at the 56-week cut-off and at the CACO (4307) or PACO (4311), respectively.

Hence, there are no new important findings compared to those presented in the summary of clinical safety included in the marketing authorisation application for the HAwI and HBwI indications.

Elevations in D-dimer were generally more pronounced with concizumab PPX as compared to no PPX (main part of trials 4307, 4311 and 4310) and placebo (trial 4159). Mean prothrombin fragment 1+2 values were increased compared to baseline in patients on concizumab PPX but not in patients on no PPX (main part of trials 4307, 4311 and 4310) or placebo (trial 4159), and levels remained stable over time up until the 56-week cut-off.

For all haemophilia subtypes (HA, HB, HAwI and HBwI), concizumab concentrations were positively correlated with levels of fibrin D-dimer and prothrombin fragment 1+2, reflecting the haemostatic effect of concizumab. The same pattern was observed across the five multiple-dose trials.

There are no new important findings compared to those presented in the summary of clinical safety included in the marketing authorisation application for the HAwI and HBwI indications in terms of changes in mean levels of the remaining coagulation parameters (fibrinogen, total TFPI, prothrombin time, INR, aPTT and antithrombin) across the five multiple-dose trials.

Mean fibrinogen levels remained stable throughout the trials, with no apparent correlation with concizumab exposure observed in the phase 3 trials 4307 and 4311 and with no clinically

significant changes seen at the different concizumab dose levels in the phase 2 trials 4255 and 4310.

Compassionate use programme

Results were overall consistent with those obtained from the multiple-dose trials.

Clinical laboratory adverse events

Haematology and biochemistry (including urinalysis)

No new AEs related to standard haematology or biochemistry clinical safety laboratory findings have been reported since submission of the marketing authorisation application for the HAwI and HBwI indications.

AEs related to standard haematology clinical safety laboratory findings were reported in 3 of the five multiple-dose trials in haemophilia (trials 4255, 4311 and 4310). No haematology clinical laboratory AEs were reported in trials 4307 or 4159.

AEs related to standard biochemistry clinical safety laboratory findings were reported in all five multiple-dose trials in haemophilia. No AEs were reported for additional biochemical parameters in trials 4307, 4310 or 4159, and few events were reported in trials 4255 and 4311. In trial 4311, all reported events were reported before the PACO.

Coagulation-related parameters

AEs pertaining to coagulation-related parameters were reported in all five multiple-dose trials in haemophilia. There are no new important findings since the marketing authorisation application for the HAwI and HBwI indications.

Similar reporting patterns were observed across haemophilia subtypes.

Among the most commonly reported PTs pertaining to coagulation-related parameters in the safety pool were 'Fibrin D-dimer increased' and 'Prothrombin fragment 1+2 increased', of which most events were judged as possibly or probably related to concizumab PPX by the investigator. Note that due to a missing PT for 'Prothrombin fragment 1+2 increased' in MedDRA version 21.0 used for coding during the main part of the phase 2 trials, AEs reported as 'Prothrombin fragment 1+2 increased' were coded as PT: Prothrombin level increased.

Compassionate use programme

One patient in the compassionate use programme reported 2 AEs pertaining to coagulation-related parameters (1 mild event of Prothrombin fragment 1+2 increased and 1 mild event of Fibrin D-dimer increased). No events pertaining to coagulation-related parameters were reported by patients treated with concizumab on an individual patient basis.

Anti-concizumab antibodies

As is the case with any therapeutic protein, concizumab may trigger development of ADAs. Assessment of ADAs against concizumab, including antibodies with in vitro-neutralising effects, was done as part of the investigational use of concizumab.

Key results from the anti-concizumab antibody assessment during clinical development are presented in the following. Note that all titre values given below are reported with prior minimum required dilution (MRD)-adjustment (of factor 100).

Incidence of ADAs in the five multiple-dose trials (4307, 4255, 4311, 4310 and 4159)

For trial 4307 and 4311, ADAs were evaluated throughout the trial (including the entire treatment pause to the extent possible).

An overview of ADA results by trial for the multiple-dose trials (trials 4307, 4255, 4311, 4310 and 4159) is given in Table .

Of the 320 patients exposed to concizumab in the five multiple-dose trials, a total of 71 (22.2%) patients tested positive for ADAs at 1 or more visits after first exposure to concizumab. No patients tested positive for ADAs in the phase 1 trial 4159. A total of 18 (5.6%) patients tested positive for ADAs with in vitro-neutralising effects. Apart from 2 patients with medium-level ADA titres (both with peak titre 25,600) and 1 patient developing high ADA titres (peak titre 204,800), all ADA-positive patients had binding ADA titres ranging from 100 to 6400, which are considered low titres given the high sensitivity of the binding ADA assay.

Table 6238: Overview of ADA-positive patients by trial - HA, HB, HAwI and HBwI – trials 4159, 4255, 4310, 4307 (56-week cut cut-off) and 4311 (56 week cut off) – safety analysis set.

	Trial ID					
	4307	**4255**	**4311**	**4310**	**4159**	**Total**
Number of patients exposed to concizumab	151	36	127	25	18	320
Number of ADA-negative patients[a] N (%)	128 (84.8)	27 (75.0)	92 (72.4)	19 (76.0)	18 (100)	249 (77.8)
Number of ADA-positive patients[b] N (%)	23 (15.2)	9 (25.0)	35 (27.6)	6 (24.0)	0	71 (22.2)
Number of *in vitro*-neutralising ADA-positive patients N (%)	6 (4.0)	1 (2.8)	8 (6.3)	3 (12.0)	0	18 (5.6)

Notes: a All samples after first exposure to concizumab were negative. b One 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 (Summary 2.7.3, Section 3.1.1). Patients exposed in both phases only count once in the "total" column, regardless of when they tested positive for ADAs. If a patient in phase 3 only tested positive for ADAs 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; N: number of patients.

Incidence of ADAs - by haemophilia subtype

Occurrence of ADAs was analysed by haemophilia subtype across the multiple-dose trials (trials 4307, 4255, 4311, 4310 and 4159). An overview of the proportion of patients from each group testing positive for binding and in vitro-neutralising ADAs is provided in Table 63.

Table 6339: Overview of ADA-positive patients - by haemophilia subtype - HA, HB, HAwI and HBwI - trials 4159, 4255, 4310, 4307 (56-week cut-off) and 4311 (56-week cut-off) - safety analysis set

	Haemophilia subtype				
	HA	HB	HAwI	HBwI	Total
Number of patients exposed to concizumab	125	64	78	53	320
Number of ADA-negative patients[a] N (%)	102 (81.6)	56 (87.5)	54 (69.2)	37 (69.8)	249 (77.8)
Number of ADA-positive patients[b] N (%)	23 (18.4)	8 (12.5)	24 (30.8)	16 (30.2)	71 (22.2)
Number of *in vitro*-neutralising ADA-positive patients N (%)	4 (3.2)	3 (4.7)	6 (7.7)	5 (9.4)	18 (5.6)

Notes: a All samples after first exposure to concizumab were negative. b One 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; N: number of patients.

Incidence of ADAs - by age

Occurrence of ADAs was analysed by age group at baseline (adults above 18 years of age vs. adolescents between 12 and 17 years of age) across trials 4307, 4255, 4311, 4310 and 4159 (Table 64).

Table 6440: Overview of ADA-positive patients - by age group - HA, HB, HAwI and HBwI - trials 4307 (56-week cut-off), 4255, 4311 (56-week cut-off), 4310 and 4159 - safety analysis set

	Age group		
	Adolescents 12-17 years	Adults 18+ years	Total
Number of patients exposed to concizumab	78	242	320
Number of ADA-negative patients[a] N (%)	56 (71.8)	193 (79.8)	249 (77.8)
Number of ADA-positive patients[b] N (%)	22 (28.2)	49 (20.2)	71 (22.2)
Number of *in vitro*-neutralising ADA-positive patients N (%)	7 (9.0)	11 (4.5)	18 (5.6)

Notes: Patients were grouped based on the age at baseline and not the age at the time of the ADA-response.

[a]All samples after first exposure to concizumab were negative.

[b]One or more samples after first exposure to concizumab were positive.

Impact of ADAs in phase 2 and 3

In 69 of the 71 (97.2%) patients testing positive for ADAs across the phase 2 and 3 clinical trials, no apparent impact of the ADAs on bleeding patterns, PK (concizumab exposure), PD (free TFPI) or AEs were observed.

Impact of anti-concizumab antibodies on safety

The safety profile in patients testing positive for ADAs at least once after first concizumab dose vs the profile in ADA-negative patients was assessed based on MedDRA searches for immunogenicity-related AEs.

Overall, there was no indication that formation of ADAs impacts the safety profile of concizumab PPX, neither in patients with HA or HB, nor in patients with HAwI or HBwI.

Based on the MedDRA searches for injection site reactions and hypersensitivity reactions, the following event rates and patient proportions were reported for the groups of ADA-positive and -negative patients:

- ADA-positive patients: 83 events in 25 (35.2%) patients (0.6 events per PYE)
- ADA-negative patients: 112 events in 64 (25.7%) patients (0.3 events per PYE)

Similar types of events were reported by the groups of ADA-positive and -negative patients. Furthermore, for the patients positive for ADAs, there was no clustering or patterns in reporting of injection site reactions and hypersensitivity reactions in relation to when ADAs occurred.

ADA cases from phase 2 and phase 3

In 1 patient treated with concizumab in the phase 2 trial 4310, high-titre binding ADAs, some with in vitro-neutralising effects to concizumab, co-occurred with restoration of free TFPI levels to baseline levels, yet the clinical impact of the ADAs remains inconclusive. Moreover, it was not possible to determine whether the high antibody titres reduced concizumab exposure, since plasma concizumab concentration measurements failed, likely due to ADA interference in the PK assay.

Note that this case was already presented in the marketing authorisation application for the HAwI and HBwI indications, and no new information has become available for the current application.

In 1 patient treated with concizumab in the phase 3 trial 4307, low-titre ADAs with in-vitro neutralising effects co-occurred with reduced plasma concizumab levels and restored free TFPI. However, the observed changes in PK and PD were unlikely to be attributed to the ADA positive status, as the decrease in the concizumab exposure and the restoration of free TFPI continued even after the titre values decreased and the patient tested negative for in vitro-neutralising ADAs. Note that the patient missed 5 consecutive doses of concizumab just before visit 16A, explaining the lowest observed concentration of concizumab recorded at that visit (2.5 ng/mL). The decrease in concizumab exposure or increase in free TFPI was not accompanied by any significant worsening in bleeding patterns or occurrence of immunogenicity-related AEs in the patient.

Occurrence of ADAs was analysed by age group at baseline (adults above 18 years of age vs. adolescents between 12 and 17 years of age) across trials 4307, 4255, 4311, 4310 and 4159.

Table 6541: Overview of ADA-positive patients - by age group - HA, HB, HAwI and HBwI - trials 4307 (56-week cut-off), 4255, 4311 (56-week cut-off), 4310 and 4159 - safety analysis set

	Age group		
	Adolescents 12-17 years	Adults 18+ years	Total
Number of patients exposed to concizumab	78	242	320
Number of ADA-negative patients[a] N (%)	56 (71.8)	193 (79.8)	249 (77.8)
Number of ADA-positive patients[b] N (%)	22 (28.2)	49 (20.2)	71 (22.2)
Number of *in vitro*-neutralising ADA-positive patients N (%)	7 (9.0)	11 (4.5)	18 (5.6)

Notes: Patients were grouped based on the age at baseline and not the age at the time of the ADA-response.

[a]All samples after first exposure to concizumab were negative.

[b]One or more samples after first exposure to concizumab were positive.

ADA results from Compassionate use of concizumab

Of the 11 patients who received concizumab in the compassionate use programme (4807), 5 patients tested positive for low-titre ADAs at one or two visits after first exposure to concizumab. One of the 5 patients reported 6 non-serious and mild injection site reactions (1 event of Injection site pain and 5 events of Injection site urticaria) from 5.5 months to 1 month prior to a single positive ADA test (visit 4). All events were reported as mild and resolved and judged as probably related to concizumab PPX by the investigator. Of note, 4 of the 6 events were experienced in the same week as the patient tested negative for ADAs (visit 3). No further AEs were reported for this patient up until the data cut-off, and Novo Nordisk assesses that the 6 reported injection site reactions are unlikely to be caused by ADAs.

Of the 19 patients who were treated with concizumab on an individual patient basis, 1 patient had a single positive test for in vitro-neutralising ADAs during a period where a reduced, though not absent, effect of concizumab was reported by the investigator. The patient remained in vitro-neutralising ADA-negative but still experienced multiple bleeds for around 1.5 years until his daily concizumab dose was increased. This suggested that it is unlikely that the increased bleeds experienced by the patient were caused by in vitro-neutralising ADAs.

Note that this case was previously included in the marketing authorisation application for the HAwI and HBwI indications.

Vital signs, body measurements and physical examinations

The results for vital signs, body measurements and physical examinations presented in the marketing authorisation application for the HAwI and HBwI indications were based on the five multiple-dose trials 4159, 4310, 4255, 4311 and 4307, with results included from trial 4311 up until the 56-week cut-off and from trial 4307 up until the CACO. Presented below are results from the five multiple-dose trials 4159, 4255, 4310, 4307 and 4311.

Results from the multiple-dose trials

Vital signs and body measurements

No apparent clinically relevant changes in vital signs (mean systolic and diastolic blood pressure and pulse) or body measurements (body weight or BMI) were observed in the multiple-dose trials in any of the treatment groups.

