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RESEARCH**

APPLICATION NUMBER:

761315Orig1s000

INTEGRATED REVIEW

CLINICAL REVIEW and SUMMARY MEMO for REGULATORY ACTION

Application Type	BLA
Application Number(s)	761315
Priority or Standard	Class 2 Resubmission (6-months)
Submit Date(s)	June 20, 2024
Received Date(s)	June 20, 2024
PDUFA Goal Date	December 20, 2024
Division/Office	Division of Nonmalignant Hematology
Reviewer Name(s)	Andrew Dmytrijuk, Carrie Diamond, Sudharshan Hariharan, Chongwoo Yu
Review Completion Date	Electronic Stamp
Established/Proper Name	concizumab-mtci
(Proposed) Trade Name	Alhemo
Applicant	Novo Nordisk Inc.
Dosage Form(s)	(b) (4) injection
Applicant Proposed Dosing Regimen(s)	The recommended dosing regimen comprise a loading dose of 1 mg/kg followed by an initial once daily dosing of 0.20 mg/kg. Based on the concizumab exposure level measured after 4 weeks of treatment, the maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg once daily
Applicant Proposed Indication(s)/Population(s)	For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	Alhemo is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients 12 years of age and older with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors

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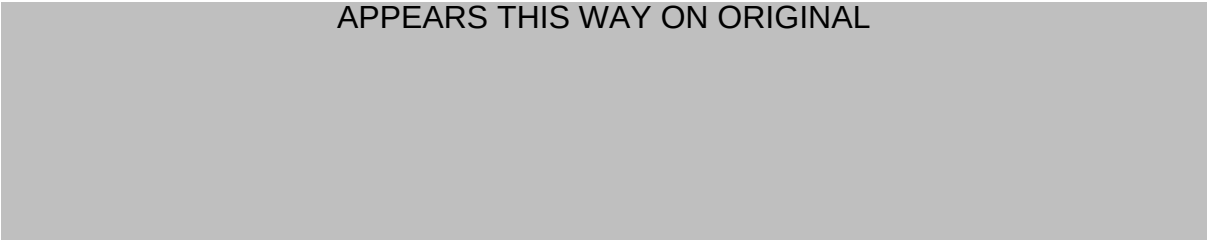
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Glossary

ABR	annualized bleeding rate
AC	advisory committee
AE	adverse event
aPCC	activated prothrombin complex concentrate
AMR	analytical measurement range
BLA	biologics license application
BRF	Benefit Risk Framework
CACO	confirmatory analysis cut-off
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CGMP	Current Good Manufacturing Practices
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CRF	case report form
CRL	Complete Response Letter
CRT	clinical review template
CS	calibration standards
CSR	clinical study report
CT	computerized tomography
CTA	clinical trial assay
CV	coefficient of variation
DARRTS	Document Archiving and Registry Tracking System
DMC	data monitoring committee
DP	drug product
DS	drug substance
eCTD	electronic common technical document
ELISA	enzyme-linked immunosorbent assay
FDA	Food and Drug Administration
FIX	factor IX
FVII	factor VII
FVIIa	activated factor VII
FVIII	factor VIII
FXa	activated Factor X
GCP	good clinical practice
HA	hemophilia A
HB	hemophilia B
HAwI	hemophilia A with inhibitor
HBwI	hemophilia B with inhibitor

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HTN	hypertension
ICH	International Council for Harmonization
ID	patient identification number
IND	Investigational New Drug Application
ISS	integrated summary of safety
ITI	immune tolerance induction
MedDRA	Medical Dictionary for Regulatory Activities
NME	new molecular entity
OSI	Office of Scientific Investigation
PD	pharmacodynamics
PI	prescribing information or package insert
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert
PPX	prior prophylaxis
PREA	Pediatric Research Equity Act
PYE	patient years of exposure
QC	quality controls
rFVII	recombinant factor VII
SAE	serious adverse event
SC	subcutaneous
SOC	standard of care
SUR	Safety Update report
TE	total error
TEAE	treatment emergent adverse event
TFPI	tissue factor pathway inhibitor
TMDD	target mediated drug disposition
USPI	United States Prescribing Information

1. Executive Summary

1.1. Summary of Regulatory Action

Novo Nordisk originally submitted their Biologic License Application (BLA) for marketing approval of concizumab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and hemophilia B (congenital factor IX deficiency) with FIX inhibitors on August 24, 2022. Concizumab is an anti-tissue factor pathway inhibitor administered by injection. During the initial review cycle of the application, multiple deficiencies were identified which precluded approval. This included concerns about inadequate monitoring for missed doses, need for clear labeling instructions regarding missed doses, need for a Medication Guide, issues regarding the interim concizumab assay proposed for product launch and product quality review issues including facilities inspectional deficiencies. The Applicant received a Complete Response Letter (CRL) on April 24, 2023. The reasons for the CRL are summarized below in Section 2, Regulatory History, of this review.

On June 20, 2024, the Applicant submitted a response to the CRL, addressing the deficiencies listed in the CRL. This resubmission review focuses only on the review of the deficiencies identified in the CRL, updated safety information, labeling and postmarketing commitments. This review is a joint review by Clinical and Clinical Pharmacology.

The Applicant has adequately addressed all deficiencies in the CRL. Each discipline recommends approval, and the signatory authority concurs that the application should be approved. The overall benefit/risk profile is favorable as described in the Benefit-Risk Framework below.

1.2. Benefit-Risk Assessment

Benefit-Risk Dimensions

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hemophilia A (HA) is an X-linked recessive disorder caused by mutations in the FVIII gene which results in a severe deficiency or absence of the clotting protein factor VIII. HA occurs in approximately 1 in 5000 live male births. Patients are typically diagnosed in infancy. Patients are at increased risk for minor and serious bleeding including life threatening spontaneous or traumatic bleeding. Disease manifestations include mucosal bleeding, easy bruising, soft tissue and muscle bleeds, hemarthrosis and excessive bleeding with procedures or trauma. Bleeding can occur in vital organs (including the brain). Adults commonly experience hemophilic arthropathy due to recurrent joint bleeds, which is associated with significant disease morbidity. • Hemophilia B (HB) is an X-linked recessive disorder caused by mutations in the FIX gene which results in a severe deficiency or absence of the clotting protein factor IX. HB occurs in approximately 1 in 30,000 live male births. Deficient factor IX levels result in an increased risk for minor and serious bleeding, including life threatening spontaneous or traumatic bleeding. Disease manifestations of HB are the same as HA described in the text above. • One of the most serious treatment complications of HA and HB is inhibitor development. Approximately 30% of patients with HA and 5-15% of patients HB develop inhibitors to factor replacement. Because bleeding is more difficult to prevent and treat, patients with inhibitors often experience increased disease morbidity and mortality.	Hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors (HAWI) and hemophilia B (congenital factor IX deficiency) with FIX inhibitors (HBWI) are serious chronic diseases with significant morbidity and mortality due to bleeding. Patients with inhibitors have a worse disease course.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• FDA approved bypassing agents are used to prevent or control bleeding in patients with inhibitors. Activated prothrombin complex concentrate (aPCC) is indicated to control and prevent bleeding episodes in patients with HAwI and HBwI. Recombinant activated coagulation factor VII (rFVIIa), is indicated for the treatment of bleeding episodes in patient with HAwI and HBwI. Efficacy of these products can be variable, and they carry a boxed warning for thrombosis. Antibodies to FVIIa can develop in patients with HAwI and HBwI and interfere with the effectiveness of these factor-based therapies. • Alloantibodies or inhibitors develop with exposure to exogenous factor, and block the activity of factor VIII or IX. Inhibitors can make it difficult to stop excessive bleeding as it leads to reduced efficacy of factor replacement. • Patients with HAwI and HBwI may undergo immune ITI to eradicate the inhibitor, but this is only successful in 60-80% of cases in patients with HAwI and 15-30% of patients with HBwI. • Emicizumab (HEMLIBRA) is a bispecific factor IXa and factor X-directed antibody that was FDA approved in 2017 for the indication of routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with HA or HAwI. Emicizumab is administered by weekly up to every 4 weeks by SC injection. Emicizumab has a boxed warning for thrombotic microangiopathy and thromboembolism associated with use with aPCC.	There is a need for available, safe and effective therapies. Patient with HA and HB can develop inhibitors after exposure to exogenous factor. For patients with HAwI and HBwI, prophylactic treatment options are very limited, in particular for patients with HBwI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	Pivotal, Phase 3 Study 4311 - Study 4311 was a multi-center, open-label, randomized-controlled study in which 52 adult and adolescent patients (27 HAWI, and 25 HBWI), previously treated with on-demand therapy, were randomized 1:2 to arm 1, no prophylaxis (on demand therapy) (N=19) or arm 2, concizumab prophylaxis (N=33) for at least 24 weeks. Arms 3 and 4 included 81 additional patients (53 HAWI and 28 HBWI) treated with concizumab prophylaxis. Any bleeds occurring in the clinical study were treated with the patient's usual bypassing product or factor. Superiority of concizumab PPX (arm 2) over no PPX (arm 1) was confirmed for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes. The annualized bleeding rate (ABR) was calculated as the number of treated spontaneous or traumatic bleeds divided by the number of days in the analysis set, multiplied by 365. The ABR was 1.7 with 95% CI (1.01, 2.87) for patients on concizumab PPX (arm 2) and 11.8 with 95% CI (7.03, 19.86) for patients on no PPX (arm 1). The estimated ABR ratio was 0.14 with 95% CI (0.07, 0.29) corresponding to an 86% reduction in ABR for patients on concizumab PPX (arm 2) compared to no PPX (arm 1). Results were statistically significant and the magnitude of reduction in bleeding rate was clinically meaningful for a patient population at risk for frequent bleeding that is difficult to treat. While there is a theoretical concern that patients may alter their behavior due to knowledge of their treatment assignment, the highly statistically significant efficacy result provides reassurance of treatment effect. - Key secondary endpoints of change in SF-36v2 bodily pain and change in SF-36v2 physical functioning were not statistically significant.	Prophylactic treatment with daily concizumab is expected to reduce spontaneous and traumatic bleeding episodes in patients with HAWI and HBWI. This was evident by the reduction in the number of bleeding events in patients treated with concizumab prophylaxis compared to on demand therapy. Concizumab will fulfill an unmet need in that there are no non-factor therapies currently approved to reduce bleeding in patients with HBWI.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	- In a descriptive analysis, 94.7% of patients in arm 1 (no PPX) had a treated bleed or discontinued before week 24 compared to 48.5% in arm 2 (concizumab PPX). Supportive, Phase 2 Study 4310 - Study 4310 was a supportive, multicenter, open-label, randomized-controlled study in which 26 patients (16 HAwI patients, 10 HBwI) patients were randomized 2:1 to concizumab PPX (n=17) and eptacog alfa (rFVIIa) on demand (N=9) for at least 24 weeks. The primary endpoint the number of bleeding episodes during at least 24 weeks from treatment onset. The ABR was significantly lower in the concizumab PPX arm compared to the eptacog arm. The estimated ABR during the entire treatment period was also lower in the concizumab arm compared to the eptacog alfa arm: 5.4 (95% CI: 3.8, 7.6) and 20.6 (95% CI: 13.7, 30.8), respectively.	
Risk and Risk Management	Overall Safety Findings - The review of safety focused on Study 4311, which included 127 patients with HAwI and HBwI exposed to concizumab, including 33 patients randomized to concizumab PPX (arm 2) compared to 19 patients randomized to no PPX (arm 1) in the main treatment period. The safety analysis was further supported by Study 4310. - TEAEs were reported in 60% of patients in concizumab PPX arm 2 compared to 42% patients in the on-demand arm 1 in the randomized main treatment portion of study 4311. The most common TEAE in the main treatment period and occurred in a higher proportion of patients in the concizumab arm compared to no PPX was local administration reactions, which occurred in 18% of patients in the concizumab arm (arm 2) compared to 0% in the on-	Several risks have been identified that will be included in the Warnings and Precautions section of the USPI, this includes risk of thrombosis, hypersensitivity reactions, and increased laboratory values of fibrin D-dimer and prothrombin fragment 1+2. Local injection site reaction was the most common AR. Patients with prolonged subtherapeutic levels (<200ng/mL) of concizumab are at increased risk of bleeding, which can be serious and life-threatening. Adherence to the daily SC dosing regimen of concizumab is critical to

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	demand therapy arm (arm 1). The most common adverse reactions ($\geq 5\%$) also includes urticaria. Thrombosis - In total, four patients across clinical trials experienced serious events of thrombosis, including arterial and venous thrombosis, after receiving concizumab, compared to no patients in the control group. Notable characteristics were additional risk factors for thrombosis (i.e., smoking, obesity and HTN), receiving factor product or a bypassing agent within 24 hours of the thrombotic event and elevated concizumab levels ($>4000\text{ng/mL}$). - The Applicant had modified the concizumab dosing regimen during the clinical development to target a concizumab level between $200\text{--}4000\text{ng/mL}$, to prevent bleeding and thrombosis. In addition, the Applicant included a number of mitigation strategies, including using the lowest labeled dose of factor or bypassing agent. Risk of Bleeding with Subtherapeutic Concizumab Levels. - Across clinical trials, the majority of patients with subtherapeutic concizumab levels ($<200\text{ ng/mL}$) had no bleeding or minor bleeding although, 6 (1.9%) patients had serious bleeding events and 2 (0.6%) patients died with subtherapeutic levels. - Large PK fluctuations were noted in clinical studies, this was in part due to issues with non-compliance. PK analysis demonstrates missed doses of concizumab can result in subtherapeutic levels within a few days, further, once the patient restarts administration it may take several days to become therapeutic.	prevent prolonged subtherapeutic levels. Therefore, the importance of adherence to daily dosing will be stressed in labeling, a Medication Guide and education materials. In addition, a plan for missed concizumab doses is described in labeling. Achieving concizumab levels $>200\text{ng/mL}$ is key to the therapeutic effect of concizumab and levels $<4000\text{ng/mL}$ is critical to decrease the risk of thrombosis. A companion diagnostic concizumab assay is necessary for effective and safe use of this product, however due to the unmet need, concizumab will be approved but not concurrently with the proposed companion diagnostic, which is under review with CDRH. In the interim, an assay (b) (4) will be made available by the Applicant to prescribers to guide dosing and management. Development of a companion diagnostic assay will be requested in a PMC.

