**Report on the Deliberation Results**

August 9, 2023
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

| | |
|---|---|
| **Brand Name** | Alhemo Subcutaneous Injection 15 mg, Alhemo Subcutaneous Injection 60 mg<br>Alhemo Subcutaneous Injection 150 mg, Alhemo Subcutaneous Injection 300 mg |
| **Non-proprietary Name** | Concizumab (Genetical Recombination) (JAN*) |
| **Applicant** | Novo Nordisk Pharma Ltd. |
| **Date of Application** | August 29, 2022 |

**Results of Deliberation**

In its meeting held on July 31, 2023, the Second Committee on New Drugs concluded that the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is classified as a biological product. The re-examination period is 10 years. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of very limited number of Japanese patients treated with the product, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of cases are obtained so as to understand the characteristics of patients treated with the product, promptly collect safety and efficacy data of the product , and take necessary measures to ensure proper use of the product.

**Japanese Accepted Name (modified INN)*

**Review Report**

July 6, 2023
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

| | |
|---|---|
| **Brand Name** | Alhemo Subcutaneous Injection 15 mg, Alhemo Subcutaneous Injection 60 mg<br>Alhemo Subcutaneous Injection 150 mg, Alhemo Subcutaneous Injection 300 mg |
| **Non-proprietary Name** | Concizumab (Genetical Recombination) |
| **Applicant** | Novo Nordisk Pharma Ltd. |
| **Date of Application** | August 29, 2022 |
| **Dosage Form/Strength** | Solution for injection: One cartridge (1.5 or 3 mL) contains 15, 60, 150, or 300 mg of Concizumab (Genetical Recombination). |
| **Application Classification** | Prescription drug, (1) Drug with a new active ingredient |

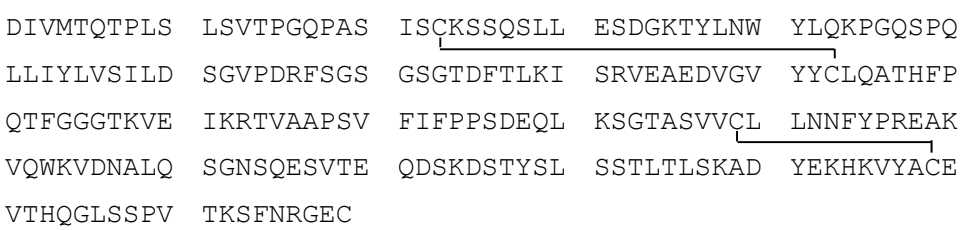
**Definition**

Concizumab is a recombinant humanized monoclonal antibody composed of complementarity-determining regions derived from mouse anti-human tissue factor pathway inhibitor (TFPI) monoclonal antibody, human framework regions and human IgG4 constant regions, whose amino acid residue at position 229 in the H-chain is substituted by Pro. Concizumab is produced in Chinese hamster ovary cells. Concizumab is a glycoprotein (molecular weight: ca. 149,000) composed of 2 H-chains (γ4-chains) consisting of 448 amino acid residues each and 2 L-chains (κ-chains) consisting of 219 amino acid residues each.

**Structure**

Amino acid sequence and disulfide bonds:

L-chain



H-chain

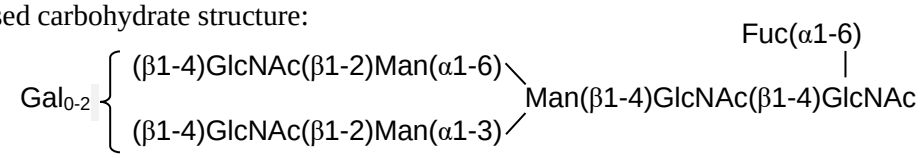
EVQLVESGGG LVKPGGSLRL SCAASGFTFS NYAMSWVRQT PEKRLEWVAT
ISRSGSYSYF PDSVQGRFTI SRDNAKNSLY LQMNSLRAED TAVYYCARLG
GYDEGDAMDS WGQGTTVTVS SASTKGPSVF PLAPCSRSTS ESTAALGCLV
KDYFPEPVTV SWNSGALTSG VHTFPAVLQS SGLYSLSSVV TVPSSSLGTK
TYTCNVDHKP SNTKVDKRVE SKYGPPCPPC PAPEFLGGPS VFLFPPKPKD
TLMISRTPEV TCVVVDVSQE DPEVQFNWYV DGVEVHNAKT KPREEQFNST
YRVVSVLTVL HQDWLNGKEY KCKVSNKGLP SSIEKTISKA KGQPREPQVY
TLPPSQEEMT KNQVSLTCLV KGFYPSDIAV EWESNGQPEN NYKTTPPVLD
SDGSFFLYSR LTVDKSRWQE GNVFSCSVMH EALHNHYTQK SLSLSLGK

H-chain N298: Glycosylation

H-chain K448: Partial processing

L-chain C219–H-chain C135, H-chain C227–H-chain C227, H-chain C230–H-chain C230: Disulfide bonds

Main proposed carbohydrate structure:




Molecular formula: $C_{6462}H_{10004}N_{1712}O_{2046}S_{46}$ (protein moiety, 4 chains)

H-chain $C_{2178}H_{3360}N_{580}O_{682}S_{17}$

L-chain $C_{1053}H_{1646}N_{276}O_{341}S_{6}$

Molecular weight: ca. 149,000

**Items Warranting Special Mention**

Orphan drug (Orphan Drug Designation No. 502 of 2021 [*R3 yaku*]; PSEHB/PED Notification No. 0219-1 dated February 19, 2021, by the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare)

**Reviewing Office** Office of Vaccines and Blood Products

**Results of Review**

On the basis of the data submitted, PMDA has concluded that the product has efficacy in controlling bleeding tendency in patients with congenital hemophilia who have coagulation factor VIII or IX inhibitors, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions.

**Indication**

Control of bleeding tendency in patients with congenital hemophilia with coagulation factor VIII or IX inhibitors

**Dosage and Administration**

The usual dosage of subcutaneous Concizumab (Genetical Recombination) for patients aged ≥12 years is the 1-mg/kg loading dose administered on Day 1, followed by a maintenance dose of 0.20 mg/kg once daily starting on Day 2.

The maintenance dose, after starting at 0.20 mg/kg, may be decreased to 0.15 mg/kg or increased to 0.25 mg/kg based on the blood concentration of concizumab or the patient's condition.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of very limited number of Japanese patients treated with the product, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of cases are obtained so as to understand characteristics of patients treated with the product, promptly collect safety and efficacy data of the product, and take necessary measures to ensure proper use of the product.

**Attachment**

# Review Report (1)

May 8, 2023

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Alhemo Subcutaneous Injection 15 mg, Alhemo Subcutaneous Injection 60 mg<br>Alhemo Subcutaneous Injection 150 mg, Alhemo Subcutaneous Injection 300 mg |
| **Non-proprietary Name** | Concizumab (Genetical Recombination) |
| **Applicant** | Novo Nordisk Pharma Ltd. |
| **Date of Application** | August 29, 2022 |
| **Dosage Form/Strength** | Solution for injection: One cartridge (1.5 or 3 mL) contains 15, 60, 150, or 300 mg of Concizumab (Genetical Recombination). |

**Proposed Indication**

Control of bleeding tendency in patients with congenital hemophilia with coagulation factor VIII or IX inhibitors

**Proposed Dosage and Administration**

The usual dosage of subcutaneous Concizumab (Genetical Recombination) for patients aged ≥12 years is the 1-mg/kg loading dose administered on Day 1, followed by a maintenance dose of 0.20 mg/kg once daily starting on Day 2.

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**List of Abbreviations**

See Appendix.

## 1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

Hemophilia (congenital coagulation factor VIII deficiency [hemophilia A] and congenital coagulation factor IX deficiency [hemophilia B]) is a bleeding disorder caused by deficiency or dysfunction of coagulation factor VIII (FVIII) or coagulation factor IX (FIX), and is a potential risk of serious bleeding symptoms.

The standard hemostatic treatment for hemophilia is FVIII or FIX replacement therapy. Some patients, however, develop inhibitors to FVIII or FIX, which markedly reduce the hemostatic effects of FVIII or FIX products and thus may make hemostasis difficult. Bypassing agents activate a coagulation cascade independently of FVIII and FIX and achieve hemostasis, which are used for symptomatic treatment of bleeding in patients with hemophilia with inhibitors. Currently, rFVIIa, FVIIa/FX, and activated prothrombin complex concentrate (aPCC) products have been approved. Prophylactic factor replacement therapy i.e., regular injections of the deficient factor over a long period of time, is used in patients with severe hemophilia to decrease the frequency of bleeding (control of bleeding tendency), etc. FVIIa/FX and aPCC products and emicizumab are the approved as medicines for routine prophylaxis in patients with hemophilia with inhibitors.

Concizumab (Genetical Recombination) (concizumab) is a recombinant humanized monoclonal antibody, which binds to tissue factor pathway inhibitor (TFPI). TFPI binds to FXa and TF/FVIIa complex inhibiting the extrinsic coagulation pathway. Concizumab binds to TFPI and reduces its inhibitory activity against FXa, which promotes the formation of FXa to increase thrombin production leading to hemostasis. This action mechanism will be effective regardless of hemophilia type (FVIII or FIX deficiency) or the presence of inhibitors to FVIII or FIX. Thus, concizumab has been developed as a medicine for routine prophylaxis in all hemophilia A and B patients with or without inhibitors.

Based on the results from a global phase III trial in patients with hemophilia with inhibitors (Trial NN7415-4311) etc., the applicant has recently filed a marketing application for concizumab. As of April 2023, concizumab has been approved in Canada, and applications are under review in the US and EU.

## 2. Quality and Outline of the Review Conducted by PMDA

### 2.1 Drug substance

#### 2.1.1 Generation and control of cell substrate

Concizumab is a humanized, full-length immunoglobulin G4 (IgG4) monoclonal antibody targeting the Kunitz-2 domain (K2) of human TFPI.

Complementarity-determining regions (CDRs) cloned from mouse hybridoma cells producing mouse anti-human TFPI monoclonal antibodies were grafted onto the framework regions of human heavy and light chain variable domains and fused with the constant domains of human IgG4 heavy chain and human κ light chain. Amino acid substitutions were introduced in the heavy chain variable and constant domains, and DNA segments were prepared. The DNA segments were cloned into expression vectors to generate the concizumab expression constructs. The expression constructs were transfected into Chinese hamster ovary (CHO) cells,

and a cell clone expressing high levels of concizumab was isolated. This cell clone was used to prepare a master cell bank (MCB) and a working cell bank (WCB).

The MCB, WCB, and cells at the limit of *in vitro* cell age used for production (CAL) were characterized and subjected to purity tests in accordance with the ICH Q5A (R1), Q5B, and Q5D guidelines. The test results demonstrated genetic stability during production, and no viral or non-viral adventitious agents were detected other than endogenous retrovirus-like particles, which are known to be present in rodent cell lines, in any of the tests conducted.

The MCB and WCB are stored in the vapor phase of liquid nitrogen. There is no plan for generating a new MCB, but a new WCB will be generated as needed.

### 2.1.2 Manufacturing process

The manufacturing process for the drug substance consists of inoculation and cell propagation, cell culture (bioreactor production), harvest clarification, [redacted] chromatography, [redacted] viral inactivation, [redacted] chromatography, filtration for virus removal, [redacted] chromatography, concentration and [redacted], filling, testing, and storage.

[redacted] viral inactivation and filtration for virus removal are critical steps.

Process validation of the commercial-scale drug substance manufacturing process was performed.

### 2.1.3 Safety evaluation of adventitious agents

Except for the host CHO cells, no raw materials of biological origin etc. are used in the drug substance manufacturing process.

The MCB, WCB, and CAL were subjected to purity tests [see Section 2.1.1]. Pre-harvest unprocessed bulk at commercial scale was subjected to transmission electron microscopy, test for bioburden, *in vitro* test for adventitious viruses, and test for mycoplasma. None of the tests revealed contamination with viral or nonviral adventitious agents other than endogenous retrovirus-like particles, which are known to be present in CHO cells. These tests excluding transmission electron microscopy for pre-harvest unprocessed bulk are included as in-process controls.

Viral clearance studies of the purification process were performed with model viruses. The results demonstrated a certain robustness of the purification process (Table 1). For calculation of virus reduction factors of the process steps, the lowest virus reduction factor value from multiple independent determinations (including the results obtained with end of lifetime resin for the chromatography steps) for each of the process steps was adopted.

**Table 1. Results of viral clearance studies**

| Process step | Virus reduction factor ($log_{10}$) | | |
|---|---|---|---|
| | Ecotropic murine leukemia virus | Minute virus of mice | Infectious bovine rhinotracheitis virus |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] |
| [redacted] viral inactivation | [redacted] | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] |
| Filtration for virus removal | [redacted] a) | [redacted] | [redacted] |
| [redacted] chromatography | [redacted] | [redacted] | [redacted] |
| Overall reduction factor | >15.2 (>20.4) b) | 12.6 | >22.5 |

a) Only 1 viral clearance study of this process step was performed with ecotropic murine leukemia virus.
b) Given a), the overall reduction factor was calculated by summing virus reduction factors from the individual process steps (Only process steps evaluated by ≥2 viral clearance studies were included in the calculation). The overall reduction factor calculated by summing the individual factors including that of the filtration for virus removal step that was evaluated by only 1 viral clearance study, is given in parenthesis as a reference value.

### 2.1.4 Manufacturing process development

The following are major changes made to the drug substance manufacturing process during development (Process A, Process B, Process C, the proposed commercial process).

- Process A→Process B: cell culture expansion, change of the drug substance container
- Process B→Process C: change of the cell bank (establishment of the WCB), manufacturing facility change, cell culture expansion
- Process C→the proposed commercial process: change of the drug substance container

The drug products produced from the drug substances manufactured by Process A or B were used in non-clinical studies. The drug product produced from the drug substance manufactured by Process B was used in phase I and II trials. The drug product produced from the drug substance manufactured by Process C was used in phase III trials. For these process changes, comparability of quality attributes between pre-change and post-change drug substances has been demonstrated.

### 2.1.5 Characterization

#### 2.1.5.1 Structure and properties

Characterization was performed as shown in Table 2.

**Table 2. Characterization attributes**

| | |
|---|---|
| Primary/high order structure | amino acid sequence, disulfide bonds, secondary structure, tertiary structure |
| Carbohydrate structure | N-glycan profile, glycosylation site |
| Physicochemical properties | molecular weight, absorbance, solubility, charge heterogeneity, hydrodynamic radius, thermal stability, colloidal stability |
| Biological properties | [redacted], specific activity |

#### 2.1.5.2 Product-related substances/Product-related impurities

Based on the results of characterization etc. in Section 2.1.5.1, high molecular weight protein (HMWP), truncated forms, Impurity A, Impurity B, and Impurity C were identified as product-related impurities. The product-related impurities are controlled by the drug substance and drug product specifications. No product-related substances have been identified.

### 2.1.5.3 Process-related impurities

Impurity D, Impurity E, Impurity F, Impurity G, Impurity H, Impurity I, host cell DNA, host cell protein (HCP), Impurity J, Impurity K, Impurity L, and Impurity M were identified as process-related impurities. HCP and Impurity J are controlled by the drug substance specification. Other process-related impurities were demonstrated to be adequately removed by the manufacturing process.

## 2.1.6 Control of drug substance

The proposed specifications for the drug substance consist of content, description, identity ([redacted], [redacted]), pH, purity (purity and total fragments, HMWP, HCP, residual Impurity J, carbohydrate map, Impurity A, [redacted]), bacterial endotoxins, microbial limits, specific activity, and assay.

## 2.1.7 Stability of drug substance

The primary stability studies on the drug substance are shown in Table 3.

**Table 3. Overview of primary stability studies on drug substance**

| Study | Number of batches | Manufacturing process | Storage conditions | Testing period | Storage package |
|---|---|---|---|---|---|
| Long-term[a)] | 3 | Proposed commercial process | −80 ± 10°C | 36 months | PET container with high density polyethylene screw-cap |
| Accelerated | 1 | Proposed commercial process | 5 ± 3°C | 6 months | |
| | 5 | Process C | | 6 months | PETG container with high density polyethylene screw-cap |
| | 1 | Process C | 25 ± 2°C | 1 month | |
| Stress (light) | 1 | Process C | An overall illumination of not less than 1.2 million lx·hr and an integrated near ultraviolet energy of not less than 200 W·h/m$^2$ | | Glass vial with chlorobutyl rubber stopper |

a) ongoing through [redacted] months.

Under the long-term condition, all batches met the proposed specifications, and no significant changes in quality attributes occurred throughout the testing period.

Under the accelerated conditions (5°C and 25°C), [redacted] tended to increase, and [redacted] tended to decrease. The results of stress testing (light) indicated that the drug substance is photosensitive.

Based on the above, a shelf life of 36 months has been proposed for the drug substance when stored in a polyethylene terephthalate (PET) container, protected from light, at −80 ± 10°C.

## 2.2 Drug product

### 2.2.1 Description and composition of drug product and formulation development

The drug product is a combination product, which consists of a cartridge containing a drug solution sealed in a dedicated pen-injector. With regard to the drug product volume and concentration, a total of 3 concentrations and 4 presentations are available: concizumab 15 mg (10 mg/mL), 60 mg (40 mg/mL), or 150 mg (100 mg/mL)/1.5 mL glass cartridge and concizumab 300 mg (100 mg/mL)/3 mL glass cartridge. The drug product contains the following excipients: L-histidine, L-arginine HCl, sodium chloride, sucrose, polysorbate 80, phenol, hydrochloric acid, sodium hydroxide, and water for injection.

### 2.2.2 Manufacturing process

The manufacturing process for the drug product consists of formulation, sterile filtration, filling, assembly, packaging, labeling, storage, inspection, and testing. Formulation, sterile filtration, and filling have been defined as critical steps.

Process validation of the commercial-scale drug product manufacturing process has been performed.

### 2.2.3 Manufacturing process development

The following are major changes made to the drug product manufacturing process during development (Process 1, Process 2, Process 3, the proposed commercial process).

- Process 1→Process 2: formulation, device specification (single-use pen→multi-dose pen)
- Process 2→Process 3: formulation, manufacturing facility, additional strength (60 mg), size of primary package
- Process 3→the proposed commercial process: manufacturing facility, additional strengths (15 mg and 300 mg), additional size of primary package

The drug product produced by Process 1 was used in non-clinical studies and phase I trials. The drug product produced by Process 2 was used in phase II trials. The drug product produced by Process 3 was used in phase III trials. For these process changes, comparability of quality attributes between pre-change and post-change drug products has been demonstrated.

### 2.2.4 Control of drug product

The proposed specifications for the drug product consist of strength, description, identity ([redacted]), osmolarity, specific activity, pH, purity (purity and total fragments, HMWP, Impurity A, [redacted]), bacterial endotoxins, extractable volume, foreign insoluble matter, insoluble particulate matter, sterility, dose accuracy, identity and content of phenol, and assay.

### 2.2.5 Stability of drug product

The primary stability studies on the drug product are shown in Table 4. In stability studies, 3 batches each of the 60- and 150-mg strengths of the drug product produced by the same pre-change process as that of the batches for phase III trials (Process C for the drug substance, Process 3 for the drug product), 3 batches of the 15-mg strength of the drug product and 2 batches of the 300-mg strength of the drug product produced by the proposed commercial process from the drug substance manufactured by Process C, and 1 batch of the 300-mg strength of the drug product produced by the proposed commercial process from the drug substance manufactured by the proposed commercial process were used.

**Table 4. Overview of primary stability studies on drug product**

| Study | Number of batches | Storage conditions | Testing period | Storage package |
|---|---|---|---|---|
| Long-term[a)] | 3 each | 5 ± 3℃ | 24 months[b)] | Glass cartridge with chlorobutyl rubber plunger |
| Accelerated | 3 each | 30 ± 2℃ | 6 months | |
| Photostability[c)] | 1 each | An overall illumination of not less than 1.2 million lx·hr and an integrated near ultraviolet energy of not less than 200 W·h/$m^2$, 5 ± 3℃ | | |

a) ongoing through [redacted] months for all batches
b) One batch of the 300-mg strength of the drug product was tested through 18 months.
c) Evaluated by tests on the drug product in a cartridge, a cartridge sealed in a dedicated pen-injector, and a cartridge wrapped in aluminum foil.

Under the long-term condition, the samples met the proposed drug product specifications for all tests. [redacted], [redacted], [redacted], and [redacted] tended to increase, and [redacted] and [redacted] tended to decrease.

Under the accelerated condition, increases in [redacted], [redacted], and [redacted] and decreases in [redacted], [redacted], and [redacted] were observed. [redacted] tended to increase in the early stage of storage and decreased at 6 months of storage.

In the photostability testing, the samples were photosensitive when stored in a cartridge only, but photostable when stored in a cartridge sealed in a dedicated pen-injector.

Based on the above, a shelf life of 24 months (the 15-, 60-, and 150-mg strengths) or 18 months (the 300-mg strength) has been proposed for the drug product when stored in a cartridge with a chlorobutyl rubber plunger as primary packaging, sealed in a dedicated pen-injector to protect from light, at 2℃ to 8℃.

## 2.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that the quality of the drug substance and the drug product is adequately controlled.

### 2.R.1 Control of visible particles of protein detected in the drug product

The applicant's explanation about the reason for setting a drug product specification for foreign insoluble matter that permits the presence of visible particles of protein, and its control strategy:

During development, translucent visible particles were detected in the drug product and analyzed using [redacted], [redacted] etc. These visible particles were identified as protein of the active substance. The visible particles of protein that arise in the drug product are formed transiently by self-association of the antibodies (the active substance), and there was no tendency towards an increase over time in stability studies.