Physical examination

Improvements in the 'musculoskeletal system' were apparent across treatment groups and trials (4307, 4255, 4311 and 4310). For patients on concizumab PPX, reductions in the proportion of patients with clinically significant abnormalities in the musculoskeletal system were observed as follows:

- Trial 4307: concizumab PPX (arms 2−4); from 21.9% at baseline to 19.4% (week 56) in patients with HA and from 18.5% at baseline to 6.3% (week 56) in patients with HB
- Trial 4255: concizumab PPX; from 19.4% at baseline to 8.0% at visit 16 (end of treatment in extension part; up until week 126)
- Trial 4311: concizumab PPX (arms 2−4); from 29.3% at baseline to 25.0% (week 56)
- Trial 4310; from 36.0% at baseline to 27.3% at visit 16 (end of treatment in extension part; up until week 118)

For the remaining parameters, no clinically relevant changes were observed by physical examination in any of the trials and no trends over time were apparent with respect to the proportion of patients with abnormal findings.

In trials 4307 and 4311, no apparent differences were observed in physical examination results between the concizumab PPX (arms 2−4) and no PPX (arm 1) treatment groups after the main part of the trials, and no differences between treatment groups were observed in trial 4310.

Safety in special populations

Safety by age group

The safety pool was divided into subgroups by baseline age in adolescents (12-17 years) and adults (>18 years).

Safety pool (trials 4307, 4255, 4311, 4310 and 4159)

Exposure by age group

A total of 21 adolescents with HA and 15 adolescents with HB have been exposed to concizumab, corresponding to 26.9 and 17.0 PYE, respectively. Further, 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. Total exposure in the adult subgroup ranged from 56.5 (HB) to 168.9 (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: 5 patients with HA and 1 patient with HBwI.

Adverse events in the adolescent vs. the adult age group

An AE overview is presented for the safety pool by age group (adolescents [12−17 years] and adults [≥18 years]) in Figure 36 (patient proportions) and Figure 37 (AE rates). The overall proportion of patients reporting AEs and corresponding event rates were slightly lower in the adolescent than the adult age group. Proportions and event rates were comparable across age groups for severe AEs and SAEs as well as for AEs leading to discontinuation of treatment, though based on very low numbers of events in the adolescent age group.

Most SAEs reported by both age groups were unlikely related to concizumab, as judged by the investigator, and were reported as 'resolved'. For both age groups, the SAEs were reported across

several SOCs with no apparent pattern or clustering of PTs. Of the 5 patients who experienced an SAE with fatal outcome, 1 patient was an adolescent and 4 were adults. The SAE with fatal outcome reported by an adolescent patient was Haemorrhage intracranial and judged as unlikely related to concizumab.

For both the adolescent and adult age group, the proportion of patients with AEs leading to permanent trial product discontinuation was low. Two (2) AEs in 2 patients in the adolescent age group (Hypersensitivity and Injection site pain) and 10 AEs in 8 patients in the adult age group (5 thromboembolic events in 3 patients; Cardiac failure; Congestive cardiomyopathy; Craniocerebral injury; Intra-abdominal haemorrhage and COVID-19 [fatal]) led to permanent discontinuation of trial product.

The proportion of patients with possibly or probably related AEs was lower for the adolescent age group as compared with the adult age group, though event rates were comparable.

The most frequently reported AEs (>5% patients in either the adult or the adolescent age group) are shown by age group in figure 38.

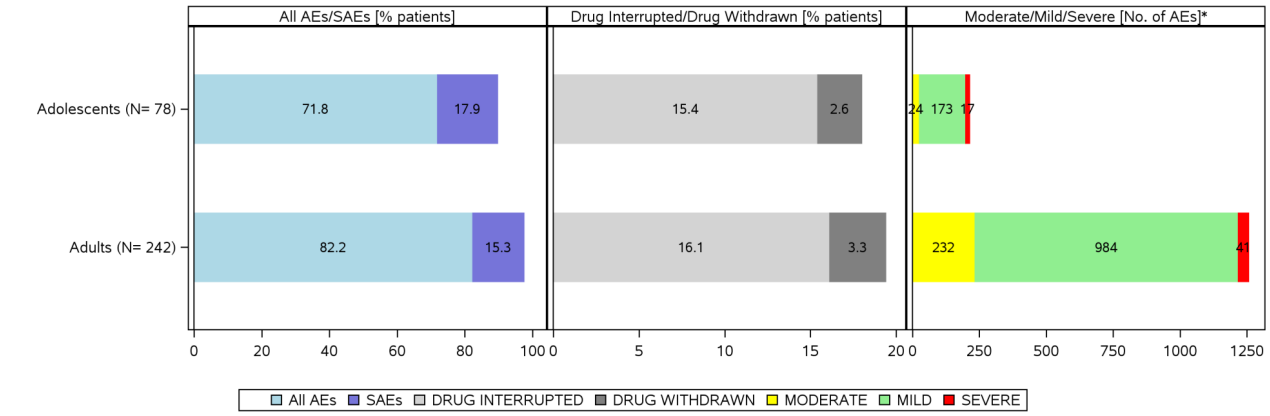
Similar event rates were observed for all commonly reported events for the adult and the adolescent age group. The proportion of adolescents with common AEs was lower or comparable to that for adults, except for the PT Viral upper respiratory tract infection, which had a higher frequency in adolescents than in adults.

Adverse events in the elderly age group

In the elderly age group, 30 AEs with onset during the on-treatment period were reported in 4 of 6 patients on concizumab PPX. All except 1 AE were non-serious, mild or moderate in severity and did not lead to action taken to trial product. One (1) SAE (Cardiac failure) was reported for the elderly age group. The event was unlikely related to concizumab as judged by the investigator, moderate in severity and led to permanent discontinuation of concizumab. The reported outcome was 'resolving'. A total of 10 AEs in concizumab-treated elderly patients were reported as 'not resolved'.

Six (6) non-serious possibly or probably related AEs were reported in 2 elderly patients with HA (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 were reported as 'resolved', with no actions taken to trial product.

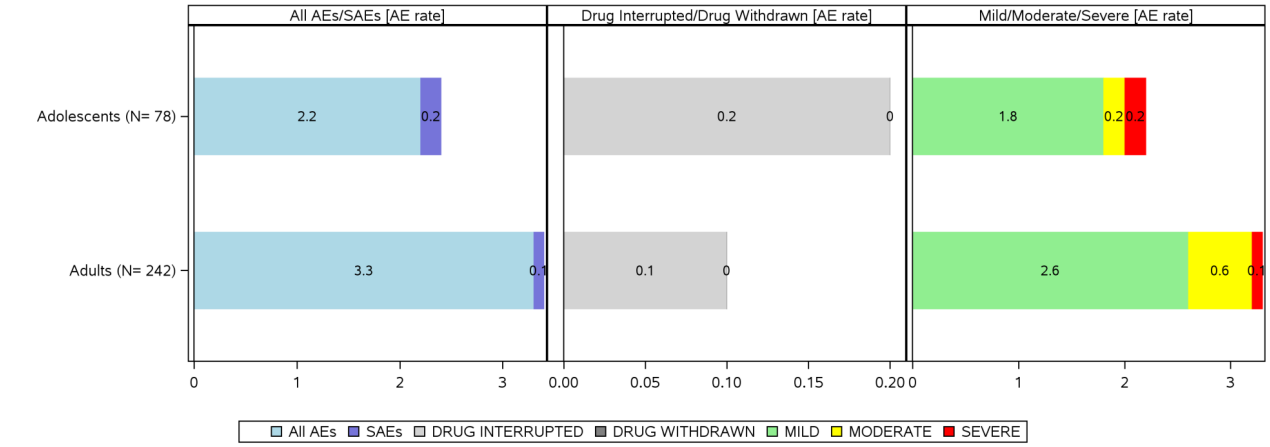
Figure 36: Overview of adverse events - percentage of patients - by age group - trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off) - HA+HB+HAwI+HBwI - safety pool - safety analysis set.



AE: adverse event, SAE: serious adverse event, HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors.
% patients: percentage of patients with adverse event.
Patients exposed to concizumab are included. This means that placebo data from 4159, Eptacog alfa 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.
* For visualization purposes the order of the AE categories are shown as Moderate/Mild/Severe in this plot.
Note that the total percentages of patients can exceed 100% as categories depicted are not mutually exclusive.

nn7415/nn7415-summary/safety_hahb_ema_20241111_er
21NOV2024:06:39:49 - f-ae-overview-byage.sas/f-ae-overview-pct-byage.png

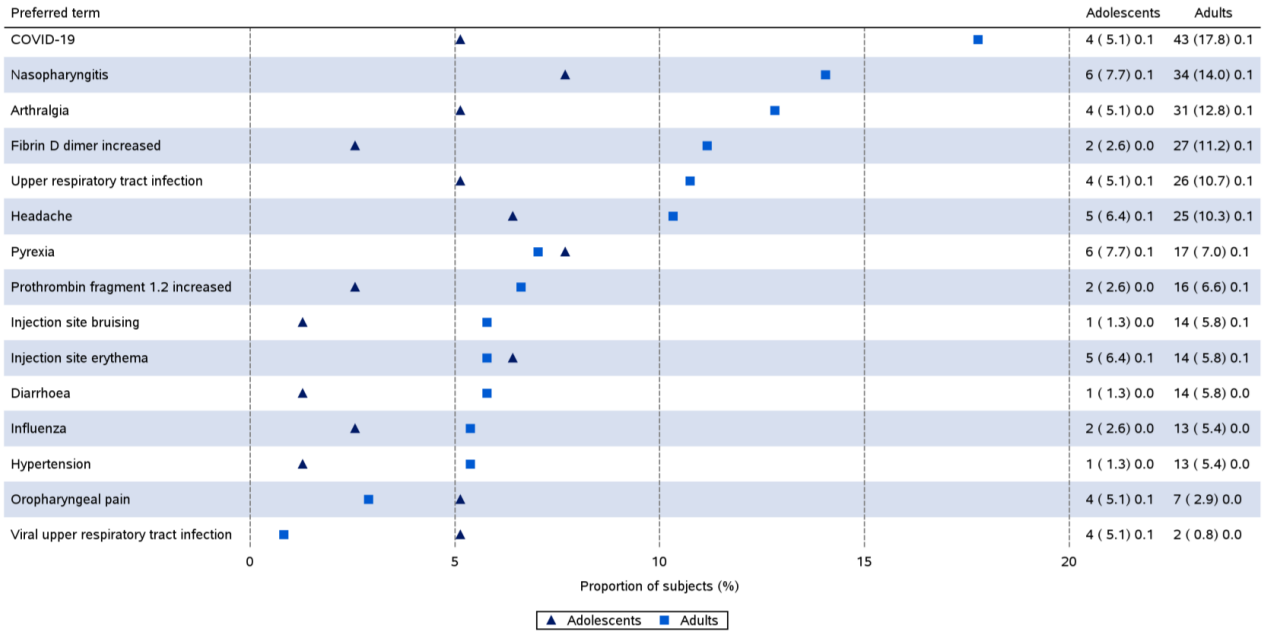
Figure 37: Overview of adverse events- AE rate - by age group - trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off) - HA+HB+HAwI+HBwI - safety pool - safety analysis set.



AE: adverse event, SAE: serious adverse event, HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors.
AE rate: rate calculated as number of adverse events per patient years of exposure.
Patients exposed to concizumab are included. This means that placebo data from 4159, Eptacog alfa 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.

nn7415/nn7415-summary/safety_hahb_ema_20241111_er
21NOV2024:06:40:00 - f-ae-overview-byage.sas/f-ae-overview-rate-byage.png

Figure 38: Adverse events on concizumab - by preferred term - most frequent (>=5%) - by age group - summary plot - HA, HB, HAwI and HBwI - safety analysis set - trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off).



HA: haemophilia A without inhibitors, HB: haemophilia B without inhibitors, HAwI: haemophilia A with inhibitors, HBwI: haemophilia B with inhibitors. MedDRA 26.0.
Patients exposed to concizumab are included. This means that placebo data from 4159, Eptacog alfa 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.
nn7415/nn7415-summary/safety_hahb_ema_20241111_er
21NOV2024:06:40:59 - f-ae-pt-agegrp-5pct.sas/f-ae-pt-agegrp-5pct.png

Safety by race

Safety pool (trials 4307, 4255, 4311, 4310 and 4159)

Overall, there were no notable differences with respect to the distribution of AEs across racial subgroups.

Few patients (14) in the concizumab clinical development programme were in the 'Black or African American' subgroup; thus, results for this subgroup should be interpreted in the light of its small size.

For 8 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. For the remaining subgroups under 'Other', patient numbers were also few.

In the total safety pool, cumulative exposure was highest within the White and Asian racial subgroups (305.3 and 130.9 PYE), where also the highest proportions of patients were observed.

The proportion of patients with AEs varied from 64.7% to 85.7% across racial subgroups and the rate of AEs ranged from 2.2 to 3.5 events per PYE.

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

Safety pool (trials 4307, 4255, 4311, 4310 and 4159)

Overall, there were no notable differences with respect to the distribution of AEs across ethnic subgroups. Ethnicity was not reported for 7 patients in the total safety pool.

A total of 126 AEs in 15 (71.4%) patients (4.3 events per PYE) were reported in patients of Hispanic or Latino ethnicity vs 1314 AEs in 235 (80.5%) non-Hispanic non-Latino patients (3.0 events per PYE).

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

Safety pool (trials 4307, 4255, 4311, 4310 and 4159)

Overall, there were no notable differences with respect to the distribution of AEs across hepatic function subgroups. The number of patients exposed to concizumab PPX and cumulative exposure (PYE) by baseline hepatic impairment subgroups are presented for the total safety pool in Table .

Few (9 of 320; 2.8%) 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).

Table 6642: Overview of patients exposed to concizumab and AEs by hepatic impairment – safety analysis set - safety pool – trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off).