*A substantial portion of the text in the benefit-risk framework was taken directly from the original BLA review, see finalized review in DARRTS dated April 24, 2023.

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Abbreviations: ABR, annualized bleeding rate; aPCC, activated prothrombin complex concentrates; CDRH, Center for Devices and Radiological Health; ELISA, enzyme-linked immunoassay; HA, hemophilia A; HB, hemophilia B; HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; HTN, hypertension; ITI, immune tolerance induction; PK, pharmacokinetic; PMC, postmarketing commitment; PPX, prophylaxis; SAEs, serious adverse events; SC, subcutaneous; TEAEs, treatment-emergent adverse events; TFPI, tissue factor pathway inhibitor; USPI, United States Prescribing Information

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Conclusions Regarding Benefit-Risk

- HAWI and HBWI are rare and serious diseases, associated with significant morbidity and mortality due to a risk of frequent and severe bleeding. Prophylactic factor-based treatment is considered standard of care to prevent bleeding related complications. However, antibodies to FVIIa can develop in patients and interfere with the effectiveness of these factor-based therapies. There is an unmet medical need for prophylactic non-factor therapy options for patients with HAWI and HBWI.

Concizumab is an anti-tissue factor pathway inhibitor which enhances FXa production during the initiation phase of coagulation which leads to improved thrombin generation and clot formation to achieve hemostasis.

The efficacy of concizumab was based on a single, adequate and well controlled trial, study 4311. Study 4311 compared ABR “on demand” treatment with a bypassing agent, eptacog alfa or activated prothrombin complex concentrate, administered at the time of bleeding with prophylaxis concizumab treatment. The efficacy results demonstrated a statistically significant reduction in median ABR for the prophylaxis concizumab treatment group when compared with the “on demand” treatment group. Confirmatory evidence included study results from study 4310, which also demonstrated a large reduction in ABR in the group on concizumab prophylaxis and mechanistic support.

The safety of concizumab was assessed in the randomized controlled portion of study 4311, along with the entire safety database in the concizumab hemophilia development plan including 320 patients with HAWI, HBWI, HA and HB. Common adverse reactions included injection site reactions and urticaria. Similar to other treatments for hemophilia, concizumab carries an increased risk of thromboembolic events. The risk of thrombosis can be decreased with adjusting the concizumab maintenance dose to the concizumab concentration target range as described in the USPI and following blood management guidelines. We will continue to assess the risk of thrombosis with postmarketing enhanced pharmacovigilance. Concizumab also carries an increased risk of serious hypersensitivity reactions.

The benefit/risk profile of concizumab is now favorable, as the Applicant has adequately addressed deficiencies in the CRL, including guidance on missed doses, emphasized the importance of drug compliance in labeling, and resolved issues related to product quality and facility inspections. At this time, there is no FDA-cleared assay to measure concizumab levels, which are used to guide safe and effective dosing. While the Applicant completes development of a companion diagnostic assay (see post-marketing commitment in Section 8) an interim assay will be used to assess concizumab levels. The unapproved interim assay was reviewed by the Agency and determined to be adequate for use for this purpose.

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2. Regulatory History

Novo Nordisk originally submitted their BLA for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors and hemophilia B (congenital factor IX deficiency) with FIX inhibitors on August 24, 2022. The Applicant received a CRL on April 24, 2023. The reasons for the CRL are briefly summarized below, see finalized CRL in DARRTS for further details.

Deficiencies identified in the CRL:

Clinical and Clinical Pharmacology: At the target exposure range of concizumab, target-mediated drug disposition (TMDD) plays a dominant role in concizumab clearance, leading to rapid drug elimination and a relatively shorter half-life at the proposed doses of 0.15 - 0.25 mg/kg. As a result, concizumab concentrations can decline steeply to subtherapeutic levels with missed doses and it may take several days of consecutive dosing to gradually return to target concentrations of >200 ng/mL. Therefore, a plan for dosing after one or more missed doses is required, including an additional concizumab pharmacokinetics (PK) monitoring and/or a repeat loading dose. In addition, the importance of adherence to daily dosing and maintenance of therapeutic concizumab levels should be stressed in a Medication Guide, labeling and educational materials.

Device: Four weeks after initiating concizumab prophylaxis, a concizumab-mtci plasma concentration will be measured by Concizumab Enzyme-Linked Immunosorbent Assay (ELISA) for dose optimization purposes. Based on the ELISA assay results, the dose of concizumab may be modified in order to maintain the target range. The Applicant's interim assay to monitor concizumab concentration was inadequate for a multitude of reasons outlined in the CRL.

Product Quality: (b) (4) are present in the concizumab drug product. The Applicant provided insufficient information and data provided to address the risk of (b) (4) on safety and efficacy and the control strategy for (b) (4) was inadequate to ensure product quality, safety, and efficacy. Other deficiencies were identified including inadequate cell bank stability protocols, inadequate reference material stability protocols, inadequate drug substance (DS) and drug product (DP) release and stability specifications, and inadequate DS and DP post-approval annual stability protocols.

Facility Inspection: Following inspection of (b) (4) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility.

Type A Meeting to Discuss Deficiencies in CRL:

On June 23, 2023, a Type A in-person meeting was held to discuss the deficiencies in the CRL

and potential path forward. Key discussion points from the meeting are listed below, see finalized meeting minutes in DARRTS for further details.

- The Applicant proposed guidance for resumed dosing after missed concizumab doses. The rationale of this plan was to ensure that patients who have missed concizumab daily injection at the maintenance dose stage could reach steady-state concizumab exposure levels as quickly as possible upon resumed dosing without exceeding steady-state levels. Overall, the Agency commented that the proposal was reasonable, however emphasized that the USPI and Medication Guide should further stress the importance of adherence to daily dosing and the consequence of missed doses.
- The Applicant proposed to include an additional concizumab plasma concentration level to be performed 8 weeks after initiation of maintenance dosing. The Agency commented that the proposal was reasonable, but additional clarification should be provided on what to do with the results of the level.
- The Agency did not agree with the Applicant's data package, characterization study and control strategy was sufficient to address concerns of safety, efficacy and product quality regarding (b) (4) in the drug product. The Agency advised the Applicant to submit a separate meeting request to discuss this issue further.
- The Agency stated that the Applicant's proposed additions to the release and shelf-life specifications, post-approval stability protocol for on-going stability in the assembled pen-injector, along with the proposal to provide analytical produce and validation of analytical procedure was reasonable.
- The Agency clarified that the facility evaluation will be performed during the resubmission review cycle.
- The Agency agreed with the proposed content of the safety update.
- The Agency stated that the (b) (4) concizumab-ELISA remains a deficiency as described in the CRL.

Type B Meeting for (b) (4)

On April 15, 2024, a Type B videoconference was held to discuss the Applicant's proposed control strategy for (b) (4) to be included in the resubmission of the BLA and gain agreement on the implementation plan for CAPA based on the identified main root cause for formation of visible particles. Key responses from the meeting are listed below, see finalized meeting minutes in DARRTS for further details.

- The Agency did not agree with the Applicant's proposed drug product control strategy and stated it was not possible to determine the clinical impact from (b) (4) in the concizumab drug product. In a post-meeting comment, the Agency emphasized given the transient nature of the particles and inability to determine if a subject received drug with particles, it will be very challenging to understand the safety profile and efficacy impact of (b) (4).
- The Applicant stated the main root cause for formation of (b) (4) is identified (b) (4). In addition, the

Applicant planned to include a comparability protocol detailing the post-approval change in the resubmission.

3. Deficiencies Identified in the CRL

3.1. Clinical and Clinical Pharmacology

To address the potential for significant fluctuations in concizumab concentration levels, which can lead to subtherapeutic levels in the setting of missed doses and thus increasing the risk of serious bleeding events, the Applicant proposed several mitigation strategies, including (1) guidance on missed doses, (2) guidance on additional concizumab measurements, and (3) additional education and guidance to emphasize the importance of adherence to the prescribed dosing regimen.

Guidance on missed doses when a patient has forgotten or neglected to take their once-daily maintenance dose

The Applicant has proposed the following plan to be included in the USPI for concizumab:

- *1 missed dose: Resume once-daily treatment at the maintenance dose level*
- *2 to 6 missed doses: Resume treatment with a double dose followed by once-daily treatment at the maintenance dose level*
- *7 or more missed doses: Physician should be contacted, and a new loading dose should be considered*

The above proposal was based on population PK modelling. The final population PK model, reviewed earlier by the Agency with original BLA submission, was used to simulate individual concentration-time profiles for 10,000 subjects with different numbers of missed doses followed by treatment being resumed with either a single dose, a double dose or a new loading dose. The maintenance dose setting was implemented as a dose increase to 0.25 mg/kg or a decrease to 0.15 mg/kg 6 weeks after first dose, based on C_{trough} values 4 weeks after first dose. In the simulations, exposure was at steady state at the time of the first missed dose and the body-weight distribution was similar to trial 4311.

In the setting of 1 missed dose, resumption of treatment at the same maintenance dose level on the following day with continued once-daily maintenance dose is shown to result in patients quickly reaching and maintaining the steady state levels (Figure 1).

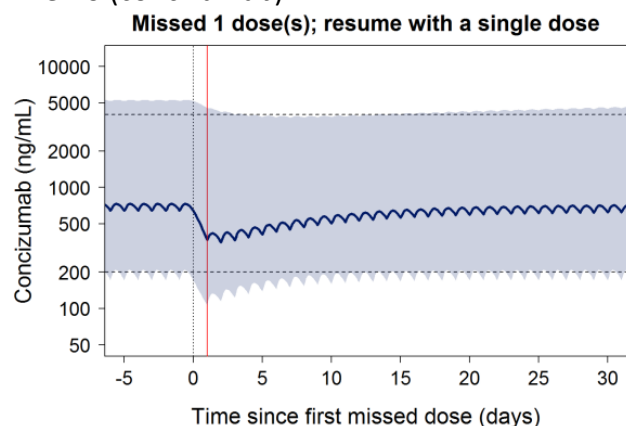


Figure 1: Simulation of concizumab plasma concentration when treatment is resumed with a single maintenance dose followed by once-daily maintenance dose after 1 missed dose.

In the setting of 2 to 6 missed doses, simulations show that doubling the maintenance dose following missed dose(s) is able to bring concizumab exposures above 200 ng/mL reasonably quickly and achieve steady state exposures with continued once-daily maintenance doses (Figure 2). Use of a loading dose to resume treatment in the scenario of 2 to 6 missed doses is not appropriate because the resulting exposures is expected to exceed the prior steady state levels.