The control strategy of visible particles of protein in the drug product is as follows.

- In the filling step of the drug product, 100% of the cartridges are tested for foreign insoluble matter, [redacted]

● When visible particles are detected by foreign insoluble matter test conducted at the time of batch release in Japan, the acceptance criteria will be met if the visible particles are identified as protein, and the number of the visible particles is within the range observed with the drug products used in clinical trials.

The drug product batches containing visible particles of protein were also used in clinical trials, and there are no reports that they affected the product quality or patient safety. Although the formation of visible particles of protein could not completely be prevented by reduction measures such as optimization of process parameters, post-marketing information on the control of visible particles of protein in the manufacturing process will be collected as part of continuous process verification. Based on the above, visible particles of protein can be controlled adequately by the above control strategy.

PMDA's conclusion:
Given the above explanation by the applicant, the proposed control strategy of visible particles of protein is acceptable.

## 3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The applicant submitted the results from primary pharmacodynamic studies (*in vitro* studies that evaluated the pharmacodynamic properties of concizumab, *in vivo* studies in rabbits), safety pharmacology studies in cynomolgus monkeys, pharmacodynamic drug interaction studies (*in vitro* studies that evaluated interactions with coagulation factors), etc. The main study results are described below.

### 3.1 Primary pharmacodynamics

#### 3.1.1 *In vitro* studies

##### 3.1.1.1 Binding affinity for TFPI (CTD4.2.1.1-2, Study 209161; CTD4.2.1.1-1, Study 210179)

Epitope mapping of concizumab was performed using the antigen-binding fragment (Fab) of mouse anti-human TFPI monoclonal antibody having the same CDRs as concizumab and the K2 of TFPI. The binding epitope for concizumab was defined as the 14 amino acid residues in the K2 of TFPI, which are conserved among human, rabbit, and monkey TFPI. As measured by surface plasmon resonance (SPR) analysis, binding constant ($K_D$) values of concizumab to human, cynomolgus monkey, and rabbit TFPI were 0.04, 0.06, and 0.22 nmol/L, respectively. Concizumab was shown to bind equally, with high affinity, to TFPI from these species.

##### 3.1.1.2 Neutralization of TFPI

Using coagulation factors (TFPI, FXa, FVIIa/TF/FXa), vascular endothelial cells, plasma, and whole blood, neutralization of TFPI by concizumab was evaluated.

#### 3.1.1.2.1 Effect on TFPI inhibition of FXa activity/generation (CTD4.2.1.1-6, Study 209144; CTD4.2.1.1-7, Study 210180; CTD4.2.1.1-9, Study [redacted]100403)

The effect of concizumab or vehicle on human TFPI inhibition of FXa catalytic activity was evaluated. Concizumab reduced the inhibitory activity of TFPI in a concentration-dependent manner. The effect of concizumab or vehicle on human TFPI inhibition of FXa generation (conversion of FX to FXa) was evaluated. Concizumab reduced the inhibitory activity of TFPI in a concentration-dependent manner.

#### 3.1.1.2.2 Effect on endothelial cell-bound TFPI inhibition of FXa generation (CTD4.2.1.1-8, Study [redacted]080802)

On HUVECs (human umbilical vein endothelial cells) and ECV304 (human endothelial-like cell line) expressing TFPI and tissue factor (TF), concizumab enhanced FVIIa/TF-mediated FXa generation, compared with vehicle.

#### 3.1.1.2.3 Effect on dilute prothrombin time in human, cynomolgus monkey, and rabbit plasma (CTD4.2.1.1-3, Study 209168)

Using human (normal and FVIII-deficient plasma), cynomolgus monkey, and rabbit plasma, the effect of concizumab on the clotting time (dilute prothrombin time) was evaluated. Concizumab concentration-dependently shortened dilute prothrombin time in all plasma samples.

#### 3.1.1.2.4 Effect on clot formation in human and cynomolgus monkey whole blood (CTD4.2.1.1-10, Study [redacted]100201; CTD4.2.1.1-5, Study [redacted]091002)

Hemophilia A or hemophilia B-like conditions were induced by incubation of human and cynomolgus monkey whole blood with an anti-FVIII antibody or an anti-FIX antibody, respectively. The effect of concizumab on the coagulation initiated by addition of TF and calcium was evaluated by thromboelastography (TEG). Concizumab shortened the clotting time in a concentration-dependent manner in hemophilia-like blood.

### 3.1.2 *In vivo* studies

#### 3.1.2.1 Effect on coagulation in rabbit models of hemophilia A (CTD4.2.1.1-12 to 4.2.1.1-17 and CTD4.2.1.4-3, Studies [redacted]110403/[redacted]110701, [redacted]100301, [redacted]090801, [redacted]100602, 300077, 209164, and [redacted]090501)

In rabbit models after induction of hemophilia A with an anti-FVIII antibody, concizumab or negative control (isotype control antibody) was administered intravenously or subcutaneously before cuticle bleeding was induced by cutting the nail, and the cuticle blood loss was measured. Concizumab reduced the blood loss in a concentration-dependent manner, compared with negative control.

#### 3.1.2.2 Effect on clot formation in a venous stasis model in rabbits (CTD4.2.1.1-18, Study [redacted]090201; CTD4.2.1.1-19, Study [redacted]090802)

After concizumab or negative control (isotype control antibody) was administered intravenously in rabbits, the facial veins were ligated to induce venous stasis. Their effects on coagulation biomarkers (platelet count, prothrombin time, thrombin-antithrombin [AT] complex, fibrinogen, fibrinogen degradation products) and local clot formation were evaluated. There were no clear differences between concizumab and negative control,

whereas administration of concizumab prior to a crush injury of the ligated facial veins resulted in increased local clot formation.

### 3.2 Safety pharmacology

The effects of concizumab on the central nervous, cardiovascular, and respiratory systems were assessed in repeated-dose toxicity studies (Table 5). There were no effects of concizumab on the safety pharmacology endpoints in any of the studies.

**Table 5. Overview of safety pharmacology studies**

| Test system | Endpoints/Method of assessment, etc. | Highest dose tested | Route of administration | Findings | CTD |
|---|---|---|---|---|---|
| Cynomolgus monkeys (1-13/sex/group) | clinical observations, cytokine release, ECG, blood pressure, urinalysis, pathological examination | 80/160/200 mg/kg (Escalating doses) | SC | No concizumab-related effects | 4.2.3.1-1 |
| | clinical observations, neurobehavioral examinations, ECG, blood pressure, respiratory function, cytokine release, urinalysis, pathological examination | 50 mg/kg | SC | | 4.2.3.2-2 |
| | | 200 mg/kg | IV | | |
| | clinical observations, ECG, urinalysis, pathological examination | 9 mg/kg | SC | | 4.2.3.2-4 |

### 3.3 Pharmacodynamic drug interactions

As to drug-drug interactions between concizumab and rFVIIa, aPCC, rFVIII, or rFIX, the results from the following *in vitro* studies using human plasma were submitted. The applicant discussed that the effects of combining concizumab with rFVIIa, aPCC, rFVIII, or rFIX were mainly additive.

#### 3.3.1 Drug interaction with rFVIIa (CTD4.2.1.4-1, Study 319076; CTD4.2.1.4-3, Study 300077)

The drug-drug interaction between concizumab and rFVIIa was evaluated by TEG analysis and thrombin generation assay, using hemophilia A human plasma. Combining concizumab with rFVIIa resulted in increased thrombin generation.

#### 3.3.2 Drug interaction with aPCC (CTD4.2.1.4-1, Study 319076)

The drug-drug interaction between concizumab and aPCC was evaluated by thrombin generation assay, using hemophilia A human plasma. Combining concizumab with aPCC resulted in increased thrombin generation.

#### 3.3.3 Drug interaction with rFVIII or rFIX (CTD4.2.1.4-2, Study 321538)

The drug-drug interaction between concizumab and rFVIII was evaluated by thrombin generation assay, using hemophilia A human plasma. The drug-drug interaction between concizumab and rFIX was evaluated by thrombin generation assay, using hemophilia B human plasma. Combining concizumab with either rFVIII or rFIX resulted in increased thrombin generation.

### 3.R Outline of the review conducted by PMDA

PMDA's view:

The results of primary pharmacodynamic studies presented indicate that concizumab binds to TFPI and is expected to have a hemostatic effect *in vivo*. The results from safety pharmacology studies presented indicate that there is no particular concern about the safety of concizumab.

The safety issues in clinical use relating to the pharmacodynamic drug interactions presented will be discussed in Section 7.R.3.1.

## 4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

The applicant submitted pharmacokinetic data, in the form of the results from studies in rabbits and cynomolgus monkeys. Plasma concentrations of concizumab were determined by an enzyme-linked immunosorbent assay (ELISA). Anti-concizumab antibodies (ADAs) were assessed by a bridging ELISA. Unless otherwise specified, pharmacologic (PK) parameters are expressed as the mean ± standard deviation (SD).

### 4.1 Absorption

The applicant submitted the results from absorption studies of concizumab in rabbits and cynomolgus monkeys. The main study results are described below.

#### 4.1.1 Single-dose studies

##### 4.1.1.1 Single-dose studies in rabbits (CTD4.2.2.2-2)

Following a single intravenous or subcutaneous dose of concizumab in rabbits, the plasma concentrations of concizumab were determined. PK parameters are shown in Table 6. Concizumab exposure (AUC) tended to increase in a greater than dose-proportional manner, and concizumab exhibited non-linear pharmacokinetics. The bioavailability of concizumab after subcutaneous administration of 20 mg/kg was 83%.

**Table 6. PK parameters of concizumab following a single-dose administration in rabbits (Study 209305)**

| Route of administration | IV | SC | | | |
|---|---|---|---|---|---|
| Dose (mg/kg) | 20 | 2 | 5 | 10 | 20 |
| Number of animals | 4 males | 4 males | 4 males | 4 males | 4 males |
| $C_{max}$ (µg/mL) | 417 ± 84.6 | 2.96 ± 0.517 | 19.5 ± 2.34 | 63.3 ± 2.44 | 175 ± 49.1 |
| $T_{max}$ (h)[a)] | 2 [2, 2] | 36 [24, 48] | 48 [48, 48] | 60 [48, 72] | 120 [96, 168] |
| $AUC_{0-\infty}$ (µg·h/mL) | 33000 ± 3810 | 144 ± 17 | 1450 ± 219 | 7490 ± 884 | 27400 ± 2820 |
| AUC/Dose[b)] | 1650 | 72 | 289 | 749 | 1370 |
| $T_{1/2}$ (h) | 32.0 ± 7.80 | 21.7 ± 3.99 | 14.5 ± 11.2 | 11.3 ± 1.67 | 31.9 ± 17.2 |
| CL (mL/kg/h) | 0.6 ± 0.1 | — | — | — | — |
| Vd (mL/kg) | 52.4 ± 4.53 | — | — | — | — |

a) Median [Range]
b) Normalized to 1 mg/kg

##### 4.1.1.2 Single-dose studies in cynomolgus monkeys (CTD4.2.2.2-5 and CTD4.2.3.1-1)

Following a single intravenous or subcutaneous dose of concizumab in cynomolgus monkeys, the plasma concentrations of concizumab were determined. PK parameters are shown in Table 7. Concizumab exposure (AUC) tended to increase in a greater than dose-proportional manner, and concizumab exhibited non-linear pharmacokinetics.

The bioavailability of concizumab after subcutaneous administration of 20 mg/kg was 77%.

The applicant's explanation:

The non-linear pharmacokinetic behavior of concizumab is caused by target-mediated drug disposition (TMDD), which occurs when concizumab binds to endothelial cell-anchored TFPI with subsequent elimination of the drug-target complex [see Section 6.R.3.1].

**Table 7. PK parameters of concizumab following a single-dose administration in cynomolgus monkeys**

| Study | 210156 | | | 208250 | |
|---|---|---|---|---|---|
| Route of administration | IV | | | IV | SC |
| Dose (mg/kg) | 0.1 | 0.5 | 1 | 20 | 20 |
| Number of animals | 2/sex | 2/sex | 2/sex | 3 males | 3 males |
| $C_{max}$ (µg/mL) | 0.256 ± 0.199 | 1.605 ± 0.451 | 20.8 ± 3.38 | 418 ± 21.6 | 145 ± 21.2 |
| $T_{max}$ (h)[a)] | 0.5 [0.5, 0.5] | 0.5 [0.5, 0.5] | 0.5 [0.5, 2] | 0.5 [0.5, 2] | 168 [120, 168] |
| $AUC_{0-\infty}$ (µg·h/mL) | 1.08 ± 0.40 | 69.7 ± 19.5 | 418 ± 77.6 | 66000 ± 15400 | 50700 ± 10300 |
| AUC/Dose[b)] | 11 | 139 | 418 | 3300 | 2540 |
| $T_{1/2}$ (h) | 24 ± 3.7 | 50 ± 6.3 | 66 ± 25 | 198 ± 36[c)] | 183 ± 46[c)] |
| CL (mL/kg/h) | 102 ± 27.3 | 7.7 ± 2.5 | 2.5 ± 0.5 | 0.313 ± 0.066 | 0.406 ± 0.090 |
| Vd (mL/kg) | 3610 ± 1120 | 1110 ± 242 | 205 ± 90.7 | — | — |

a) Median [Range]
b) Normalized to 1 mg/kg
c) Calculated when concizumab plasma concentration was saturated (>20000 ng/mL).

### 4.1.2 Repeated-dose studies

#### 4.1.2.1 Repeated-dose toxicity studies in cynomolgus monkeys (CTD4.2.3.2-1 to 4.2.3.2-4 and CTD4.2.3.7.7-8)

Concizumab was administered intravenously or subcutaneously for 4 to 52 weeks in cynomolgus monkeys, and the plasma concentrations of concizumab were determined. PK parameters are shown in Table 8.

After repeated once daily subcutaneous dosing, accumulation of concizumab was considerable, particularly at low dose (the mean ratio of accumulation [Rac] was up to approximately 400).

ADAs were assessed, and formation of ADAs reduced concizumab exposure in some of the animals.

**Table 8. PK parameters of concizumab following repeated dosing in cynomolgus monkeys**

| Study | Dosing duration | Route of administration | Dose (mg/kg/day) | Number of animals | $C_{max}$ (µg/mL) | $AUC_{tau}$ (µg·h/mL)[a)] | $R_{ac}$ |
|---|---|---|---|---|---|---|---|
| 210130 | 4 weeks | SC | 3 | 3/sex | 638 ± 117 | 14100 ± 2290 | 162 ± 63 |
| | | SC | 9 | 3/sex | 1730 ± 249 | 37400 ± 4840 | 73 ± 16 |
| | | IV | 30 | 3/sex | 1290 ± 134 | 154000 ± 18200 | 2.7 ± 0.15 |
| 209206 | 13 weeks | SC | 1 | 5/sex | 282 ± 53.1 | 5930 ± 952 | 385 ± 351 |
| | | SC | 10 | 5/sex | 4200 ± 535 | 83600 ± 8790 | 108 ± 47 |
| | | SC | 50 | 5/sex | 14700 ± 2780 | 326000 ± 57800 | 58 ± 10 |
| | | IV | 200 | 5/sex | 11800 ± 2220 | 1580000 ± 280000 | 2.8 ± 0.72 |
| 211087 | 26 weeks | SC | 3 | 5/sex | 992 ± 389 | 21400 ± 6810 | 130 ± 49 |
| | | SC | 9 | 5/sex | 3310 ± 618 | 76500 ± 14300 | 58 ± 24 |
| | | IV | 30 | 5/sex | 2650 ± 646 | 307000 ± 93100 | 3.8 ± 1.4 |
| 213542 | 52 weeks | SC | 0.5[b)] | 9/sex | 82.6 ± 10.3 | 1910 ± 354 | —[c)] |
| | | SC | 1[b)] | 9/sex | 309 ± 55.8 | 6890 ± 1140 | 232 ± 175 |
| | | SC | 9 | 13/sex | 5070 ± 1480 | 99300 ± 21000 | 88 ± 135 |

a) $AUC_{0-24h}$ for SC dosing, $AUC_{0-168h}$ for IV dosing
b) Exposure in ADA-negative animals (0.5 mg/kg/day) or animals with inconclusive ADA/lower-titer ADAs (1.0 mg/kg/day)
c) $R_{ac}$ could not be calculated due to very low exposure in most animals.

### 4.2 Distribution

Although no dedicated distribution studies have been performed with concizumab, tissue cross-reactivity studies with cynomolgus monkey and human tissues and immunohistochemistry in rabbits and cynomolgus monkeys showed that concizumab is seen in blood and associated with the endothelium.

The applicant's explanation:
Although placental transfer of concizumab has not been studied, as monoclonal antibodies are generally known to cross the placenta in humans, concizumab may also cross the placenta into the fetus.

### 4.3 Metabolism and excretion

Concizumab is a monoclonal antibody consisting of natural amino acids. It is expected to be catabolized into peptides and amino acids and then reused by or eliminated from the body. Thus, no metabolism or excretion studies have been conducted, in line with the ICH S6 (R1) guideline.

### 4.4 Pharmacokinetic drug interactions

A 4-week drug-drug interaction study in cynomolgus monkeys on concizumab (CTD4.2.3.7.7-3, Study 215431) evaluated the drug-drug interaction between concizumab and rFVIIa. Concizumab did not affect the PK of rFVIIa.

### 4.R Outline of the review conducted by PMDA

Based on the submitted pharmacokinetic data, PMDA considers that there is no particular problem with the non-clinical pharmacokinetic evaluation of concizumab.

## 5. Toxicity and Outline of the Review Conducted by PMDA

The applicant submitted the results from single-dose and repeated-dose toxicity studies etc. The main study results are described below.

### 5.1 Single-dose toxicity

A single subcutaneous dose toxicity study was conducted in cynomolgus monkeys (Table 9). There were no concizumab-related effects.

**Table 9. Overview of single-dose toxicity study**

| Test system | Route of administration | Doses (mg/kg)[a)] | Noteworthy findings | Approximate lethal dose (mg/kg) | CTD |
|---|---|---|---|---|---|
| Male and female cynomolgus monkeys | SC | 2,[b)] 20, 80, 160, 200 | None | >200 | 4.2.3.1-1 (Reference data) |

a) Three single escalating subcutaneous doses of concizumab (2/20/80, 20/80/160, and 80/160/200 mg/kg/groups) were administered 2 weeks apart.
b) Vehicle: 34 mM histidine, 251 mM sucrose, and 0.03% Tween 80 solution, pH 6.5

### 5.2 Repeated-dose toxicity

Repeated subcutaneous or intravenous dose toxicity studies were conducted in cynomolgus monkeys (Table 10). The noteworthy toxicological findings were vascular and perivascular changes in the choroid plexus in the

brain, the lungs, and the liver (inflammation, endothelial hypertrophy/hyperplasia, smooth muscle hypertrophy, medial thickening, etc.).

**Table 10. Overview of repeated-dose toxicity studies**

| Test system | Route of administration | Dosing Duration | Doses (mg/kg) | Noteworthy findings | NOAEL (mg/kg) | CTD |
|---|---|---|---|---|---|---|
| Male and female cynomolgus monkeys | SC or IV | 4 weeks (SC: once daily IV: once weekly) | SC[a)]: 3, 9<br>IV[a)]: 0, 30 | ≥3: decreased fibrinogen | SC: 9<br>IV: 30 | 4.2.3.2-1 |
| | | 13 weeks (SC: once daily IV: once weekly) + 11-week recovery period | SC[a)]: 0, 1, 10, 50<br>IV[a)]: 200 | ≥ 1: decreased fibrinogen<br>≥10: thrombi<br>50: intimal proliferation in the lung<br><br>These findings were reversible. | SC: 1<br>IV: none | 4.2.3.2-2 |
| | | 26 weeks (SC: once daily IV: once weekly) +13-week recovery period | SC[a)]: 0, 3, 9<br>IV[b)]: 30 | ≥3: decreased fibrinogen, thrombi, vascular and perivascular changes in the choroid plexus in the brain and the lungs[c)] (inflammation, endothelial hypertrophy/hyperplasia, smooth muscle hypertrophy, medial thickening)<br>9: mortality [d)]<br><br>These findings were reversible. | SC: none<br>IV: none | 4.2.3.2-3 |
| | SC | 52 weeks (SC: once daily) | SC[b)]: 0, 0.5, 1, 9 | ≥0.5: decreases in platelet counts and fibrinogen, inflammatory cell infiltration in the choroid plexus in the brain,[c)] increased immune complexes in blood<br>≥1: thrombi, subendothelial intimal thickening in the lung[c)]<br>9: subendothelial intimal thickening in the liver | SC: 0.5 | 4.2.3.2-4 |

a) Vehicle: 34 mM histidine, 251 mM sucrose, and 0.03% polysorbate solution, pH 6.5
b) Vehicle: 33 mM histidine, 150 mM sucrose, 0.01 mg/mL Tween 80, 25 mM arginine, and 25 mM sodium chloride solution, pH 6.0
c) Immune complexes (consisting of concizumab and monkey IgG, IgM, or complement component C3a) were found in each lesion.
d) One female monkey in the 9 mg/kg/day group experienced adverse clinical signs (decrease in movement, pale gum, slowness of movement, shallow respiration, etc.) and was euthanized. The cause for adverse clinical signs was determined to be pulmonary thrombosis and necrosis with severe anemia.

### 5.3 Genotoxicity

Since concizumab is a protein produced by recombinant DNA technology, no genotoxicity studies with concizumab have been conducted.