	Normal ALT and AST	Elevated ALT or AST	Total[b]
N	310	9	320
Total exposure (PYE)	464.3	9.3	474.7
Patients with adverse event, N (%)	248 (80.0)	6 (66.7)	255 (79.7)
Number of adverse events	1400	45	1471
Event rate[a]	3.0	4.8	3.1

Notes: Normal: ALT and AST levels below 1.5 times above ULN; elevated ALT or AST: ALT and/or AST levels at 1.5 times ULN or above. For trials 4307 and 4311, the 56-week cut-off is used. aRate calculated as number of AEs per patient years of exposure. bFor 1 patient classification of hepatic function was missing. MedDRA version 26.0 is used. Abbreviations: AE: adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; MedDRA: medical dictionary for regulatory activities; N (%): number and percentage of patients; PYE: patient years of exposure; ULN: upper limit of the normal range.

In the 'elevated ALT or AST' subgroup, only non-serious events of Injection site reaction' (2 events in 2 patients) and Hypertension (3 events in 3 patients) were reported in more than 1 patient. The remaining AEs were distributed across several SOCs with no clear pattern.

Seven (7) SAEs spread across multiple SOCs and PTs were reported in 3 (of 9) patients in the elevated ALT or AST' subgroup (Hand fracture, Puncture site haemorrhage, Shock haemorrhage, Muscle haemorrhage and Subdural haemorrhage [same patient]; Acute Myocardial infarction and COVID-19). Only the event of Acute myocardial infarction was judged as possibly related to concizumab by the investigator. Except for the event of COVID-19, which was fatal, all SAEs had the outcome 'resolved'.

Safety in patients with renal impairment

The safety pool was divided into subgroups by baseline renal function, normal renal function (eGFR ≥90 mL/min per 1.73 m2) and reduced renal function (eGFR <90 mL/min per 1.73 m2)

In the phase 1 trial 4159, eGFR was not assessed. Instead, patients with renal dysfunction were excluded if they were receiving dialysis and/or based on creatinine level ≥ 1.25 x ULN according to central laboratory ranges at screening (Trial 4159). Therefore, patients exposed to concizumab in

trial 4159 were excluded from the safety evaluation of concizumab in patients with reduced eGFR. As per exclusion criteria, no patients with eGFR <30 mL/min per 1.73 m2 were enrolled in the phase 3 (4307 and 4311) and phase 2 (4255 and 4310) clinical trials with concizumab.

Phase 2 and 3

Overall, there were no notable differences with respect to the distribution of AEs across renal function subgroups.

The number of patients exposed to concizumab PPX and cumulative exposure (PYE) by baseline renal function subgroups are presented for the total safety pool (excluding trial 4159) in Table . Few (19 of 302; 6.3%) patients in the concizumab clinical development programme had reduced renal function; thus, results for this subgroup should be interpreted in the light of its small size.

Table 6743: Overview of patients exposed to concizumab and AEs by baseline renal function - safety analysis set - safety pool - trials 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

	Reduced	Normal	Total[b]
N	19	283	302
Total exposure (PYE)	30.1	440.8	470.9
Patients with adverse event, N (%)	14 (73.7)	225 (79.5)	239 (79.1)
Number of adverse events	97	1327	1424
Event rate[a]	3.2	3.0	3.0

Notes: Normal renal function: eGFR ≥90 mL/min per 1.73 m2; reduced eGFR: eGFR <90 mL/min/1.73 m2. Patients exposed to concizumab in trial 4159 (N=18) were excluded from the evaluation, as eGFR was not assessed in the trial. aRate calculated as number of AEs per patient years of exposure. bFor the 18 patients exposed to concizumab in trial 4159, classification of renal function is missing. MedDRA version 26.0 is used. Abbreviations: AE: adverse event; eGFR: estimated glomerular filtration rate; MedDRA: medical dictionary for regulatory activities; N (%): number and percentage of patients; PYE: patient years of exposure.

Similar proportions of patients reported AEs across renal function subgroups. For both renal function subgroups, the most frequently reported AEs were similar to those in the total safety pool.

In the reduced renal function subgroup, only non-serious injection site reactions (Injection site haemorrhage [6 AEs in 2 patients], Injection site bruising [4 AEs in 2 patients] and Injection site erythema [2 events in 2 patients]) and non-serious events of COVID-19 (6 events in 6 patients), Arthralgia (3 events in 2 patients), Oedema peripheral (3 events in 2 patients), Fall (2 events in 2 patients), Fibrin D-dimer increased (2 events in 2 patients) and Hepatic enzyme increased (2 events in 2 patients) were reported in more than 1 patient. The remaining AEs were distributed across several SOCs with no clear pattern.

Four (4) SAEs were reported in the reduced renal function subgroup, including the 3 thromboembolic events reported in 1 patient with HA in trial 4307 prior to the treatment pause and an event of Dizziness which led to temporary discontinuation of concizumab.

Safety in patients with thromboembolic risk factors

Thromboembolic risk factors in the total safety pool (trials 4307, 4255, 4311, 4310 and 4159)

Thromboembolic risk factors at screening based on the MedDRA search are presented for the total safety pool and by haemophilia subtype. Thromboembolic risk factors were present in 73 (22.8%) patients of the total safety pool population, with comparable proportions across haemophilia subtypes (Table 68).

The most frequently reported thromboembolic risk factor across all haemophilia subtypes was 'Hypertension' (SOC Vascular disorders), followed by 'BMI >35 kg/m2'. The remaining risk factors were spread across multiple SOCs and reported in up to 3 patients across haemophilia subtypes.

Table 6844: Thromboembolic risk factors at screening - based on MedDRA search in medical history - by system organ class and preferred term - by haemophilia subtype - summary - HA, HB, HAwI and HBwI - safety analysis set - trials 4159, 4310, 4255, 4307 (56-week cut).

	HA N (%)	HB N (%)	HAwI N (%)	HBwI N (%)	Total N (%)
N in SAS	125	64	78	53	320
Thromboembolic risk factors					
Yes	31 (24.8)	13 (20.3)	16 (20.5)	13 (24.5)	73 (22.8)
No	94 (75.2)	51 (79.7)	62 (79.5)	40 (75.5)	247 (77.2)
BMI > 35 kg/m^2	5 (4.0)	4 (6.3)	1 (1.3)	6 (11.3)	16 (5.0)
Risk factors by SOC and PT					
Vascular disorders	22 (17.6)	7 (10.9)	11 (14.1)	9 (17.0)	49 (15.3)
Hypertension	22 (17.6)	6 (9.4)	11 (14.1)	9 (17.0)	48 (15.0)
Aortic stenosis	0	1 (1.6)	0	0	1 (0.3)
Essential hypertension	0	1 (1.6)	0	0	1 (0.3)
Metabolism and nutrition disorders	4 (3.2)	0	2 (2.6)	3 (5.7)	9 (2.8)
Hypercholesterolaemia	1 (0.8)	0	1 (1.3)	1 (1.9)	3 (0.9)
Dyslipidaemia	1 (0.8)	0	1 (1.3)	0	2 (0.6)
Type 2 diabetes mellitus	2 (1.6)	0	0	0	2 (0.6)
Hyperlipidaemia	1 (0.8)	0	0	1 (1.9)	2 (0.6)
Diabetes mellitus	1 (0.8)	0	0	0	1 (0.3)
Hypertriglyceridaemia	0	0	0	1 (1.9)	1 (0.3)
Nervous system disorders	0	1 (1.6)	3 (3.8)	0	4 (1.3)
Cerebrovascular accident	0	0	2 (2.6)	0	2 (0.6)
Haemorrhagic stroke	0	0	1 (1.3)	0	1 (0.3)
Hemiparesis	0	0	1 (1.3)	0	1 (0.3)
Vascular encephalopathy	0	1 (1.6)	0	0	1 (0.3)
Surgical and medical procedures	1 (0.8)	1 (1.6)	0	1 (1.9)	3 (0.9)
Central venous catheterisation	1 (0.8)	1 (1.6)	0	1 (1.9)	3 (0.9)
Catheterisation venous	0	0	0	1 (1.9)	1 (0.3)
Cardiac disorders	1 (0.8)	0	1 (1.3)	0	2 (0.6)
Atrial fibrillation	1 (0.8)	0	0	0	1 (0.3)
Angina pectoris	0	0	1 (1.3)	0	1 (0.3)
Investigations	2 (1.6)	0	0	0	2 (0.6)
Blood pressure increased	2 (1.6)	0	0	0	2 (0.6)
Congenital, familial and genetic disorders	1 (0.8)	0	0	0	1 (0.3)
Factor V Leiden mutation	1 (0.8)	0	0	0	1 (0.3)
Gastrointestinal disorders	0	0	0	1 (1.9)	1 (0.3)
Gastrointestinal necrosis	0	0	0	1 (1.9)	1 (0.3)
Musculoskeletal and connective tissue disorders	0	0	1 (1.3)	0	1 (0.3)
Osteonecrosis	0	0	1 (1.3)	0	1 (0.3)

Safety in patients with thromboembolic risk factors – Total safety pool (trials 4307, 4255, 4311, 4310 and 4159)

AEs were spread across multiple SOCs with similar event rates and overall similar patterns between the 2 subgroups (thromboembolic risk factors vs no thromboembolic risk factors). With few exceptions, the most common AEs (>5%) were similar across subgroups and reflected the most frequently reported AEs in the total safety pool.

The overall 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 the corresponding event rates were comparable between the 2 subgroups (thromboembolic risk factors vs no thromboembolic risk factors).

Thromboembolic risk factors were also found present in patients treated with concizumab PPX who did not report thromboembolic events, which supports the multi-factorial aetiology of these events.

Safety in relation to major surgery

Major surgery cases from the multiple-dose trials

Major surgeries were reported for patients on concizumab PPX in the trials 4307, 4311 and 4310. No patients treated with concizumab PPX in phase 1 trial 4159 or phase 2 trial 4255 underwent major surgery.

No AEs of concern were reported in relation to the major surgeries from the phase 2 and 3 trials except for 1 case from phase 2, where 2 SAEs were caused by postoperative blood sampling, and 1 case from phase 3, where the surgery (intracranial haemorrhage drainage) was performed acutely to save the life of the patient, yet, the patient died from the bleed.

Trial 4307

Up until the 56-week cut-off, 4 major surgeries were reported in 4 patients on concizumab PPX:

- An adolescent with HB treated with concizumab PPX in arm 2 underwent major surgery on study day 155. The indication for the surgery was reported as 'right ankle arthropathy unresponsive to steroid injection'. The surgery was not reported as an SAE. The last concizumab dose prior to surgery was reported as 1 day before surgery and the first dose after surgery was reported as 4 days after surgery. The patient received Benefix (nonacog alfa) as haemostatic medication in relation to the surgery.
- An adolescent with HB treated with concizumab PPX in arm 2 underwent major surgery on study day 371 after suffering a traumatic abdominal bleed. The surgery was a diagnostic laparoscopy with removal of blood from the abdominal cavity with the indication reported as 'suspected intra-abdominal bleeding'. An SAE with PT 'Abdominal injury' (reported term: 'Closed abdominal injury') was reported with the surgery. The last concizumab dose prior to surgery was reported as 9 days before surgery and the first dose after surgery was reported as 9 days after surgery. Haemostatic medications given in relation to the surgery included Factor IX and tranexamic acid, the latter a per-protocol prohibited medication. The use of tranexamic acid was reported as an important protocol deviation, and it was noted that use of the prohibited medication was vital (Trial 4307 56wk). The outcome of the co-reported SAE was reported as resolved.
- A patient with HA treated with concizumab PPX in arm 2 underwent major surgery on study day 713. The surgery was a total knee arthroplasty. No SAE was reported in relation to the surgery. According to an important protocol deviation, concizumab PPX was not interrupted during the whole period of surgery including hospitalisation. It was noted that this did not lead to a safety risk (Trial 4307 56wk). The patient received recombinant factor VIII on the day of the surgery.
- A patient with HA treated with concizumab PPX in arm 4 underwent major surgery on study day 389. The surgery was a total knee replacement. An SAE with PT 'cartilage injury' (reported term: 'cartilage rupture') was reported in relation to the surgery. The last dose of concizumab was taken 5 days before the surgery and reported to be resumed 44 days after surgery (Trial 4307 56wk). The outcome of the co-reported SAE was reported as resolved. Haemostatic medications included Advate (octocog alfa) and enoxaparin.

Trial 4311

Up until the 56-week cut-off, 4 major surgeries were reported in 4 patients on concizumab PPX, including one surgery which was only reported as an SAE:

- A patient with HAwI treated with concizumab PPX in arm 4 underwent an elective major surgery on study day 759. The surgery was a total hip alloplasty with the indication reported as haemophilic arthropathy. An SAE was co-reported with the surgery with PT 'hip arthroplasty' (reported term: 'Total left hip alloplasty [surgery no. 4]'). The last concizumab dose prior to surgery was reported as 82 days before surgery and the first dose after surgery was reported as 37 days after surgery. Haemostatic medication given in relation to the surgery included FEIBA and Exacyl (Tranexamic acid). The outcome of the co-reported SAE was reported as resolved.
- An adolescent with HBwI treated with concizumab PPX in arm 2 underwent acute surgery (intracranial haematoma drainage) on study day 346 due to intracranial haemorrhage, which was reported as an SAE with onset the day before surgery. The last dose of concizumab was taken the day before the surgery. NovoSeven (5 mg/kg) was given as haemostatic medication in relation to the surgery. A protocol deviation was registered, as it was not possible to obtain dosing details for the haemostatic treatment from the local hospital where the surgery was performed. The co-reported SAE was reported with outcome 'fatal' 6 days after surgery.
- A patient with HBwI treated with concizumab PPX in arm 3 underwent major surgery on study day 822. The surgery was a total hip arthroplasty. An SAE with PT 'Femoral neck fracture' (reported term: 'fractured neck of femur') was reported in relation to the surgery. The last concizumab dose prior to surgery was reported as 4 days before surgery and the first dose after surgery was reported as 17 days after surgery. Haemostatic medication given in relation to surgery included BeneFIX (nonacog alfa) and NovoSeven (eptacog alfa). The outcome of the co-reported SAE was reported as resolved.
- A patient with HBwI treated with concizumab PPX in arm 2 underwent major surgery on study day 726. The surgery was a bilateral total hip prosthesis. An SAE was co-reported with the surgery with PT 'Osteoarthritis' (reported term 'Bilateral coxarthrosis'). Concizumab PPX was paused prior to and re-initiated after the surgery. The outcome of the SAE was reported as resolved. Haemostatic medication included Exacyl (tranexamic acid) given during surgery and until 12 days after surgery.