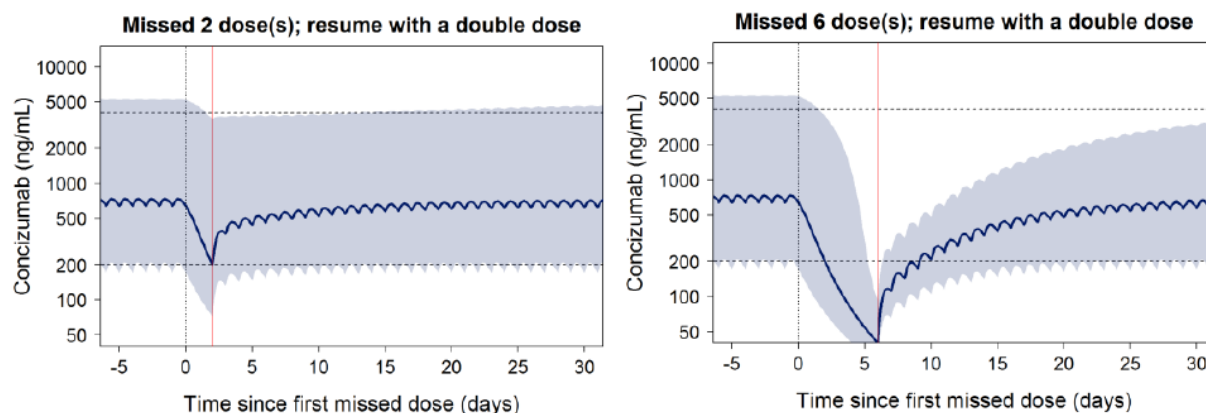


Figure 2: Simulation of concizumab plasma concentration when treatment is resumed with a double maintenance dose followed by once-daily maintenance dose after 2 (left) or 6 (right) missed doses.

In the setting of 7 or more missed doses, a loading dose of 1 mg/kg followed by once-daily maintenance doses is more appropriate as it results in concizumab exposures achieving steady state levels as quickly as possible without exceeding the prior steady state levels (Figure 3).

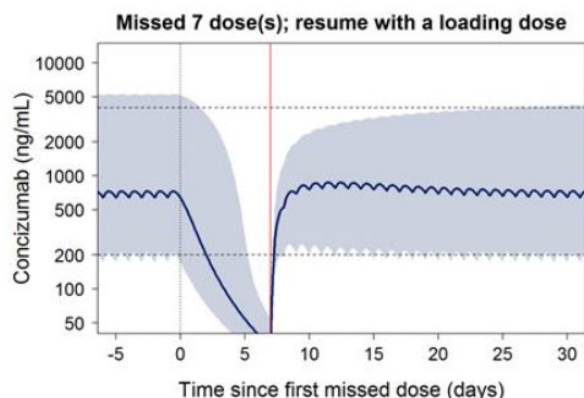


Figure 3: Simulation of concizumab plasma concentration when treatment is resumed with a loading dose followed by once-daily maintenance dose after 7 missed doses.

Guidance on Concizumab Measurements

Four weeks after initiation of concizumab, prescribers are advised to check concizumab-mtci plasma concentration by Concizumab ELISA prior to administration of next scheduled dose for dose optimization. Based on the results the concizumab dose may be adjusted. In order to further monitor patient compliance, Novo Nordisk proposed to add the following guidance for additional monitoring of concizumab plasma concentration to the USPI:

Based on the patient's condition, additional measurements of concizumab-mtci plasma concentration (b) (4) be taken (b) (4) so long as the patient has been on the same maintenance dose for 8 weeks of treatment to ensure steady-state plasma concentration.

The timing of the additional measurement i.e., 8 weeks beyond the dose adjustment period is reasonable, as it ensures achievement of new steady state levels in 90% of patients who underwent dose-adjustment. The Agency clarified further in the USPI that additional measurements of concizumab-mtci plasma concentration can be used to assess compliance.

Guidance and Education on Compliance

In order to stress the importance of adherence to daily dosing during the initial dosing period for appropriate maintenance dose setting, Novo Nordisk further proposed including the following guidance in the USPI and the corresponding instructions to be included in the Medication Guide:

Adherence to daily dosing of Alhemo is important to maintain protection against bleeding. This is especially important during the initial 4 weeks of treatment to ensure a correct maintenance dose is established. Patients who miss a dose during the initial 4-week period should inform their healthcare professional and resume once-daily dosing at the initial 0.2 mg/kg dose level.

Advise patients on the importance of adherence to daily dosing and to speak with their healthcare provider before discontinuing treatment with Alhemo as patients who are not

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adhering to daily dosing or stop treatment with Alhemo may no longer be protected against bleeding.

The Medication Guide will replace the Patient Product Insert (PPI) and text will be added on the carton with directions regarding dispensing the Medication Guide to each patient. The Medication Guide will include the following statement:

It is important to follow the daily dosing schedule to stay protected against bleeding. Take ALHEMO exactly as prescribed by your healthcare provider.

In addition, Novo Nordisk commits to developing educational material conveying similar messages based on the final approved labeling text.

Summary

The Applicant has adequately addressed the clinical and clinical pharmacology concerns regarding missed doses and strategies to monitor and promote patient compliance. The Agency agrees with the additional guidance on missed doses to be included in labeling, the recommendation for an additional concizumab level anytime beyond 8 weeks post-dose adjustment and guidance along with education materials to stress the importance of adherence to the prescribed dosing regimen.

3.2. Device

Concizumab Enzyme Linked Immunosorbent Assay (ELISA) and Intended Use:

- [REDACTED] (b) (4)
- [REDACTED]
- It is intended for concizumab concentration measurements in human 3.2% citrated plasma samples from patients after 4 weeks from the initiation of treatment for maintenance dose adjustment decision.
- It will be used in an **interim period** to bridge the time gap from concizumab BLA approval until a [REDACTED] (b) (4) PMA-approved concizumab ELISA companion diagnostic is available.

Complete Response Letter (CRL) Issue 2: Cross-validation between concizumab ELISA [REDACTED] (b) (4) vs [REDACTED] (b) (4) clinical trial assay (CTA)

Include sufficient number of native patient samples and samples that cover a range that are pertinent to dose adjustment decisions.

Applicant's Response:

The Applicant repeated the cross-validation study using 120 individual patient samples (i.e., native samples from Phase 3 clinical trials, NN7415-4311 and NN7415-4307). The sample material was residual PK assay samples which were left-over from PK samples derived from clinical trial visits other than dose decision visit. The dose decision visit samples are being used for [REDACTED] (b) (4) cross-validation and the proposed plan was accepted by the Agency. [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Reviewer's Assessment:

Reference is made to the *ICH M10 Bioanalytical Method Validation and Sample Analysis guidance*. Cross validation should be assessed by measuring the same set of QCs (low, medium, and high) at least in triplicate and study samples (if available) that span the study sample concentration range ($n \geq 30$) with both methods, or in both laboratories. The performance of calibration standards (CSs) and quality controls (QCs) for each method was not reported for the cross validation. However, it was noted that the performance of the CSs and QCs of the concizumab ELISA at (b) (4) and concizumab ELISA CTA at (b) (4) were evaluated as a part of their own method validation and the validation results were found to be acceptable.

(b) (4)

Overall, the Applicant's response regarding cross validation is acceptable.

CRL Issue 3: Assessment of instrument-to-instrument and lot-to-lot precision**Applicant's Response:**

(b) (4)

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Reviewer's Assessment:

The Applicant's assessment and conclusion appears to be reasonable.

CRL Issue 4: Assay specificity/interference study



Reviewer's Assessment:

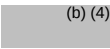
The Applicant's assessment and conclusion appears to be reasonable.

CRL Issue 5: Sample stability

Applicant's response:



Reviewer's Assessment:

The Applicant's assessment and conclusion appear to be reasonable. It should be noted that long term sample stability under frozen conditions has been established previously by  and Novo-Nordisk for 2 years.

CRL Issue 6: Root-cause analysis

Applicant's response:

CDER Clinical Review Template

Version date: March 8, 2019 for all NDAs and BLAs

Reviewer's Assessment:

The Applicant's assessment and conclusion appear to be reasonable.

Recommendation:

Overall, all of the Applicant's responses to the CRL issues related to the bioanalytical methods were found to be reasonable and therefore, the proposed interim concizumab ELISA assay (b) (4) is found to be reliable of its intended use.

3.3. Product Quality

The original BLA 761315 submission received a CR recommendation due to multiple product quality and device constituent deficiencies related to inadequate control of drug substance, drug product and device constituent.

The Applicant submitted updated information to Chemistry, Manufacturing, and Controls modules in response to the complete response comments and additional comments provided in the Complete Response Action Letter on April 24, 2023, which have been addressed adequately in the current assessment period.

The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761315 for Alhemo manufactured by Novo Nordisk Inc. The data submitted in the application were determined to be adequate to support the conclusion that the manufacture of Alhemo is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert. A PMC will be requested for the post-approval change (b) (4). See final review dated December 13, 2024.

3.4. Facility Inspection

Per the product quality review, adequate descriptions of the facilities, equipment, environmental controls, cleaning, and contamination control strategy were provided for (b) (4) and Novo Nordisk A/S (FEI: 3000151819) proposed for concizumab DS and DP manufacture. All proposed manufacturing and testing facilities are acceptable based on their current CGMP compliance status and recent relevant inspectional coverage.

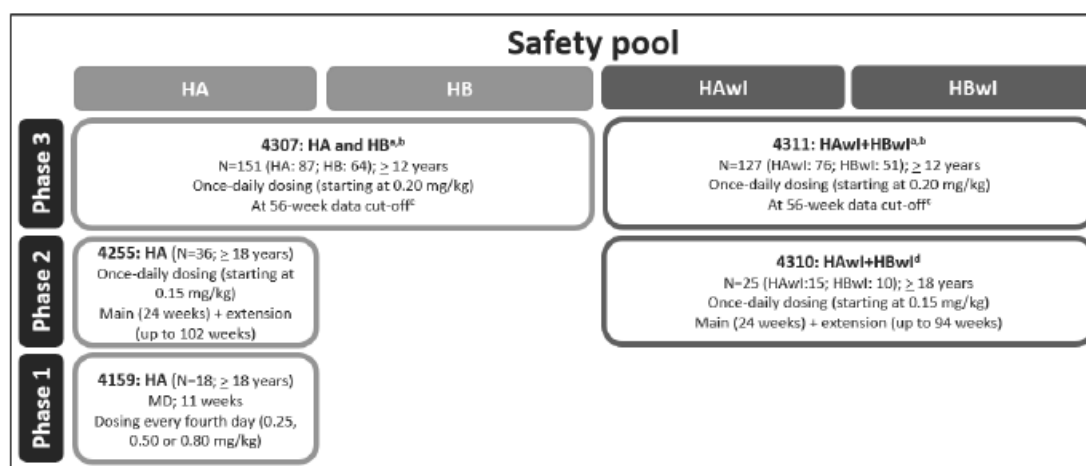
4. Review of Safety Update

4.1. Safety Review Approach

As requested in the CRL, the Applicant submitted a Safety Update Report with this resubmission.

The updated safety database for trials supporting the safety analysis of concizumab consists of multiple-dose trials (i.e., 4307, 4255, 4311, 4310 and 4159) (see Table 12 in the Appendix for an overview of the clinical trials). The Applicant's figure below shows that 320 patients total are included in the trials in patients with hemophilia before and/or after the treatment pause. Since the initial HAwI and HBwI application, results from a new (56-week) cut-off for phase 3 trial 4311 (HAwI and HBwI) and from two cut-offs (confirmatory analysis cut-off (CACO) and the 56-week cut-off) for phase 3 trial 4307 (HA and HB) were reviewed. The resubmission data cutoff date was March 31, 2024. Compassionate use data was also submitted from 27 patients.

Figure 5. Safety Database Pool by Trial



Notes: ^a16 patients with HA from trial 4255 were transferred to trial 4307 (cross-reference: ADSL.sas7bdat [Trial 4307]) and 21 patients from trial 4310 were transferred to trial 4311 (Trial 4311 PACO [M5.3.5.1], Table 10-1 [arm 3]). ^bPatients randomised to on demand treatment who were exposed to at least one dose of concizumab following the main part of the trial, contributed to the pooled safety evaluation. ^cThe 56-week cut-off was defined as when all patients in arms 2, 3 and 4 had completed visit 13a (or permanently discontinued treatment). ^dPatients randomised to on-demand treatment in the main part, who have been exposed to at least one dose of concizumab in the extension part of the trial, contribute to the pooled safety evaluation. Further details on exposure to concizumab are available in Section 1.2.