### 5.4 Reproductive and developmental toxicity

The effect of concizumab on fertility was evaluated in a 26-week repeated-dose toxicity study in cynomolgus monkeys, and there were no effects on the reproductive organs. On the other hand, since thrombi resulting from an exaggerated pharmacological response can lead to miscarriage (*Nat Rev Rheumatol*. 2011; 7: 330-339, *Obstet Gynecol*. 2007; 109: 1146-1155), it was considered difficult to evaluate the effect of concizumab on the offspring (the embryo/fetus and pup) in normal animals, and no reproductive and developmental toxicity studies have been conducted.

### 5.5 Carcinogenicity

Since concizumab is a protein produced by recombinant DNA technology, no carcinogenicity studies with concizumab have been conducted.

### 5.6 Local tolerance

Local tolerance assessment was integrated in repeated-dose toxicity studies in cynomolgus monkeys (CTD 4.2.3.2-1 to 4.2.3.2-4), and it was concluded that concizumab does not induce local irritation.

### 5.7 Other toxicity studies

#### 5.7.1 Cross-reactivity

For the selection of animal species for non-clinical safety evaluation of concizumab, a cross-reactivity study with human and cynomolgus monkey tissue panels was conducted (Table 11). The staining pattern observed in human tissues was similar to that observed in cynomolgus monkey tissues.

**Table 11. Overview of cross-reactivity study**

| Type of study | Test system | Test method | Noteworthy findings | CTD |
|---|---|---|---|---|
| Cross-reactivity | Human and cynomolgus monkey tissue panels | Tissue panels were prepared, and tissue cross-reactivity analyses were conducted by immunostaining using concizumab. | Concizumab binding was present in the following cells.<br>Human:<br>the cytoplasm in vascular endothelial cells, haematopoietic precursor cells and leucocytes, spindle cells, placental decidual cells<br>Cynomolgus monkey:<br>the cytoplasm in vascular endothelial cells, haematopoietic precursor cells and leucocytes, spindle cells | 4.2.3.7.7-2 |

### 5.R Outline of the review conducted by PMDA

Based on the submitted data and the following considerations, PMDA concluded that there is no particular problem with the toxicity of concizumab.

#### 5.R.1 Vascular and perivascular changes

Vascular and perivascular changes in the choroid plexus in the brain, the lungs, etc., were observed in 26-week and 52-week repeated-dose toxicity studies in monkeys (CTD4.2.3.2-3 and CTD4.2.3.2-4). PMDA asked the applicant to explain their pathogenesis and safety in humans.

The applicant's explanation:

Vascular and perivascular changes observed in 26-week and 52-week repeated-dose toxicity studies in monkeys were endothelial hypertrophy, subendothelial thickening, or inflammatory cell infiltration, etc., mainly in the choroid plexus in the brain and the lungs. Based on the biodistribution of concizumab, the development of ADA and immune complexes, immunohistochemistry, etc., in repeated-dose toxicity studies in monkeys, these findings are considered to result from local deposition of immune complexes secondary to ADA formation, as observed after administration of other antibody drugs (*Toxicol Pathol.* 2014; 42: 725-764). The plasma exposure of concizumab at the no-observed-adverse-effect-level (NOAEL) (0.5 mg/kg/day) in the 52-week study in which these findings were observed was ≥70-fold the human exposure, and the findings were reversible in the 26-week study. Thus, these findings do not suggest the risk associated with concizumab in humans.

PMDA's view:

From the standpoint of non-clinical safety evaluation, the applicant's explanation that the risk relating to vascular/perivascular changes in the choroid plexus in the brain, the lungs, etc., is low in humans is acceptable.

However, as there are limitations to evaluating human immunogenic risk in animals, the safety consequences of ADA formation in humans will be reviewed in Section 6.R.2.

### 5.R.2 Effects on the offspring

Since no reproductive and developmental toxicity studies with concizumab (embryo-fetal development, pre- and postnatal development) have been conducted, PMDA asked the applicant to explain the risk associated with concizumab in pregnant women, taking account of its biological properties etc.

The applicant's explanation:

Fetal exposure to human IgGs including concizumab increases from the second to third trimesters of pregnancy after completion of organogenesis and reaches maternal plasma exposure at birth (*Crit Rev Toxicol*. 2012; 42: 185-210). In a 52-week repeated-dose toxicity study in monkeys (CTD4.2.3.2-4), though the pharmacology-mediated formation of thrombi was observed, as there was a ≥70-fold safety margin relative to human exposure, and generally, human fetal hemostasis evolves towards the adult state (*Semi Thromb*. 2003; 29: 329-338, *Bio Neonat*. 1966; 10: 108-112, *Blood*. 1996; 88: 900-906), the risk of thrombus formation associated with concizumab in the fetuses and infants should be low. As to maternal effects, concizumab is expected to normalize the coagulation system in patients with hemophilia. Since the maternal concentrations of circulating coagulation factors increase during pregnancy even in healthy women, patients with hemophilia treated with concizumab also are at risk of miscarriage due to thrombus formation, but the risk should be similar to that in pregnant women with normal coagulation function. Thus, there should be no particular concerns about administration of concizumab. However, taking into account that there are no data on the use of concizumab during pregnancy such as a reproductive and developmental toxicity study, the package insert will advise that concizumab may be used in pregnant women or women who may be pregnant only if the expected therapeutic benefits outweigh the possible risks.

PMDA's view:

The applicant's explanation that concizumab's risk to embryo-fetal and pre- and postnatal development is low is acceptable. Prior to the use of concizumab in pregnant women, in addition to the precaution information in the package insert, the information about concizumab's risk of thrombus formation, which can lead to miscarriage etc., should be provided appropriately.

## 6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

### 6.1 Summary of biopharmaceutic studies and associated analytical methods

Plasma concentrations of concizumab were determined by an ELISA, and the lower limit of quantification (LLOQ) was 5 ng/mL. Plasma free TFPI concentrations were determined by an ELISA, and the LLOQ was 9.6 to 17.1 ng/mL depending on the laboratory. Thrombin generation was measured by the calibrated automated thrombogram method.

ADAs were measured by a bridging ELISA/electrochemiluminescence assay using labeled concizumab. Positive samples were assessed for neutralizing activity *in vitro* by a chromogenic substrate assay or a ligand binding assay.

The Concizumab-ELISA kit as an *in vitro* companion diagnostic intended for use as an aid to dose adjustment, is under development by Randox.

## 6.2 Clinical pharmacology

The applicant submitted clinical pharmacology evaluation data, in the form of the results of clinical trials in healthy subjects or patients with hemophilia, a population pharmacokinetic analysis, and exposure-response analyses. The main study results are described below.

### 6.2.1 Single-dose studies

#### 6.2.1.1 Foreign phase I trial of concizumab administered intravenously or subcutaneously in non-Japanese healthy subjects and patients with hemophilia without inhibitors (CTD5.3.3.1-3, Trial NN7415-3813; Trial period, October 2010 to September 2012)

Single intravenous doses of 0.0005 to 0.25 mg/kg of concizumab or single subcutaneous doses of 0.05 to 1 mg/kg of concizumab were administered to non-Japanese healthy subjects (≥18 and ≤65 years of age). Single intravenous doses of 0.25 to 9 mg/kg of concizumab or a single subcutaneous dose of 1 or 3 mg/kg of concizumab were administered to patients with hemophilia (HA or HB, ≥18 and ≤65 years of age). PK parameters are shown in Tables 12 and 13. Regardless of the route of administration, concizumab exposure ($C_{max}$, AUC) increased with increasing dose, but was non-linear, with a large inter-subject variability.

**Table 12. PK parameters following a single intravenous administration (Geometric mean [CV%])**

| | Healthy subjects | | | | Patients with hemophilia with inhibitors | | | |
|---|---|---|---|---|---|---|---|---|
| Dose (mg/kg) | 0.0005[a)] | 0.005 | 0.05 | 0.25 | 0.25 | 1 | 3 | 9 |
| N | 2 | 3 | 3 | 3 | 3 | 3 | 3 | 3 |
| $C_{max}$ (ng/mL) | 6.19 (15.3) | 45.3 (36.7) | 785 (16.0) | 4457 (5.9) | 3997 (8.7) | 35252 (14.7) | 74342 (3.1) | 239053 (30.8) |
| $AUC_{0-\infty}$ (ng·h/mL) | 0.288 (11.1) | 28.5 (81.0) | 1513 (33.6) | 44575 (15.1) | 38256 (9.8) | 1175441 (24.5) | 5176337 (9.3) | 32865565 (30.0) |
| CL (mL/h/kg) | 1750 (10.0) | 176 (75.9) | 33.4 (38.2) | 5.78 (16.6) | 6.53 (11.0) | 0.913 (24.5) | 0.564 (13.0) | 0.27 (30.2) |
| $T_{1/2}$ (h) | - | - | - | 25.7 (4.4) | 31 (12.3) | 49.3 (9.8) | 73.1 (21.6) | 65.2 (16.7) |

a) One of 3 subjects dosed with concizumab in the cohort had concizumab plasma measurements below the LLOQ.

**Table 13. PK parameters following a single subcutaneous administration (Geometric mean [CV%])**

| | Healthy subjects | | | Patients with hemophilia without inhibitors | |
|---|---|---|---|---|---|
| Dose (mg/kg) | 0.05[b)] | 0.25 | 1 | 1 | 3 |
| N | 3 | 3 | 3 | 3 | 3 |
| $C_{max}$ (ng/mL) | 8.93 (27.3) | 35.5 (18.8) | 934 (42.7) | 838 (88.6) | 15437 (42.4) |
| $AUC_{0-\infty}$ (ng·h/mL) | - | 8197 (93.4) | 52375 (36.8) | 83244 (70.8) | 2163346 (52.0) |
| CL/F (mL/h/kg) | - | 30.6 (60.7) | 19.1 (33.6) | 12 (103.0) | 1.39 (71.9) |
| $T_{1/2}$ (h) | - | 89.4 (20.1) | 114 (4.8) | 104 (59.5) | 69.4 (42.0) |
| $T_{max}$ (h)[a)] | 12 | 24 | 36 | 46.4 | 70.4 |

a) Median
b) $AUC_{0-\infty}$, CL/F, or $T_{1/2}$ was not calculated, as no subjects in the cohort had continuous profiles above the LLOQ.

#### 6.2.1.2 Foreign phase I trial of concizumab administered subcutaneously in Japanese healthy subjects (CTD5.3.3.1-1, Trial NN7415-3981; Trial period, March 2012 to May 2012)

Table 14 shows the PK parameters of concizumab following a single subcutaneous dose of 0.25 or 1 mg/kg in Japanese healthy subjects living in the UK (≥20 and ≤64 years of age). The applicant explained that there were no clear differences in the PK parameters of concizumab between Japanese healthy subjects and non-Japanese healthy subjects in Trial 3813.

**Table 14. PK parameters following a single subcutaneous administration in Japanese healthy subjects living in the UK (Geometric mean [CV%])**

| Dose (mg/kg) | 0.25 | 1 |
|---|---|---|
| N | 3 | 3 |
| $C_{max}$ (ng/mL) | 55.1 (7.0) | 252.4 (55.2) |
| $AUC_{0-\infty}$ (ng·h/mL) | 7067.8 (9.7) | 24988.0 (23.3) |
| CL/F (mL/h/kg) | 35.5 (8.6) | 40.0 (20.9) |
| $T_{1/2}$ (h) | 96.1 (10.5) | 109.0 (15.1) |
| $T_{max}$ (h)[a)] | 12.1 | 11.8 |

a) Median

### 6.2.2 Multiple-dose studies

#### 6.2.2.1 Subcutaneous administration study in patients with hemophilia A or B with inhibitors

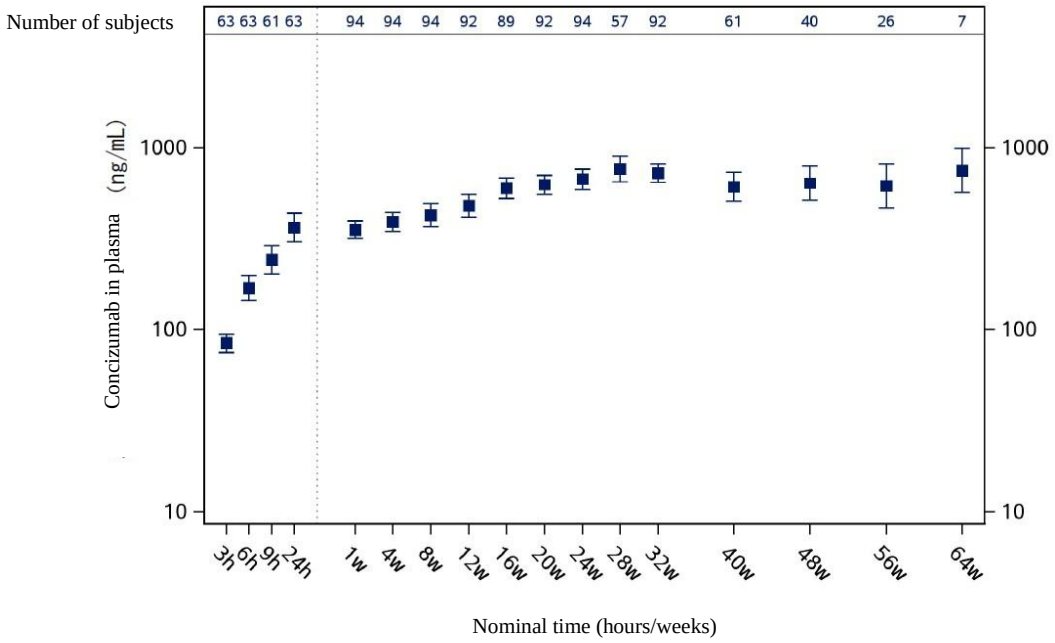
##### 6.2.2.1.1 Global phase III trial (CTD5.3.5.1-3, Trial NN7415-4311; Trial period, ongoing since October 2019 [data cutoff date of December 27, 2021])

Patients with hemophilia A with inhibitors (HAwI) or hemophilia B with inhibitors (HBwI) aged ≥12 years received the 1-mg/kg loading dose of subcutaneous concizumab on Day 1, followed by an initial maintenance dose of 0.20 mg/kg once daily starting on Day 2. Plasma concentrations of concizumab were measured after Week 4, based on which patients received subsequent maintenance doses of 0.15, 0.20, or 0.25 mg/kg.[1)] Figure 1 shows change over time in concizumab plasma concentration in subjects on concizumab prophylaxis (treatment arms 2-4). After the loading dose of concizumab on Day 1, the concizumab plasma concentration rapidly reached a steady state and remained stable with a once daily maintenance dose of concizumab. The geometric mean $C_{trough}$ at Week 24 (geometric coefficient of variation [GCV])[2)] was 665.4 (2.2) ng/mL, and other PK parameters are shown in Table 15. These parameters were similar between patients with hemophilia A and B. As the key pharmacodynamic parameter, plasma free TFPI concentrations were measured, and the results are shown in Figure 2.

[1)] For the details of trial design including treatment arms, see Section 7.3.1.

[2)] In Trial 4311, GCV was calculated with the following formula (σ denotes the SD of log-transformed value): $GCV = \sqrt{\exp(\sigma 2) - 1}$

**Figure 1. Change over time in concizumab plasma concentration (Geometric mean plots, Arms 2-4)[a) to c)]**



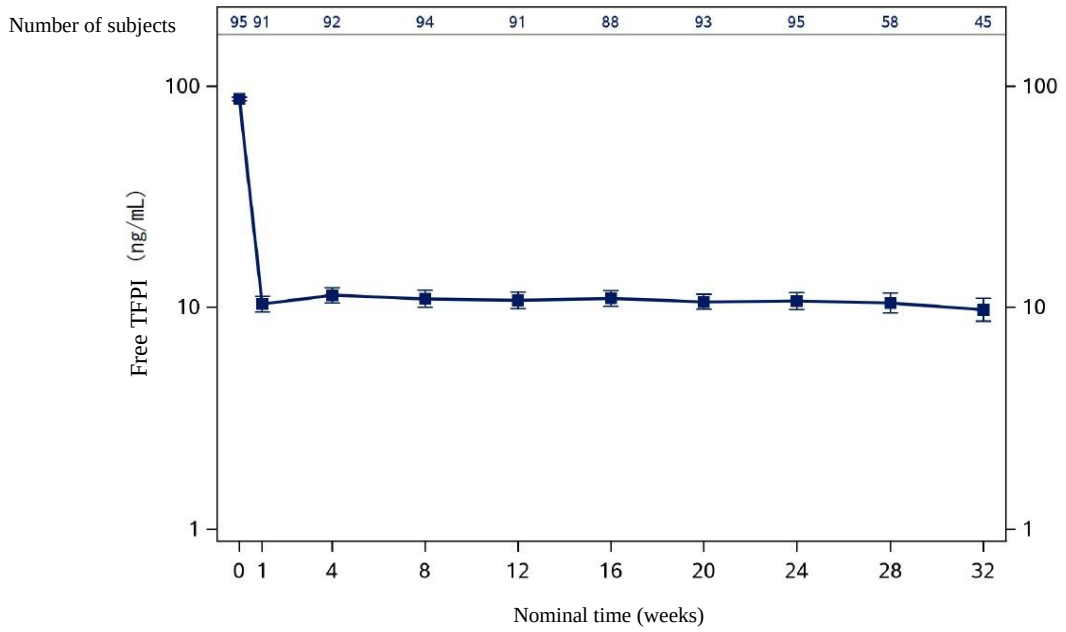

a) SAS and on treatment without data on the initial regimen [see Section 7.3.1] (OTexIR)
b) Error bars represent ± standard error of the geometric mean.
c) Plasma concentrations below the LLOQ are set to half of the LLOQ.

**Table 15. PK parameters following multiple doses in patients with hemophilia with inhibitors (Arms 2-4)[a)]**

| | HAwI | | HBwI | |
|---|---|---|---|---|
| | Baseline | Week 24[b)] | Baseline | Week 24[b)] |
| N | 42 | 42 | 21 | 27 |
| $C_{max}$ (ng/mL) (Geometric mean [GCV]) | 336.7 (2.8) | 1165.9 (1.5) | 495.8 (2.0) | 1168.9 (1.0) |
| $AUC_{0\text{-}24h}$ (ng·h/mL) (Geometric mean [GCV]) | 5209.8 (2.4) | 22327.7 (1.4) | 7258.0 (1.9) | 22511.7 (1.1) |
| $C_{max}/C_{trough}$ ratio (Mean ± SD) | — | 2.6 ± 6.6 | — | 1.5 ± 0.5 |

a) SAS and OTexIR
b) Week 24 is relative to the relevant baseline.

**Figure 2. Change over time in plasma free TFPI concentration (Geometric mean plots, Arms 2-4)[a) to c)]**




a) SAS and OTexIR
b) Error bars represent ± standard error of the geometric mean.
c) Plasma concentrations below the LLOQ are set to half of the LLOQ.

### 6.2.2.2 Multiple subcutaneous administration studies in hemophilia A patients without inhibitors

#### 6.2.2.2.1 Foreign phase I trial (CTD5.3.4.2-1, Trial NN7415-4159; Trial period, September 2015 to October 2016)

Concizumab 0.25, 0.50, or 0.80 mg/kg was administered subcutaneously every 4 days for 12 doses in patients with HA aged 18 to 64 years. Table 16 shows PK parameters.

**Table 16. PK parameters following multiple doses in patients with HA (Geometric mean [CV%])**

| Dose (mg/kg) | 0.25 | 0.50 | 0.80 |
|---|---|---|---|
| N | 6 | 6 | 6 |
| $AUC_{tau}$ (ng·days/mL)[a)] | 135 (20.9) | 396 (10.3) | 1470 (174.1) |
| $C_{max}$ (ng/mL)[b)] | 52 (25.0) | 265 (180.0) | 1442 (179.6) |
| $C_{trough}$ (ng/mL)[c)] | 30 (26.2) | 67 (25.4) | 350 (121.5) |

a) AUC over the dosing interval from the penultimate dose administration (Day 38) to the last dose administration (Day 42)
b) Measured 4 hours after the first concizumab dose.
c) Measured prior to the last dose on Day 42.

#### 6.2.2.2.2 Global phase II trial (CTD5.3.5.2-1 to 5.3.5.2-2, Trial NN7415-4255; Trial period, August 2017 to June 2020)

Patients with HA aged ≥18 years were treated with once daily subcutaneous injections of 0.15 mg/kg concizumab (with potential dose escalation up to 0.25 mg/kg according to bleeding tendency). Table 17 shows concizumab plasma concentrations prior to the last dose administration at Week 24 (the main part) and after ≥76 weeks of treatment (the extension part). Table 18 shows plasma free TFPI concentrations.