Trial 4310

Two (2) patients treated with concizumab PPX (0.15 mg/kg) in trial 4310 underwent major surgery during the extension part of the trial. A protocol deviation was registered for both surgeries:

- A patient with HBwI underwent a total knee replacement due to worsening of arthropathy. An SAE with PT 'Arthropathy' (reported term 'worsening of right knee arthropathy'; Trial 4310 extension part was reported for the patient. Haemostatic mediation given in relation to the surgery included eptacog alfa. Concizumab PPX treatment was not discontinued before surgery. The outcome of the co-reported SAE was reported as resolved.
- A patient with HBwI underwent major surgery after an accident caused fracture to three fingers on his left hand. An SAE with PT Hand fracture was reported for the case (Trial 4310 extension part). Haemostatic medication given in relation to the surgery and the 2 other SAEs (Puncture site haemorrhage and Shock haemorrhagic) with onset on the same day as the surgery (Trial 4310) included ByClot, FEIBA (activated prothrombin complex concentrates) and NovoSeven. Concizumab PPX was discontinued the day after surgery and resumed after 50 days of interruption (Trial 4310 extension part). The outcome of the co-reported SAE was reported as Resolving.

Summary of safety in relation to major surgeries performed during phase 2 and 3

A total of 4 major surgeries were reported in 4 patients on concizumab PPX in each of the phase 3 trials 4307 and 4311 (including 1 surgery from trial 4311 only reported as an SAE). All 8 surgeries were reported after treatment restart. One (1) of the cases was an acute intracranial haemorrhage drainage performed to save the life of the patient who experienced an SAE of Intracranial haemorrhage. The outcome of this event was fatal. In 6 of the remaining 7 cases of major surgery, concizumab treatment was discontinued before the surgery and reinitiated after surgery with varying lengths of the discontinuation period. For 1 case where a patient underwent total knee replacement, concizumab PPX was not interrupted at any point during the peri-/postoperative period.

No major surgery was reported in the phase 1 trial 4159 or in the phase 2 trial 4255. In the phase 2 trial 4310, 2 patients underwent major surgery while on 0.15 mg/kg concizumab PPX during the extension part of the trial. In one of the cases (hand fracture surgery), concizumab PPX was discontinued from the day after surgery, and in the other case (total knee replacement), the patient did not discontinue concizumab PPX in relation to the surgery.

No thromboembolic events, and no other AEs of concern, were reported in the peri-/postoperative period for 8 of the 9 cases of major surgery reported in the multiple-dose trials with concizumab (excluding the fatal case of Intracranial haemorrhage from trial 4311). The exception is the hand fracture surgery case from phase 2 trial 4310, where the patient went into haemorrhagic shock (reported as SAE) on the same day as the surgery was performed after he experienced an SAE of femoral artery puncture site haemorrhage due to blood sampling.

Use in pregnancy and lactation

Fertility

There is no clinical experience with concizumab use in pregnancy or lactation, and its potential effects on male and female fertility are unknown. Women of childbearing potential are recommended to use contraception during treatment with concizumab and until 7 weeks after end of treatment.

No evidence of direct or indirect harmful effects were observed on male or female fertility in cynomolgus monkeys dosed s.c. with concizumab at doses up to 9 mg/kg/day (corresponding to 3400-fold the human exposure, based on area under the concentration-time curve from time zero to 24 hours [AUC0-24h]).

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.

Medication errors leading to overdose were reported in clinical trials with 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 apart from 1 case where a non-serious and mild event of Tachycardia, resolved within 1 day, was co-reported with an event of Accidental overdose.

Drug abuse

The available results on the pharmacology, nonclinical and clinical studies do not suggest any potential for drug abuse with concizumab. Concizumab is unlikely to be associated with abuse, based on its mechanism of action.

Withdrawal and rebound

Based on results from clinical trials, there is no indication that patients cannot safely discontinue concizumab PPX, 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. However, it is unlikely that concizumab affects the ability to drive and use machines.

Technical complaints

Technical complaints were reported in trials 4307, 4255, 4311 and 4310, and 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 the trials, there were 7 AEs (6 events in trial 4311 and 1 event in trial 4310) related to a trial product 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 resolved and did not lead to any action taken 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 and is described in Section 2.2.4. No clinical consequences arose from the medication error.

No HA or HB patients reported AEs related to trial product technical complaints.

Safety related to drug-drug interactions and other interactions

Drug interactions

No formal drug-drug interaction clinical studies have been performed and no interactions of concizumab with other medicinal products have been reported.

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.

Since the marketing authorisation application for the HAwI and HBwI indications, results from an in vitro drug-drug interaction study with concizumab and a sequence-identical analogue of emicizumab (emicizumab-SIA) have become available. The interaction was evaluated in a thrombin generation assay to address if any exaggerated thrombin generation could be observed when

concizumab and emicizumab were present in plasma simultaneously (with or without rFVIIa, FVIII or aPCC). The combined effects were mainly additive, with only minor extra contribution from drug-interaction. These data are in line with previous data and published data.

In conclusion, there is no evidence of clinically relevant drug-drug interactions based on in vitro and ex vivo drug-drug interaction studies performed up until the application cut-off with rFVIIa, aPCC, recombinant FVIII, recombinant FIX or emicizumab in blood from haemophilia patients on prophylactic treatment with concizumab.

Laboratory assay interference

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.

Discontinuation due to adverse events

Adverse events leading to permanent or temporary treatment discontinuation

By trial (trials 4307, 4255, 4311, 4310 and 4159)

Patients who experienced any of the following events were to permanently discontinue trial product: significant thromboembolic event, 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 discontinuation of concizumab PPX are listed by trial in Table 69.

A total of 12 AEs in 10 (3.1%) patients led to permanent discontinuation of trial product, of which 9 AEs in 7 patients were judged by the investigator as possibly or probably related to concizumab and 62 AEs in 51 (15.9%) patients (including the cases of discontinuation due to COVID-19) 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 4307:

- 6 possibly or probably related SAEs 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 and Injection site pain
- 2 possibly or probably related AEs in 2 patients led to temporary treatment discontinuation (Tachycardia [co-reported with an event of Accidental overdose] and Neutropenia)

Trial 4255:

- No patients discontinued concizumab treatment permanently due to AEs
- 3 possibly or probably related AEs in 2 patients led to temporary treatment discontinuation (episcleritis; and prothrombin level increased and atypical pneumonia [same patient])

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 as per protocol discontinuation criterion, see Section 2.2.2]; Injection site rash [the patient later permanently discontinued treatment due to the event of Hypersensitivity listed above (first bullet); Haematemesis and Melaena; and Dizziness).

Trial 4310:

- No patients discontinued concizumab treatment permanently due to AEs
- 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'])

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. All 11 SAEs had resolved or were resolving at the data cut-off, except for the events of Renal infarct, which was reported as 'resolved with sequelae' ('patient will have ongoing scarring secondary to the thrombosis event, despite normal renal function') and the events of Deep vein thrombosis, Pulmonary embolism and Superficial vein thrombosis (in the same patient from 4307), which were resolving by the time the patient withdrew from the trial.

Table 6945: Listing of patients with AEs leading to permanent discontinuation of trial product by trial (trials 4307 and 4311) - on-treatment - safety analysis set.

Haem type /	AE no.	Study day[a]/ Duration (days)	SOC / PT	Serious / Severity/ Causality	Outcome
HB	1	3/48	Gastrointestinal disorders/ Intra-abdominal haemorrhage	Yes/ Severe/ Possible	Recovered/ Resolved
HA	1	25/48	Injury, poisoning and procedural complications/ Craniocerebral injury	Yes/ Severe/ Unlikely	Recovered/ Resolved with Sequelae
HA	4	59/15	Cardiac disorders/Acute myocardial infarction (AESI: Section 2.2.1)	Yes/ Severe/ Possible	Recovered/ Resolved
HA	9	644/26	Cardiac disorders/Cardiac failure	Yes/ Moderate/ Unlikely	Recovering/ Resolving
HA	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
HB	1	1/79	General disorders and administration site conditions/ Injection site pain	No/ Moderate/ Probable	Recovered/ Resolved
HAwI/	1	501/ 39	Cardiac disorders/ Congestive cardiomyopathy	No/ Moderate/ Possible	Recovering/ Resolving
HBwI/	2	21/ 205	Renal and urinary disorders/ Renal infarct (AESI: Section 2.2.1)	Yes/ Severe/ Possible	Recovered/ Resolved with Sequelae
HBwI/	2	18/ 10	Immune system disorders/ Hypersensitivity	No/ Moderate/ Possible	Recovered/ Resolved
HBwI/	5	553/ 22	Infections and infestations/ COVID-19	Yes/ Severe/ Unlikely	Fatal

Notes: [a]Study day is calculated based on the treatment start date. Patient age and BMI are reported at baseline in years and kg/m^2, respectively. Abbreviations: AE: adverse event; BMI: body mass index; haem type: haemophilia subtype; HA: haemophilia A without inhibitors; HAwI: haemophilia A with inhibitors; HB: haemophilia B without inhibitors; HBwI: haemophilia B with inhibitors; no.: number; SOC: system organ class; PT: preferred term.

Adverse events leading to a change in concizumab dose

AEs leading to changes in dose were only reported in trials 4307, 4255 and 4311 are summarised below.

Trial 4307

Two (2) events leading to a change in concizumab dose in trial 4307 were reported up until the 56-week cut-off. Both were reported prior to the CACO. One (1) patient with HB on concizumab PPX

experienced an event of Injection site reaction (AE no. 3) which led to a single dose reduction from 25 increments (18.75 mg) to 16 increments (12 mg). 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. In another patient with HB, a dose increase was reported for 1 event of 'Underdose'. The event was also reported as a medication error.

Trial 4255

Two (2) patients on concizumab PPX (0.25 mg/kg) had their dose reduced due to a non-serious AE (Fibrin D dimer increased and Prothrombin level increased, respectively) in the main part of trial 4255. Both AEs were mild in severity, judged as possibly/probably related to concizumab PPX by the investigator and resolved.

Trial 4311

Five (5) events leading to a change in concizumab dose in trial 4311 were reported up until the 56-week cut-off. All of these were reported prior to the PACO. Based on the AE form, 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. An additional 2 patients experienced an AE (Injection site erythema and Synovitis) after treatment restart with action taken 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.

Safety pool – by haemophilia subtype

In the total safety pool, 60 (18.8%) patients discontinued treatment temporarily or permanently due to 74 AEs:

- 10 (3.1%) patients permanently discontinued trial product due to 12 AEs (0.0 AEs per PYE)
- 51 (15.9%) patients temporary discontinued trial product due to 62 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, except for events of COVID-19, which per protocol required temporary treatment discontinuation.

Safety from ongoing clinical trials and compassionate use

Narratives on new events for deaths, other SAEs and AESIs from the three ongoing phase 3 trials with concizumab (4307, 4311 and 4616), as well as for patients treated with concizumab via compassionate use, were extracted from the ARGUS safety database with a cut-off of 30-Sep-2024, corresponding to the cut-off date for this application. These narratives form the basis for the safety evaluation presented in this section.

Trial 4307 – phase 3 – HA and HB

A total of 129 patients were exposed to concizumab in trial 4307 between the 56-week cut-off and the application cut-off (data on file).

Updates to deaths, other SAEs and AESIs

No updates to existing information on deaths, other SAEs or AESIs reported in trial 4307 were registered in the period between the 56-week safety database cut-off and the application cut-off of 30-Sep-2024.

New deaths, other SAEs and AESIs reported after the 56-week cut-off

No new deaths have been reported between the 56-week cut-off for trial 4307 and the cut-off date for this application.

A total of 18 SAEs were reported by 9 patients treated with concizumab PPX between the 56-week cut-off and the application cut-off. Two (2) of the SAEs (1 event of PT Ischaemic stroke and 1 event of Cerebral infarction) were reported as AESIs. Of the 18 SAEs, 13 events were severe, 2 were moderate, and 3 were mild. All of the reported SAEs, except 1 event of Ischaemic stroke (judged as possibly related), were judged as unlikely related to concizumab PPX by the investigator.

Most of the 18 events led to temporary (9 events) or permanent (4 events) treatment discontinuation. Fourteen (14) events were reported as resolved, 2 were reported as resolved with sequelae, and 2 were reported as not resolved at the application cut-off.

Three (3) SAEs, including the 2 AESIs, are presented briefly below:

- SAE of PT Ischaemic stroke in a patient with HA, reported as resolved. The investigator judged the event of Ischaemic stroke as possibly related to concizumab PPX, although the case has alternative aetiologies of underlying disease, fluctuating hypertension and previous stroke.
- SAE of PT Cerebral infarction in a patient with HA reported as 'resolved'. The investigator judged the event as 'unlikely related' to concizumab PPX, as hypertension being a risk factor for ischemic as well as haemorrhagic stroke, the patient's advanced age is also considered a risk factor.
- The SAEs of Traumatic haemorrhage in a patient with HB, as the patient injured his veins. The SAE was reported resolved and judged as unlikely related to concizumab PPX by the investigator.