Abbreviations: HA: haemophilia A without inhibitors; HB: haemophilia B without inhibitors; HAwI: haemophilia A with inhibitors; HBwI: haemophilia B with inhibitors; MD: multiple-dose; N: number of patients exposed to at least one dose of concizumab

Source: Safety Update Report

4.2. Review of the Safety Database

4.2.1. Overall Exposure

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A total of 320 patients with HA, HB, HAwI and HBwI from the updated safety pool have been exposed to concizumab in the clinical trials 4307, 4255, 4311, 4310 and 4159, corresponding to a total of 474.7 patient years of exposure (PYE). The initial safety pool comprised a total of 185 patients exposed to concizumab for a total of 232.8 PYE. The Applicant's table below shows the total duration of exposure to concizumab by hemophilia subtype for the updated safety pool. The total exposure for the HAwI and HBwI group was 121.3 and 84.0 PYE, respectively. Total exposure in the HA and HB group was 195.8 and 73.5 PYE, respectively.

Table 3. Concizumab Exposure by Hemophilia Type Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

Patient years of exposure	HA N=125	HB N=64	HAwI N=78	HBwI N=53	HAwI + HBwI N=131	Total N=320
Total	195.8	73.5	121.3	84	205.3	474.7
Median (range)	1.2 (0, 4.7)	1.1 (0, 2.3)	1.3 (0.1, 4.2)	1.4 (0.2, 4.4)	1.4 (0.1, 4.4)	1.2 (0, 4.7)
Mean (SD)	1.6 (1.2)	1.1 (0.5)	1.6 (0.9)	1.6 (1.1)	1.6 (0.96)	1.5 (0.99)

Source: Safety Update Report

4.2.2. Relevant characteristics of the safety population:

In the total safety pool, mean (SD) age at screening was 31.2 (13.9) years. The majority of patients were age ≥ 18 years (76.3%), or $12 \leq 18$ years (23.7%). There were 6 patients (1.8%) age 65-84 years. No patients under age 12 years were enrolled in the trials. The ethnicity most frequently reported among enrolled patients was non-Hispanic or Latino (309 patients (91.4%)). The most commonly reported race was white (217 patients (64.2%)). The majority of patients enrolled in the trials were non-US (93.1%). See table below for demographic information reported in the Safety Update Report.

Table 4. Demographics Reported in Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

	HA N=134 n (%)	HB N=66 n (%)	HAwI N=83 n (%)	HBwI N=55 n (%)	HAwI + HBwI N=138 n (%)	Total N=338 n (%)
Age group (years)						
Adolescents (12-17yr)	23 (17)	15 (23)	22 (27)	20 (36)	42 (30)	80 (24)
Adults (≥ 18 yr)	111 (83)	51 (77)	61 (74)	35 (64)	96 (70)	258 (76)
Elderly (65-84 yr)	3 (2.2)	1 (1.5)	1 (1.2)	1 (1.8)	2 (1.4)	6 (1.8)
Ethnicity						
Hispanic	10 (8)	5 (8)	1 (1.2)	5 (9)	6 (4.3)	21 (6)
Not Hispanic or Latino	121 (90)	61 (92)	81 (98)	46 (84)	127 (92)	309 (91)
Not reported	3 (2.2)	0	1 (1.2)	4 (7)	5 (3.6)	8 (2.4)
Race						
American Indian or	2 (1.5)	1 (1.5)	1 (1.2)	2 (3.6)	3 (2.2)	6 (1.8)

	HA N=134 n (%)	HB N=66 n (%)	HAwI N=83 n (%)	HBwI N=55 n (%)	HAwI + HBwI N=138 n (%)	Total N=338 n (%)
Alaska Native						
Asian	33 (25)	17 (26)	22 (27)	17 (31)	39 (28)	89 (26)
Black or African American	3 (2.2)	2 (3)	7 (8)	2 (3.6)	9 (7)	14 (4.1)
White	91 (68)	45 (68)	52 (63)	29 (53)	81 (59)	217 (64)
Not Reported	3 (2.2)	0	1 (1.2)	5 (9)	6 (4.3)	9 (2.7)
Other	2 (1.5)	1 (1.5)	0	0	0	3 (0.9)

Source: Safety Update Report

Clinical reviewer comment: Patients younger than age 12 years of age were not included in clinical trials. (b) (4)

4.2.3. Adequacy of the safety database:

In total, 320 patients with HAwI, HBwI, HA and HB were exposed to concizumab in clinical trials. The safety update is adequate for review.

4.3. Adequacy of Applicant's Clinical Safety Assessments

4.3.1. Issues Regarding Data Integrity and Submission Quality

In the original BLA submission, a clinical inspection summary was completed by Dr. Anthony Orenca in the Office of Scientific Investigations, final signature date March 2, 2023, and no major issues were identified. For the safety update, no issues identified regarding data integrity and submission quality.

4.3.2. Categorization of Adverse Events

Adverse events were coded as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms (version 17.0 to 26.0). The Applicant used version 26.0 of MedDRA for the outputs based on the pooled data. The majority of adverse events were analyzed using standardized MedDRA queries. Hypersensitivity was analyzed using FDA Medical Query.

4.4. Safety Results

4.4.1. Deaths

In the original safety pool, there were 4 patient deaths including events of road traffic accident, COVID-19, alcoholic coma and intracranial hemorrhage. The event of intracranial hemorrhage occurred in an adolescent with subtherapeutic concizumab levels (see finalized Integrated Review dated April 24, 2023, for further details).

One new death in a patient with HA (treated on study 4307) was reported in the Safety Update Report. Patient (b) (6), was a 54-year-old male, with HA treated with concizumab PPX who was reported to have died due to intra-abdominal hemorrhage. In Trial 4307, on study day 276, the patient was found dead at home. The exact event onset date remains unknown. The cause of death based on autopsy was reported bleeding to death by diffuse intra-abdominal bleed of 1.7 L of blood without a clearly localizable bleeding source. The event was judged by the investigator as possibly related to concizumab, with alternative causality reported as “underlying disease severe hemophilia A”.

This patient was treated with concizumab PPX at a dose of 0.15 mg/kg in trial 4255 for approximately 2 years and 8 months. The patient was then enrolled in Trial 4307 and was treated with concizumab PPX (0.25 mg/kg) for approximately 8 months prior to the onset of the fatal event. There were no bleeding events reported for the patient in either trial up until the fatal event. Of note, the patient had an ongoing concomitant illness of hypertension treated with bisoprolol. Blood pressure measurements performed at the last 5 visits before event onset were reported to have from around 120-140/80 mmHg to around 155-170 /100-110mmHg.

An Information Request was sent to the Applicant to provide additional information regarding concizumab level(s) and compliance. The Applicant reported that all concizumab plasma concentration measurements performed for the patient after the maintenance dose setting were below 200 ng/mL. The concizumab plasma concentration gradually increased from approximately 70 ng/mL to fluctuating between approximately 90 and 175 ng/mL from week 8 up until the last measurement at week 32. There was seemingly only a minor effect of the maintenance dose increase to 0.25 mg/kg.

Despite the low plasma concizumab levels, free TFPI in plasma was well-suppressed at all visits where measured. The patient did not test positive for anti-concizumab antibodies (ADAs) at any visit. No protocol deviations related to missed doses or compliance issues were registered for the patient.

Reviewer comment: The cause for this patient’s intra-abdominal bleeding event is not clear. Although concizumab levels were consistently below the recommended levels of 200ng/mL the patient did not have other bleeding events. Notably, there was no evidence of antidrug antibodies. As described in the original BLA review, with low concentration of concizumab (<200ng/mL) patients are at risk for serious and life-threatening bleeding events. In fact, there was one other case of a fatal bleed described in the original review; however, this patient/caregiver may have had compliance issues. Per the Applicant the other patient who died due to intra-abdominal hemorrhage was compliant, but uncertainty remains.

To minimize risk of serious and life-threatening bleeding with subtherapeutic concizumab levels, the label should include instructions to advise prescribers/patients to consider alternative

therapies if the therapeutic range for concizumab cannot be achieved. Additional concizumab level monitoring to assess for subtherapeutic levels needs to be clearly stated in the label.

4.4.2 Serious Adverse Events

In total, 51 (15.9%) patients reported 71 serious adverse events (SAEs) (0.1 events per PYE). Similar proportions of patients reported SAEs in the updated (n=320 patient) and the initial safety pool (n=185 patient), 13.0% and 15.9%, respectively, and the rate was 0.1 events per PYE in both pools. Among patients with HAwI and HBwI there were 26/131 (19.8%) who reported SAEs. The table below shows that 10 patients with SAEs required discontinuation of the study drug. Cases with thrombotic adverse events of special interest were previously discussed in the Integrated Review final signature date April 24, 2023.

Table 5. Proportion of Patients with Serious Adverse Events Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

	HA N= 125 n (%)	HB N=64 n (%)	HAwI N=78 n (%)	HBwI N=53 n (%)	HAwI + HBwI N=131 n (%)	Total N=320 n (%)
SAE (yes)	17 (14)	8 (13)	9 (12)	17 (32)	26 (20)	51 (16)
Outcome						
Fatal	1 (0.8)	0	0	4 (8)	4 (3.1)	5 (1.6)
Not recovered	1 (0.8)	1 (1.6)	0	1 (1.9)	1 (0.8)	3 (0.9)
Recovered with sequelae	1 (0.8)	0	0	1 (1.9)	1 (0.8)	2 (0.6)
Recovering	2 (1.6)	0	0	1 (1.9)	1 (0.8)	3 (0.9)
Recovered	14 (11)	7 (11)	9 (12)	12 (23)	21 (16)	42 (13)
Unknown	0	0	0	0	0	0
Action taken with concizumab						
Drug withdrawn	4 (3.2)	1 (1.6)	0	2 (3.8)	2 (1.5)	7 (2.2)
Drug interrupted	5 (4)	1 (1.6)	5 (6)	5 (9)	10 (8)	16 (5)
Dose reduced	0	0	0	0	0	0
Dose increased	0	0	0	0	0	0
Dose not changed	9 (7)	6 (9.4)	3 (3.8)	11 (21)	14 (11)	29 (9)

Source: Safety Update Report

All SAEs by preferred term occurred in <1% of patients. The reviewer's table below shows the SAEs that were reported in ≥ 2 patients in the pooled population (patients with HA, HB, HAwI, and HBwI).

Table 6. SAEs Reported in ≥ 2 patients Trials 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

Preferred Term	N=320 n, (%)
Ligament sprain	3, (0.9%)
COVID-19 Infection	3, (0.9%)
Pneumonia	2, (0.6%)
Intra-abdominal hemorrhage	2, (0.6%)
Muscle hemorrhage	2, (0.6%)
Dizziness	2, (0.6%)

Source: Adapted from Safety Update Report

In total, 14 (4.4%) patients had serious bleeding events. This included events of pharyngeal hemorrhage, gastrointestinal hemorrhage, intra-abdominal hemorrhage, renal hematoma, post procedural hematoma, traumatic hematoma, retroperitoneal hemorrhage/hematoma, muscle hematoma/hemorrhage, hemorrhagic shock, puncture site hemorrhage, subdural hemorrhage, hemorrhage intracranial, melaena, hematemesis, and hemarthrosis. The majority of serious bleeding events were related to GI bleeding. Gastrointestinal bleeding disorders includes the pooled terms intra-abdominal hemorrhage, gastrointestinal hemorrhage, hematemesis, melena, retroperitoneal hematoma, and retroperitoneal hemorrhage, were reported in 7/320 (2.2%) of patients.

Reviewer comment: In the Information Request Response dated December 2, 2024, the Applicant responded to the query if there were subjects who may have had a subtherapeutic concizumab level and also had a serious bleeding adverse event reported after the 56-week cut off. The Applicant responded that a total of 14 patients reported a total of 19 bleed-related SAEs in trials 4311 (17 events in 12 patients) and 4307 (2 events in 2 patients) after the 56-week cut-offs i.e., based on on-going trial data. Among the 14 patients who reported bleeding SAEs after the 56-week cut-offs in trials 4311 and 4307 there are 6 patients whose plasma concizumab concentration was reported to be low (i.e., below 200 ng/mL) around the time of onset of the event. These patients had maintenance concizumab doses ranging from 0.20mg/kg to 0.25mg/kg. It is not clear why patients on 0.20mg/kg did not have a dose increase. Three of the 6 patients with low concizumab concentration were reported to have one protocol deviation. The 6 patients are presented in the table below, note the patient described in Section 4.4.1 that died due to intra-abdominal hemorrhage is not included as one of the 6 patients.