**Table 17. Concizumab plasma concentrations following long-term treatment in patients with HA (prior to the last dose administration,[a)] Mean ± SD)**

| Treatment duration | 24 weeks | | | ≥76 weeks[b)] | | |
|---|---|---|---|---|---|---|
| Last dose level (mg/kg) | 0.15 | 0.20 | 0.25 | 0.15 | 0.20 | 0.25 |
| N | 18 | 4 | 6 | 13 | 10 | 7 |
| Concentration (ng/mL) | 195.2 ± 147.0 | 374.4 ± 644.0 | 2640.8 ± 4085.6 | 195.1 ± 161.7 | 392.3 ± 427.9 | 4015.1 ± 2902.0 |

a) Prior to the last dose administration of trial drug after ≥76 weeks of treatment
b) Concizumab plasma concentration at the last visit during study treatment for subjects affected by the trial pause

**Table 18. Plasma free TFPI concentrations following long-term treatment in patients with HA (prior to the last dose administration,[a)] Mean ± SD)**

| | 24 weeks | | | ≥76 weeks[b)] | | |
|---|---|---|---|---|---|---|
| Last dose level (mg/kg) | 0.15 | 0.20 | 0.25 | 0.15 | 0.20 | 0.25 |
| N | 18 | 4 | 6 | 13 | 10 | 7 |
| Concentration (ng/mL) | 30.1 ± 15.6 | 64.4 ± 35.3 | 12.4 ± 2.2 | 26.9 ± 17.1 | 36.1 ± 33.1 | 10.1 ± 5.7 |

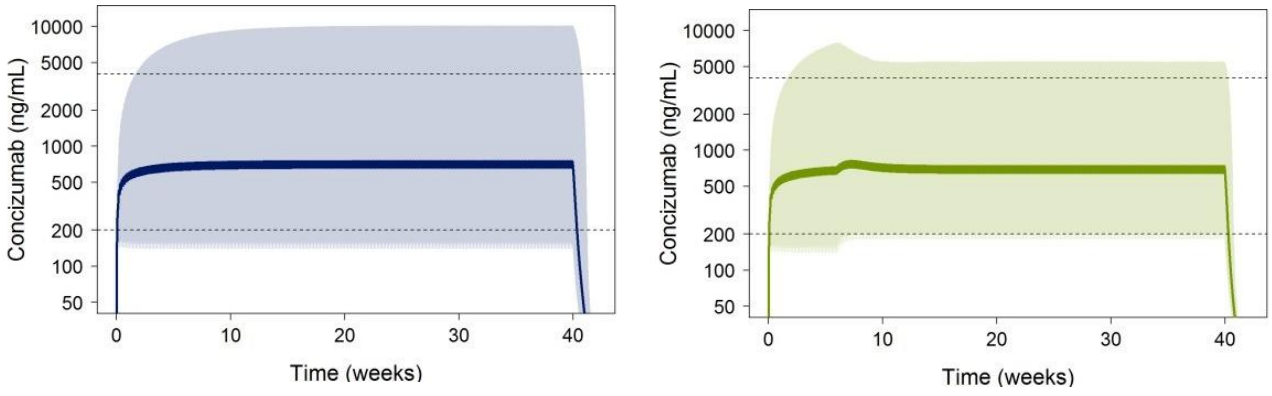
a) Prior to the last dose administration of trial drug after ≥76 weeks of treatment
b) Plasma free TFPI concentration at the last visit during study treatment for subjects affected by the trial pause

## 6.3 Population pharmacokinetic analysis (CTD5.3.3.5-2)

Using concizumab plasma concentration data from a total of 232 subjects (4145 sampling points) in foreign phase I trials (Trials 3813, 3981, 3986,[3)] and 4159), global phase II trials (Trials 4255 and 4310[4)]), and a global phase III trial (Trial 4311), a population pharmacokinetic analysis was performed with NONMEM (version 7.3). The pharmacokinetics of concizumab were described by a 2-compartment model with linear clearance and target-mediated drug disposition (TMDD). Based on the results of covariate exploration, body weight as the most important covariate was included in the model.

Based on this model, the concizumab plasma concentration-time profiles with and without dose adjustment after Week 4 were simulated. The results are shown in Figure 3. The applicant explained that these simulations indicated that individual maintenance dose setting would reduce concizumab exposure variability at the population level.

**Figure 3. Simulated exposure profiles with (right) and without (left) dose adjustment after Week 4[a)]**




a) Based on the final model that includes the same distribution of body weight as in Trial 4311, individual concentration-time profiles (without the residual variability) were simulated for 10000 subjects.
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 (with residual variability) occurring at Week 4.

[3)] A foreign phase I trial in healthy subjects and patients with HA or HB [for the details of the trial, see Section 7, Table 22]
[4)] A global phase II trial in patients with HAwI or HBwI [for the details of the trial, see Section 7.2.2]

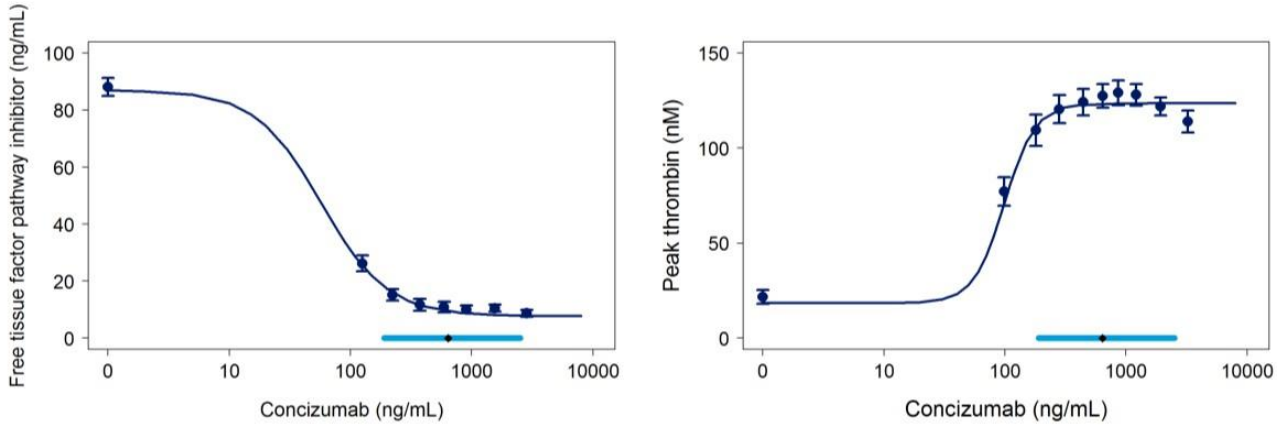
## 6.4 Exposure-response analyses (CTD5.3.3.5-2)

Based on the data after the restart of Trial 4311,[5)] exposure-response models for plasma free TFPI and peak thrombin generation were constructed. The exposure-response analyses showed that doses of concizumab used in Trial 4311 maintain the concizumab exposure level which kept plasma free TFPI concentration or peak thrombin generation almost unchanged (Figure 4). The exposure-response analysis of bleeding episodes (annualised bleeding rate [ABR][6)]) showed that doses of concizumab used in Trial 4311 maintain concizumab exposure which allows its effect on ABR to remain flat (Figure 5).

The applicant explained that the above results also support the dosing regimen of concizumab.

**Figure 4. Exposure-response relationship for plasma free TFPI or peak thrombin generation**

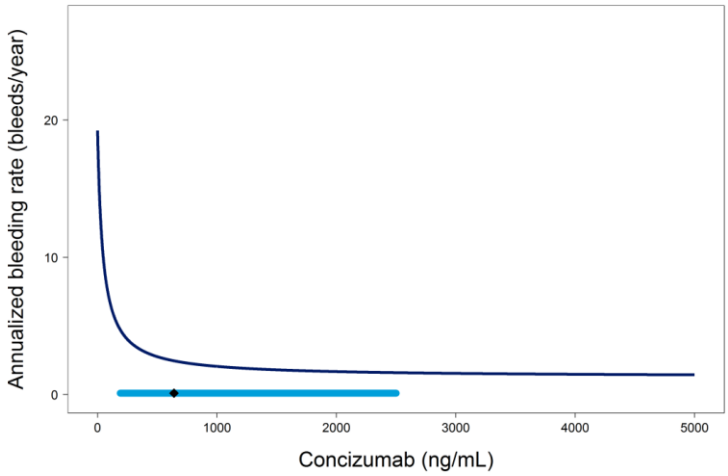
**(A) Plasma free TFPI concentration** **(B) Peak thrombin generation**




Plots with error bars: the mean and 95% CI of observed plasma free TFPI concentrations (A) or observed thrombin peak levels (B) versus concizumab plasma concentrations
The dark blue line: the mean model prediction
The horizontal light blue line at the bottom: the median (diamond) and the 5% to 95% range of the individual average plasma exposure predicted across the trial duration (only including data after restart of Trial 4311), using a PPK model that includes BOV

[5)] Including concizumab plasma concentrations and simultaneous plasma free TFPI concentrations and peak thrombin generation up to the primary analysis cutoff in subjects on concizumab prophylaxis (only after starting concizumab treatment in Arm 1).
[6)] ABR (episodes/year) = (the number of treated spontaneous and traumatic bleeding episodes/the number of days in the analysis data set) × 365.25

**Figure 5. Exposure-response relationship for ABR**




The dark blue line: the mean model prediction
The horizontal light blue line at the bottom: the median (diamond) and the 5% to 95% range of the individual average plasma exposure predicted across the trial duration (only including data after restart of Trial 4311), using a PPK model that includes BOV

## 6.R Outline of the review conducted by PMDA

### 6.R.1 Pharmacokinetic differences between Japanese and non-Japanese populations

The applicant's explanation about pharmacokinetic differences between Japanese and non-Japanese populations:

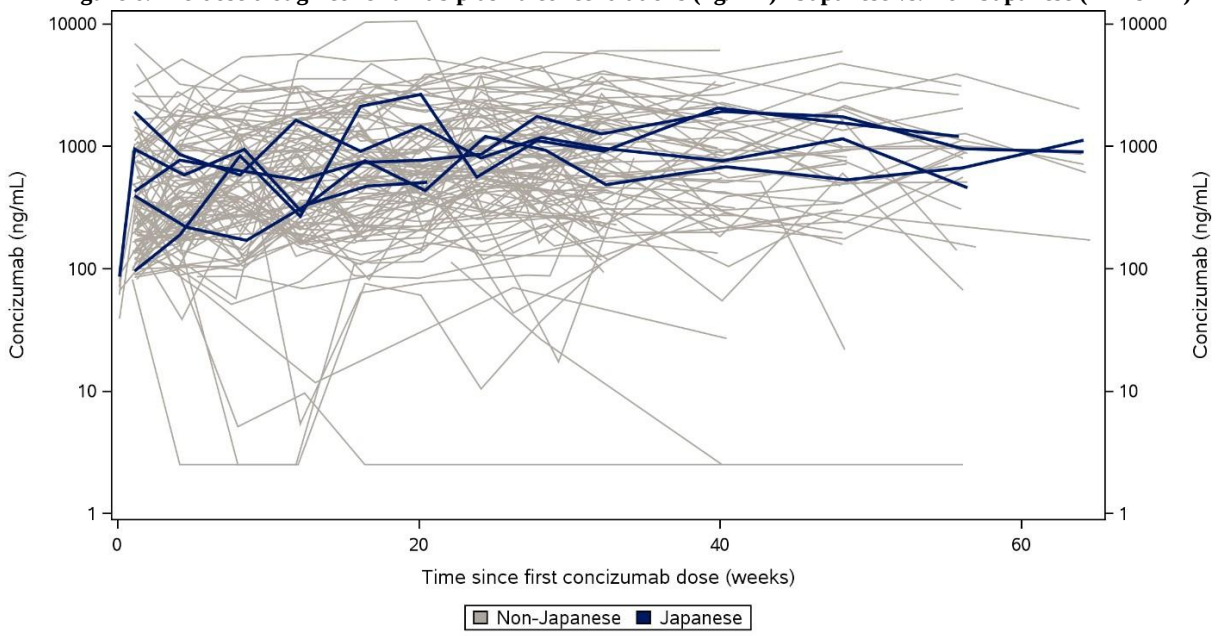
In the treatment arms 2 to 4 after the restart of Trial 4311, the geometric mean $C_{trough}$ values at Week 24 (GCV) in Japanese subjects (1 subject with HAwI, 3 subjects with HBwI) and non-Japanese subjects were 823.8 (0.3) and 659.1 (2.3) ng/mL, respectively, and other PK parameters are shown in Table 19. The plasma concentrations of concizumab over time in Japanese subjects were within the exposure range of the overall population (Figure 6), and there were no clear differences in the pharmacokinetic profile between Japanese and non-Japanese subjects. There were also no clear differences in plasma free TFPI concentrations.

**Table 19. PK parameters following multiple doses in Japanese and non-Japanese subjects (Arms 2-4)[a)]**

| | Japanese | | Non-Japanese | |
|---|---|---|---|---|
| | Baseline | Week 24[c)] | Baseline | Week 24[c)] |
| N | — | 4 | 63 | 65 |
| $C_{max}$ (ng/mL) (Geometric mean [GCV]) | — | 1007.4 (0.1) | 383.0 (2.5) | 1177.7 (1.3) |
| $AUC_{tau}$ (ng·h/mL) (Geometric mean [GCV])[b)] | — | 19307.3 (0.1) | 5818.6 (2.2) | 22605.3 (1.3) |
| $C_{max}/C_{trough}$ ratio (Mean ± SD) | — | 1.3 ± 0.4 | — | 2.2 ± 5.3 |

a) SAS and OTexIR
b) $AUC_{0\text{-}24h}$
c) Week 24 is relative to the relevant baseline.

**Figure 6. Pre-dose trough concizumab plasma concentrations (ng/mL) - Japanese vs. Non-Japanese (Arms 2-4)[a)b)]**




a) SAS and OTexIR
b) Plasma concentrations below the LLOQ are set to half of the LLOQ.

A total of 4 Japanese patients with HA were enrolled in Trial 4255, and 2 Japanese patients with HBwI (including 1 patient assigned to the concizumab group) were enrolled in Trial 4310. In either trial, there were no major differences in concizumab exposure or decreases in plasma free TFPI after dosing between Japanese and non-Japanese subjects. Also in phase I trials in healthy subjects (Trials 3813 and 3981), there were no clear differences in concizumab plasma concentration or free TFPI concentration over time after dosing between Japanese and non-Japanese subjects.

PMDA accepted the applicant's explanation, and considers that regarding the use of the data from global trials involving Japan and foreign clinical trials as the basis for the efficacy and safety of concizumab, no particular problem has been suggested from a pharmacokinetic perspective.

### 6.R.2 ADA

The applicant's explanation about the incidence of ADAs and the impact of ADAs on the PK/PD, efficacy, and safety of concizumab:

ADAs and neutralizing antibodies (*in vitro* neutralizing ADAs) were assessed across clinical trials. No ADAs were detected in phase I trials, and 15 of 61 subjects treated with concizumab (24%-25%) developed ADAs, and ADAs were neutralizing *in vitro* in 4 subjects (6.6%) in phase II trials (Trials 4310 and 4255). In the 1 subject with ADAs in Trial 4310, plasma free TFPI concentration returned to baseline, but there was no evident worsening of the bleeding pattern (the frequency and timing of bleeding events). In a phase III trial (Trial 4311), 33 of 127 subjects treated with concizumab (treatment arms 1-4) (26%) developed ADAs, and ADAs were neutralizing *in vitro* in 8 subjects (6.3%). Among patients treated with concizumab via compassionate use,[7)]

[7)] A total of 14 patients (8 on an individual patient basis and 6 through the concizumab compassionate use program) were treated with concizumab via compassionate use.

ADAs and neutralizing antibodies were detected in 1 patient each, and the detection of neutralizing antibodies coincided with a reduction of concizumab activity (multiple target joint bleeds) in the 1 patient with neutralizing antibodies. On the other hand, the patient continued to receive concizumab, and neutralizing antibodies were negative in samples collected at ≥2.5 months after the detection of neutralizing antibodies. Moreover, as the detection of neutralizing antibodies did not always coincide with a bleeding episode, it cannot be concluded that neutralizing antibodies worsened the bleeding pattern in this patient. Bleeding patterns in patients with ADAs in clinical trials were also assessed. Regardless of the presence or absence of ADAs (the periods with or without ADAs), the bleeding pattern was largely similar, and the presence of ADAs is not considered to affect efficacy.

Plasma concizumab concentration and plasma free TFPI concentration were used as PK/PD markers. The effects of ADAs and the timing of ADA formation were assessed based on the over-time plots of concentrations in individual subjects. Plasma concizumab concentrations and plasma free TFPI concentrations showed similar profiles, regardless of the presence or absence of ADAs. Thus, ADAs are not considered to affect the PK/PD of concizumab.

The safety analysis indicated no major differences in the incidence of adverse events according to ADA status (Table 20).

**Table 20. Adverse events by ADA status (Pooled data from Trials 4311, 4310, 4255, and 4159, SAS)**

| | | ADA-negative (N = 138) | ADA-positive (N = 47) |
|---|---|---|---|
| All adverse events | | 101 (73.2) | 36 (76.6) |
| Serious adverse events | | 15 (10.9) | 9 (19.1) |
| Severity | Severe | 13 ( 9.4) | 6 (12.8) |
| | Moderate | 34 (24.6) | 18 (38.3) |
| | Mild | 93 (67.4) | 32 (68.1) |

N: Number of subjects analyzed
Number of subjects with event (%)

Based on the above, ADAs and neutralizing antibodies have no major impact on the PK/PD, efficacy, and safety of concizumab. However, information on the incidences of ADAs and neutralizing antibodies will be provided in the package insert, etc.

PMDA's view:
According to the presented data etc., there were no clear effects of ADAs on the efficacy, safety, and PK/PD of concizumab, and neutralizing antibodies were found in multiple subjects in clinical trials. Given these points, information on ADAs and neutralizing antibodies should be provided in the package insert, etc. It is also necessary to continue to collect information on the incidences of ADAs and neutralizing antibodies in the ongoing clinical trials, etc. Package insert information should be updated appropriately based on new findings available.

### 6.R.3 Dosage and administration

#### 6.R.3.1 Non-linear PK of concizumab

The results of pharmacokinetic studies showed that systemic exposure to concizumab based on the $C_{max}$ and AUC increased with increasing dose in a greater than dose-proportional manner.

The applicant's explanation about the non-linear PK of concizumab:
The target for concizumab, TFPI is present on endothelial cells (approximately 92%) and in platelets (approximately 1%) and plasma (approximately 7%). Since concizumab binds to TFPI on endothelial cells and is then cleared by endocytosis and degradation (target-mediated clearance), the non-linear PK behavior is caused by TMDD.

A population pharmacokinetic analysis (Modeling and Simulation [M&S]) indicated complete saturation of non-linear clearance process at concizumab plasma concentrations >10000 ng/mL (body weight of 75 kg). Thus, the clearance of concizumab is expected to be non-linear at the exposure levels observed in Trial 4311 (Section 6.2.2 Table 15). Although between-subject and within-subject variabilities in concizumab exposure are likely to be attributable to differences in the endothelial TFPI pool, as the endothelial TFPI pool cannot be measured, this has not been demonstrated experimentally.

PMDA's view:
The dose should be adjusted, considering the non-linear PK of concizumab, large between-subject and within-subject variabilities in concizumab exposure, and poorly predictable variability over time. This point will be discussed in Section 7.R.5, taking also account of the following considerations in Sections 6.R.3.2 and 6.R.3.3.

#### 6.R.3.2 Loading dose as the first dose and maintenance dose

Global phase III trials (Trials 4311 and 4307[8)]) were paused owing to thromboembolic events and resumed after changing the maintenance dose from 0.25 mg/kg to 0.20 mg/kg [see Section 7.3.1]. The selection of the loading and maintenance doses for Trial 4311 was based on (1) at the time of start of the trial and (2) after the temporary pause and restart of the trial.

**(1) At the time of start of Trial 4311**

Based on PK/PD, efficacy, and safety data from phase II trials and pharmacokinetic modelling, a loading dose of 1 mg/kg (excluding patients transferred from a phase II trial) and a maintenance dose of 0.25 mg/kg were chosen. Exploratory exposure-response analyses based on the results of the main parts of phase II trials (Trials 4255 and 4310) (Table 21) showed relatively high bleeding rates at exposure levels up to 200 ng/mL. Simulations indicated that the majority of subjects would have exposure levels of ≥200 ng/mL at a maintenance dose of 0.25 mg/kg.

[8)] A global phase III trial to evaluate the efficacy and safety of multiple subcutaneous injections of concizumab in patients with HA or HB aged ≥12 years (including Japan). A 1.0 mg/kg loading dose of concizumab was followed by a maintenance dose of 0.20 mg/kg once daily. Within the initial 5- to 8-week period, the maintenance dose was adjusted to 0.15, 0.20, or 0.25 mg/kg.

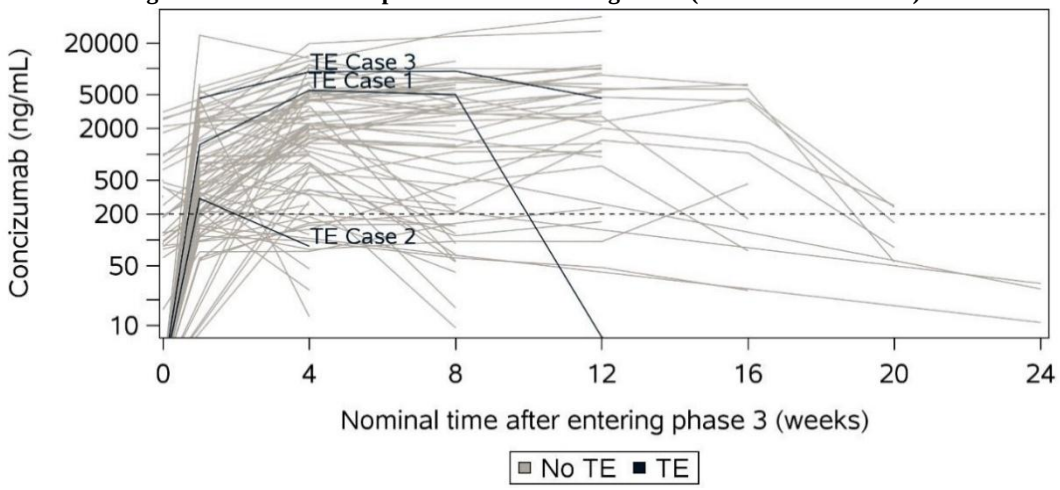
**Table 21. Exposure-response analyses of model-estimated ABR**

| Exposure (ng/mL) | Number of subjects | Proportion of subjects with bleeding episodes (%) | Number of bleeding episodes | Exposure time (years) | ABR estimate [95% CI] (episodes/year) |
|---|---|---|---|---|---|
| 0-100 | 53 | 55 | 65 | 6.72 | 15.6 [10.1-24.1] |
| 100-200 | 48 | 62 | 92 | 8.88 | 14.5 [8.1-26.2] |
| 200-500 | 26 | 46 | 22 | 5.06 | 4.9 [2.2-10.7] |
| 500-1000 | 13 | 38 | 8 | 2.35 | 3.7 [1.2-10.8] |
| >1000 | 8 | 38 | 5 | 0.98 | 5.4 [1.4-19.2] |

**(2) After restart of Trial 4311**

A total of 2 out of 3 subjects with thromboembolic events had high exposure levels (>5000 ng/mL, Figure 7). Concizumab exposure at the original maintenance dose of 0.25 mg/kg was higher than predicted by population pharmacokinetic modelling at the time of the start of the trial and the results of phase II trials.