Other SAEs (PT) included: Severe posttraumatic bleeding, concizumab discontinued, Post procedural haemorrhage/ post brain surgery intracranial bleed, which resolved with sequelae, fracture, injury (3), Hydrocephalus/Malresorptivus, myocarditis, Wound infection, Transient vertigo symptoms, Soft tissue damage grade 1 of the left lower leg, Wound healing disorder in ankle joint, Wound infection on the sole. The Wound infection was not resolved, the post procedural haemorrhage/ post brain surgery intracranial bleed, and Hydrocephalus/Malresorptivus resolved with sequelae; all other SAEs were resolved. All other SAEs were judged as unlikely related to concizumab.

Trial 4311 – phase 3 - HAwI and HBwI

A total of 104 patients were exposed to concizumab in trial 4311 between the 56-week cut-off and the application cut-off (data on file).

Updates to deaths, other SAEs and AESIs

No updates on deaths, other SAEs or AESIs reported in trial 4311 were registered in the period between the 56-week safety database cut-off and the application cut-off.

New deaths, other SAEs and AESIs reported after the 56-week cut-off

No new deaths have been reported between the 56-week cut-off and the cut-off date for this application. A total of 38 SAEs in 20 patients treated with concizumab PPX were reported in trial 4311 after the 56-week cut-off. Two (2) of the SAEs (1 event of PT Haemothorax and 1 event of Gastrointestinal haemorrhage) were incorrectly registered as AESIs. For the event of Haemothorax, the investigator has noted that she has no safety concerns related to thromboembolic events for the patient.

Of the 38 SAEs, 1 event was mild, 17 were moderate and 20 were severe. All the reported SAEs were judged as unlikely related to concizumab PPX by the investigator, except 1 SAE of PT Haematuria, reported as recovered, was judged as possibly related to concizumab PPX.

Seven (7) of the events led to temporary treatment discontinuation and 1 event led to permanent treatment discontinuation. Most of the events were reported as resolved (33 events) or resolved with sequelae (3 events) at the application cut-off.

Three (3) of the reported SAEs are presented below:

- SAE of Subdural haematoma in a patient with HBwI. The patient suffered a seizure, fell and hit his head, resulting in a subdermal haematoma in the left frontal lobe. Concizumab PPX was discontinued temporarily and the subdermal haematoma was treated and stabilised. The accident had caused a flare up of the patient's pre-existing condition of nephrotic syndrome. The SAE was reported as 'resolved with sequelae' (sequelae described as 'chronic kidney disease stage 3b, minimal change disease and chronic pain syndrome secondary to recurrent haemarthroses), and the investigator judged it to be unlikely related to concizumab PPX.
- SAE of Intra-abdominal haematoma in patient with HBwI. The patient was hospitalised for intra-abdominal bleeding due to pain in his abdomen. The patient underwent lifesaving surgery, as he was critically low on haemoglobin and unconscious. The patient recovered and NovoSeven was given on the day of surgery as well as in the days after the surgery. Concizumab was restarted 12 days after he was hospitalised for the bleed. The investigator judged the SAE as unlikely related to concizumab PPX; alternative aetiology reported as the patient's HBwI.
- SAEs with PT Gastrointestinal haemorrhage and Gastritis in a patient with HBwI. The patient was treated with concizumab PPX for around 3.5 years before event onset. On the day of event onset, the patient was admitted to hospital and presented with pallor, dizziness and low Hb. Oesophagogastroscopy was performed, and gastritis was confirmed. The patient received blood and was discharged 4 days later. No action was taken to trial product, and the SAE of Gastrointestinal haemorrhage was reported as resolved 8 days after onset. The SAE of Gastritis was not resolved. The investigator judged both events as unlikely related to concizumab PPX.

Trial 4616 – ongoing phase 3 – HA, HB, HAwI and HBwI in paediatric patients <12 years

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. In addition, male patients (regardless of age) on compassionate use of concizumab are included in arm 2 to allow for a structured collection of data in these patients for additional assessment of safety. The trial was initiated in March 2022 (FPFV 24-Mar-2022). More information on trial 4616 can be found in the efficacy section. At application cut-off (30-Sep-2024), 61 patients had been exposed to concizumab in trial 4616.Deaths, SAEs and AESIs in trial 4616 up until the application cut-off

No deaths or AESIs were reported for patients in trial 4616 from FPFV up until the application cut-off.
A total of 14 SAEs were reported by 9 patients treated with concizumab PPX. Of these, 6 events were severe, 5 were moderate, and 3 were mild. All events were reported as unlikely related to concizumab PPX, except the SAE of Peripheral ischaemia (judged as possibly related). Five events led to temporary treatment discontinuation. All 14 events were reported as resolved.
The case of Epistaxis as well as the linked cases of Haematoma and Peripheral ischaemia are described below:

- Severe SAE of spontaneous Epistaxis in a HBwI child. The patient received blood transfusion, tranexamic acid and vitamin K. No NovoSeven was given. No action was taken to trial product and SAE was reported as resolved within 6 days. The SAE was judged unlikely related to concizumab by the investigator.
- Two (2) severe SAEs of Haematoma and Peripheral ischaemia (reported terms: 'left iliopsoas haematoma' and 'Peripheral ischaemia [left hand and forearm]') in a HBwI child treated with concizumab for 11 months. Three days after Haematoma onset, ultrasound showed enlargement of the left iliopsoas and NovoSeven was initiated; a Midline catheter was placed in the patient's left forearm for the bleed treatment. The next day Peripheral ischaemia occurred with progressive cyanosis of the patient's left forearm and hand. An ultrasound showed arterial insertion of the Midline catheter. The catheter was removed, treatment with NovoSeven was withdrawn, and concizumab PPX discontinued temporarily. The investigator judged the Haematoma unlikely related to concizumab PPX, but the Peripheral ischaemia as possibly related. The MAH assesses that the Peripheral ischaemia is more likely to be caused by a combination of the arterial misplacement of the Midline catheter and treatment with NovoSeven through the catheter than by concizumab PPX. This assessment is in line with the alternative aetiologies for the event provided by the investigator: 'concomitant medication NovoSeven' and 'arterial insertion of Midline catheter (left forearm)'. Both events resolved.

Compassionate use

No deaths have been reported for patients in the compassionate use programme or patients treated with concizumab on an individual patient basis between 28-Feb-2024 and the application cut-off. No patient discontinued treatment permanently in the period.

Compassionate use programme (4807) - HBwI

A total of 14 patients were exposed to concizumab in the compassionate use programme between 28-Feb-2024 and the application cut-off (data on file).

In this period, 1 SAE (PT: Vascular device infection) of moderate severity was reported which was judged unlikely related to concizumab PPX by the investigator, did not lead to a change in trial product and was reported as resolved.

Post marketing experience

Concizumab has been marketed as Alhemo since December 2023. Total post-marketing exposure to Alhemo at the application cut-off, estimated from the sales volume of approximately 54,750 mg, was 10 PYE. No significant safety cases have been reported for patients treated with Alhemo.

2.5.1. Discussion on clinical safety

In the initial MAA, the **safety evaluation** of concizumab for the HAwI and HBwI indications was primarily based on results from the safety pool of five phase 1-3 multiple-dose trials conducted in patients with HAwI, HBwI, HA, and HB (trials 4159, 4310, 4255, 4311 and 4307), and the safety data collected in the randomized main part up to 24/32 weeks plus OLE 56-week cut-off of phase 3 study 4311 in patients with HAwI and HBwI, and the randomized main part (confirmatory analysis (CACO)) up to 24/32 weeks of phase 3 study 4307 in patients with HA and HB.

In the current application, the safety evaluation is based on an **updated safety pool** of concizumab, with newly presented **safety data from the OLE** up to 56-week cut-off (cut-off date: 27-Dec-2022) of pivotal **study 4307** in HA and HB patients. Also, results from the latest interim cut-off of the **compassionate use programme (trial 4807**; cut-off date: 28-Feb-2024) in HBWi patients.
The two trials 4307 and 4311, with randomised data of 24/32 weeks collected in arm 1 and arm 2, and longer term 56-weeks 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.
The updated safety pool, including all patients who had taken at least one dose of concizumab, is prepared to supplement the safety data of the separate studies with an aggregated evaluation of the safety of concizumab and increases the likelihood of detecting potential safety signals and to detect potential differences in the safety profile between haemophilia subtype group (HA, and HB, HAwI, HBwI). This approach, including the integrated populations by haemophilia subtype group, appears acceptable as supportive safety data source.
In addition to this, also latest safety information of the ongoing trials, i.e. trial 4307, 4311, 4616 and compassionate use, have been submitted to further support the safety evaluation for concizumab, i.e. information from the safety database concerning narratives for deaths, other serious adverse events (SAEs) and adverse events of special interest (AESIs), i.e. thromboembolic events provided up until the application cut-off date of 30-Sep-2024.

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. However, it can be considered that there were no significant consequences for the available study results on safety.

The **dose regimen** used after the treatment pause in the phase 3 trial 4307 (and trial 4311) is similar to the approved dose regimen included section 4.2 of the SmPC for the current indications of HAwI and HBwI patients, which consists of several steps: a loading dose of 1 mg/kg, followed by daily dosing of 0.20 mg/kg from day 2 up to 4 weeks at which time point concizumab through level is measured. The individual maintenance dose is based on a concizumab through plasma level. Before the treatment pause, all patients in the pivotal study 4307 (and trial 4311) received a higher dose regimen of 0.25 mg/kg, which is similar in the phase 3 trial 4311 in HAwI and HBwI patients. In the phase 2 dose-response trials 4255 and 4310 and in phase 1 trial 4159 a lower maintenance dosing of concizumab of 0.15 mg/kg was used, 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. 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 are presented, this approach was considered acceptable.
The dosing pattern in HA and HB patients in phase 3 trial 4307 was generally similar as previously observed in trial 4311 in HAwI and HBwI patients. Of 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**, in the safety pool, 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 195.8 PYE and 73.5 PYE for patients with HA and HB, respectively, and 121.3 PYE, and 84.0 PYE for patients with HAwI and HBwI, respectively. Of these 320 patients, 249 (78%) patients were exposed for more than 12 months, and 63 (20%) patients were exposed for more than 24 months.
With inclusion of the newly submitted OLE data of pivotal trial 4307 up until the 56-week cut-off, a total of 151 patients were exposed to concizumab, of which 87 and 64 were HA and HB patients respectively. Of these, 115 HA and HB patients had completed 56 weeks of concizumab treatment. According to the guideline ICH-E1 100 patients exposed for a minimum of one-year at dosage levels intended for clinical use is considered to be acceptable for appropriate safety evaluation, thus the updated safety pool consisting of 249 patients, and the 115 patients in the pivotal trial 4301 do, therefore, fulfil the requirements of ICH-E1.

In pivotal study 4307, the percentage of HA and HB patients who reported **adverse events** (AEs) were in the same range as noted in study 4311, with 69% (n=104), up until CACO. The most frequently reported AEs (>5%) were COVID-19 (n=19 (13%) patients), fibrin D dimer increased (n=12 (8%) patients) and upper respiratory tract infection (n=10 (7%) patients). The number of patients with events in the no PPX arm was lower with 15 AEs in 6 (29%) patients, as expected. Up until the 56-week cut-off, a total of 118 of 151 (78.1%) patients reported 528 AEs (2.7/PYE) with concizumab. The most frequently reported AEs (>5%) in patients with either haemophilia subtype were generally similar with the data up until CACO, and included (in descending order) COVID-19, fibrin D dimer increased, nasopharyngitis and upper respiratory tract infection.
In general, the adverse event pattern up to 56 weeks of treatment noted in the HA and HB patients in study 3407 appears comparable with that observed in HAwI and HBwI patients in study 3411.

Regarding the **serious AEs** (SAEs), up until CACO in study 4307, 22 SAEs (0.2/PYE) were reported in 14 (9.3%) patients exposed to concizumab, with a similar proportion of patients with SAEs and similar event rates across HA and HB. Most SAEs were judged as unlikely related to concizumab (16 SAEs in 10 [6.6%] patients) and resolved (14 SAEs in 10 [6.6%] patients).
In total, 8 SAEs were reported by 8 patients after the 56-week cut-off, which makes this in total 30 reported SAEs (0.2 events per PYE) in 20 (13.2%) patients exposed to concizumab, with a similar proportion of patients with SAEs and similar event rates across HA and HB. The SAEs were distributed across multiple SOCs and PTs, and mostly reported as isolated cases. No apparent clustering across SOCs and PTs was observed. No SAEs were reported in ≥5% of HA and HB patients. Most SAEs were judged as unlikely related to concizumab (24 SAEs in 16 [10.6%] patients) and resolved (22 SAEs in 16 [10.6%] patients). SAEs were in the same range as observed in study 4311.

Regarding **compassionate use** data in patients with HBwI, in the new update, a total of 24 SAEs were reported in 11 patients until data lock point 28-Feb-2024. Fourteen SAEs were reported as part of 6 cases for patients treated on an individual patient basis. Most SAEs consisted of hemarthrosis, and haematoma. One SAE of intra-abdominal haematoma without known cause was reported in a patient with HBwI who suffered from platelet delta storage pool disorder, which could had contributed to the event. The patient recovered. No new safety signals have been reported with these data.