Table 7. Serious Bleeding Events and Subtherapeutic Concizumab Levels

Study ID/Pt ID	Hemophilia Subtype	Concizumab Maintenance Dose	Concizumab Levels	Bleed-Related SAE	Report of Non-compliance	ADAs Against Concizumab
4311/ (b) (6)	HAwI	0.2 mg/kg	Within target range for the first 72 weeks, after which exposure levels	Muscle hemorrhage	Yes	No

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Study ID/Pt ID	Hemophilia Subtype	Concizumab Maintenance Dose	Concizumab Levels	Bleed-Related SAE	Report of Non-compliance	ADAs Against Concizumab
			declined to below 200 ng/mL.			
4311/ (b) (6)	HBwl	0.2 mg/kg	Within target range for the first 56 weeks, after which exposure levels declined to below 200 ng/mL.	Hematuria, traumatic hemorrhage, traumatic arthrosis, hemarthrosis	No	Yes
4311/ (b) (6)	HAwl	0.2 mg/kg	All plasma concizumab concentration measurements were below 200 ng/mL with minor fluctuations.	Hematuria	Yes	No
4311/ (b) (6)	HBwl	0.25 mg/kg	Fluctuations throughout the treatment period with long periods of exposure below 200 ng/mL and only 4 visits where levels were above 200 ng/mL.	Intra-abdominal hemorrhage	No	No
4307/ (b) (6)	HB	0.25 mg/kg	The had subtherapeutic levels after discontinuing concizumab for surgery.	Post-procedural hemorrhage	No	No
4307/ (b) (6)	HB	0.2 mg/kg	All levels were below 200 ng/mL at all visits.	Traumatic hemorrhage; relation to a suicide attempt	Yes	No

Source: Applicant's IR Response December 4, 2024

The Agency requested the Applicant to include additional mitigation strategies in the label to decrease the risk of serious bleeding with subtherapeutic levels, such as requiring patients to

check additional measurement(s) to ensure a therapeutic level is achieved, in addition to advice on what the prescriber should do if a therapeutic level is not achieved.

4.4.2. Dropouts and/or Discontinuations Due to Adverse Effects

In the updated total safety pool, 60 (18.8%) patients who temporarily interrupted treatment or permanently discontinued therapy compared to 21 (16.9% patients originally reported in study 4311 and 4310). There were 10 (3.1%) patients who permanently discontinued study drug. AEs leading to study drug discontinuation were all reported in 1 patient each, including, intra-abdominal hemorrhage, procedural complication, acute myocardial infarction, cardiac failure, deep vein thrombosis, injection site pain, cardiomyopathy, renal infarct, hypersensitivity and COVID-19 infection. Patients with permanent study drug discontinuation ranged in age from 13-67 years. The duration of therapy prior to discontinuation ranged from 10-205 days. Of note, protocols required temporary treatment discontinuation for COVID-19 infection.

Table 8. Serious Adverse Events Leading to Study Drug Discontinuation Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

Study ID/Pt ID	Hemophilia Subtype	Age (years)	Study Day ¹	Reported SAE Term
4307/ (b) (6)	HB	43	3	Gastrointestinal bleed
4307/ (b) (6)	HB	15	1	Injection site pain
4307/ (b) (6)	HA	38	25	Cranial trauma
4307/ (b) (6)*	HA	46	59	Myocardial infarct
4307/ (b) (6)	HA	67	644	Cardiac failure
4307/ (b) (6)*	HA	43	86	Deep vein thrombosis
4311/ (b) (6)*	HBwl	28	21	Renal infarct
4311/ (b) (6)	HBwl	41	553	COVID-19 Infection
4311/ (b) (6)	HBwl	13	18	Hypersensitivity
4311/ (b) (6)	HAwl	61	501	Decompensated cardiomyopathy

¹Calculated from the start of treatment. *Cases with thrombotic serious adverse events previous discussed in the Integrated Review final signature date April 24, 2023

Clinical reviewer comment: Patient (b) (6) had a serious event of intra-abdominal bleeding. The patient was a 43-year-old male with HB who was treated with concizumab on study 4307. On day 2 of therapy the patient was admitted to hospital due to right upper quadrant abdominal pain. The patient underwent a CT scan of the abdomen and chest which showed blood in the area of the spleen and liver, and a lung mass, respectively. The lung mass was biopsied which was subsequently shown to have lymphocytic changes but no malignancy. The patient's concizumab therapy was discontinued at the time of the event. Although abdominal bleeding is not a common site for bleeding in patients with hemophilia it has been reported. This serious bleeding event is likely due to the underlying disease as the patient had just initiated concizumab therapy.

The majority of events leading to treatment discontinuation are included in labeling with mitigation strategies (i.e., bleeding due to subtherapeutic levels, thrombosis, and hypersensitivity reaction).

4.4.3. Treatment-Emergent Adverse Events

In the total safety pool, the most frequently reported TEAEs by PT were COVID-19 (14.7%), nasopharyngitis (12.5%), arthralgia (10.9%), headache and upper respiratory tract infection (both 9.4%), fibrin D-dimer increased (9.1%), pyrexia (7.2%), injection site erythema (5.9%) and prothrombin fragment 1+2 increased (5.6%). See table below.

Table 9. Most Common (>5%) TEAEs by Preferred Term in Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

Preferred Term	HA N=125 n (%)	HB N=64 n (%)	HAwI N=78 n (%)	HBwI N=53 n (%)	HAwI + HBwI N=131 n (%)	Total N=120 n (%)
COVID-19	20 (16)	12 (19)	8 (10)	7 (13)	15 (12)	47 (15)
Nasopharyngitis	25 (20)	3 (5)	5 (6)	7 (13)	12 (9)	40 (13)
Arthralgia	12 (10)	4 (6)	8 (10)	11 (21)	19 (15)	35 (11)
Headache	15 (12)	5 (8)	7 (9)	3 (6)	10 (8)	30 (9)
URI	14 (11)	5 (8)	7 (9)	4 (8)	11 (8)	30 (9)
Fibrin D-dimer increased	17 (14)	4 (6)	5 (6)	3 (6)	8 (6)	29 (9)
Pyrexia	9 (7)	2 (3)	5 (6)	7 (13)	12 (9)	23 (7)
Injection site erythema	6 (5)	3 (5)	4 (5)	6 (11)	10 (8)	19 (6)
Prothrombin fragment 1+2 increased	9 (7.2)	2 (3)	5 (6)	2 (4)	7 (5)	18 (6)

Source: Clinical reviewer

Abbreviations: URI, upper respiratory tract infection

4.4.4. Adverse Events of Special Interest

1. Thromboembolic events

In the Safety Update Report, 4 (1.3%) patients experienced SAEs of thromboembolic events, 3 out the 4 patients were reported in the original review. The one new case of serious thromboembolic event (cerebral infarction) occurred in a 63 year-old male with HA. The patient had a medical history of hypertension since 2013 and was treated with 2 anti-hypertensive medications. The patient was previously enrolled in the phase 2 trial 4255 and had more than 5 years of concizumab exposure up until onset of the SAE, including exposure before and after the treatment pause in trial 4307. On the day of event onset, the patient experienced visual disturbance, facial weakness, ataxia and slurred speech. The patient was diagnosed with an ischemic stroke. Different scans, MRI brain scans, were performed, and a small recent infarction was detected in 2 different areas (left hemipons and corona radiata). According to the investigator, the MRI images of the patient's brain as well as the CT scans taken after event onset were shared with a specialist (neuro-radiologist) to get a second opinion. According to the specialist, the specific lesions (perforating arteries) found on the scans are most seen in patients with a medical history of hypertension. The patient discontinued concizumab treatment permanently.

Clinical reviewer comment: Thrombosis is a serious adverse reaction associated with concizumab, likely due to exaggerated pharmacologic effect and will be included in the Warnings and Precautions section of the USPI. While providing specific guidance for use of the lowest labeled dose of factor product or bypassing agent while on concizumab PPX and a concizumab dosing regimen which targets concizumab levels <4000ng/mL, this risk remains, as evident by the event of cerebral infarction. Risk factors for thromboembolism further increase the risk of thrombosis and may include the use of high and/or frequent doses of breakthrough bleed treatments (factor products or bypassing agents) or conditions in which tissue factor is overexpressed (e.g., atherosclerotic disease, crush injury, cancer, disseminated intravascular coagulation, thrombotic microangiopathy, or septicemia). Thromboembolic events occurred in patients with multiple risk factors for thromboembolism, including the use of high doses or prolonged treatment with factor product or bypassing agent (2 of 4 events). Enhanced pharmacovigilance is recommended to further monitor the risk of thrombosis.

2. Hypersensitivity reactions

In the Safety Update Report, the search for FDA Medical Query (FMQ) for hypersensitivity reactions was reported in 30 (9.4%) patients totaling 55 events (0.1 events per PYE). The most common terms reported in ≥ 4 (approximately $\geq 1\%$) patients were 'hypersensitivity', 'injection site reaction', and 'pruritis'. The reviewer's table below shows the proportion of patients with hypersensitivity reactions reported in

≥ 4 patients using the FMQ search by disease subtype. One event of serious hypersensitivity reaction (anaphylaxis) was reported in the original review, no new events of anaphylaxis were reported. No events were fatal. Two events led to permanent treatment discontinuation. All but one event was characterized mild-moderate severity.

Table 10. Hypersensitivity Reactions Reported In ≥ 4 Patients in Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

Preferred Term	HA N=125 n, (%)	HB N=64 n, (%)	HAwI N=78 n, (%)	HBwI N=53 n, (%)	Total N=320 n, %
Pruritis	3 (2.4%)	0 (0.0%)	2 (2.6%)	0 (0.0%)	5 (1.6%)
Hypersensitivity	1 (0.8%)	0 (0.0%)	0 (0.0%)	3 (5.7%)	4 (1.3%)
Injection site rash	1 (0.8%)	1 (1.6%)	1 (1.3%)	1 (1.9%)	4 (1.3%)

Source: Adapted from Safety Update Report

Clinical reviewer comment: Hypersensitivity reactions remain a serious adverse reaction and will be included in the Warnings and Precautions section of the USPI.

3. Increased Laboratory Values of Fibrin D-dimer and Prothrombin Fragment 1+2

In the Safety Update Report, increased fibrin D-dimer and prothrombin fragment 1+2 was reported in 29/320 (9.1%) patients and 18/320 (5.6%) patients, respectively. The table below shows the proportion of patients by hemophilia subtype with fibrin D-dimer increased and prothrombin 1+2 increased.

Table 11. Proportion of Patients with Fibrin D-Dimer/Prothrombin 1+2 Increased in Trials 4159, 4310, 4255, 4307 (56-week cut-off) and 4311 (56-week cut-off)

Preferred Term	HA N=125 n, (%)	HB N=64 n, (%)	HAwI N=78 n, (%)	HBwI N=53 n, (%)	Total N=320 n, (%)
Fibrin D-dimer Increased	17 (13.6%)	4 (6.3%)	5 (6.4%)	3 (5.7%)	29 (9.1%)
Prothrombin 1+2 Increased	9 (7.2%)	2 (3.1%)	5 (6.4%)	2 (3.8%)	18 (5.6%)

Source: Adapted from Safety Update Report

Clinical reviewer comment: The plasma concentration of concizumab is positively correlated with fibrin D-dimer and prothrombin fragments 1.2 indicating a hemostatic effect of concizumab. For patients taking concizumab, these coagulation biomarkers may not be reliable predictive markers for clinical decision-making with suspicion of

thrombosis such as deep vein thrombosis (DVT) and pulmonary embolism (PE), therefore this risk will be included in the Warnings and Precautions section of the USPI.

5. Advisory Committee Meeting and Other External Consultations

An advisory committee (AC) meeting was not convened to discuss this application. No issues were identified that would have benefitted from a public discussion with external experts.

6. Labeling Recommendations

6.1. Prescription Drug Labeling

Alhemo will be approved with Prescribing Information, Medication Guide, and 3 Instructions for Use (one per pen strength).

CDER chose to approve concizumab without its companion diagnostic given the unmet need for patients with hemophilia with inhibitors. A postmarketing commitment is recommended for the development of the companion diagnostic. The label will state there are no FDA authorized tests. This is the same approach we have consistently used when CDER chooses to approve a drug without its companion diagnostic. The Center for Devices and Radiological Health (CDRH) agreed with CDER's approach and advised on labeling related to the use of an unauthorized concizumab-ELISA.