**Figure 7. Concizumab exposure at the initial regimen[a] (Trials 4311 and 4307)[b]**




No TE: subjects without thromboembolic events; TE: subjects with thromboembolic events
a) Loading dose of 1 mg/kg, maintenance dose of 0.25 mg/kg
b) Data cutoff date of April 27, 2020

Based on the above, concizumab exposure at a lower maintenance dose was simulated using the updated population pharmacokinetic model, which predicted that concizumab exposure at a maintenance dose of 0.20 mg/kg is within the exposure range observed in the phase II trials. Given these findings, a maintenance dose of 0.20 mg/kg was chosen from an efficacy and safety standpoint.

PMDA concluded that the selection of loading and maintenance doses are acceptable from a clinical pharmacology standpoint. As the appropriateness of the dosing regimen of concizumab needs to be discussed, including the efficacy and safety results from clinical trials, this is covered in Section 7.R.5.

### 6.R.3.3 Dose adjustment

For the restart of phase III trials (Trials 4311 and 4307), the following dose adjustment was scheduled after Week 4 in addition to the change in the maintenance dose.

- Measure blood concizumab concentration after Week 4 of concizumab prophylaxis.
- Based on blood concizumab concentration at Week 4, increase the maintenance dose to 0.25 mg/kg for

subjects with blood concentration of <200 ng/mL, and decrease to 0.15 mg/kg for subjects with blood concentration of >4000 ng/mL.

The applicant's explanation about the reason for including a dose-adjustment step and the appropriateness of dose adjustment (including the selection of lower and upper cutoffs for concizumab exposure):
Exploratory exposure-response analyses based on the results from phase II trials (Trials 4255 and 4310) showed a trend toward lower bleeding rates at exposure levels ≥200 ng/mL (Section 6.R.3.2 Table 21). The 200 ng/mL cutoff for individual maintenance dose setting (dose adjustment) was based on this finding. Although there are no data showing that thromboembolic events were caused directly by high exposure levels itself, as high exposure levels combined with other risk factors can become a factor in causing thromboembolism, the 4000-ng/mL cutoff was set as an additional safety precaution to avoid constant, high concizumab exposure levels.

A population pharmacokinetic analysis (M&S) based on the data after the restart of Trial 4311, etc. predicted that inclusion of the above dose-adjustment step would reduce concizumab exposure variability at the population level (Section 6.3 Figure 3). According to the exposure-response analyses of efficacy (ABR) and biomarkers (plasma free TFPI, peak thrombin generation), dose adjustment can only maintain concizumab exposure that keeps the same levels of outcomes (Section 6.4 Figures 4 and 5), and no further benefit is expected in efficacy at even higher exposure levels.

Actually in Trial 4311, the maintenance dose was decreased in 1 subject (1.0%), increased in 24 subjects (24.7%), and maintained in 72 subjects (74.2%) by the above-mentioned dose adjustment. After individual maintenance dose setting, between-subject variability was observed in concizumab exposure, but concizumab exposure levels remained stable during the trial period (Section 6.2.2 Figure 1 and Section 6.R.1 Figure 6). The efficacy and safety results of Trial 4311 also support the appropriateness of dose adjustment.

PMDA's conclusion:
Taking account of the applicant's explanation, dose adjustment based on blood concentration at Week 4 is acceptable from a clinical pharmacology standpoint. The appropriateness of dose adjustment is discussed in Section 7.R.5.

## 7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted efficacy and safety evaluation data, in the form of the results from foreign phase I trials, global phase II trials, and global phase III trials presented in Table 22.

**Table 22. Listing of clinical trials**

| Geographical location | Trial | Phase | Trial population | Number of subjects treated | Dosing regimen | Main endpoints |
|---|---|---|---|---|---|---|
| Foreign | 3813 | I | Healthy subjects and patients with HA or HB (18-65 years) | N = 52<br>28 healthy subjects<br>24 hemophilia patients<br>(each dose of concizumab : placebo = 3 : 1) | Single intravenous doses of 0.5, 5, 50, or 250 µg/kg of concizumab or placebo in healthy subjects. Single intravenous doses of 250, 1000, 3000, or 9000 µg/kg or placebo in hemophilia patients.<br>Single subcutaneous doses of 50, 250, or 1000 µg/kg of concizumab or placebo in healthy subjects. Single subcutaneous doses of 1000 or 3000 µg/kg of concizumab or placebo in hemophilia patients. | Safety<br>PK |
| | 3981 | I | Japanese healthy subjects living in the UK (20-64 years) | N = 8<br>concizumab : placebo = 3 : 1 | A single subcutaneous dose of concizumab (250 or 1000 µg/kg) or placebo | PK<br>Safety |
| | 3986 | I | Healthy subjects and patients with HA (18-64 years) | N = 4<br>(4 each in dose cohorts according to the initial plan) | Concizumab 250 µg/kg (healthy subjects), 500 µg/kg, or 1000 µg/kg (hemophilia patients) administered subcutaneously every other day for 8 doses. Since the trial was halted, concizumab was administered at a dose of 250 µg/kg only. | Safety<br>PK |
| | 4159 | I | Patients with HA (18-64 years) | N = 24<br>each dose of concizumab : placebo = 3 : 1 | Concizumab (0.25, 0.50, or 0.80 mg/kg) or placebo administered subcutaneously every 4 days for 12 doses. | Safety<br>PK |
| Global | 4310 | II | Patients with HAwI or HBwI (≥18 years) | N = 26<br>17 in the concizumab group<br>9 in the control group | Concizumab group: A 0.5 mg/kg loading dose of subcutaneous concizumab followed by 0.15 mg/kg (with potential stepwise dose escalation to 0.20 and 0.25 mg/kg) once daily for 76-118 weeks (≥24 weeks in the main part).<br>Control group: main part (24 weeks, on-demand treatment with rFVIIa) followed by extension part (a 0.5 mg/kg loading dose of subcutaneous concizumab followed by 0.15 mg/kg once daily)<br>Both groups: treatment of breakthrough bleeding episodes with rFVIIa | Efficacy<br>Safety |
| | 4255 | II | Patients with HA (≥18 years) | N = 36 | Concizumab 0.15 mg/kg (with potential stepwise dose escalation to 0.20 and 0.25 mg/kg) administered subcutaneously once daily for 76-126 weeks (≥24 weeks in the main part). | Efficacy<br>Safety |
| | 4322 | III | Patients with HA, HB, HAwI, or HBwI (≥12 years) | N = 231 | Investigate the number of bleeding episodes in routine clinical treatment practice in patients with hemophilia. | Non-interventional study in patients treated according to routine clinical treatment practice |
| | 4311 | III | Patients with HAwI or HBwI (including subjects transferred from Trial 4310 or Study 4322) (≥12 years) | N = 133<br>80 patients with HAwI<br>53 patients with HBwI<br>21 from Trial 4310, 64 from Study 4322 | Arm: Previous treatment: Main part 24-32 weeks: Extension part 128-136 weeks<br>Arm 1: On-demand treatment: On-demand treatment: Concizumab prophylaxis<br>Arm 2: On-demand treatment: Concizumab prophylaxis: Concizumab prophylaxis<br>Arm 3: Trial 4310: Concizumab prophylaxis: Concizumab prophylaxis | Efficacy<br>Safety |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | | | | Arm 4 | Prophylaxis with by-passing agents and on-demand treatment | Concizumab prophylaxis | Concizumab prophylaxis | |
| | | | | | A 1.0 mg/kg loading dose of subcutaneous concizumab followed by a maintenance dose of 0.20 mg/kg once daily. Within the initial 5-8-week period, the maintenance dose was adjusted to 0.15, 0.20, or 0.25 mg/kg.[a)] | | | | |

a) The modified dosing regimen [see Section 7.3.1]

Clinical trials are summarized below. Pharmacokinetic and pharmacodynamic results from phase I trials are described in Section 6.2.

## 7.1 Phase I trials

### 7.1.1 Foreign phase I trial (CTD5.3.3.1-3, Trial NN7415-3813; Trial period, October 2010 to September 2012)

A randomized, double-blind, placebo-controlled, dose escalation trial was conducted at 13 sites in 9 foreign countries to investigate the safety, pharmacokinetics, and pharmacodynamics of concizumab in healthy male subjects and patients with hemophilia aged 18 to 65 years. A single intravenous or subcutaneous dose of concizumab was administered as per the regimens shown in Table 23.

**Table 23. Dosing regimens in Trial 3813**

| | IV administration (µg/kg) | | | | | SC administration (µg/kg) | | | |
|---|---|---|---|---|---|---|---|---|---|
| Healthy male subjects | 0.5 (N = 3) | 5 (N = 3) | 50 (N = 3) | 250 (N = 3) | Placebo (N = 4) | 50 (N = 3) | 250 (N = 3) | 1000 (N = 3) | Placebo (N = 3) |
| Patients with Hemophilia | 250 (N = 3) | 1000 (N = 3) | 3000 (N = 3) | 9000 (N = 3) | Placebo (N = 4) | 1000 (N = 3) | 3000 (N = 3) | Placebo (N = 2) | |

A total of 52 subjects enrolled in the trial received trial drug (concizumab or placebo), all of whom were included in the safety analysis set (SAS).

The safety analysis revealed 76 adverse events occurring in 65.4% (34 of 52) of subjects. Adverse events reported by ≥2 subjects treated with concizumab were nasopharyngitis (concizumab [2 subjects, 2 events], placebo [1 subject, 1 event]), contusion (concizumab [4 subjects, 5 events]), headache (concizumab [4 subjects, 5 events], placebo [1 subject, 1 event), arthralgia (concizumab [2 subjects, 2 events], placebo [1 subject, 1 event]), haemarthrosis (concizumab [6 subjects, 10 events], placebo [3 subjects, 4 events]), and pain in extremity (concizumab [2 subjects, 2 events]). A total of 5 subjects experienced 5 adverse drug reactions (protein urine [concizumab 250 µg/kg IV], abdominal pain (concizumab 9000 µg/kg IV), and hypersensitivity [placebo IV] in patients with hemophilia; superficial thrombophlebitis [concizumab 1000 µg/kg SC] and injection site discomfort [placebo SC] in healthy male subjects), and the outcomes of those events were all reported as "resolved." There were no serious adverse events or adverse events leading to death or trial discontinuation.

### 7.1.2 Foreign phase I trial (CTD5.3.3.1-1, Trial NN7415-3981; Trial period, March 2012 to May 2012)

A randomized, double-blind, placebo-controlled trial was conducted at 1 site overseas to assess the pharmacokinetics of a single subcutaneous dose of concizumab in Japanese healthy male subjects aged 20 to 64 years.

A single subcutaneous dose of concizumab or placebo was administered. Treatment began with the low-dose cohort (3 subjects for concizumab 250 μg/kg, 1 subject for placebo), followed by the high-dose cohort (3 subjects for concizumab 1000 μg/kg, 1 subject for placebo).

A total of 8 subjects enrolled in the trial received the trial drug (concizumab or placebo), all of whom were included in the SAS.

The safety analysis revealed 5 adverse events occurring in 50.0% (4 of 8) of subjects. Adverse events reported by ≥2 subjects treated with concizumab were nasopharyngitis[9)] (concizumab [2 subjects, 2 events], placebo [1 subject, 1 event]). There were no adverse drug reactions, serious adverse events, deaths, or adverse events leading to trial discontinuation.

### 7.1.3 Foreign phase I trial (CTD5.3.4.2-1, Trial NN7415-4159; Trial period, September 2015 to October 2016)

A randomized, double-blind, placebo-controlled, dose escalation trial was conducted at 18 sites in 13 foreign countries to investigate the safety, pharmacokinetics, and pharmacodynamics of concizumab subcutaneously administered in hemophilia A patients aged 18 to 64 years.

Concizumab 0.25, 0.50, or 0.80 mg/kg or placebo was administered subcutaneously daily for the first 2 days and then every 4 days for a total of 12 doses.

A total of 24 subjects enrolled in the trial (6 subjects receiving concizumab and 2 subjects receiving placebo for each dose level) received the trial drug, all of whom were included in the SAS.

The safety analysis revealed 56 adverse events occurring in 79.2% (19 of 24) of subjects. Adverse events reported by ≥2 subjects treated with concizumab were injection site erythema (concizumab [2 subjects, 2 events], placebo [1 subject, 1 event), fatigue (concizumab [2 subjects, 2 events]), nasopharyngitis [10)] (concizumab [3 subjects, 4 events], placebo [1 subject, 1 event), upper respiratory tract infection (concizumab [2 subjects, 2 events]), headache (concizumab [4 subjects, 6 events]), and myalgia (concizumab [2 subjects, 2 events]). Thirteen adverse drug reactions occurred in 33.3% (8 of 24) of subjects, which were injection site erythema (concizumab [2 subjects, 2 events], placebo [1 subject, 1 event]), injection site pain (placebo [1 subject, 2 events]), fatigue (concizumab [1 subject, 1 event]), headache (concizumab [1 subject, 3 events]), subcutaneous haemorrhage (placebo [1 subject, 1 event]), maculo-papular rash (concizumab [1 subject, 1

[9)] Nasopharyngitis (MedDRA/J ver.15.1)
[10)] Nasopharyngitis (MedDRA/J ver.19.0)

event]), flatulence (placebo [1 subject, 1 event]), and myalgia (concizumab [1 subject, 1 event]), and all of those events had an outcome of "resolved." There were no serious adverse events, deaths, or adverse events leading to trial discontinuation.

## 7.2 Phase II trials

### 7.2.1 Global phase II trial (CTD5.3.5.2-1 to 5.3.5.2-2, Trial NN7415-4255; Trial period, August 2017 to June 2020)

A global, open-label, uncontrolled, dose escalation trial was conducted at 26 sites in 11 countries including Japan to evaluate the efficacy and safety of prophylactic administration of concizumab in patients with severe hemophilia A without inhibitors aged ≥18 years.

Subjects were treated with once daily subcutaneous injections of concizumab 0.15 mg/kg, with potential stepwise dose escalation to 0.20 and 0.25 mg/kg if they experienced ≥3 spontaneous bleeding episodes within the preceding 12 weeks of concizumab treatment. The trial consisted of the main and extension parts. The main part of the trial ended when all subjects had completed 24 weeks of treatment. The extension part lasted 52 to 102 weeks.

A total of 36 subjects enrolled in the trial received concizumab, all of whom were included in the SAS and the full analysis set (FAS). Of these, 4 subjects withdrew from the trial before the end of the main part and did not enter the extension part.

The efficacy of concizumab was evaluated based on the number of treated bleeding episodes during the treatment period of each subject in which their last dose level was reached. The ABR[6)] estimates [95% CI] from a negative binomial regression model were 7.0 [4.6, 10.7] episodes/year (main part) and 6.4 [4.1, 9.9] episodes/year (main part + extension part). Table 24 shows ABR by last dose level.

**Table 24. ABR by last dose level (main part + extension part, FAS)**

| Last dose level | 0.15 mg/kg | 0.20 mg/kg | 0.25 mg/kg | Total |
|---|---|---|---|---|
| Number of subjects analyzed | 15 | 10 | 10 | 35 |
| Total observation period (years) | 28.8 | 10.1 | 12.1 | 51.0 |
| Total number of bleeding episodes | 67 | 42 | 123 | 232 |
| ABR estimate [95% CI] | — | — | — | 6.4 [4.1, 9.9] |
| Median ABR [Range] | 3.0 [0.0, 45.7] | 2.6 [0.0, 20.6] | 12.9 [0.0, 28.2] | 3.8 [0.4, 45.7] |

The safety analysis revealed 298 adverse events occurring in 91.7% (33 of 36) of subjects and 76 adverse drug reactions in 58.3% (21 of 36) of subjects during the trial period (≥76 weeks in the main and extension parts). Table 25 shows adverse events or adverse drug reactions reported by ≥2 subjects.

**Table 25. Adverse events or adverse drug reactions reported by ≥2 subjects (SAS)**

| | Adverse events (N = 36) | | Adverse drug reactions (N = 36) | |
|---|---|---|---|---|
| | n (%) | Number of events | n (%) | Number of events |
| Total | 33 (91.7) | 298 | 21 (58.3) | 76 |
| Gastrointestinal infection | 3 ( 8.3) | 3 | 0 | 0 |
| Influenza | 4 (11.1) | 4 | 0 | 0 |
| Nasopharyngitis | 12 (33.3) | 22 | 0 | 0 |
| Periodontitis | 2 ( 5.6) | 2 | 0 | 0 |
| Pharyngitis | 3 ( 8.3) | 3 | 0 | 0 |
| Rhinitis | 2 ( 5.6) | 2 | 0 | 0 |
| Upper respiratory tract infection | 5 (13.9) | 7 | 0 | 0 |
| Influenza like illness | 2 ( 5.6) | 2 | 1 ( 2.8) | 1 |
| Injection site bruising | 6 (16.7) | 10 | 5 (13.9) | 9 |
| Injection site haematoma | 5 (13.9) | 7 | 2 ( 5.6) | 3 |
| Injection site haemorrhage | 4 (11.1) | 8 | 3 ( 8.3) | 3 |
| Injection site pruritus | 2 ( 5.6) | 2 | 2 ( 5.6) | 2 |
| Pyrexia | 3 ( 8.3) | 4 | 0 | 0 |
| Fibrin D dimer increased | 9 (25.0) | 12 | 9 (25.0) | 12 |
| Prothrombin level increased | 7 (19.4) | 12 | 7 (19.4) | 12 |
| Thrombin-antithrombin III complex increased | 2 ( 5.6) | 5 | 2 ( 5.6) | 5 |
| Arthralgia | 4 (11.1) | 6 | 0 | 0 |
| Back pain | 5 (13.9) | 7 | 0 | 0 |
| Groin pain | 2 ( 5.6) | 3 | 1 ( 2.8) | 1 |
| Haemophilic arthropathy | 2 ( 5.6) | 3 | 0 | 0 |
| Musculoskeletal chest pain | 2 ( 5.6) | 3 | 0 | 0 |
| Neck pain | 2 ( 5.6) | 9 | 0 | 0 |
| Contusion | 2 ( 5.6) | 11 | 1 ( 2.8) | 2 |
| Fall | 2 ( 5.6) | 2 | 0 | 0 |
| Ligament sprain | 2 ( 5.6) | 3 | 0 | 0 |
| Chronic gastritis | 2 ( 5.6) | 2 | 0 | 0 |
| Dental caries | 3 ( 8.3) | 6 | 0 | 0 |
| Headache | 8 (22.2) | 12 | 1 ( 2.8) | 2 |
| Cough | 4 (11.1) | 4 | 0 | 0 |
| Oropharyngeal pain | 2 ( 5.6) | 5 | 0 | 0 |
| Pruritus | 2 ( 5.6) | 2 | 0 | 0 |
| Type 2 diabetes mellitus | 2 ( 5.6) | 2 | 0 | 0 |

N: Number of subjects analyzed
MedDRA/J ver.22.1

The incidence of serious adverse events was 13.9% (5 of 36 subjects) (5 events) (atypical pneumonia, ligament sprain, pharyngeal haemorrhage, gastrointestinal haemorrhage, gastrointestinal infection). A causal relationship to concizumab was denied except for atypical pneumonia, and all those events had an outcome of "resolved." There were no deaths or adverse events leading to discontinuation. In addition, 1 serious adverse event (abortion missed) was reported by a subject's partner.

### 7.2.2 Global phase II trial (CTD5.3.5.1-1 to 5.3.5.1-2, Trial NN7415-4310; Trial period, August 2017 to January 2020)

A global, open-label, randomized, parallel-group (dose escalation) trial was conducted at 17 sites in 12 countries including Japan to evaluate the efficacy and safety of prophylactic administration of concizumab in patients with hemophilia with inhibitors aged ≥18 years.

Subjects were randomized to receive concizumab prophylaxis or on-demand treatment with rFVIIa. A 0.5-mg/kg loading dose of subcutaneous concizumab was administered as the first dose, followed by a maintenance dose of 0.15 mg/kg once daily. For subjects experiencing ≥3 spontaneous bleeding episodes within the

preceding 12 weeks of treatment with concizumab, the maintenance dose could be escalated to 0.20 mg/kg and then to 0.25 mg/kg. The trial consisted of the main and extension parts. The main part of the trial ended when all subjects had completed 24 weeks of treatment. The extension part lasted 52 to 94 weeks. After completion of the main part, subjects in the rFVIIa group were switched to prophylactic treatment with concizumab.

Twenty-six subjects enrolled in the trial received trial drug (17 in the concizumab group, 9 in the rFVIIa group), all of whom were included in the SAS and the FAS. One subject who discontinued treatment before the end of the main part did not enter the extension part.

The efficacy of concizumab was evaluated based on the number of treated bleeding episodes during the treatment period of each subject in which their last dose level was reached. The ABR estimates [95% CI] from a negative binomial regression model were 4.5 [3.2, 6.4] episodes/year (main part) and 4.8 [3.2, 7.2] episodes/year (main part + extension part) in the concizumab group and 20.4 [14.4, 29.1] episodes/year (main part) in the rFVIIa group. Table 26 shows ABR by last dose level.