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 **thromboembolic events** (TE) with concizumab due to exaggerated pharmacology. 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. In the newly submitted data of study 4307 up to 56 week cut-off, no new TEs were reported.
  As assessed and discussed in the initial MAA, in total, 11 events in 6 of 320 (1.9%) patients were reported as TEs in the safety pool. All these cases occurred before the treatment pause. In 6 of the events a causal relationship with the use of concizumab was considered unlikely. A total of 5 non-fatal serious TEs (including the event of renal infarct) in 3 patients in the two phase 3 clinical trials (4311 and 4307), have led to the concizumab treatment pause.
  After the treatment pause, risk mitigation measures have been implemented and trial protocols had been updated. The MAH revised the concizumab dose regimen and implemented more restrictive dosing with regard to the use of breakthrough bleed treatment, i.e. the revised phase 3 protocols are in line with the lower end of the WFH dosing recommendations. Further, training of investigators and patients had been implemented. Also, TE was considered an ADR and the current SmPC contains extensive warnings in section 4.4 with regard to this risk.
  However, in the period after the 56-week cut-off and up to application cut-off, 2 serious TEs were reported in the ongoing OLE of trial 4307 (2 patients with HA), which both were reported to have recovered: One SAE of cerebral infarction in a patient who presented with thromboembolic risk factors (hypertension and advanced age), which could have contributed to the occurrence of the event and one SAE of Ischaemic stroke. One SAE of Ischaemic stroke in a patient who presented with thromboembolic risk factors (previous stroke and uncontrolled hypertension), which could have contributed to the occurrence of the event. The reporting of two new cases of TE in patients does not render a further update of the currently included warnings present in the current SmPC.
- Based on the newly provided study information, no new safety signals have been reported on **hypersensitivity reactions, injection site reactions**, which are already included as ADRs in the SmPC. Further, no new safety concerns have been revealed on **medication errors, rare events suspected transmission of an infectious agent, increased inflammatory response** or **renal events**.
- When the coagulation system is excessively activated, not only thrombosis, but also **increased bleeding tendency** could potentially occur due to consumption of coagulation factors. In the multiple-dose trials, 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 haemophilia subtypes. It is noted that the mean (SD) change from baseline to week 56 for concizumab PPX was -0.43 (0.91) g/L for patients with HA and -0.18 (0.90) g/L for patients with HB is less than observed from baseline to week 24 for concizumab PPX arms 2−4 (-0.47 (0.89) g/L for patients with HA and -0.30 (0.94) g/L for patients with HB). The initial conclusion that from these data a causal relationship of increased bleeding tendency with the use of concizumab could not be observed, is maintained.
- **Hepatic events.** Based on the updated data of study 4307 provided, there were no cases reported that fulfilled Hy's law criteria for severe hepatotoxicity. A total of 18 AEs on hepatic disorders in 15 (4.7%) patients were reported with similar rate across haemophilia subtypes, which percentage is considered low. No SAEs were reported. In 3 patients during the CACO, hepatic events were reported as related to the use of concizumab by the investigator: 1 patient with had elevated AST and bilirubin levels, who had previously experienced fluctuations in AST, which could have played in the role in the current occurrence of the events. No changes to the

drug use were made; one patient who had increased AST levels only at one visit one week after start of study medication with all other AST levels measured at following visits within the normal range, and one patient who had elevated hepatic enzymes at one visit, who suffered from Hepatitis C and HIV infection, which could also have contributed to the elevation of enzymes. Summarized, there is no indication that concizumab induces liver toxicity based on the evaluation of biochemical markers of liver function overall. No new hepatic events that were related to the use of concizumab have been reported in comparison to the cases reported in the initial MAA.

No changes have been proposed for section 4.8 in the current SmPC, which are agreed, as the additional safety data up to week 56 cut-off have not revealed any new safety issues.

In the initial MAA, no apparent clinically relevant changes in the **clinical laboratory haematology and biochemistry parameters** have been observed. Regarding coagulation-related parameters, concizumab concentrations were positively correlated with increased D-dimer and prothrombin fragments 1+2, reflecting the haemostatic effect of concizumab, while fibrinogen levels remained within the normal range. Across trials, no differences in coagulation-related parameters between haemophilia subtypes could be observed and increase in D-dimer and prothrombin fragments 1+2 were included as ADRs in the SmPC. No new relevant changes have been observed with the newly provided data.

In the current application, no relevant differences on immunology events with the initial MAA have been observed within the trials.
A total of 71/320 (22.2%; 3 more patients compared to ADA data in the initial MAA) patients exposed to concizumab (total safety pool) tested positive for anti-concizumab antibodies (ADAs) and 18 (5.8%; one more patient compared to ADA data in initial MAA) patients tested positive for ADAs with in-vitro neutralising effects, with more ADA-positive HAwI and HBwI patients (24/78 [30.8%] and 16/53 [30.2%], resp.) versus HA and HB patients (23/125 [18.4%] and 8/64 [12.5%0, resp.), and a slight increase was seen in adolescents (28% vs 20%). Seroconversion most frequently took place from around 12 weeks after first concizumab dose and onward, and the ADA response was transient in the majority of cases (68%), lasting $\leq$ 24 weeks in 75% of cases. The frequency of binding antibodies and in-vitro neutralising antidrug antibodies are in line with frequency of other IgG4 based therapeutics like emicizumab (5.1% and 2.7%, respectively; see assessment 'on persistence of efficacy').
Two relevant ADA cases in the total safety pool were discussed. One patient (phase 2 trial 4310) was already presented in the initial MAA, in whom the clinical impact of the high-titre binding **ADAs**, some with in vitro-neutralising effects to concizumab, remained inconclusive, since ADAs co-occurred with restoration of free TFPI levels to baseline levels, and plasma concizumab concentration measurements failed, likely due to ADA interference in the PK assay. The second patient has been newly reported within this procedure (phase 3 trial 4307) and experienced low-titre ADAs with in-vitro neutralising effects co-occurring with reduced plasma concizumab levels and restored free TFPI. The decrease in the concizumab exposure and the restoration of free TFPI continued even after the titre values decreased and the patient tested was negative for in vitro-neutralising ADAs and was not accompanied by any significant worsening in bleeding patterns or occurrence of immunogenicity-related AEs in the patient.
Further, in the compassionate use data, 5 patients (one more compared to ADA data in initial MAA) were tested positive for low-titre ADAs, at one or two visits after first exposure to concizumab. In the 19 patients who were treated on an individual patient bases no new relevant ADA cases were reported. One patient was discussed earlier in the initial MAA, who experienced multiple bleeds during the period of a single positive test for *in vitro*-neutralising ADAs. The bleeds lasted 1.5 years, while the patient returned to ADA-negative until his daily concizumab dose was increased,

which did not suggest an association between the presence of the in-vitro neutralising ADAs with concizumab.

In the initial MAA, regarding the **vital signs, body measurements and physical examinations**, no clinically meaningful changes have been observed in the blood pressure and weight measurements over the total duration of treatment. Regarding the outcome of physical examinations, the MAH reported that improvements in the 'musculoskeletal system' were apparent across treatment groups and trials (4307, 4255, 4311 and 4310), with clinically significant abnormalities in the musculoskeletal system from 20.5% at baseline to 14.7% at week 32 and 13.9% at week 56 in trial 4307, and from 29.3% at baseline to 25.0% at weeks 32 and 56 in trial 4311.

As in the initial MAA, no new relevant concerns have been observed in **special populations**. Subgroup analyses were performed for the intrinsic factors of age, race, ethnicity, hepatic, and renal function groups, and with and without thromboembolic risk factors.
Similar trends and no new relevant information have been revealed from data obtained after initial MAA on extrinsic factors, including use in pregnancy and lactation, overdose, drug abuse, withdrawal and rebound, effects on ability to drive and technical complaints. Data on these special populations are in general already sufficiently covered in the current SmPC.
Regarding **major surgeries**, for which no information was available in the initial MAA, a total of 10 major surgeries were performed in 2 patients who were on concizumab PPX in the phase 2 trial 4310, in 4 patients in phase 3 trial 4307 and in 4 patients in phase 3 trial 4311. Concizumab PPX was either discontinued before surgery (7 cases), discontinued from the day after surgery (1 case) or not discontinued at any time in relation to the surgery (2 cases of total knee replacement). Of note, in the SmPC it is recommended to pause concizumab at least 4 days prior to elective major surgery and to resume concizumab treatment 10-14 days after surgery. No thromboembolic events, or any other AEs of concern were reported in the peri-/postoperative period. However, in a patient in trial 4307 who underwent major surgery for intracranial haemorrhage, an intracranial haematoma drainage was performed acutely to save his life, but the patient died from the bleed. The last dose of concizumab was taken the day before the surgery, and NovoSeven (5 mg/kg) was given as haemostatic medication during the surgery. A protocol deviation for this case was registered. Further, in relation to a hand fracture surgery in trial 4310, 2 SAEs (Puncture site haemorrhage and Shock haemorrhagic) were reported due to postoperative blood sampling. However, concizumab PPX was discontinued the day after surgery which is not in line with the SmPC recommendations, concizumab was resumed 50 days of interruption. No further concerns have been identified in relation with major surgery.

Results from a recently completed in vitro **drug-drug interaction** study with concizumab and a sequence-identical analogue of emicizumab (emicizumab-SIA) have become available. Based on the results of study no. 323801, which investigated the combined effect of concizumab and emicizumab-SIA, alone or together with rFVIIa, aPCC or rFVIII, in thrombin generation assay in haemophilia A pooled plasma initiated with low amount of tissue factor (TF), it was shown that a drug interaction between concizumab and emicizumab-SIA was up to 33% extra effect. The presence of concizumab did not reinforce the known, strong positive drug interaction between emicizumab-SIA and aPCC, or the small negative drug interaction between emicizumab-SIA and rFVIII. Further, drug interaction with rFVIIa was present for concizumab both alone and when combined with emicizumab-SIA. Overall, no unexpected drug interactions with haemostatic agents used to treat breakthrough bleeds were observed when concizumab was added to plasma containing emicizumab-SIA. This information has been reflected in section 4.5 of 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 15.9% (n=51 patients) who temporary discontinued trial product due to AEs. 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 or pattern, which is reassuring.

New SAEs in **ongoing extensions of phase 3 studies 4307 and 4311** have been reported until the application cut-off date of 30-Sept-2024, in comparison to the 4 SAEs of carpal tunnel syndrome, renal impairment, haematuria and laryngeal haematoma treated with eptacog alfa, which resolved, in the initial MAA. All were agreed to be unlikely related to the use of concizumab, except for the SAEs (AESI) of Ischaemic stroke in a patient with HA and the SAE of PT Haematuria (study 4311), which were judged as possibly related to concizumab PPX. No new relevant information has been reported in the latest update from the paediatric data from ongoing paediatric trial 4616 (patients <12 years) and compassionate use (patients >18 years).

The MAH reported a total **post-marketing exposure** of 10 patient years (PYs) since marketing authorization in December 2024. Exposure is therefore considered still low.

2.5.2. Conclusions on clinical safety

Based on the currently available data in HA and HB patients ≥ 12 years of age, concizumab appears to be generally well tolerated with only 3.1% patients, who permanently discontinued trial product due to AEs and 15.9% patients, who temporary discontinued trial product due to AEs in the updated safety pool. Up until the 56-week cut-off, the most common treatment-related AEs in HA and HB patients in pivotal trial 4307 were injection site reactions, hypersensitivity, fibrin D dimer increased, and prothrombin fragment 1+2, which were of mild or moderate nature. These were comparable with findings in trial 4311 and in the total updated safety pool with generally similar outcomes across the haemophilia subtypes.

Based on assessment of the initial and the newly submitted OLE data in this patient population, no change in the already identified risks of thromboembolic or increased bleeding tendency, and ADAs could be revealed with the use of concizumab, and no specific risk was observed during new cases of major surgery in patients who had temporary interrupted treatment.

2.5.3. PSUR cycle

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.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The (main) proposed RMP changes were the following:

- Update RMP relevant sections for HA and HB
- Update data for clinical study NN7415-4307 (56-week data)
- Update data for compassionate use

No significant changes to the summary of safety concerns, pharmacovigilance plan and risk

minimisation measures have been proposed.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 2.1 is acceptable.

The CHMP endorsed the Risk Management Plan version 2.1 with the following content:

Safety concerns

Table 70: Safety concerns

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

Pharmacovigilance plan

Table 71: Pharmacovigilance plan

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.

Risk minimisation measures

Table 72: Pharmacovigilance and risk minimisation activities by safety concern

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

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

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly. Minor changes were also made to other sections of the PI.

2.7.1. User consultation

A justification for not performing a full user consultation with target patient groups on the package leaflet has been submitted by the MAH and has been found acceptable for the following reasons: The format, design, layout and writing style of the daughter PL and parent PL are identical. The daughter PL includes an update to the content compared to the parent PL and these updates are justified not to alter the key messages for safe use and thus the readability. As a result, the key messages for safe use have not changed and therefore it is considered that this update does not affect readability, providing sufficient justification for not performing a readability test to the daughter PL to support the addition of the new indications.

2.7.2. 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.

2.8. Therapeutic Context

2.8.1. Disease or condition

This application concerns the additional indications in patients with HA and HB without inhibitors, as follows:

- *severe haemophilia A (congenital factor VIII deficiency, FVIII <1%) without FVIII inhibitors and of 12 years of age or more.*
- *moderate/severe haemophilia B (congenital factor IX deficiency, FIX ≤2%) without FIX inhibitors and of 12 years of age or more.*

2.8.2. 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.

2.8.3. Main clinical studies

Concizumab recently (2024) received MA for the **indication of routine prophylaxis of bleeding in HAwI and HBwI patients of 12 years of age or more**. Main data to support this indication came from **study 4311 (explorer 7)** in HAwI and HBwI patients, supported by phase 3 **study 4307 (explorer 8)** of similar design in HA and HB patients, proof-of-concept dose-response study 4310, dose-response study 4255, as well as data from the compassionate use programme.