Summary of Significant Labeling Changes (High Level Changes)		
Section	Proposed Labeling	Approved Labeling
1 Indications and Usage	The Applicant proposed the following indication statement: Alhemo is a tissue factor pathway inhibitor (TFPI) antagonist indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients - hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors - hemophilia B (congenital factor IX deficiency) with FIX inhibitors	The established pharmacologic class (EPC) was edited to replace "(b) (4)". The EPC for this drug is "tissue factor pathway inhibitor antagonist." The Agency added that the indication is for pediatric patients at least 12 years of age, as this is the population included in clinical trials.
2 Dosage and Administration	The Applicant proposed guidance on dosing of concizumab.	Additional guidance on monitoring for subtherapeutic levels was added. Additional language added to stress the importance of adherence.

Summary of Significant Labeling Changes (High Level Changes)		
Section	Proposed Labeling	Approved Labeling
		Text added to provide guidance to prescribers on how to change to Alhemo from other hemostatic products. Revised text in 2.4 to clarify that self-administration may occur only after appropriate training. Added required language regarding inspection for particulate matter for parenteral drug products.
4 Contraindications	Applicant proposed to contraindicate in patients with known hypersensitivity to Alhemo or its components.	Revised to include those with a history of known serious hypersensitivity to Alhemo or its components or the inactive ingredients.
5 Warnings and Precautions	Applicant proposed Warnings for thromboembolic events and hypersensitivity reactions.	Revised the order to list the most clinically important risk first (thromboembolic events). Overall changed wording to active voice. Thromboembolic events (TE)- added additional description including the proportion of patients who experienced a TE and noted that cases occurred in patients with multiple risk factors for thromboembolism, including the use of high doses or prolonged treatment with factor product or bypassing agent (2 of 4 events). Hypersensitivity reactions- added additional description of the symptoms that were included in hypersensitivity reactions and the case of anaphylaxis. The Agency requested to add "Increased Laboratory Values of Fibrin D dimer and Prothrombin Fragment 1+2" as a Warning, as for patients taking concizumab, these coagulation biomarkers may not be reliable predictive markers for clinical decision-making with suspicion of thrombosis such as deep vein thrombosis (DVT)

Summary of Significant Labeling Changes (High Level Changes)		
Section	Proposed Labeling	Approved Labeling
6 Adverse Reactions	The Applicant presented pooled safety data.	and pulmonary embolism (PE). Information provided on the pooled studies that were used to provide data in Warnings and Precautions. Section 6.1 reported safety findings from the randomized, controlled trial (Explorer 7 or Study 4311) in patients with HAWI and HBWI. During labeling negotiations the clinical team agreed infectious related AEs were not related due to the MOA of the drug and no infectious toxicities were reported in animal data. The clinical team also agreed that arthralgia was most likely related to the underlying disease and comorbid conditions.
7 Drug Interactions	The Applicant did not propose text here.	The Agency added Bypassing Agents and described how to manage this interaction.
8 Use in Specific Populations	Pregnancy: (b) (4) Lactation: The Applicant stated that there was no information on the presence of drug in human milk. Females and Males of Reproductive Potential: The Applicant recommended use of contraception in women of childbearing potential. Pediatric Use: The Applicant described the age groups that had been studied with Alhemo.	The Agency revised this subsection to be consistent with the PLLR guidance. Added risk based on mechanism of action and known transport of monoclonal antibodies across the placenta. The background risk statement was revised. The Agency added that no information was available on the presence of the drug in animal milk. The Agency added a recommendation to conduct pregnancy testing in this population before starting treatment. The Agency revised this subsection to be consistent with the Pediatric Use labeling guidance which includes a required pediatric use statement, the basis of approval, and a limitation statement for those <12 years of age.

Summary of Significant Labeling Changes (High Level Changes)		
Section	Proposed Labeling	Approved Labeling
	Geriatric Use: (b) (4)	The Agency revised this subsection to be consistent with the Geriatric Use Subsection of Labeling Guidance which describes that the studies did not include sufficient numbers of geriatric patients to determine a different response. The Agency added a new subsection titled "Increased Body Weight" to describe the decreased clearance and volume of distribution in increased body weight. No dose adjustment is needed based on this.
12 Clinical Pharmacology		The Agency added a subsection 12.7 for Interference of Concizumab-mtci with Laboratory tests regarding the lack of clinically significant interference with standard PT/aPTT or FVIII or FIX activity measurement based on in vitro studies. These tests are used frequently in these patients.
14 Clinical Studies	(b) (4)	Only included prespecified, alpha-controlled endpoints.

7. Risk Evaluation and Mitigation Strategies (REMS)

Based on the available data, a risk evaluation and mitigation strategy is not necessary to ensure the benefits of concizumab in patients with HAWI and HBWI outweigh the risks.

8. Postmarketing Requirements and Commitments

PMC 4761-1: Conduct adequate analytical and clinical validation testing to establish and support labeling of an FDA cleared or approved in vitro diagnostic device to accurately and reliably detect concizumab concentration in human 3.2% citrated plasma that is safe and effective for concizumab dose adjustment decisions for Hemophilia A and B patients (with and without inhibitors) after 4 weeks from the initiation of treatment with concizumab. The results of the validation studies are intended to inform product labeling.

PMC 4761-2: To implement the change (b) (4) in the concizumab drug product (DP). The final report includes updates to the concizumab DP manufacturing process and all supporting studies of the pre- and post-change concizumab DP will be reported per 21 CFR 601.12
Final Report Submission: 10/2027

PMC 4761-3: To commit to re-evaluate the shelf-life (b) (4) after sufficient release and stability data from is collected no later than 3 years post-approval to support the concizumab-mtci drug product lifecycle. The revised shelf-life (b) (4) and adequate justifications will be reported per 21 CFR 601.12.
Final Report Submission: 04/2028

9. Appendices

9.1. Summary of Clinical Trials

Table 12. Summary of Clinical Trials 4307, 4255, 4311, 4310 and 4159

Trial ID	Trial Description	Population	Concizumab dose	Status
Study 4159	Phase 1, Safety, PK and PD Randomized, DB, placebo controlled, multiple-dose 11 weeks	N = 24 HA patients (18–64 years)	s.c. 0.25, 0.5, and 0.8 mg/kg every 4 days, 12 doses	Completed
Study 4255	Phase 2, efficacy and safety OL, multiple-dose Main part: ≥ 24 weeks Extension part: 52-102 weeks (Full trial: ≥76 weeks)	N = 36 HA patients (≥18 years)	Daily s.c. dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks.	Completed
Study 4310	Phase 2, efficacy and safety	N = 25 HAWI: 16	Day 1: Single s.c. loading dose of 0.5 mg/kg	Completed

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Trial ID	Trial Description	Population	Concizumab dose	Status
	Randomized, OL, controlled, multiple-dose Main part: ≥ 24 weeks Extension part: 52-94 Weeks (Full trial: ≥76 weeks)	HBwl: 10 (≥18 years)	concizumab. Day 2 and onwards: Daily s.c. dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks.	
Study 4307	Phase 3, efficacy, PK, PD and safety Randomized, OL, controlled, multiple-dose Main part: 24 weeks for arm 1 and 32 weeks for arms 2, 3 and 4. Extension part: up to 265 weeks.	N = 151 HA: 87 HB: 64 (≥12 years)	Day 1: Single s.c. loading dose of 1 mg/kg concizumab. Day 2 and onwards: Initial daily s.c. dose of 0.20 mg/kg. Individual maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment	CACO and 56-week cut-off reached (extension part ongoing)
Study 4311	Phase 3, efficacy, PK, PD and safety Randomized, OL, controlled, multiple-dose Main part: 24 weeks for arm 1 and 32 weeks for arms 2, 3 and 4. Extension part: up to 265 weeks.	N = 127 HAWl: 76 HBwl: 51 (≥12 years)	Day 1: Single s.c. loading dose of 1 mg/kg concizumab. Day 2 and onwards: Initial daily s.c. dose of 0.20 mg/kg. Individual maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment.	PACO and 56-week cut-off reached (extension part ongoing)

Source: Adapted from Applicant's Clinical Study Report

Abbreviations: CACO, confirmatory analyses cut-off; DB, double-blind; HA, hemophilia A; HAWl, hemophilia A with inhibitors; hemophilia B; HBwl, hemophilia B with inhibitors; OL, open-label; PACO, primary analysis cut-off; PD, pharmacodynamic; PK, pharmacokinetic; S.C., subcutaneous

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Integrated Review

Table 1. Application Information

Application type	BLA
Application number(s)	761315
Priority or standard	Priority
Submit date(s)	8/24/2022
Received date(s)	8/24/2022
PDUFA goal date	4/24/2023
Division/office	Division of Nonmalignant Hematology (DNH)
Review completion date	Electronic stamp
Established/proper name	concizumab
(Proposed) proprietary name	ALHEMO®
Pharmacologic class	Anti-tissue factor pathway inhibitor
Other product name(s)	NNC0172-2021
Applicant	Novo Nordisk
Dosage form(s)/formulation(s)	(b) (4) injection
Dosing regimen	The recommended dosing regimen comprise a loading dose of 1 mg/kg followed by an initial once daily dosing of 0.20 mg/kg. Based on the concizumab exposure level measured after 4 weeks of treatment, the maintenance dose will be set to 0.15, 0.20 or 0.25 mg/kg once daily.
Applicant-proposed indication(s)/ population(s)	For routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with: • hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors • hemophilia B (congenital factor IX deficiency) with FIX inhibitors
SNOMED CT code for proposed indication disease term(s) ¹	Click or tap to enter text.
Regulatory action	Complete response
Approved dosage (if applicable)	Not applicable.
Approved indication(s)/ population(s) (if applicable)	Not applicable.
SNOMED CT code for approved indication disease term(s) ¹	Not applicable.

¹ For internal tracking purposes only.

Abbreviations: PDUFA, Prescription Drug User Fee Act; SNOMED CT, Systematized Nomenclature of Medicine Clinical Terms

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Glossary

ABR	annualized bleeding rate
ADA	anti-drug antibody
AE	adverse event
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
AST	aspartate aminotransferase
BLA	biologics license application
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
C _{max}	maximum plasma concentration
CR	complete response
CSR	clinical study report
EC ₅₀	half maximal effective concentration
ECG	electrocardiogram
ELISA	enzyme-linked immunoassay
FDA	Food and Drug Administration
FIX	coagulation factor IX
FMQ	Food and Drug Administration Medical Dictionary for Regulatory Activities query
FVII	coagulation factor VII
FVIII	coagulation factor VIII
FXa	coagulation factor Xa
GLP	good laboratory practice
HA	hemophilia A
HAwI	hemophilia A with inhibitors
HB	hemophilia B
HBwI	hemophilia B with inhibitors
ICH	International Council for Harmonization
IEC	independent ethics committee
IND	investigational new drug
IRB	institutional review board
ISS	integrated summary of safety
ITI	immune tolerance induction
IV	intravenous
NDA	new drug application
NOAEL	no observed adverse effect level
PD	pharmacodynamic
PK	pharmacokinetic
PPX	prophylaxis
PRO	patient-reported outcome
PT	prothrombin time
SAE	serious adverse event

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SD	standard deviation
SOC	system organ class
TEAE	treatment-emergent adverse event
TF	tissue factor
TFPI	tissue factor pathway inhibitor
T _{max}	time to maximum concentration
ULN	upper limit of normal

I. Executive Summary

1. Summary of Regulatory Action

On August 24, 2022, Novo Nordisk submitted BLA 761315 for concizumab for the following indications: ALHEMO® is a tissue factor pathway inhibitor (TFPI)-directed antibody indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors (HAWI) and hemophilia B (congenital factor IX deficiency) with coagulation factor IX (FIX) inhibitors (HBwI). This application was reviewed by a multidisciplinary team. This application was given priority review because the proposed indication would have addressed an unmet medical need of a prophylaxis treatment for patients with HBwI.

In 2018 and 2019, concizumab received orphan designation for hemophilia A (HA) and hemophilia B (HB), and in 2019 received Breakthrough Therapy designation for HBwI.

In clinical studies, concizumab prophylaxis use demonstrated an improvement in the annualized bleeding rate (ABR) compared to on demand treatment using a blood product approved for the on-demand treatment of bleeding events for patients with HA and HB. ABR endpoint has been used for product approval for decades for products to treat bleeding events due to hemophilia.

The application has multiple deficiencies including concern about inadequate monitoring for missed doses, need for clear labeling instructions regarding missed doses, need for a Medication Guide, the interim assay proposed for product launch and product quality review issues including facilities inspectional deficiencies which preclude approval.