**Table 26. ABR by last dose level (main part + extension part, FAS)**

| Last dose level | 0.15 mg/kg | 0.20 mg/kg | 0.25 mg/kg | Total |
|---|---|---|---|---|
| Number of subjects analyzed | 12 | 9 | 4 | 25 |
| Total observation period (years) | 21.7 | 6.3 | 2.4 | 30.4 |
| Total number of bleeding episodes | 97 | 19 | 20 | 136 |
| ABR estimate [95% CI] | — | — | — | 4.8 [3.2, 7.2] |
| Median ABR [Range] | 4.9 [0.0, 8.9] | 1.6 [0.0, 13.4] | 11.6 [0.0, 17.4] | 3.6 [0.0, 17.4] |

The safety analysis revealed 131 adverse events occurring in 88.0% (22 of 25) of subjects and 13 adverse drug reactions in 36.0% (9 of 25) of subjects during the trial period (≥76 weeks in the main and extension parts). Table 27 shows adverse events or adverse drug reactions reported by ≥2 subjects.

**Table 27. Adverse events or adverse drug reactions reported by ≥2 subjects (SAS)**

| | Adverse events (N = 25) | | Adverse drug reactions (N = 25) | |
|---|---|---|---|---|
| | n (%) | Number of events | n (%) | Number of events |
| Total | 22 (88.0) | 131 | 9 (36.0) | 13 |
| Viral gastroenteritis | 2 ( 8.0) | 2 | 0 | 0 |
| Nasopharyngitis | 3 (12.0) | 6 | 0 | 0 |
| Respiratory tract infection | 2 ( 8.0) | 2 | 0 | 0 |
| Rhinitis | 2 ( 8.0) | 2 | 0 | 0 |
| Upper respiratory tract infection | 4 (16.0) | 8 | 0 | 0 |
| Injection site bruising | 2 ( 8.0) | 3 | 2 ( 8.0) | 3 |
| Injection site haematoma | 3 (12.0) | 10 | 0 | 0 |
| Pyrexia | 2 ( 8.0) | 2 | 0 | 0 |
| Diarrhoea | 4 (16.0) | 5 | 0 | 0 |
| Gastritis | 2 ( 8.0) | 2 | 0 | 0 |
| Toothache | 2 ( 8.0) | 2 | 0 | 0 |
| Vomiting | 2 ( 8.0) | 2 | 0 | 0 |
| Arthralgia | 3 (12.0) | 3 | 0 | 0 |
| Fibrin D dimer increased | 2 ( 8.0) | 2 | 2 ( 8.0) | 2 |
| Prothrombin level increased | 2 ( 8.0) | 2 | 2 ( 8.0) | 2 |
| Headache | 2 ( 8.0) | 2 | 1 ( 4.0) | 1 |
| Anaemia | 2 ( 8.0) | 2 | 0 | 0 |
| Insomnia | 2 ( 8.0) | 2 | 0 | 0 |

N: Number of subjects analyzed
MedDRA/J ver.22.1

The incidence of serious adverse events was 20% (5 of 25 subjects) (9 events) (central venous catheter removal, arthropathy, loss of consciousness, hand fracture, puncture site haemorrhage, haemorrhagic shock, muscle haemorrhage, subdural haemorrhage, sleep apnoea syndrome). A causal relationship to concizumab was ruled out for all those events, and their outcomes were reported as "resolved" except for sleep apnoea syndrome. There were no deaths or adverse events leading to trial discontinuation.

## 7.3 Phase III trial

### 7.3.1 Global phase III trial (CTD5.3.5.1-3, Trial NN7415-4311; Trial period, ongoing since October 2019 [data cutoff date of December 27, 2021, data cutoff date of February 2, 2022 for serious adverse events])

An open-label, partially randomized trial was conducted at 70 sites in 27 countries including Japan to assess the efficacy and safety of daily subcutaneous concizumab prophylaxis in patients with hemophilia A or B with inhibitors aged ≥12 years (including subjects transferred from Trial 4310 or Study 4322).

The trial included 2 randomization arms and 2 nonrandomization arms (a total of 4 treatment arms), and subjects were randomized or assigned to treatment arms, based on their treatment regimen before entering the trial. The trial consisted of the main part (24 weeks) and the extension part (up to 136 weeks). The trial was designed as described in (1) below at the start, but the applicant paused this trial and Trial 4307[8)] in March 2020 due to 5 serious thromboembolic events in 3 patients in these trials (Section 7.R.3.1 Table 37). Concizumab treatment was also paused during the trial pause. The trials resumed after August 2020 following the implementation of risk mitigation measures such as a new dosing regimen and updated breakthrough bleeding management guidance. The trial designs before and after the trial pause are shown below.

(1) Trial design before the trial pause

(i) Randomization arms: Subjects receiving on-demand treatment before enrollment (target sample size, 48 subjects[11)]) were randomly assigned at a ratio of 1:2 to Arm 1 (on-demand treatment) or Arm 2 (concizumab prophylaxis). The randomization was stratified by type of hemophilia and bleeding frequency.[12)] A 1.0-mg/kg loading dose of concizumab was administered subcutaneously on Day 1 followed by a maintenance dose of 0.25 mg/kg once daily starting on Day 2 ("the initial dosing regimen").

Arm 1: On-demand treatment with bypassing agents in the main part and concizumab prophylaxis with the initial dosing regimen in the extension part

Arm 2: Concizumab prophylaxis with the initial dosing regimen in the main and extension parts

(ii) Nonrandomization arms:

Arm 3: A loading dose was omitted, and concizumab prophylaxis with the initial dosing regimen in the main and extension parts for subjects who consented to be transferred from Trial 4310 to this trial (target sample size, 25 subjects)

[11)] With a treatment duration of approximately 6 months, assuming a yearly overdispersion of 13, and ABR of 18 episodes in Arm 1 and 3 to 5 episodes in Arm 2, a sample size of 42 patients would provide ≥97% power to detect the superiority of Arm 2 (concizumab prophylaxis) over Arm 1 (on-demand treatment) (two-sided significance level of 0.05).

[12)] The number of bleeding episodes during the 24 weeks before screening (<9, ≥9)

Arm 4: Concizumab prophylaxis with the initial dosing regimen in the main and extension parts for subjects who had received prophylaxis with a bypassing agent before enrollment and subjects receiving on-demand treatment before enrollment who were screened at a timepoint where the required number of patients in Arms 1 and 2 had been randomized (target sample size, 60 subjects).

(2) Trial design after the restart of the trial

Since approximately 85% of the planned sample size for Arms 1 and 2 had been enrolled (41 of 48 subjects: 13 in Arm 1 and 28 in Arm 2) at the time of the trial pause, the trial resumed with no substantial change in the target sample size, and subjects before and after the pause were evaluated together (target sample size, 51 subjects[13)]). Subjects enrolled before the pause remained in the same treatment arms. New enrolled subjects were randomized to Arm 1 or 2 according to the randomization schedule used before the pause if the randomization criteria were met, or assigned to Arm 4.

The resumed trial consisted of the main part (≥24 weeks [Arm 1] or ≥32 weeks [Arms 2-4]) and the extension part (up to 136 weeks). A new dosing regimen of concizumab ("the new dosing regimen") was as follows.

New dosing regimen: A 1.0-mg/kg loading dose of subcutaneous concizumab on Day 1 followed by a maintenance dose of 0.20 mg/kg once daily starting on Day 2. During the dose adjustment period of Weeks 5 to 8, a maintenance dose of 0.15 mg/kg, 0.20 mg/kg, or 0.25 mg/kg was selected based on the concizumab plasma concentration measured after Week 4.

Arm 1 (on-demand treatment): No concizumab prophylaxis and on-demand treatment with bypassing agents in the main part (≥24 weeks) followed by concizumab prophylaxis with the new dosing regimen in the extension part

Arms 2, 3, and 4 (concizumab prophylaxis): Concizumab prophylaxis with the new dosing regimen in the main part (≥32 weeks) and the extension part

All of 133 subjects enrolled in the trial were included in the FAS and the SAS. Among the SAS, 127 subjects received ≥1 dose of concizumab.[14)] Table 28 shows subject disposition.

[13)] With treatment durations of 24 weeks (Arm 1) and 32 weeks (Arm 2) based on the updated protocol, assuming the same other values as in the initial protocol, a sample size of 42 patients would detect superiority (two-sided significance level of 0.05) with ≥88% power. Allowing for dropouts, a target sample size of 51 randomized patients was chosen.

[14)] The reasons for treatment discontinuations (19 subjects) were adverse events (5 subjects), discretion of the investigator (3 subjects), and others (11 subjects). The reasons for trial withdrawals (25 subjects) were consent withdrawal (17 subjects: 5 in Arm 1, 2 in Arm 2, 3 in Arm 3, 7 in Arm 4), the investigator decision (3 subjects: 1 in Arm 2, 2 in Arm 3), and death (5 subjects: 1 in Arm 1, 3 in Arm 2, 1 in Arm 3).

**Table 28. Subject enrollment in Trial 4311**

| | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Total |
|---|---|---|---|---|---|
| Number of enrolled subjects (Total) | 19 | 33 | 21 | 60 | 133 |
| Enrolled before pause | 13 | 28 | 21 | 18 | 80 |
| Not restarted | 5 | 4 | 6 | 5 | 20 |
| Enrolled after restart | 6 | 5 | 0 | 42 | 53 |
| Number of subjects who received ≥1 dose of concizumab | — (13)[a)] | 33 | 21 | 60 | 114 (127)[a)] |
| Number of Japanese subjects | 0 | 1 | 1 | 4 | 6 |

a) Number of subjects in the main and extension parts in parenthesis (Subjects in Arm 1 received concizumab prophylaxis in the extension part)

Endpoints related to bleeding episodes were analyzed using the FAS and the OTwoATexIR analysis data set (On-treatment without ancillary therapy excl. data on the initial regimen for patients exposed to both regimens). The following data are included in OTwoATexIR.

On-demand treatment (Arm 1): All on-demand treatment data before, during, and after the pause
Concizumab prophylaxis:

- Subjects exposed to both initial and new regimens: Data on the new regimen excluding data on the initial regimen
- Subjects exposed only to the initial regimen: Data on the initial regimen
- Subjects exposed only to the new regimen: Data on the new regimen

For both on-demand treatment and concizumab prophylaxis, periods with ancillary therapy (use of factor-containing products not related to treatment of a bleeding episode) were excluded.

At the primary analysis cutoff,[15)] the median observation period [range] was 31.1 [3.9, 72.9] weeks in Arm 1 (until the start of concizumab prophylaxis), 40.1 [3.1, 56.3] weeks in Arm 2, 56.0 [3.6, 64.1] weeks in Arm 3, and 32.8 [2.0, 64.4] weeks in Arm 4.

The primary efficacy endpoint was the number of treated spontaneous and traumatic bleeding episodes. For Arm 1 (on-demand treatment) and Arm 2 (concizumab prophylaxis), the estimated ABRs were calculated using a negative binomial regression model. The ABR was significantly lower in Arm 2 than in Arm 1 (Table 29). The ABRs in Japanese subjects were 3.2 episodes/year in Arm 1 (N = 1) and 16.8 episodes/year in Arm 2 (N = 1).

**Table 29. Between-arm comparison of ABR for treated spontaneous and traumatic bleeding episodes (FAS, OTwoATexIR)**

| Treatment arm | Arm 1 (N = 19) | Arm 2 (N = 33) | ABR ratio | *P*-value |
|---|---|---|---|---|
| Estimated mean ABR[a)] [95% CI] | 11.8 [7.03, 19.86] bleeds/patient-year | 1.7 [1.01, 2.87] bleeds/patient-year | 0.14 [0.07, 0.29] | <0.001 |

N: Number of subjects analyzed
a) A negative binomial regression model that included treatment, type of hemophilia, and the number of bleeding episodes during the 24 weeks before screening (<9 or ≥9) as factors and the logarithm of the length of the observation period as offset.

[15)] The primary analysis cutoff was defined as the date when all subjects on on-demand treatment (Arm 1) had completed the Week 24 visit (or had withdrawn), and all subjects on concizumab prophylaxis (Arm 2) had completed the Week 32 visit (or had withdrawn).

The safety evaluation was based on the data collected during the entire trial period (the on-treatment period during which subjects were exposed to on-demand treatment with bypassing agents or concizumab treatment, irrespective of the dosing regimen of concizumab) (On treatment analysis data set). As of the primary analysis cutoff (December 27, 2021), 42.1% (8 of 19) of subjects in Arm 1 experienced 25 adverse events in the main part, 38.5% (5 of 13) of subjects in Arm 1 experienced 16 adverse events in the extension part, and 65.8% (75 of 114) of subjects in Arms 2 to 4 experienced 340 adverse events (60.6% [20 of 33] of subjects in Arm 2 experienced 60 adverse events; 76.2% [16 of 21] of subjects in Arm 3 experienced 83 adverse events; 65.0% [39 of 60] of subjects in Arm 4 experienced 197 adverse events). Table 30 shows adverse events reported by >3% of subjects in the SAS (127 subjects).

**Table 30. Adverse events reported by >3% of subjects (SAS, On treatment)**

| | On-demand treatment | | Concizumab prophylaxis | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Treatment arm | 1 (main part) N = 19 | | 1 (extension part) N = 13 | | 2 N = 33 | | 3 N = 21 | | 4 N = 60 | | Total N = 127 | |
| | n (%) | Number of events | n (%) | Number of events | n (%) | Number of events | n (%) | Number of events | n (%) | Number of events | n (%) | Number of events |
| Arthralgia | 0 | 0 | 0 | 0 | 2 (6.1) | 2 | 4 (19.0) | 8 | 7 (11.7) | 13 | 13 (10.2) | 23 |
| Upper respiratory tract infection | 1 (5.3) | 1 | 0 | 0 | 2 (6.1) | 2 | 4 (19.0) | 4 | 2 ( 3.3) | 2 | 8 (6.3) | 8 |
| COVID-19 | 1 (5.3) | 1 | 0 | 0 | 2 (6.1) | 2 | 3 (14.3) | 3 | 1 ( 1.7) | 1 | 6 (4.7) | 6 |
| Nasopharyngitis | 1 (5.3) | 1 | 0 | 0 | 1 (3.0) | 1 | 3 (14.3) | 3 | 2 ( 3.3) | 2 | 6 (4.7) | 6 |
| Injection site erythema | 0 | 0 | 0 | 0 | 1 (3.0) | 1 | 1 ( 4.8) | 1 | 7 (11.7) | 11 | 9 (7.1) | 13 |
| Injection site bruising | 0 | 0 | 0 | 0 | 1 (3.0) | 1 | 1 ( 4.8) | 1 | 2 ( 3.3) | 5 | 4 (3.1) | 7 |
| Pyrexia | 1 (5.3) | 1 | 0 | 0 | 2 (6.1) | 2 | 2 ( 9.5) | 2 | 2 ( 3.3) | 2 | 6 (4.7) | 6 |
| Prothrombin fragment 1.2 increased | 0 | 0 | 0 | 0 | 1 (3.0) | 1 | 1 ( 4.8) | 2 | 5 ( 8.3) | 9 | 7 (5.5) | 12 |
| Fibrin D dimer increased | 0 | 0 | 0 | 0 | 1 (3.0) | 1 | 0 | 0 | 5 ( 8.3) | 10 | 6 (4.7) | 11 |
| Headache | 0 | 0 | 0 | 0 | 1 (3.0) | 1 | 1 ( 4.8) | 1 | 4 ( 6.7) | 8 | 6 (4.7) | 10 |
| Pain in extremity | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 4 ( 6.7) | 4 | 4 (3.1) | 4 |
| Vaccination complication | 0 | 0 | 0 | 0 | 0 | 0 | 1 ( 4.8) | 1 | 3 ( 5.0) | 5 | 4 (3.1) | 6 |
| Hypertension | 0 | 0 | 0 | 0 | 1 (3.0) | 1 | 1 ( 4.8) | 1 | 2 ( 3.3) | 2 | 4 (3.1) | 4 |

N: Number of subjects analyzed, MedDRA/J ver. 24.1

The incidence of adverse drug reactions was 26.0% (33 of 127 subjects: 1 in Arm 1, 8 in Arm 2, 4 in Arm 3, 20 in Arm 4) (103 events) (injection site erythema [n = 13], migraine and prothrombin fragment 1.2 increased [n = 12 each], fibrin D dimer increased [n = 11], injection site urticaria [n = 7], injection site bruising and injection site haematoma [n = 5 each], injection site pruritus, migraine with aura, and arthralgia [n = 4 each], injection site reaction, injection site swelling, hypersensitivity, and pruritus [n = 2 each], injection site haemorrhage, injection site induration, injection site pain, injection site rash, blood fibrinogen decreased, C-reactive protein increased, fibrinolysis, aura, dizziness, headache, musculoskeletal stiffness, spinal osteoarthritis, abdominal pain, haematemesis, melaena, congestive cardiomyopathy, vitreous floaters, and renal infarct [n = 1 each]).

During concizumab prophylaxis, 11.0% (14 of 127) of subjects experienced 18 serious adverse events (0 subjects [0 events] in Arm 1, 6 subjects [9 events] in Arm 2 [road traffic accident, femur fracture, humerus fracture, COVID-19, encephalitis, haematemesis, melaena, hypersensitivity, and renal infarct (n = 1 each)], 1 subject [1 event] in Arm 3 [haemoglobin decreased (n = 1)], 7 subjects [8 events] in Arm 4 [ligament sprain, COVID-19, catheter site infection, fibrin D dimer increased, prothrombin fragment 1.2 increased, haemarthrosis, muscle haemorrhage, and dizziness (n = 1)]). Among those events, haematemesis and melaena (occurring in the same subject), fibrin D dimer increased and prothrombin fragment 1.2 increased (occurring in the same subject), hypersensitivity (n = 1), renal infarct (n = 1), and dizziness (n = 1) were classified as serious adverse drug reactions. The outcome of renal infarct was reported as "resolved with sequelae," and all other events had an outcome of "resolved." During the period of no concizumab prophylaxis, 15.8% (3 of 19) of subjects in Arm 1 experienced 5 serious adverse events (road traffic accident, lower limb fracture, COVID-19, pneumonitis, and haematoma [n = 1 each]).

There were 3 deaths (2 in Arm 2, 1 in Arm 1). The causes of deaths were reported to be road traffic accident, femur fracture, and humerus fracture occurring in the same subject in Arm 2, COVID-19 occurring in the other subject in Arm 2, and pneumonitis in the 1 subject in Arm 1 who had not transferred to receive concizumab. During the trial pause, 2 deaths (1 each in Arms 2 and 3) occurred, and the causes of deaths were reported to be gastrointestinal haemorrhage and haematoma, respectively. A causal relationship to trial drug was denied for all 5 cases. There were no adverse events leading to trial discontinuation.

Among Japanese subjects, as of the primary analysis cutoff, 83.3% (5 of 6) experienced 34 adverse events, and 66.7% (4 of 6) of subjects experienced 9 adverse drug reactions (prothrombin fragment 1.2 increased [n = 4], fibrin D dimer increased [n = 2], injection site swelling, injection site urticaria, and injection site reaction [n = 1 each]). The outcomes of prothrombin fragment 1.2 increased (n = 2) and fibrin D dimer increased (n = 1) were reported as "unresolved," but all other events had an outcome of "resolved." Though 2 subjects experienced 2 serious adverse events (haemarthrosis and muscle haemorrhage [n = 1 each]), their causal relationship to concizumab was denied, and the outcomes of these events were both reported as "resolved."

## 7.R Outline of the review conducted by PMDA

### 7.R.1 Clinical data package

The applicant's explanation about the clinical data package for the present application:

Given its mechanism of action, concizumab is expected to be effective in patients with hemophilia with or without inhibitors. Thus, concizumab has been developed for all patients with hemophilia A or B. The present application has been submitted for concizumab in patients with hemophilia A or B with inhibitors. Since hemophilia with inhibitors is a rare disease, and the number of patients is very limited across all countries including Japan (112 patients in Japan [including 95 patients with hemophilia A with inhibitors and 17 patients with hemophilia B with inhibitors], Nationwide Survey on Coagulation Disorders 2021), global clinical trials were conducted to enroll a sufficient number of subjects. The proposed indication for concizumab is "control of bleeding tendency in patients with congenital hemophilia with coagulation factor VIII or IX inhibitors." The efficacy of concizumab for the proposed indication was evaluated by comparing the number of bleeding episodes in subjects randomly assigned to on-demand treatment with bypassing agents or concizumab prophylaxis in Trial 4311. The safety of concizumab was evaluated based on the data from a global phase II trial in patients with hemophilia without inhibitors (Trial 4255) and 4 foreign phase I trials in healthy subjects and patients with hemophilia without inhibitors, in addition to Trials 4310 and 4311 in patients with inhibitors.

PMDA's view:

The epidemiological profile of patients with hemophilia A or B with inhibitors, the condition of bleeding tendency, the concept of treatment, etc., are similar between Japan and overseas. There were no clear differences in the PK/PD of concizumab between Japanese and non-Japanese subjects (Section 6.R.1). Thus, the impact of intrinsic and extrinsic ethnic factors on the efficacy and safety of concizumab is not considered significant.

Accordingly, the efficacy of concizumab prophylaxis in controlling bleeding tendency was evaluated based on a global phase III trial, Trial 4311, as the pivotal trial. Safety was assessed based on the incidences of adverse events, etc. in all clinical trials submitted as evaluation data. The safety information from the ongoing Trial 4311 after the data cutoff date, which is not included in the clinical data package for the present application, was also used to review the occurrence of adverse events.