For the current application intended to extend the indication with **routine prophylaxis of bleeding in patients with severe HA (FVIII<1%) and moderate/severe HB (FIX≤2%), without inhibitors, and 12 years of age or more**, the main data came from the pivotal phase 3 study 4307 (explorer 8), which was already assessed in the initial MAA, supported by newly

submitted data from the ongoing open label extension up to 56-week data cut-off, and summarized results of study 4311 in patients with HAwI or HBwI.

As discussed in the initial MAA, the clinical program of concizumab was put on hold due to the occurrence of 5 thromboembolic events in 3 subjects (1 in study 4311, 2 in 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, 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 is advised in line with the WFH guidelines.

Study 4307 is a 4-armed, open-label, pivotal phase 3 trial of similar design as study 3411 in HA and HB patients, including a comparison of on-demand treatment with FVIII/FIX containing products (no PPX) with concizumab PPX in randomized arms 1 and 2. The main part of the study has a duration of 24-32 weeks, i.e. the confirmatory analysis cut-off (CACO), followed by an open-label, uncontrolled extension treatment period of 136 weeks, for which data have been provided at 56-week cut-off. In the randomized part (**arm 1 + 2**), patients in arm 1 (no PPX) continued on-demand treatment with their usual factor replacement therapy, and patients in arm 2 received concizumab PPX. In (non-randomised) **arm 3**, patients were enrolled who already completed trial 4255 prior to treatment pause. In (non-randomised) **arm 4**, patients who completed study 4255 after the treatment pause were enrolled as well as from the non-interventional study (NIS) study 4322, enabling a within-patient comparison with historical ABR previously obtained with factor-containing prophylaxis. In the CACO, 27 HA patients and 36 HB patients were randomized (1:2) to arm 1 on-demand treatment (n=9 for HA, n=12 for HB) or to arm 2 concizumab PPX (n=18 HA, n=24 HB) for a period of 24-32 weeks. In addition, a total of 52 patients (n=29 HA, n=22 HB) who had been on stable FVIII/FIX containing PPX for at least 24 weeks in non-interventional (NIS) study 4322, were allocated to arm 4 of study 4307. **Key inclusion criteria** were patients aged ≥12 years with a diagnosis of congenital severe HA (FVIII <1%) or moderate/severe HB (FIX ≤2%) with a documented treatment with coagulation factor containing product in the last 24 weeks. **Key exclusion criterium** was a history of (arterial or venous) thromboembolism (TE) or considered to be at increased risk for TE. The **primary efficacy endpoint** analysis consisted of demonstration of superiority of concizumab PPX over no PPX (on-demand treatment with FVII/FIX products) in reduction of the number of treated spontaneous and traumatic bleeding episodes expressed as annualised bleeding rate (ABR). 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).

Further, supportive phase 3 **study 4311**, a 4-armed, open-label study with an almost similar design was performed in HAwI and HBwI subjects ≥12 years of age. In the randomized part, 52 HAwI or HBwI subjects were randomized (1:2) to arm 1 on-demand treatment (n=9 HAwI, n=10 HBwI) or to arm 2 concizumab PPX (n=17 HAwI, n=12 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. **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. For feasibility, HAwI and HBwI patients were analysed together due to rarity of the condition.

2.9. Favourable effects

Regarding the primary analysis, superiority for the **primary efficacy endpoint** of study 4307 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 3.5 [2.18; 5.54] for **HA** patients on concizumab PPX versus 24.5 [14.50; 41.48] 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 estimated mean **ABR** was 3.2 [2.00; 5.22] and 15.4 [8.55; 27.78] for **HB** patients on concizumab PPX versus 14.8 (95% CI 8.14-26.86) for patients receiving on-demand treatment only; the estimated **ABR ratio** between patients on concizumab PPX and on-demand treatment was 0.21 (95% CI 0.10-0.45; p<0.001), corresponding to an 79% statistically significant reduction in ABR.

The **observed reduction in ABR** relative to on-demand treatment of 86% and 79%, respectively, is indicative of a clinically relevant improvement. The outcome of the **sensitivity and supplementary analyses** were all consistent with the primary endpoint.

Regarding the **secondary endpoint – intra-patient comparison**, non-inferiority of concizumab PPX (trial 4307) over previous PPX (study 4322) was not confirmed for both HA and HB patients: while the lower limit of the 95% CI was below 1, the upper limit was above the pre-defined non-inferiority margin of 2, see below:

- The estimated ABR was 3.7 (95%CI 2.51-5.42) for **HA** patients (n=29) on previous PPX (study 4322) and 5.1 (95% CI 2.71-9.65) for patients on concizumab PPX (study 4307); the estimated ABR ratio was 1.39 (95%CI 0.73-2.63).
- The estimated ABR was 3.1 (95%CI 2.07-4.62) for **HB** patients (n=22) on previous PPX (study 4322) and 5.4 (95% CI 2.27-12.91) for patients on concizumab PPX (study 4307). The estimated ABR ratio was 1.75 (95%CI 0.81-3.78).

In patients with HA, observed median ABR (treated spontaneous and traumatic bleedings) was 2.2 (0.0; 13.5) on previous routine prophylaxis compared to 2.3 (0.0; 46.7) on concizumab prophylaxis. In patients with HB, observed median ABR was 2.1 (0.0; 10.6) on previous routine prophylaxis compared to 1.4 (0.0; 50.6)) on concizumab prophylaxis.

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 33.3% (n=6/16) versus 0% (n=0/9) for HA, and 45.8% (n=10/24) versus 8.3% (n=1/12) for HB patients, further supporting the efficacy of concizumab in prevention of bleeding events. In the IPAS, the proportion of patients with zero treated spontaneous and traumatic bleeding episodes during the first 24 weeks after starting stable treatment was 37.9% on concizumab PPX (study 4307) and 34.5% on previous FVIII/FIX PPX (study 4322) for HA patients, and 45.5% on concizumab PPX (study 4307) and 31.8% on previous FVIII/FIX PPX (study 4322) for HB patients.

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.

In general, **explorative endpoints on QoL** suggested a more favourable outcome on concizumab as compared to on demand treatment or prophylaxis with FVIII/FIX products.

Descriptive efficacy at 56 weeks cut-off (newly submitted data) of trial 4307

At the 56-week cut-off, the descriptive results for all bleed related endpoints and assessments were consistent with descriptive results seen at the CACO, both for HA and HB patients. For the patients in arm 1, who switched from no PPX to concizumab PPX after completing 24 weeks in the main part, the median ABR on concizumab PPX (arm 1 at 56-week cut-off) was consistently lower than the median ABR on no PPX (arm 1 at the CACO).

For the 80 **HA** patients on concizumab PPX (arms 1−4), the overall median ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 1.7. For the 7 HA patients in arm 1 (who switched from no PPX to concizumab PPX treatment after at least 24 weeks), the median ABR at the 56-week cut-off was 2.6. At the CACO, the median ABR for the 9 HA patients on no PPX (arm 1) was 19.6.

For the 64 **HB** patients on concizumab PPX (arms 1−4), the overall median ABR for treated spontaneous and traumatic bleeding episodes at the 56-week cut-off was 2.8. For the 10 HB patients in arm 1 (who switched from no PPX to concizumab PPX treatment after at least 24 weeks), the median ABR at the 56-week cut-off was 3.3. At the CACO, the median ABR for the 12 HB patients on no PPX (arm 1) was 14.9.

These results are confirmative of **maintenance of treatment effect** of concizumab PPX on ABR during longer-term treatment up to 56 weeks.

At 56-weeks, **target-joints**, defined as three or more spontaneous bleeds into a single joint within a consecutive 6-month period, were evaluated for the first time to assess frequency of resolution. For patients on concizumab PPX (arms 1-4) reporting pre-existing target joints at baseline, the majority (~85% for both HA and HB) of these target joints were resolved.

For **study 4311**, the primary endpoint in HA and HB subjects, the results were in line with the above-mentioned results in study 4307. 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 reduction in ABR was maintained during **long-term treatment** up to 56-week cut-off. The primary efficacy outcome was of similar magnitude as noted in study 4307 in HA and HB patients, indicating that efficacy is independent of haemophilia subtype and the presence or absence of inhibitors.

2.10. Uncertainties and limitations about favourable effects

Non-inferiority could not be established in the intra-patient comparison against prior routine prophylaxis, as the upper limits of the 95% CIs were above the prespecified non-inferiority margin of 2 on the relative scale in both patient populations.

Sample size for the intra-patient comparison to routine prophylaxis was low (HA: n=29, HB: n=22).

2.11. Unfavourable effects

In general, the **exposure** to concizumab in haemophilia patients in the safety database is considered sufficient. With inclusion of the newly submitted OLE data of pivotal trial 4307, a total of 151 patients were exposed to concizumab, of which 87 and 64 were HA and HB patients respectively. Of these, 115 HA and HB patients had completed 56 weeks of concizumab treatment.

No changes regarding safety are needed in the current SmPC, as the new safety data up to week 56 cut-off have not revealed any new safety issues.

In pivotal study 4307, the percentage of HA and HB patients who reported adverse events (AEs) were in the same range as noted in study 4311, with 69%, up until CACO. The **most frequently reported AEs** (>5%) were COVID-19 (13%), fibrin D dimer increased (8%) and upper respiratory tract infection (7%). Up until the 56-week cut-off, 78.1% patients reported 528 AEs (2.7/PYE) with concizumab. 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 were in SOC general disorders/injection site disorders with injection site erythema/reaction (8%), and investigations with fibrin D dimer increased (6.6%) and prothrombin fragment 1.2 increased (5.3%). The most frequently reported AEs in patients with either haemophilia subtype were generally similar up until CACO.
In general, the AE pattern up to 56 weeks of treatment noted in the HA and HB patients in study 3407 appears to be comparable with that observed in HAwI and HBwI patients in study 3411.

Regarding the **serious AEs** (SAEs), up until CACO in study 4307, 22 SAEs (0.2/PYE) were reported in 14 (9.3%) patients exposed to concizumab, with a similar proportion of patients with SAEs and similar event rates across HA and HB. Six possibly or probably related SAEs in 4 patients were reported, including deep vein thrombosis, pulmonary embolism and superficial vein thrombosis [in one patient]; acute myocardial infarction and 2 events of Intra-abdominal haemorrhage in 2 patients (of which 1 had fatal outcome), which were severe. Apart from the fatal event, remaining events recovered or were recovering. In 3 patients, the SAE led to permanent discontinuation of concizumab.
In total, 8 SAEs were reported by 8 patients after the 56-week cut-off, which makes this in total 30 reported SAEs (0.2 events per PYE) in 20 (13.2%) patients exposed to concizumab, with a similar proportion of patients with SAEs and similar event rates across HA and HB. The SAEs were distributed across multiple SOCs and PTs, and mostly reported as isolated cases. No apparent clustering across SOCs and PTs was observed. No new SAEs were considered possibly or probably related by the investigator.
Results from study 4311 were comparable with above-mentioned SAE data in trial 4307.
Regarding compassionate use data in patients with HBwI, the new update, reported a total of 24 SAEs in 11 patients until data lock point of 28-Feb-2024. Most SAEs consisted of hemarthrosis, and haematoma. No new safety signals have been identified in this update.

An in-depth evaluation of the following **areas of medical focus/special interest** was performed:

- Based on the newly provided study information, no new safety signals have been reported on **hypersensitivity reactions,** and **injection site reactions**, which are already included as ADRs in the SmPC. Further, no new safety concerns have been identified regarding **medication errors, rare events**, **suspected transmission of an infectious agent, increased inflammatory response,** and **renal** or **hepatic events**.
- In the newly submitted data of study 4307 up to 56 week cut-off, no new **thromboembolic events** (TEs) were reported.

As assessed and discussed in the initial MAA, in total 11 TE events in 6 of 320 (1.9%) patients were reported in the safety pool. All these cases occurred before the treatment pause. In 6 TE events a causal relationship with the use of concizumab was considered unlikely. A total of 5 non-fatal serious TEs (including the event of renal infarct) in 3 patients in the two phase 3 clinical trials (4311 and 4307), have led to the concizumab treatment pause. After the treatment pause, risk mitigation measures have been implemented and trial protocols had been updated. The MAH revised the concizumab dose regimen, and implemented more restrictive dosing with regard to the use of breakthrough bleed treatment, i.e. the revised phase 3 protocols are in line with the lower end of the WFH dosing recommendations. Further, training of investigators and patients had been implemented. TE was included as an ADR and the current SmPC contains extensive warnings in section 4.4 with regard to this risk of TE.
In the period after the 56-week cut-off and up to application cut-off, 2 serious TEs were reported in the ongoing OLE of trial 4307 (2 HA patients). The reporting of two new cases of TE in patients does not render a further update of the currently included warnings present in the current SmPC.

- In the multiple-dose trials, 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 haemophilia subtypes. It is noted that the mean (SD) change from baseline to week 56 for concizumab PPX was -0.43 (0.91) g/L for HA patients and -0.18 (0.90) g/L for HB patients is less than observed from baseline to week 24 for concizumab PPX arms 2−4 (-0.47 (0.89) g/L for HA patients and -0.30 (0.94) g/L for HB patients). The initial conclusion that from these data a causal relationship of **increased bleeding tendency** with the use of concizumab could not be observed, is considered maintained.

No new relevant changes have been observed with the newly provided data in the **clinical laboratory haematology and biochemistry parameters or vital signs**. Also, no relevant differences have been observed within the trials on **immunology events** in comparison with the initial MAA.