2. Benefit-Risk Assessment

2.1. Benefit-Risk Framework

Table 2. Benefit-Risk Framework

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of condition	- HA is an X-linked recessive disorder caused by mutations in the FVIII gene which results in a severe deficiency or absence of the clotting protein factor VIII. HA occurs in approximately 1 in 5000 live male births. Patients are typically diagnosed in infancy. Patients are at increased risk for minor and serious bleeding including life threatening spontaneous or traumatic bleeding. Disease manifestations include mucosal bleeding, easy bruising, soft tissue and muscle bleeds, hemarthrosis and excessive bleeding with procedures or trauma. Bleeding can occur in vital organs (including the brain). Adults commonly experience hemophilic arthropathy due to recurrent joint bleeds, which is associated with significant disease morbidity. - HB is an X-linked recessive disorder caused by mutations in the FIX gene which results in a severe deficiency or absence of the clotting protein factor IX. HB occurs in approximately 1 in 30,000 live male births. Deficient factor IX levels results in an increased risk for minor and serious bleeding, including life threatening spontaneous or traumatic bleeding. Disease manifestations of HB are the same as HA described in the text above. - One of the most serious complications of HA and HB is inhibitor development. Approximately 30% of patients with HA and 5-15% of patients HB develop inhibitors. Because bleeding is more difficult to prevent and treat, patients with inhibitors often experience increased disease morbidity and mortality.	Hemophilia A (congenital factor VIII deficiency) with FVIII inhibitors (HAWI) and hemophilia B (congenital factor IX deficiency) with FIX inhibitors (HBWI) are serious chronic diseases with significant morbidity and mortality due to bleeding. Patients with inhibitors have a worse disease course.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current treatment options	- FDA approved bypassing agents are used to prevent or control bleeding in patients with inhibitors. Activated prothrombin complex concentrate (aPCC) is indicated to control and prevent bleeding episodes in patients with HAwI and HBwI. Recombinant activated coagulation factor VII (rFVIIa), is indicated for the treatment of bleeding episodes in patient with HAwI and HBwI. Efficacy of these products can be variable, and they carry a boxed warning for thrombosis. - Alloantibodies or inhibitors develop with exposure to exogenous factor, and block the activity of factor VIII or IX. Inhibitors can make it difficult to stop excessive bleeding as it leads to reduced efficacy of factor replacement. - Patients with HAwI and HBwI may undergo immune ITI to eradicate the inhibitor, but this is only successful in 60-80% of cases in patients with HAwI and 15-30% of patients with HBwI. - Emicizumab (HEMLIBRA) is a bispecific factor IXa and factor X-directed antibody that was FDA approved in 2017 for the indication of routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with HA or HAwI. Emicizumab is administered by weekly up to every 4 weeks by SC injection. Emicizumab has a boxed warning for thrombotic microangiopathy and thromboembolism associated with use with aPCC.	There is a need for available, safe and effective therapies. Patient with HA and HB can develop inhibitors after exposure to exogenous factor. For patients with HAwI and HBwI, prophylactic treatment options are very limited, in particular for patients with HBwI.
Benefit	Pivotal, Phase 3 Study 4311 Study 4311 was a multi-center, open-label, randomized-controlled study in which 52 adult and adolescent patients (27 HAwI, and 25 HBwI), previously treated with on-demand therapy, were randomized 1:2 to arm 1, no prophylaxis (on demand therapy) (N=19) or arm 2, concizumab prophylaxis (N=33) for at least 24 weeks. Arms 3 and 4 included 81 additional patients (53 HAwI and 28 HBwI) treated with concizumab prophylaxis. Any bleeds occurring in the clinical study were treated with the patient's usual bypassing	The benefit of concizumab was clearly demonstrated in Study 4311, in which prophylactic treatment with daily concizumab reduced spontaneous and traumatic bleeding episodes in patients with HAwI and HBwI. This was evident by the reduction in the number of bleeding events in patients treated with concizumab prophylaxis compared to on demand therapy. While there is a concern that patients may alter their behavior due to knowledge of their treatment assignment, the highly statistically significant efficacy result provides reassurance of treatment effect.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	product or factor. Superiority of concizumab PPX (arm 2) over no PPX (arm 1) was confirmed for the primary endpoint of number of treated spontaneous and traumatic bleeding episodes. The annualized bleeding rate (ABR) was calculated as the number of treated spontaneous or traumatic bleeds divided by the number of days in the analysis set, multiplied by 365. The ABR was 1.7 with 95% CI (1.01, 2.87) for patients on concizumab PPX (arm 2) and 11.8 with 95% CI (7.03, 19.86) for patients on no PPX (arm 1). The estimated ABR ratio was 0.14 with 95% CI (0.07, 0.29), corresponding to an 86% reduction in ABR for patients on concizumab PPX (arm 2) compared to no PPX (arm 1). Results were statistically significant and the magnitude of reduction in bleeding rate was clinically meaningful for a patient population at risk for frequent bleeding that is difficult to treat. • Key secondary endpoints of change in SF-36v2 bodily pain and change in SF-36v2 physical functioning were not statistically significant. • In a descriptive analysis, 94.7% of patients in arm 1 (no PPX) had a treated bleed or discontinued before week 24 compared to 48.5% in arm 2 (concizumab PPX).) Supportive, Phase 2 Study 4310 • Study 4310 was a supportive, multicenter, open-label, randomized-controlled study in which 26 patients (16 HAWI patients, 10 HBWI) patients were randomized 2:1 to concizumab PPX (n=17) and eptacog alfa (rFVIIa) on demand (N=9) for at least 24 weeks. The primary endpoint was the number of bleeding episodes during at least 24 weeks from treatment onset. The ABR was significantly lower in the concizumab PPX arm compared to the eptacog arm. The estimated ABR during the entire treatment period was also lower in the concizumab arm compared to the eptacog alfa arm: 5.4 (95% CI: 3.8, 7.6) and 20.6 (95% CI 13.7, 30.8), respectively.	Substantial evidence of effectiveness of concizumab for prophylaxis in patients with HAWI and HBWI was based on one adequate and well controlled study, Study 4311, and confirmatory evidence. Confirmatory evidence was provided from Study 4310 based on a large reduction in ABR in the concizumab arm compared to the eptacog alfa arm in patients with HAWI and HBWI, along with mechanistic support of reduction in TFPI with corresponding increased thrombin generation.

Risk and risk management	Overall Safety Findings - The review of safety focused on Study 4311, which included 127 patients with HAWL and HBWL exposed to concizumab, including 33 patients randomized to concizumab PPX (arm 2) compared to 19 patients randomized to no PPX (arm 1) in the main treatment period. The safety analysis was further supported by Study 4310. - TEAEs were reported in 60% of patients in concizumab PPX arm 2 compared to 42% patients in the on-demand arm 1 in the randomized main treatment portion of study 4311. The most common TEAE (>10%) in the main treatment period and occurred in a higher proportion of patients in the concizumab arm compared to no PPX was local administration reactions, which occurred in 18% of patients in the concizumab arm (arm 2) compared to 0% in the on-demand therapy arm (arm 1). The most common ARs (>10%) at any timepoint (main and extension parts) after exposure to concizumab were local administration reaction (23.7%), nasopharyngitis (14.9%), and arthralgia (11.4%). Additional notable safety findings included one patient (<1%) with an AR of serious hypersensitivity reaction, prothrombin fragment 1.2 increased (6.1%), and fibrin d-dimer increased (5.3%). Thrombosis - In total, three patients experienced non-fatal events of thrombosis, including arterial and venous thrombosis, after receiving concizumab, compared to no patients in the control group. Notable characteristics were additional risk factors for thrombosis (i.e., smoking, obesity and HTN), receiving factor product or a bypassing agent within 24 hours of the thrombotic event and elevated concizumab levels (>4000ng/mL). - The Applicant had modified the concizumab dosing regimen during the clinical development to target a concizumab level between 200-4000ng/mL, to prevent bleeding and thrombosis. In addition, the Applicant	Several risks have been identified that should be included in the Warnings and Precautions section of the USPI if concizumab is approved, this includes risk of thrombosis, hypersensitivity reactions, and increased laboratory values of fibrin D-dimer and prothrombin fragment 1+2. Local injection site reaction was the most common AR. Patients with prolonged subtherapeutic levels (<200ng/mL) of concizumab are at increased risk of bleeding, which can be serious and life-threatening. Compliance to the daily SC dosing regimen of concizumab is critical to prevent prolonged subtherapeutic levels. Therefore, the importance of adherence to daily dosing should be stressed in labeling and a Medication Guide. In addition, a plan for missed concizumab doses should be described in labeling. Concizumab levels >200ng/mL is key to the therapeutic effect of concizumab and levels <4000ng/mL is critical to decrease the risk of thrombosis, therefore it is necessary to have an accurate and reliable concizumab ELISA in order to dose adjust concizumab to a safe and efficacious concentration. CDRH has identified multiple issues with the concizumab ELISA and has determined it is inadequate for postmarket use.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	included a number of mitigation strategies, including using the lowest labeled dose of factor or bypassing agent. After the new dosing regimen was put in place along additional mitigation strategies, no additional thrombotic events occurred in clinical studies. Risk of Bleeding with Subtherapeutic Concizumab Levels. • The majority of patients with subtherapeutic concizumab levels (<200 ng/mL) had no bleeding or minor bleeding although, a serious bleeding event of muscle hemorrhage and a fatal intracranial bleed occurred with subtherapeutic levels. • Large PK fluctuations were noted in clinical studies, this was in part due to issues with non-compliance. PK analysis demonstrates missed doses of concizumab can result in subtherapeutic levels within a few days, further, once the patient restarts administration it may take several days to become therapeutic.	

Abbreviations: ABR, annualized bleeding rate; aPCC, activated prothrombin complex concentrates; ELISA, enzyme-linked immunoassay; HA, hemophilia A; HB, hemophilia B; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; HTN, hypertension; ITI, immune tolerance induction; PK, pharmacokinetic; PPX, prophylaxis; SAEs, serious adverse events; SC, subcutaneous; TEAEs, treatment-emergent adverse events; TFPI, tissue factor pathway inhibitor; USPI, United States Prescribing Information

2.2. Conclusions Regarding Benefit-Risk

BLA 761315, ALHEMO® (concizumab), provided substantial evidence of effectiveness based on data from clinical studies. However, the application will receive a Complete Response letter because of the inspection, multiple product quality deficiencies, an inadequate interim assay to monitor concizumab concentration after dose adjustment and an inadequate plan for monitoring for missed doses that preclude approval.

The review teams acknowledged that the hemophilias are serious and life-threatening diseases with few to no treatment options depending upon the subtype. If left untreated, hemophilia will result in significant morbidity and early mortality from uncontrolled bleeding arising spontaneously, following injury, or related to surgery. Thus, affected patients start on a life-long treatment program of blood products or recombinant factor concentrates designed to “bypass” the absent clotting factor, or emicizumab to prevent severe bleeding for patients with hemophilia A with and without inhibitors. Some patients treated with blood products and recombinant factor concentrates will develop antibody inhibitors which render the treatment ineffective, leaving these patients with few to no options depending upon the subtype.

Concizumab focuses on providing a prophylaxis treatment for those with congenital hemophilia A or B with inhibitors. For the subgroup of patients with congenital hemophilia B with inhibitors this product has the potential to address an unmet medical need because of a lack of available therapies available for prophylaxis. The nonclinical, clinical, statistical and clinical pharmacology teams support the approval based on the nonclinical and clinical data packages and did not identify any deficiencies. No important differences of opinion were voiced during the review process.

The clinical data package consisted of several clinical studies that demonstrated an effect on ABR, an endpoint that has been used for the approval of other monoclonal antibodies or blood products for the treatment of hemophilia. The main study was 4311, an international, multicenter, open-label, randomized controlled study. Study 4311 was designed to compare “on demand” treatment with a bypassing agent, eptacog alfa or activated prothrombin complex concentrate, administered at the time of bleeding with prophylaxis concizumab treatment. The efficacy results demonstrated a markedly lower reduction in median annualized bleeding rates for the prophylaxis concizumab treatment when compared with the “on demand” eptacog alfa or activated prothrombin complex concentrate treatment. Median ABR for the concizumab combined arms was 1.7 [1.01, 2.87] bleeds compared with 11.8 [7.03, 19.86] bleeds for the eptacog alfa treatment “on demand” arm. During the initial part of the study, an increase in thrombotic events occurred in the concizumab treatment arm which resulted in a study pause and clinical hold because of concerns of excessive TFPI inhibition. Thus, Novo Nordisk developed an algorithm based on concizumab pharmacokinetics (PK) levels to adjust concizumab dose if needed. The study resumed and no further thrombotic events were observed. The major Study 4311 concizumab safety findings were bleeding, thrombosis, hypersensitivity reactions, and injection site reactions.