### 7.R.2 Efficacy

The applicant's explanation about the efficacy of concizumab:

#### 7.R.2.1 Efficacy of concizumab

The primary analysis of the primary endpoint of the number of treated spontaneous and traumatic bleeding episodes for Trial 4311 was performed based on the ABR. The ABR was significantly reduced in Arm 2 (concizumab prophylaxis) than in Arm 1 (on-demand treatment) (Section 7.3.1 Table 29). The median ABRs [range] (descriptive statistics) for treated spontaneous and traumatic bleeding episodes were 0.0 [0, 66.4] episodes/year in 33 subjects on concizumab prophylaxis in Arm 2, 0.0 [0, 66.4] episodes/year in 127 subjects in Arms 1 to 4, and 9.8 [0, 94.7] episodes/year in 19 subjects receiving on-demand treatment in Arm 1 (Table 31).

**Table 31. Descriptive statistics of ABR for treated spontaneous and traumatic bleeding episodes (episodes/year) in the FAS (FAS, OTwoATexIR)**

| | On-demand treatment | Concizumab prophylaxis | | | | | |
|---|---|---|---|---|---|---|---|
| | Arm 1 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arms 2-4 | Arms 1-4 |
| Number of subjects analyzed | 19 | 13 | 33 | 21 | 60 | 114 | 127 |
| Mean exposure time (weeks) | 31.9 | 37.5 | 38.3 | 44.4 | 35.9 | 38.2 | 38.1 |
| Number of bleeding episodes | 166 | 22 | 59 | 47 | 152 | 258 | 280 |
| Median ABR [Range] | 9.8 [0, 94.7] | 1.9 [0, 4.7] | 0.0 [0, 66.4] | 0.8 [0, 13.2] | 0.0 [0, 47.5] | 0.0 [0, 66.4] | 0.0 [0, 66.4] |
| ABR Mean ± SD | 18.4 ± 24.7 | 2.1 ± 1.9 | 3.8 ± 11.7 | 2.1 ± 3.3 | 3.2 ± 7.8 | 3.2 ± 8.5 | 3.1 ± 8.1 |

The efficacy results from the ongoing Trial 4311 at Week 56 were similar to the above results at the primary analysis cutoff (Table 32).

**Table 32. Descriptive statistics of ABR for treated spontaneous and traumatic bleeding episodes (**episodes/**year) in the FAS at Week 56 (FAS, OTwoATexIR)**

| | On-demand treatment | Concizumab prophylaxis | | | | | |
|---|---|---|---|---|---|---|---|
| | Arm 1 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arms 2-4 | Arms 1-4 |
| Number of subjects analyzed | 19 | 13 | 33 | 21 | 60 | 114 | 127 |
| Mean exposure time (weeks) | 31.9 | 59.7 | 57.3 | 61.2 | 56.4 | 57.5 | 57.8 |
| Number of bleeding episodes | 166 | 24 | 89 | 69 | 221 | 379 | 403 |
| Median ABR [Range] | 9.8 [0, 94.7] | 1.3 [0, 4.3] | 0.9 [0, 66.4] | 0.7 [0, 10.1] | 0.7 [0, 48.3] | 0.7 [0, 66.4] | 0.8 [0, 66.4] |
| ABR 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 |

### 7.R.2.2 Impact of changes in the design of Trial 4311 on efficacy assessment

Phase III trials were paused owing to thromboembolic events in 3 patients [see Section 7.R.3.1]. At the time of the trial pause, approximately 85% of the planned sample size for the randomization arms in Trial 4311 had been enrolled (41 of 48 subjects: 13 in Arm 1 and 28 in Arm 2). Hemophilia with inhibitors is a rare disease, and the feasibility of conducting a new clinical trial is low. Thus, the randomization was maintained for previously enrolled subjects, and new subjects were also randomized according to the initial randomization schedule (Section 7.3.1 Table 28). Following the treatment pause, plasma concentrations of concizumab fell below the LLOQ by the restart of the trial.

Prior to the restart of the trial, the protocol was updated, including the updated usage of additional hemostatic agents to treat breakthrough bleeding and a new reduced dosing regimen of concizumab (Section 7.3.1 (2) New dosing regimen), in order to reduce the risk of thromboembolic events [see Section 7.R.3.1]. Along with the changes in the protocol, the primary statistical analysis plan was also reviewed.

An analysis based on the initial randomization could not be performed. In order to address this issue, the data were handled as follows according to the dosing regimen used in subjects in Arm 2 included in the primary analysis.

(1) Subjects exposed to both initial and new regimens: Data on the new regimen excluding data on the initial regimen
(2) Subjects exposed only to the initial regimen: Data on the initial regimen
(3) Subjects exposed only to the new regimen: Data on the new regimen

The above is the OTwoATexIR analysis data set. The primary efficacy analysis of Trial 4311 was based on the FAS and OTwoATexIR. The following sensitivity analyses were performed to assess the impact of the trial pause and the changes in the protocol on efficacy assessment. Table 33 shows the ABRs derived from the sensitivity analyses.

Sensitivity analysis 1:
Since there were no data on the number of bleeding episodes with the new dosing regimen for 4 subjects in Arm 2 who had been exposed only to the initial dosing regimen [the above (2)], the missing data were imputed by multiple imputation based on the number of bleeding episodes with the initial dosing regimen in the same subject, and then the same analysis as the primary analysis was performed. The data on the initial dosing regimen were excluded from the analysis.

Sensitivity analysis 2:
Irrespective of the dosing regimen, the same analysis as the primary analysis was performed using all data from subjects in Arm 2 who had been exposed to concizumab at the primary analysis cutoff.

Sensitivity analysis 3:

The ABR by the timing of randomization (before or after the pause) was calculated using the same method as the primary analysis. For subjects exposed to both regimens [the above (1)], the data on the initial dosing regimen were excluded from the analysis.

**Table 33. ABRs (episodes/year) derived from sensitivity analyses (FAS)**

| | Arm 1 | | Arm 2 | | |
|---|---|---|---|---|---|
| | N | ABR[a)] [95% CI] | N | ABR[a)] [95% CI] | ABR ratio |
| Sensitivity analysis 1 | 19 | 11.7 [6.93, 19.90] | 33 | 1.6 [0.92, 2.88] | 0.14 [0.07, 0.29] |
| Sensitivity analysis 2 | 19 | 11.8 [7.03, 19.66] | 33 | 1.7 [1.03, 2.83] | 0.14 [0.07, 0.29] |
| Sensitivity analysis 3 | | | | | |
| Subjects who underwent randomization before the pause | 13 | 11.7 [6.34, 21.45] | 28 | 1.9 [1.07, 3.30] | |
| Subjects who underwent randomization afterward | 6 | 13.0 [5.14, 32.62] | 5 | 0.8 [0.14, 4.26] | |

a) Estimated mean ABR from a negative binomial regression model that included treatment, type of hemophilia, and the number of bleeding episodes during the 24 weeks before screening (<9 or ≥9) as factors and the logarithm of the length of the observation period as offset

The results of sensitivity analyses 1 and 2 were not substantially different from the results of the primary analysis. Sensitivity analysis 3 indicated similar efficacy between subjects who had undergone randomization before the pause and those who had undergone randomization afterward. The above results of sensitivity analyses support the robustness of the superiority conclusion of the primary endpoint, and it is inferred that the results of the primary analysis were not significantly affected by the trial pause and the changes in the trial design.

### 7.R.2.3 Consistency of results between overall population and Japanese subgroup

Descriptive statistics of ABRs for treated spontaneous and traumatic bleeding episodes in all 127 subjects who received concizumab prophylaxis (Arms 1-4) (Section 7.R.2.1 Table 31) and Japanese subjects (Table 34) indicated no clear differences in efficacy between the Japanese subgroup and the overall population. Though it should be noted that 1 Japanese subject in Arm 2 had an ABR of 16.8 episodes/year, a high bleeding tendency, as this subject had an ABR of 49.4 episodes/year when treated on-demand in a non-interventional study, Study 4322 (the subject participated in Study 4322 before entering Trial 4311), the observed reduction in the ABR for concizumab prophylaxis vs. on-demand treatment was clinically meaningful also in this subject.

**Table 34. Descriptive statistics of ABR in Japanese subjects (FAS)**

| | On-demand treatment | Concizumab prophylaxis | | | | | |
|---|---|---|---|---|---|---|---|
| | Arm 1 | Arm 1 | Arm 2 | Arm 3 | Arm 4 | Arms 2-4 | Total |
| Number of subjects analyzed[a)] | 1 | 0 | 1 | 1 | 4[a)] | 6 | 6 |
| Mean exposure time (weeks) | 16.3 | 0 | 55.9 | 64.1 | 40.3 | 46.9 | 46.9 |
| Number of bleeding episodes | 1 | 0 | 18 | 2 | 11 | 31 | 31 |
| Median ABR [Range] | 3.2 | — | 16.8[b)] | 1.6 | 3.0 [0, 12.0] | 3.0 [0, 16.8] | 3.0 [0, 16.8] |
| ABR Mean ± SD | — | — | — | — | 4.5 ± 5.2 | 6.1 ± 6.7 | 6.1 ± 6.7 |

a) Including 1 subject who did not restart concizumab treatment after the pause.

b) The subject transferred from Study 4322 had an ABR of 49.4 episodes/year in Study 4322.

Based on the considerations in Sections 7.R.2.1 to 7.R.2.3, the efficacy of concizumab was demonstrated in patients with hemophilia with inhibitors including Japanese patients.

PMDA's view:
The applicant's explanation that it was difficult to conduct a new clinical trial due to the limited number of patients with hemophilia with inhibitors is understandable. Since the trial pause period (March to August 2020) was long relative to the half-life of concizumab (approximately 100 hours, see Section 6.2.1, Tables 12 and 13), the effect of the initial dosing regimen at the restart of the trial seemed sufficiently small, etc. Thus, an efficacy analysis including subjects enrolled before the pause, without conducing another confirmatory trial with the new dosing regimen, is acceptable. The results of the primary analysis and sensitivity analyses demonstrated the efficacy of concizumab.

### 7.R.3 Safety

At the data cutoff date for the present application (March 10, 2022), the incidences of serious adverse events were 16.7% (6 of 36 subjects) (6 events) in Trial 4255, 20.0% (5 of 25 subjects) (9 events) in Trial 4310, and 12.6% (16 of 127 subjects) (20 events) in Trial 4311. In Trial 4311, 5 subjects died, of whom 2 subjects receiving concizumab died after the restart of the trial. The both 2 subjects were in Arm 2, and the causes of deaths were road traffic accident, femur fracture, and humerus fracture for 1 subject and COVID-19 for the other subject. The remaining 3 deaths were reported during the trial pause, including 1 in Arm 1 (the cause of death was pneumonitis), 1 in Arm 2 (the cause of death was gastrointestinal haemorrhage), and 1 in Arm 3 (the cause of death was haematoma).

Shock or anaphylaxis was not reported in any clinical trial. Hypersensitivity occurred in 0 subjects in Trial 4310, 3 subjects (5 events) (1 subject [1 event] in Arm 2 and 2 subjects [4 events] in Arm 4) in Trial 4311, 1 subject treated with concizumab 0.15 mg/kg (3 events) in Trial 4255, and 0 subjects in Trial 4159. Except for 3 events reported by 1 subject in Arm 4 of Trial 4311, all those events were considered related to concizumab, but the outcomes of all events were reported as "resolved." The 1 subject in Trial 4311 had serious hypersensitivity leading to trial drug discontinuation.

During the period between the data cutoff date (March 10, 2022) and April 11, 2023, 11 subjects experienced 14 serious adverse events in Trial 4311 (abdominal pain [n = 2], osteoarthritis, alcoholic coma, muscle haemorrhage, laryngeal haematoma, head injury, presyncope, malignant neoplasm, carpal tunnel syndrome, hip arthroplasty, intracranial haemorrhage, functional gastrointestinal disorder, and haematuria [n = 1 each]), but a causal relationship to concizumab was denied except for haematuria. Alcoholic coma in 1 subject and intracranial haemorrhage in 1 subject had a fatal outcome, and muscle haemorrhage (1 subject, 1 event), malignant neoplasm (1 subject, 1 event), and carpal tunnel syndrome (1 subject, 1 event) remained unresolved. Other events had an outcome of "resolved" or "resolving."

Table 35 shows the incidence of adverse events by age group, and Table 36 shows adverse events reported by ≥3% of subjects in either age group, based on the safety pool (Trials 4159, 4255, 4310, and 4311). The incidences of most adverse events were higher in adult subjects, and the incidences of injection site erythema, pyrexia, and hypersensitivity were higher in adolescent subjects. There was no trend towards the occurrence of specific adverse events according to age group, and the nature of reported events in adult or adolescent subjects was similar to that in the overall population.

**Table 35. Incidence of adverse events by age group (Trials 4159, 4255, 4310, and 4311,[a)] SAS)**

| Age group | | Adolescent (12-17 years) (N = 42) | | Adult (≥18 years) (N = 143) | |
|---|---|---|---|---|---|
| | | n (%) | Number of events | n (%) | Number of events |
| Adverse events | | 24 (57.1) | 80 | 113 (79.0) | 752 |
| Serious adverse events | | 5 (11.9) | 6 | 19 (13.3) | 26 |
| Adverse drug reactions | | 11 (26.2) | 19 | 56 (39.2) | 181 |
| Adverse events leading to trial discontinuation | | 1 ( 2.4) | 1 | 3 ( 2.1) | 3 |
| Severity | Severe | 5 (11.9) | 6 | 14 ( 9.8) | 21 |
| | Moderate | 5 (11.9) | 8 | 47 (32.9) | 139 |
| | Mild | 19 (45.2) | 66 | 106 (74.1) | 592 |

N: Number of subjects analyzed
a) Data cutoff date of February 2, 2022

**Table 36. Adverse events reported by ≥3% of subjects in either age group (Trials 4159, 4255, 4310, and 4311,[a)] SAS)**

| Age group | Adolescent (12-17 years) (N = 42) | | Adult (≥18 years) (N = 143) | |
|---|---|---|---|---|
| | n (%) | Number of events | n (%) | Number of events |
| Nasopharyngitis | 2 (4.8) | 2 | 22 (15.4) | 36 |
| Upper respiratory tract infection | 1 (2.4) | 1 | 15 (10.5) | 24 |
| Pharyngitis | 0 | 0 | 7 (4.9) | 8 |
| Rhinitis | 0 | 0 | 5 (3.5) | 6 |
| COVID-19 | 1 (2.4) | 1 | 5 (3.5) | 5 |
| Influenza | 0 | 0 | 5 (3.5) | 5 |
| Viral upper respiratory tract infection | 2 (4.8) | 2 | 1 (0.7) | 1 |
| Injection site bruising | 1 (2.4) | 1 | 11 (7.7) | 19 |
| Injection site haematoma | 1 (2.4) | 1 | 9 (6.3) | 22 |
| Injection site erythema | 4 (9.5) | 6 | 9 (6.3) | 11 |
| Pyrexia | 3 (7.1) | 3 | 9 (6.3) | 10 |
| Injection site haemorrhage | 0 | 0 | 8 (5.6) | 17 |
| Injection site urticaria | 2 (4.8) | 4 | 1 (0.7) | 3 |
| Arthralgia | 2 (4.8) | 2 | 18 (12.6) | 32 |
| Back pain | 0 | 0 | 7 (4.9) | 9 |
| Myalgia | 1 (2.4) | 1 | 5 (3.5) | 7 |
| Joint swelling | 2 (4.8) | 2 | 3 (2.1) | 3 |
| Fibrin D dimer increased | 0 | 0 | 17 (11.9) | 25 |
| Prothrombin level increased | 0 | 0 | 9 (6.3) | 14 |
| Prothrombin fragment 1.2 increased | 0 | 0 | 8 (5.6) | 14 |
| Diarrhoea | 0 | 0 | 9 (6.3) | 10 |
| Toothache | 0 | 0 | 5 (3.5) | 6 |
| Vomiting | 1 (2.4) | 1 | 5 (3.5) | 5 |
| Headache | 1 (2.4) | 1 | 19 (13.3) | 29 |
| Cough | 2 (4.8) | 2 | 6 (4.2) | 6 |
| Hypertension | 0 | 0 | 6 (4.2) | 6 |
| Hypersensitivity | 3 (7.1) | 5 | 1 (0.7) | 3 |
| Gilbert's syndrome | 2 (4.8) | 2 | 0 | 0 |

N: Number of subjects analyzed, MedDRA/J ver. 24.1
a) Data cutoff date of February 2, 2022

PMDA's view:

Based on the submitted clinical trial data, there were no major differences in the safety profile of concizumab between adolescent and adult subjects. Phase III trials of concizumab (Trials 4311 and 4307) were paused owing to thromboembolic events. These thromboembolic events are described in Section 7.R.3.1, and ADA is described in Section 6.R.2.

### 7.R.3.1 Thromboembolic events reported in clinical trials

The applicant's explanation about thromboembolic events reported in Trials 4311 and 4307:

Table 37 shows an overview of subjects with thromboembolic events reported during concizumab prophylaxis. All those events were serious adverse events, and their causal relationship to concizumab could not be ruled out. Patients with previous history of thromboembolic disease, patients with current clinical signs of thromboembolic disease, patients on treatment for thromboembolic disease, and patients who in the judgement of the investigator were considered at high risk of thromboembolic events were excluded from the clinical trials, from the beginning. However, all those subjects had multiple thromboembolic risk factors: Subject A had hypertension, had received FVIII product on multiple occasions (treatment of a joint bleed and prophylaxis before tooth extraction), and had 11 years of smoking history. Subject B had obesity, had received daily treatment with FVIII product, and had hypertension. Subject C had obesity, had received FVIIa product (during 3 days prior to the onset of the event), and had a history of multiple removals and replacements of a central venous access device due to catheter-related infection, etc.

**Table 37. Overview of serious thromboembolic events that led to temporary pause of trial**

| Subject | Trial | Age | Hemophilia subtype | Treatment arm | Event term | Day of onset | Use of concomitant medications | Severity | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| A | 4307 | 4[redacted] | HA | Concizumab | Acute myocardial infarction | Day 59 | Treatment of a knee joint bleed with FVIII 70 IU/kg (on the day of onset of the event) | Severe | Resolved |
| B | 4307 | 4[redacted] | HA | Concizumab | Deep vein thrombosis,<br>Pulmonary embolism,<br>Superficial vein thrombosis | Day 86<br>Day 92<br>Day 92 | Daily treatment with FVIII 35 IU/kg since start of concizumab (except for 3 days) | Moderate<br>Moderate<br>Mild | Resolving<br>Resolving<br>Resolving |
| C | 4311 | 2[redacted] | HBwI | Arm 2 | Renal infarct | Day 21 | rFVIIa 90-130 μg/kg/8h to treat a wrist bleed (during 3 days prior to the onset of the event) | Severe | Resolved with sequelae |

At the onset of thromboembolic events, 2 of the 3 subjects had high concizumab plasma concentrations (>5000 ng/mL, Section 6.R.3.2 Figure 7), the necessity of dose adjustment based on the concizumab plasma concentration was investigated [see Section 6.R.3.3], and the following changes were made to the protocol, including the dosing regimen, to reduce the risk of thromboembolic events.

- The breakthrough bleeding management guidance was revised so that, under concizumab prophylaxis, any factor replacement products (Trial 4307) or bypassing agents (Trial 4311) would be administered at their lowest approved dose to treat mild and moderate breakthrough bleeding (The dose levels of factor replacement products for Trial 4307 or rFVIIa for Trial 4311 were not specified before the revision).

- Ensure that subjects with a potential bleed would contact the clinical trial site.
- After changes in the dosing regimen, subjects were treated with the same 1-mg/kg loading dose of concizumab on Day 1 and the maintenance dose decreased to 0.20 mg/kg from 0.25 mg/kg starting on Day 2. During the dose adjustment period after 5 to 8 weeks of concizumab prophylaxis, the maintenance dose was to be increased to 0.25 mg/kg or decreased to 0.15 mg/kg based on the concizumab blood concentration measured after Week 4.
- Major elective surgery was not permitted during the trial after the protocol change.
- A trial pause for the assessment of a serious thromboembolic event, etc. and consultation with a data monitoring committee (DMC) would occur after the onset of 1 event, which was previously specified as after the onset of 2 events.

In addition to the above changes in the protocol, subjects were informed of the trial-related information including the occurrence of thromboembolic events in the clinical trials and then gave reconsent, and subjects and the trial site staff etc. received training, prior to the restart of the trial. After the restart of the trial (after the above measures were implemented), no thromboembolic events have been reported.

Based on the safety pool (Trials 4311, 4310, 4255, and 4159), a certain proportion of subjects (23.7% [47 of 198 subjects]) had thromboembolic risk factors based on BMI at baseline, medical history, and concomitant illness. Especially, the proportion of subjects with hypertension (15.7% [31 of 198 subjects]) or BMI >35 $kg/m^2$ (4.5% [9 of 198 subjects]) was high. As hemophilia is a bleeding disorder, patients have not received appropriate prophylactic treatment or intervention for cardiovascular risk factors, and therefore may be more susceptible to cardiovascular risk factors. Given the above situation, the following precautionary statements about the possible occurrence of thromboembolic events during treatment with concizumab will be included in the package insert etc.

- Patients should be fully informed of the signs and symptoms of thromboembolic events.
- The patient's condition should be monitored for the possible occurrence of thromboembolic events.
- In case of suspicion of thromboembolic events, concizumab should be discontinued, and appropriate medical treatment should be initiated.