As in the initial MAA, no new relevant concerns have been observed in **special populations**, i.e. related to age, race, ethnicity, hepatic, and renal function groups, and with and without baseline thromboembolic risk factors.
Regarding **major surgeries**, no information was available in the initial MAA, but in the new data a total of 10 major surgeries were reported which were performed in 2 patients using concizumab in the phase 2 trial 4310, in 4 patients in phase 3 trial 4307 and in 4 patients in phase 3 trial 4311. Concizumab was either discontinued before surgery (7 cases), discontinued from the day after surgery (1 case) or not discontinued at any time in relation to the surgery (2 cases of total knee replacement). No thromboembolic events, or any other AEs of concern were reported in the peri-/postoperative period. In conclusion, no significant concerns have been identified in relation to major surgery.

The incidence of AEs leading to discontinuations in the total safety pool remained overall low with a total of 3.1% of patients who permanently discontinued trial product due to AEs, and 15.9% who temporary discontinued trial product due to AEs. No pattern with respect to type of AE leading to discontinuation of study drug could be observed.

2.12. Uncertainties and limitations about unfavourable effects

Extremely limited data are available in subjects ≥65 years of age, and only limited data are available in patients with renal and hepatic impairment as stated in Section 4.2 of the SmPC

2.13. Effects Table

Table 73: Effects Table for concizumab in routine prophylaxis of bleeding in patients with HA (congenital FVIII deficiency) and HB (congenital FIX deficiency) without inhibitors aged 12 years or more (data cut-off: 30 September 2024)

Effect	Short Description	Unit	Concizumab PPX	On-demand treatment	Uncertainties/ Strength of evidence	Ref
Favourable Effects						
All treated spontaneous and traumatic bleeding episodes Baseline to week 32	Estimated ABR in **HA** without inhibitors (n=18 concizumab PPX, n=9 on-demand)	Mean (95% CI)	3.5 [2.18; 5.54]	24.5 [14.50; 41.48]	**Primary endpoint (study 4307)** **SoE:** • Consistent with results in patients with inhibitors (study 4311) • Consistent in 4 sensitivity and in 2 supplementary analyses • Consistent for all types of bleeding episodes • Maintenance of effect over >56 weeks (based on descriptive analysis)	[8]
		Mean estimated ABR ratio (95%CI, p-value)	0.14 (0.0- 0.29; p<0.001)			
	Estimated ABR in **HB** without inhibitors (n=24 for concizumab PPX, n=12 on demand)	Mean (95%CI)	3.1 (1.91-5.04)	14.8 (8.14-26.86)		
		Mean ABR ratio (95%CI, p-value)	0.21 (0.10- 0.45; p<0.001)			
All treated spontaneous and traumatic bleeding episodes 24 week prior to baseline-week 24	ABR vs. historical ABRs	Within-patient comparison	Concizumab PPX	PPX with Factor VIII/IX product	**Key secondary endpoint** **SoE:** • Within-patient comparison with PPX with FVIII/FIX products **Unc:** • Non-inferiority margin of 2 not met. Non-inferiority not demonstrated. • Small sample size with a total of 29 patients with HA and 22 patients with HB enrolled. Planned sample size not met, wide variation and skewed distribution	[8]
	Estimated ABR in **HA** without inhibitors	Mean (95% CI)	5.1 (2.71, 9.65)	3.7 (2.51, 5.42)		
		Mean estimated ABR ratio (95% CI, p-value)	1.39 (0.73, 2.63)			
	Estimated ABR in **HB** without inhibitors	Mean (95% CI)	5.4 (2.27; 12.91)	3.1 (2.07, 4.62)		
		Mean estimated ABR ratio (95% CI, p-value)	1.75 (0.81, 3.78)			
All treated spontaneous and traumatic bleeding episodes Baseline to week 32	Estimated ABR in **HAwI and HbwI c**ombined	Mean (95% CI)	1.7 (1.01, 2.87)	11.8 (7.03, 19.86)	**Primary endpoint (study 4311)** **SoE:** • Consistent with study 4307 • 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	[7]
		ABR ratio Mean (95%CI, p-value)	0.14 (0.07, 0.29, p<0.001)			
Unfavourable Effects						
Thromboembolic events (TEs):	Thromboembolic events (TEs): frequency of TE AEs after treatment pause	N (%)	0 (0%)	-	**Key safety concern** **SoE:** • Consistent with study 4311 • Lower as compared to TE cases before treatment pause (6/320 (1.9%)) **Unc:** • Low numbers • Maintenance of risk as >56 weeks, as 2 new cases reported.	[8]
ADAs	Anti-concizumab antibodies (ADAs): frequency of AEs	N of N (%)	18 of 320 (5.8%)	-	**Unc:** • Low numbers • Decrease in incidence over time is noted in in period >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

2.14. Benefit-risk assessment and discussion

2.14.1. Importance of favourable and unfavourable effects

The pivotal evidence for efficacy is based on the randomised part (CACO) of pivotal phase 3 study 4307 of 24/32 weeks and supported by newly submitted OLE data of this study for up to 56 weeks to evaluate durability of efficacy. The pivotal study included male patients aged ≥12 years, with congenital severe HA (FVIII <1%) and moderate/severe HB (FIX ≤2%) without inhibitors. This study is of similar design as study 4311 in patients with HAwI and HBwI, and both studies were already considered well conducted in the initial MAA.

Study 4307 showed a considerable statistically significant, and clinically meaningful reduction in annual bleeding rate (ABR) of 86% and 79%, respectively, in HA and HB patients from baseline to week 24/32 with concizumab PPX compared to on demand treatment of bleeding with factor replacement treatment. Treatment with concizumab PPX resulted also in a higher proportion of patients with zero bleeds compared to on demand treatment. Outcomes of other bleed-related endpoints were supportive of the primary endpoint. The effect sustained over 56 weeks.

Although non-inferiority for the in-patient comparison of ABR on concizumab PPX versus ABR on previous FVIII/FIX PPX was not confirmed, results were impacted by three patients (2 HA, 1 HB) with substantially increased ABR values during concizumab prophylaxis and the estimated point estimates of the ABR ratios were not suggestive of a large difference in effect on ABR noted in the primary analysis. In line with the observed reductions in ABR, additional beneficial effects were seen in PROs, including the SF-36v2 health survey and the haemophilia-specific Haem-A-QoL, and the Hemo-TEM, as compared to no PPX.

The results are consistent with results noted in study 4311 in subjects with HAwI or HbwI, in whom a reduction in annual bleeding rate (ABR) of 86% from baseline to week 24/32 with concizumab PPX compared to on demand treatment was demonstrated. Taken together, the data obtained in study 4307 and 4311 are considered robust evidence that the effect of concizumab PPX on ABR is similar across haemophilia subtype and presence or absence of inhibitors.

Notably, although based on an indirect comparison, the reduction in ABR achieved with concizumab PPX appears comparable to the reduction in ABR achieved in HA and HB patients treated with marstacimab (Hympavzi), another anti-TFPI antibody recently approved by centralised procedure.

The clinical safety database is in general adequate, and the exposure up to one year in 115 HA and HB patients in study 4307 is sufficient. The patients were dosed according to the dose regimen of concizumab in the current SmPC. The update of the presented clinical data with open label extension data up to 56 weeks of study 3407 do not raise particular safety concerns. Concizumab remains well-tolerated in HA and HB patients with a safety pattern comparable with that noted for patients with HAwI and HBwI, with hypersensitivity, injection site reactions, thromboembolism, and fibrin D dimer and prothrombin fragment 1.2 increased, which is inherently due to the MoA of concizumab, being the most common adverse events (AEs). The majority of the AEs were mild to moderate in severity, without relevant differences between the haemophilia subtypes, and the discontinuations due to drug-related AEs are low (3.1%). Based on assessment of the initial and the newly submitted OLE data in this patient population, no change in the already identified risk of thromboembolic events or bleeding tendency, and ADAs could be revealed with the use of concizumab, and no specific risk was observed during new cases of major surgery in patients who had temporary interrupted treatment.

2.14.2. Balance of benefits and risks

In terms of benefit, concizumab PPX provides a significant and clinically meaningful benefit over no PPX (on demand treatment) in reduction of spontaneous and traumatic bleeding episodes in patients aged of 12 years of age or more with congenital severe HA (FVIII <1%) and moderate/severe HB (FIX ≤2%) without inhibitors, as measured by reductions in ABR during a treatment period of at least 24 weeks. Although non-inferiority of concizumab PPX as compared with previous FVIII/FIX PPX in the same patient was not established, no substantial difference in ABR between both prophylactic treatments is observed. The reduction in frequency of bleeding episodes was accompanied by trends for improvement in PROs on health-related and haemophilia-specific QoL. Of note, while based on indirect comparison, the magnitude of the ABR reduction noted with concizumab PPX is suggested in the same range as observed for marstacimab, another anti-tissue factor pathway inhibitor (anti-TFPI) antibody. The use of concizumab appeared to be well tolerated with an acceptable safety profile, especially on thromboembolic events, and without major safety signals in HA and HB patients.

2.14.3. Additional considerations on the benefit-risk balance

None.

2.15. Conclusions

The overall B/R of Alhemo is considered positive for this extension of indication to include treatment of haemophilia A without inhibitors and haemophilia B without inhibitors.

3. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a Addition of a new therapeutic indication or modification of an approved one	Variation type II	I and IIIB

Extension of indication to include treatment of haemophilia A without inhibitors and haemophilia B without inhibitors for Alhemo based on final results from study NN7415-4307; this is an interventional study to investigate efficacy and safety of concizumab prophylaxis in patients with haemophilia A or B without inhibitors; as a consequence, sections 4.1, 4.2, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package Leaflet is updated in accordance. Version 2.1 of the RMP has also been submitted. In addition, the MAH took the opportunity to introduce minor changes to the PI.

The variation leads to amendments to the annexes I and IIIB and to the Risk Management Plan (RMP).

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I and IIIB and to the Risk Management Plan are recommended.

Conditions or restrictions with regards to the safe and effective use of the medicinal product

- **Risk management plan (RMP)**

The 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.

In addition, 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:
    - Physicians should discuss with the patient and/or the caregiver about the dose and schedule of bypassing agents, if required while receiving concizumab prophylaxis.
    - Caution should be exercised when the patient is at high risk of developing thromboembolic events.
    - Patients should be informed of and monitored for the occurrence of signs and symptoms of thromboembolic events.
    - 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.

Paediatric data

Furthermore, the CHMP reviewed the available paediatric data of studies subject to the agreed Paediatric Investigation Plan PIP P/0358/2023 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Alhemo is not similar to Alprolix, Idelvion, Hemgenix, Roctavian, Altuvoct within the meaning of Article 3 of Commission Regulation (EC) No. 847/200.

4. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the "EPAR-Procedural steps taken and scientific information after authorisation" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Alhemo-H-C-5938-VR/0000244862'

Reminders to the MAH

1. In accordance with Article 13(3) of Regulation (EC) No 726/2004 the Agency makes available a European Public Assessment Report (EPAR) on the medicinal product assessed by the Committee for Medicinal Products for Human Use. The EPAR is first published after the granting of the initial marketing authorisation (MA) and is continuously updated during the lifecycle of the medicinal product. In particular, following a major change to the MA, the Agency further publishes the assessment report of the CHMP and the reasons for its opinion in favour of granting the change to the authorisation, after deletion of any information of a commercially confidential nature.

   Should you consider that the CHMP assessment report contains commercially confidential information, **please provide the EMA Procedure Assistant your proposal for deletion of commercially confidential information** (CCI) in "track changes" and with detailed justification by **7th August 2025**. The principles to be applied for the deletion of CCI are published on the EMA website at https://www.ema.europa.eu/en/documents/other/heads-medicines-agencies/european-medicines-agency-guidance-document-identification-commercially-confidential-information_en.pdf

   In addition, should you consider that the CHMP assessment report contains personal data, please provide the EMA Procedure Assistant your proposal for deletion of these data in "track changes" and with detailed justification by **7th August 2025**. We would like to remind you that, according to Article 4(1) of Regulation (EU) 2016/679 (General Data Protection Regulation, "GDPR") 'personal data' means any information, relating to an identified or identifiable natural person (the 'data subject'). An identifiable natural person is one who can be identified, directly or indirectly, in particular by reference to an identifier such as a name, an identification number, location data, an online identifier or to one or more factors specific to the physical, physiological, genetic, mental, economic, cultural or social identity of that natural person.

   It is important to clarify that pseudonymised data are also considered personal data. According to Article 4(5) of GDPR pseudonymisation means that personal data is processed in a manner that the personal data can no longer be attributed to a specific data subject without the use of additional information (e.g. key-coded data).

   Accordingly, the name and the patient identification number are two examples of personal data which may relate to an identified or identifiable natural person. The definitions also encompass for instance: office e-mail address or phone number of a company, data concerning health, e.g. information in medical records, clinical reports or case narratives which relates to an identifiable individual."

2. The MAH is reminded to submit an eCTD closing sequence with the final documents provided by Eudralink during the procedure (including final PI translations, if applicable) **within 15 days** after the Commission Decision, if there will be one within 2 months from adoption of the CHMP Opinion, or prior to the next regulatory activity, whichever is first. If the Commission Decision will be adopted within 12 months from CHMP Opinion, the closing sequence should be submitted within 30 days after the Opinion. For additional guidance see chapter 4.1 of the Harmonised Technical Guidance for eCTD Submissions in the EU.

3. If a revised RMP is being approved as part of this procedure, **please send to the EMA Procedure Assistant** one redacted PDF document containing the RMP body, Annex 4 and

Annex 6, as applicable, together with a redacted RMP file that can show the content that is proposed for redaction, and the signed RMP Publication Declaration, **by 7th August 2025**.