In drug interaction studies using plasma from patients with hemophilia dosed with concizumab, combining concizumab with rFVIIa, aPCC, rFVIII, or rFIX resulted in increased thrombin generation [see Section 3.3]. Taking also account of concomitant use of these products in the patients with thromboembolism, the package insert will advise about additional treatment with bypassing agents for breakthrough bleeding during concizumab prophylaxis: the lowest approved dose is recommended; and patients should be advised on the dose and dose interval etc. of bypassing agents if required, etc.

PMDA's view:

All of the subjects experiencing serious thromboembolic events during concizumab prophylaxis as per the initial regimen had been at risk of thromboembolism and treated with multiple or frequent self-injections of

factor-containing products for bleeding episodes since baseline. According to the clinical trial plan for concizumab, patients with previous history of thromboembolic disease were excluded, and breakthrough bleeding management guidance was provided. Despite such risk-mitigation measures taken before the trial pause, thromboembolic events can be triggered by a combination of multiple factors even if each factor has a small impact, as shown in Table 37 in Section 7.R.3.1., and this suggests the need for extra attention to these cases,

Although the new dosing regimen included a dose-adjustment step, as the cutoff for concizumab concentration at 4000 ng/mL for decreasing the maintenance dose was based on only 2 patients with high exposure levels (>5000 ng/mL) at the onset of thromboembolism, it is important to take other measures together with the management of concizumab concentrations in order to reduce the risk of thromboembolism.

After risk-mitigation measures for thromboembolic events were implemented, no thromboembolic events have been reported to date in clinical trials. A certain level of safety has been assured by additional risk-mitigation measures implemented by the applicant prior to the restart of the trial. On the other hand, patients with hemophilia on concizumab will require additional treatment with self-injection of factor-containing products for mild or moderate breakthrough bleeding, as with patients on similar drugs. Thus, after the market launch of concizumab, it is important that healthcare professionals and patients are provided with information comparable with the risk-mitigation measures taken after the restart of clinical trial, i.e., advice on dealing with breakthrough bleeding and adverse drug reactions, etc., in addition to the precautionary statements in the package insert proposed by the applicant.

### 7.R.4 Indication and clinical positioning

PMDA's conclusion:

Since the results from clinical trials in patients with congenital hemophilia with inhibitors indicate that the efficacy of concizumab prophylaxis is expected, the proposed indication of "control of bleeding tendency in patients with congenital hemophilia with coagulation factor VIII or IX inhibitors" is acceptable.

PMDA's view on the clinical positioning of concizumab:

As medications for routine prophylaxis in patients with hemophilia with inhibitors, aPCC and FVIIa/FX products and emicizumab (hemophilia A with inhibitors) have been approved in Japan. Since aPCC and FVIIa/FX products are plasma derivatives, the risk of infection from the raw material (plasma) cannot completely be excluded. In addition, as these products need to be administered intravenously every other day, it may be difficult for patients with difficult vascular access to use these products for routine prophylaxis. Emicizumab prophylaxis cannot be continued in some patients with ADAs (*Haemophilia.* 2021; 27:984-92, *Jpn J Thromb Hemost.* 2020; 31:93-104). On the other hand, given that concizumab can be used for routine subcutaneous prophylaxis also in hemophilia B patients with inhibitors, concizumab is positioned as a new option for patients with congenital hemophilia with inhibitors.

### 7.R.5 Dosage and administration

The applicant's explanation about the dosing rationale:

The initial dosing regimen for phase III trials (Trials 4311 and 4307) was determined, taking account of exploratory exposure-response analyses based on the results of the main parts of phase II trials (Trials 4255 and 4310, see Section 7.2.2), the NOAEL for thrombi in a non-clinical toxicity study, etc. [see Section 6.R.3.3]. The treatment started with a 1.0-mg/kg loading dose of subcutaneous concizumab on Day 1, followed by a maintenance dose of 0.25 mg/kg once daily starting on Day 2.

The phase III trials (Trials 4311 and 4307) were paused due to serious thromboembolic events. After the restart of the trials, the dosing regimen was modified [see Sections 7.3.1 and 7.R.2.2], and the individual maintenance dose was determined as follows, based on the concizumab pre-dose plasma concentration measured at Week 4.

- Concizumab concentration <200 ng/mL: a maintenance dose of 0.25 mg/kg once daily
- Concizumab concentration of 200 to 4000 ng/mL: a maintenance dose of 0.20 mg/kg once daily
- Concizumab concentration >4000 ng/mL: a maintenance dose of 0.15 mg/kg once daily

In Trial 4311, among 97 subjects treated with the new dosing regimen of concizumab prophylaxis in Arms 2 to 4, the maintenance dose was maintained in 72 subjects (74.2%), increased to 0.25 mg/kg in 24 subjects (24.7%), and decreased to 0.15 mg/kg in 1 subject (1.0%). Adjustment of the maintenance dose reduced variability in concizumab plasma concentration [see Section 6.R.3.3].

Based on the above considerations and demonstration of the efficacy and safety of the new dosing regimen of concizumab [see Sections 7.R.2 and 7.R.3], the following statements have been included in the “DOSAGE AND ADMINISTRATION” section of the draft package insert.

**Dosage and Administration** (The proposed text has been amended.)

The usual dosage of subcutaneous Concizumab (Genetical Recombination) for patients aged ≥12 years is the 1-mg/kg loading dose administered on Day 1, followed by a maintenance dose of 0.20 mg/kg once daily starting on Day 2.

The maintenance dose, after starting at 0.20 mg/kg, may be decreased to 0.15 mg/kg or increased to 0.25 mg/kg based on the blood concentration of concizumab or the patient's condition.

On the basis of the concizumab blood concentration measured after 4 weeks of concizumab prophylaxis, the individual maintenance dose should be adjusted no later than 8 weeks of concizumab prophylaxis, as in the clinical trials. According to concizumab concentration vs. time in Trial 4311 (Section 6.2.2 Figure 1), concizumab concentration did not increase substantially after maintenance dose adjustment. Thus, after the first dose adjustment after 4 to 8 weeks of concizumab prophylaxis, an additional dose adjustment may not be necessary. However, as dose adjustment may be needed depending on the patient's clinical symptoms etc.,

concizumab plasma concentration should be measured as needed, and an additional dose adjustment should be considered. These points for the timing of dose adjustment will be noted in the “PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION” section.

For measurement of concizumab plasma concentrations, an *in vitro* companion diagnostic, which is equivalent to an ELISA used in clinical trials, has been developed, but it is not included in the present application [see Section 6.1]. Until the approval of this *in vitro* companion diagnostic, concizumab concentrations will be measured by the applicant.

In Trials 4255, 4310, and 4311, subjects were trained in self-injection at the clinical trial site and then self-administered ≥99% of doses (approximately 80000 doses) at home. In the clinical trials, technical complaints (appearance, problems related to devices, etc.) were also collected separately from adverse events. Adverse events assessed by the investigator as related to technical complaints were injection site erythema (n = 1) and overdose (n = 1) only, and no efficacy and safety problems related to self-administration have been reported to date.

Trial 4311 included patients aged ≥12 years, and therefore the dosage and administration description mentions "aged ≥12 years." Meanwhile, the development of concizumab for patients aged <12 years is underway. Appropriate actions will be taken for the description after obtaining the results from the ongoing clinical trial.

PMDA's view:
The amended dosage and administration statement proposed by the applicant and inclusion of the points to note for the timing of dose adjustment etc. in the “PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION” section are acceptable. However, some between-subject or within-subject variability occurred also in Trial 4311 that included a dose-adjustment step (Section 6.R.1 Figure 6); there is little knowledge of the source of variability in concizumab concentration (Section 6.R.3.2); and multiple thromboembolic risk factors exist, and continuous attention is needed also after dose adjustment. Given these concerns, concizumab concentration should be measured and dose adjustment should be considered as necessary even later than after 4 to 8 weeks of concizumab treatment.

The measurement of concizumab concentrations was required for dose adjustment after the pause of the phase III trials during the late development stage. Given this, it will be unavoidable that the applicant assumes the role of concizumab concentration measurement, until the approval of the *in vitro* companion diagnostic.

The statement "Concizumab should be used as routine prophylaxis only" should be included in the “PRECAUTIONS CONCERNING DOSAGE AND ADMINISTRATION” section because the hemostatic effect of concizumab in on-demand and surgical bleed management has not been evaluated in clinical trials. Since clinical trials have suggested no particular problem with self-administration, concizumab may be self-administered, provided that appropriate precautions and information are included in the package insert etc.

### 7.R.6 Post-marketing investigations

The applicant's explanation about post-marketing surveillance etc. of concizumab:

The applicant plans to conduct a general use-results survey, covering all patients treated with concizumab (enrollment period, 4.5 years; observation period, 2 years), to assess the safety etc. of concizumab in clinical practice, and approximately 23 patients are expected to be enrolled over 4.5 years. After the marketing approval of concizumab in Japan, Trial 4311 will be reclassified as a post-marketing clinical study (evaluation period, 167 weeks; planned sample size, 136 subjects including 7 Japanese subjects) to evaluate the long-term safety etc. of concizumab. In these survey/study, information on the incidence of adverse events including shock, anaphylaxis, and thromboembolism will be collected.

PMDA's view:

The number of Japanese subjects included in clinical trials of concizumab is very limited, and there is limited clinical experience with concizumab under the Japanese medical environment. Thus, it is necessary to conduct post-marketing surveillance, covering all patients treated with concizumab, in clinical practice, in order to collect information on the characteristics of patients treated with concizumab, safety, etc. as much as possible. A post-marketing clinical study as an extension of Trial 4311 is also important in terms of collecting information on the long-term safety of concizumab. It is important to evaluate the safety information obtained from these survey/study, compared with the safety information from clinical trials, and determine the need for further information. Post-marketing safety information should be provided appropriately and promptly to healthcare professionals in clinical practice as needed.

## 8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

### 8.1 PMDA’s conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

### 8.2 PMDA’s conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-3) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

## 9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has concluded that concizumab has efficacy in controlling bleeding tendency in patients with congenital hemophilia with coagulation factor VIII or IX inhibitors, and that concizumab has acceptable safety in view of its benefits. Concizumab is clinically meaningful because it offers a new option for routine prophylaxis in patients with congenital hemophilia with inhibitors. PMDA considers that the safety of concizumab, dosage and administration, etc. need to be further discussed.

PMDA has concluded that concizumab may be approved if concizumab is not considered to have any particular problems based on comments from the Expert Discussion.

**Review Report (2)**

July 6, 2023

**Product Submitted for Approval**

| | |
|---|---|
| **Brand Name** | Alhemo Subcutaneous Injection 15 mg, Alhemo Subcutaneous Injection 60 mg<br>Alhemo Subcutaneous Injection 150 mg, Alhemo Subcutaneous Injection 300 mg |
| **Non-proprietary Name** | Concizumab (Genetical Recombination) |
| **Applicant** | Novo Nordisk Pharma Ltd. |
| **Date of Application** | August 29, 2022 |

**List of Abbreviations**

See Appendix.

## 1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors supported PMDA’s conclusions on the issues presented in the Review Report (1) (Section "7.R.2 Efficacy" and Section "7.R.4 Indication and clinical positioning").

PMDA also discussed the following points and took actions as necessary.

### 1.1 Safety and dosage and administration

The expert advisors supported PMDA’s conclusions presented in "7.R.3 Safety" and "7.R.5 Dosage and administration" in the Review Report (1), and made the following comments.

- Thromboembolic events were reported in only 3 patients in the clinical trials. The behaviors, etc. of concizumab and the target molecule TFPI on endothelial cells are not measurable, which is an obstacle in obtaining adequate basic information, etc. It is therefore difficult even for physicians with expert knowledge to predict the thromboembolic risk factors before starting the treatment with concizumab. Thus, the applicant should provide extensive information, including not only the characteristics of the patients experiencing thromboembolic events in the clinical trials but also other possible risk factors. Physicians should be advised to carefully check the patient's history of thromboembolism and thromboembolic risk factors before starting

the treatment with concizumab.

- Both healthcare professionals and patients need to be explained and educated about the risk of thromboembolism associated with concizumab and appropriate dose/usage of additional hemostatic agents, etc. to treat breakthrough bleeding. In case of breakthrough bleeding, it is important to monitor the patient's condition by coagulation testing, etc.
- The necessity of maintenance dose adjustment based on the concizumab plasma concentration is understandable. At the same time, inter-individual variability in concizumab plasma concentration was large, and the 4000 ng/mL cutoff was determined based on information from the limited number of patients. A case of a subject who experienced thromboembolism despite low concizumab plasma concentrations was suggestive of thromboembolic risk factors other than concizumab plasma concentrations. Such current limited information precludes the definitive conclusion that the management of concizumab plasma concentrations is the most important safety measure, and the management of concizumab plasma concentrations should preferably be advised along with other safety measures. Inevitably, the measurement of concizumab plasma concentration will need to be assumed by the applicant until the approval of the *in vitro* companion diagnostic in Japan.

Based on the comments from the Expert Discussion, PMDA requested the applicant to take the following actions with the package insert, etc. The applicant agreed.

- Advise that patients should be checked carefully for thromboembolic risk factors prior to the treatment with concizumab. Specific risk factors should be communicated via information materials, etc.
- Offer the following advice: Before starting the treatment, patients must understand cautions to be taken when breakthrough bleeding occurs with an awareness of their importance. In case of breakthrough bleeding, the patient's condition should be closely monitored through coagulation testing, other related diagnostic procedures, etc. The dose and dose interval of breakthrough bleeding treatment performed in the clinical trials should be communicated via information materials, etc.
- Mention in the package insert, etc. that the cutoff for concizumab plasma concentration is 4000 ng/mL for maintenance dose adjustment, with a note that the value is not definitive.

In April 2023, the applicant received a Complete Response Letter from the FDA (the US) for concizumab, which presented the following main issues to be addressed.

- [redacted]
- [redacted]
- [redacted]

PMDA confirmed that the necessary actions had been taken to address the above issues in the present review. Concerning [redacted], PMDA instructed the applicant to advise [redacted] via the package insert etc., and the applicant responded accordingly.

In addition, PMDA considers that [redacted].

### 1.2 Risk management plan (draft)

In view of the discussions presented in Section "7.R.6 Post-marketing investigations" in the Review Report (1) and comments from the expert advisers at the Expert Discussion, PMDA considers that the following should be additionally addressed in the post-marketing surveillance.

- Collection of extensive information on the possible risk factors for thromboembolism attributable to patient characteristics
- Collection of information on the amount of concomitant bypassing agents used, etc.
- Collection of time points and results of coagulation testing and concizumab plasma concentration measurement

PMDA requested that the applicant to investigate these issues via the post-marketing surveillance, and the applicant agreed.

In view of the discussion above, PMDA has concluded that the risk management plan (draft) for concizumab should include the safety specification presented in Table 38, and that the applicant should conduct additional pharmacovigilance activities and risk minimization activities presented in Tables 39 and 40.

**Table 38. Safety specification in the risk management plan (draft)**

| Safety specification | | |
|---|---|---|
| Important identified risks | Important potential risks | Important missing information |
| · Thromboembolism | · Shock, anaphylaxis<br>· Immunogenicity | None |

**Table 39. Summary of additional pharmacovigilance activities and risk minimization activities included under the risk management plan (draft)**

| Additional pharmacovigilance activities | Additional risk minimization activities |
|---|---|
| · Post-marketing clinical study[a)] | · Disseminate information to healthcare professionals (Preparation and dissemination of materials on the proper use of concizumab) |
| · General use-results survey (all-case surveillance) | · Disseminate information to patients (Preparation and dissemination of materials on the proper use of concizumab, issuing portable patient contact cards) |
| · Early post-marketing phase vigilance | · Disseminate data from early post-marketing phase vigilance |

a) The ongoing Trial 4311 will be reclassified as a post-marketing clinical study after approval and continued through Week 167.

**Table 40. Outline of use-results survey (draft)**

| | |
|---|---|
| Objective | To evaluate the safety of concizumab in clinical practice. |
| Survey method | All-case surveillance |
| Population | Concizumab-treated patients with hemophilia with inhibitors |
| Observation period | 2 years |
| Planned sample size | All patients treated with concizumab |
| Main survey items | Patient characteristics, medical history, concomitant illness, concomitant medications, adverse events (including thromboembolism, shock, and anaphylaxis), bleeding episodes, clinical parameters (including coagulation testing), plasma concizumab concentrations, the use of concizumab |

### 1.3 Shelf life of the drug product

The 18-month data from 1 batch of the 300-mg strength of the drug product, previously submitted as long-term stability data as in Table 4 [see Section 2.2.5 in the Review Report (1)], were later updated with 24-month data. The long-term stability data on 3 batches including this 1 batch demonstrated that the 300-mg strength drug product is stable after 24 months of storage. Thus, the applicant explained that a shelf life of 24 months had been proposed for the drug products of 300 mg and other strengths. PMDA accepted the proposed shelf life of the drug product.

## 2. Overall Evaluation

As a result of the above review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following conditions. As the product has been designated as an orphan drug, the re-examination period is 10 years. The product is classified as a biological product. Neither the drug product nor its drug substance is classified as a poisonous drug or a powerful drug.

**Indication**

Control of bleeding tendency in patients with congenital hemophilia with coagulation factor VIII or IX inhibitors

**Dosage and Administration**

The usual dosage of subcutaneous Concizumab (Genetical Recombination) for patients aged ≥12 years is the 1-mg/kg loading dose administered on Day 1, followed by a maintenance dose of 0.20 mg/kg once daily starting on Day 2.

The maintenance dose, after starting at 0.20 mg/kg, may be decreased to 0.15 mg/kg or increased to 0.25 mg/kg based on the blood concentration of concizumab or the patient's condition.

**Approval Conditions**

1. The applicant is required to develop and appropriately implement a risk management plan.
2. Because of very limited number of Japanese patients treated with the product, the applicant is required to conduct a post-marketing use-results survey, covering all patients treated with the product until data from a specified number of cases are obtained so as to understand the characteristics of patients treated with the product, promptly collect safety and efficacy data of the product, and take necessary measures to ensure proper use of the product.

**Appendix**

**List of Abbreviations**

| | |
|---|---|
| ABR | Annualised bleeding rate |
| ADA | Anti-drug antibody |
| aPCC | Activated prothrombin complex concentrates |
| aPCC product | Anti-inhibitor coagulant complex<br>Feiba NF Intravenous 1000 |
| AT | Antithrombin |
| AUC | Area under the plasma concentration-time curve |
| $AUC_{0-t}$ | Area under the plasma concentration–time curve from time zero to t |
| $AUC_{0-\infty}$ | Area under the plasma concentration–time curve from time zero to infinity |
| $AUC_{tau}$ | Area under the plasma concentration-time curve over a dosing interval (tau) |
| BMI | Body mass index |
| BOV | Between-occasion (within-subject) variability |
| CAL | Cells at the limit of *in vitro* cell age used for production |
| CDR | Complementarity-determining regions |
| CHO | Chinese Hamster Ovary |
| CL, CL/F | (Apparent) Clearance |
| $C_{max}$ | Maximum plasma concentration |
| concizumab | Concizumab (Genetical Recombination) |
| CV | Coefficient of variation |
| ELISA | Enzyme-linked immunosorbent assay |
| Emicizumab | Emicizumab (Genetical Recombination)<br>Hemlibra for Subcutaneous Injection 30 mg<br>Hemlibra for Subcutaneous Injection 60 mg<br>Hemlibra for Subcutaneous Injection 90 mg<br>Hemlibra for Subcutaneous Injection 105 mg<br>Hemlibra for Subcutaneous Injection 150 mg |
| F | Bioavailability |
| FAS | Full analysis set |
| FDA | Food and Drug Administration |
| FVIIa/FX product | Freeze-dried activated human blood coagulation factor VII concentrate containing factor X (Byclot Combination Intravenous Injection) |
| FX (a) | (Activated) coagulation factor X |
| GCV | Geometric coefficient of variation |
| HA (wI) | Haemophilia A (with inhibitors) |
| HB (wI) | Haemophilia B (with inhibitors) |
| HCP | Host cell protein |
| HMWP | High molecular weight protein |
| ICH | International Committee for Harmonization |
| IgG | Immunoglobulin G |
| IgM | Immunoglobulin M |
| Impurity D | [redacted] |
| Impurity E | [redacted] |
| K2 | Kunitz domain 2 |
| [redacted] | [redacted] |
| M&S | Modeling and Simulation |
| MCB | Master cell bank |
| MedDRA/J | Medical Dictionary for Regulatory Activities Japanese version |
| 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 |

| | |
|---|---|
| PD | Pharmacodynamic(s) |
| PET | Polyethylene terephthalate |
| PETG | Polyethylene terephthalate, glycol modified |
| PF1/PF2 | Prothrombin fragment 1/Prothrombin fragment 2 |
| PK | Pharmacokinetic(s) |
| PMDA | Pharmaceuticals and Medical Devices Agency |
| QbD | Quality by design |
| Rac | Ratio of accumulation |
| (r)FIX | (Recombinant) coagulation factor IX |
| (r)FVIIa | (Recombinant) (Activated) coagulation factor VII |
| rFVIIa product | Eptacog alfa (activated) (genetical recombination)<br>NovoSeven HI Syringe for i.v. injection 1 mg<br>NovoSeven HI Syringe for i.v. injection 2 mg<br>NovoSeven HI Syringe for i.v. injection 5 mg |
| (r)FVIII | (Recombinant) Coagulation factor VIII |
| SAS | Safety analysis set |
| SPR | Surface plasmon resonance |
| TEG | Thromboelastography |
| TF | Tissue factor |
| TFPI | Tissue factor pathway inhibitor |
| $T_{max}$ | Time to reach maximum plasma concentration |
| TMDD | Target-mediated drug disposition |
| $T_{1/2}$ | Terminal half-life |
| Vd | Volume of distribution |
| WCB | Working cell bank |