The clinical pharmacology review concurred with the Applicant’s assessment of 200 ng/mL as the lower end of the target concentration for concizumab. Levels lower than 200 ng/mL are associated with increased risk for bleeding. During the review, the team noted that for some

patients there was significant intrasubject PK fluctuation, which the Applicant attributed to target mediated drug disposition (TMDD). The clinical pharmacology review team considered other scenarios potentially accounting for the observed results including antidrug antibodies, problems with the PK assay, and membrane bound TFPI and treatment compliance issues. The issue of missed dosing (compliance) is a significant concern because there would be a potential for bleeding risk for the few patients whose exposure falls below 200 ng/mL. Because spontaneous bleeding events and sites cannot be predicted, understanding how patients and their healthcare providers should handle missed doses is an important key to the safe and effective use of concizumab. The importance of adherence to daily dosing and maintenance of adequate levels should be stressed in any labeling, Medication Guide and educational material.

The nonclinical review did not identify any unexpected risks with concizumab. The nonclinical toxicology studies' results were consistent with the expected mechanism of action of TFPI inhibition. Toxicities observed reflected the expected consequence of higher-than-expected exposures than those anticipated at the proposed therapeutic dose.

(b) (4)

ovo Nordisk proposed an interim assay and process which would be available for a concizumab launch. CDRH's review identified deficiencies for the interim assay and plan which include assay accuracy, precision, sample handling, and methodology.

Besides the issues with the interim assay, the Agency's product reviewers identified chemistry, manufacturing, and controls issues: the failed facilities inspection and multiple deficiencies including inadequate cell bank stability protocols, inadequate reference material stability protocols, inadequate DS and DP release and stability specifications, and inadequate DS and DP post-approval annual stability protocols.

II. Interdisciplinary Assessment

3. Introduction

Product Introduction

Concizumab (proposed proprietary name, ALHEMO[®]), a new molecular entity (NME), is a monoclonal antibody antagonist of endogenous tissue factor pathway inhibitor (TFPI). It is directed against TFPI which allows increased downstream Fxa production by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex and further downstream generation of thrombin in the coagulation cascade. Concizumab acts independently from FVIII and coagulation factor IX (FIX).

The Applicant proposes the following indication: for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients with hemophilia A with inhibitors (HAWI) and hemophilia B with inhibitors (HBWI).

The proposed dosing regimen:

- Day 1: Loading dose of 1 mg/kg
- Day 2: Once-daily dose of 0.20 mg/kg until individualization of maintenance dose (see below)
- 4 weeks after initiation of treatment: For dose optimization measure concizumab plasma concentration once by concizumab enzyme-linked immunoassay (ELISA) prior to administration of next scheduled dose
- After concizumab plasma concentration result is available but recommended no later than 8 weeks after initiation of treatment: Individualize maintenance dose of concizumab once based on the following concizumab plasma concentrations:
 - <200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
 - 200 to 4000 ng/mL: continue once-daily dose of 0.20 mg/kg
 - >4000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg

Disease Background

Patients with congenital hemophilia A or B lack specific clotting factors (factor VIII or IX, respectively) and thus have spontaneous bleeding events which can affect critical organs and be fatal. Patients with hemophilia A and B are typically treated with blood/recombinant factor concentrates which supply the necessary missing clotting factors. Some patients with hemophilia will develop antibodies (also known as inhibitors) to the factor concentrates rendering the factor concentrates ineffective to prevent bleeding events. These patients who have hemophilia and inhibitors are then treated with a bypassing strategy designed to overcome the missing factor and its inhibitor.

HAwI

Congenital hemophilia A (HA) is an X-linked bleeding disorder characterized by the deficiency or absence of factor VIII (FVIII). Hemophilia A occurs in 1 in 5000 live male births, without ethnic predominance, which results in an incidence in the US of about 20,000 people and 400,000 people worldwide ([Soucie et al. 1998](#)). The absence of functional FVIII interrupts the coagulation cascade and the ability to form a stable clot in response to trauma. The resulting bleeding complications can be severe and life threatening and can lead to long-term morbidity from joint damage due to recurrent bleeds. The standard of care in patients with HA is treatment with recombinant or plasma-derived FVIII concentrates. Treatment can either be in response to a bleeding event (episodic or “on demand” treatment) or scheduled treatment to prevent bleeds (prophylactic treatment). In resource-rich countries, prophylactic treatment initiated prior to any joint bleeds is preferred. In 30-35% of patients with hemophilia A, a neutralizing antibody, known as a FVIII inhibitor, forms which renders exogenous and endogenous FVIII nonfunctional. Patients with FVIII inhibitors are more difficult to treat in response to bleeding events, leading to a higher rate of progressive joint disease from frequent joint bleeds and an increased risk of death from uncontrolled bleeding.

HBwI

Congenital hemophilia B (HB) is an X-linked bleeding disorder caused by the deficiency of FIX, a vitamin K-dependent plasma protease that participates in the intrinsic blood coagulation pathway and whose function is to cleave and activate FX within the coagulation cascade. The prevalence of the disease is estimated to be 1:30,000 males ([Santoro et al. 2018](#)). Bleeding tendency in HB is in accordance with the severity of factor deficiency. Patients with the severe form (FIX <1%), who account approximately for 30 to 45% of persons with HB, usually suffer from recurrent joint, soft-tissue, and muscle bleedings. FIX concentrates are administered in order to reduce bleeding complications ([Santoro et al. 2018](#)). The reported rate of FIX inhibitors is 1 to 15% of all patients with HB ([Male et al. 2021](#)).

Current Therapy Options

Current therapeutic options for patients with HAwI and HBwI are summarized below ([Table 3](#)).

HAwI

Patients with inhibitors cannot be treated with FVIII replacement as the inhibitor would clear the exogenous FVIII and likely increase the inhibitor titer. To clear the FVIII inhibitor, patients may undergo immune tolerance induction (ITI). ITI involves frequent administrations of high-dose FVIII to eliminate the antibody over time and allows patients to resume their prophylactic treatment with FVIII. While this is successful in some patients, there is a failure rate of 20-40%, and those patients who have a resurgence of their antibody after ITI tend to be even more refractory to treatment. ITI also presents a heavy burden to patients both in terms of effort and cost from daily high dose factor VIII infusions. The available treatments in patients with FVIII inhibitors are episodic treatment with a bypassing agent which bypasses FVIII in the coagulation cascade, often during ITI. Unfortunately, the efficacies of these agents are unstable compared to FVIII infusions for patients without inhibitors. [Table 3](#) below summarizes the available therapies

for the treatment of HAwI. NovoSeven® and FEIBA® are available agents have product-specific characteristics that limit their usability. NovoSeven is a recombinant activated factor VII (rFVIIa) product which has a short half-life and requires intravenous (IV) treatment every two to three hours. FEIBA, or Factor Eight Inhibitor Bypassing Activity, is a plasma-derived activated prothrombin complex concentrate (aPCC) which is predominately composed of prothrombin and Factor X, but also contains lesser amounts of Factors VII and IX. This product requires a long infusion time which can limit its use. It also contains small amounts of FVIII, resulting in the risk of augmenting inhibitor formation in patients not currently undergoing ITI. Patients with FVIII inhibitors can also receive prophylactic treatment with a bypassing agent. FEIBA was approved in 2013 for this indication. The primary efficacy outcome for the registration study was annualized bleeding rate (ABR), which is the rate of bleeds normalized to one year. Patients on FEIBA prophylaxis had a median ABR of 8 compared to 29 for patients receiving episodic treatment with FEIBA. Prophylactic treatment is costly and burdensome given the need for every-other-day IV infusions of FEIBA. NovoSeven is not approved for prophylaxis with the exception of prevention of bleeding during surgical or invasive procedures, and therefore the dosing regimens used are not standardized and with variable rates of efficacy.

Emicizumab is a humanized monoclonal modified immunoglobulin G4 (IgG4) bispecific factor IXa- and factor X-directed antibody, which was approved for marketing on November 16, 2017, under BLA 761083. Emicizumab is indicated for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with HA with or without factor VIII inhibitors (i.e., HA and HAwI). The recommended loading dose of emicizumab is 3 mg/kg administered by SC injection once weekly for the first 4 weeks, followed by a maintenance dose of 1.5 mg/kg once every week, or 3 mg/kg once every two weeks, or 6 mg/kg once every four weeks. The selection of a maintenance emicizumab dose is based on healthcare provider preference with consideration of regimens that may increase patient adherence. The emicizumab product label contains a boxed warning that states cases of thrombotic microangiopathy and thrombotic events were reported when on average a cumulative amount of >100 U/kg/24 hours of aPCC was administered for 24 hours or more to patients receiving emicizumab prophylaxis. The boxed warning contains the recommendation to monitor for the development of thrombotic microangiopathy and thrombotic events if aPCC is administered, and to discontinue aPCC and suspend dosing of emicizumab if symptoms occur. The most common adverse reactions (incidence $\geq 10\%$ of patients) reported in clinical studies are injection site reactions, headache, and arthralgia.

HBwI

Treatment of hemorrhagic episodes in patients with HBwI must be individualized. The choice of therapy depends on the type of bleeding episode, the inhibitor titer, and the history and severity of previous infusion reactions. Bypassing agents (activated prothrombin complex concentrate [aPCC]; activated recombinant FVII [rFVIIa]) are therapeutic options for treatment or prevention of bleeding episodes in high-responding inhibitor patients. Bypassing agents have been shown to be effective in acute bleeding control in ~80% of patients with HBwI ([Santoro et al. 2018](#)). The presence of FIX in aPCC, in patients with previous inhibitor recognition, generally requires administration of rFVIIa. In cases of life-threatening bleeding episodes and failure of treatment with bypassing agents, plasmapheresis or immunoabsorption with staphylococcal protein A may

be considered to remove anti-FIX antibodies, and to transiently restore replacement therapy with FIX ([Santoro et al. 2018](#)). Because of the lack of therapeutic options for a large subpopulation of patients with HBwI, concizumab would address an unmet medical need.

Table 3. Therapeutic Options HAwI and HBwI

Product Name	Relevant Information	Year of Original Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
FEIBA® (activated prothrombin complex concentrate, aPCC)	For use in hemophilia A and B patients with inhibitors for: - Control and prevention of bleeding episodes - Perioperative management - Routine prophylaxis to prevent or reduce the frequency of bleeding episodes.	1979	- Control of bleeding episodes: 50-100 U/kg, frequency by type of bleed - Routine prophylaxis, 85 U/kg, every other day	On demand, median ABR 28.7 Prophylaxis, median ABR 7.9 72% reduction	Boxed warning for thromboembolic events Other serious adverse reactions, hypersensitivity	Given via IV infusion, not to exceed 2 U/kg/min, therefore each infusion for prophylaxis is approximately 45 minutes
NovoSeven® (recombinant factor VIIa, rFVIIa)	- Treatment of bleeding episodes in hemophilia A or B with inhibitors and in acquired hemophilia - Prevention of bleeding in surgical interventions or invasive procedures in hemophilia A or B with inhibitors and in acquired hemophilia	1999	- Bleeding episodes: 90 mcg/kg, every 2 hours until hemostasis is achieved - Routine prophylaxis: No standard dosing	Published information of prophylaxis report 2-3 bleeds per month (Konkle et al. 2007) .	Boxed warning for thrombotic events	Due to the short half-life, the utility of rFVIIa for routine prophylaxis is limited.

Product Name	Relevant Information	Year of Original Approval	Dosing/ Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Hemlibra® (emicizumab)	Routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and pediatric patients ages newborn and older with HA with or without factor VIII inhibitors	2017	Loading dose 3 mg/kg SC once weekly for 4 weeks, followed by maintenance dosing of 1.5 mg/kg once weekly, or 3 mg/kg once every 2 weeks, or 6 mg/kg once every four weeks.	HA (age ≥12 years) – Percent reduction annualized bleeding rate compared to no prophylaxis (95% CI) Emicizumab 1.5 mg/kg once every week 96% (92.5%, 98%); p < 0.0001 Emicizumab 3 mg/kg once every two weeks 97% (93.4%, 98.3%); p < 0.0001 HAWI (age ≥ 12 years) – Percent reduction annualized bleeding rate compared to no prophylaxis (95% CI) Emicizumab 1.5 mg/kg once every week 87% (72.3%, 94.3%); p < 0.0001	Boxed warning for thromboembolic events	Emicizumab interferes with coagulation laboratory tests, i.e., ACT, aPTT, APC-R, Bethesda clotting based assay

Source: FDA Clinical reviewer

Abbreviations: ABR, annualized bleeding rate; ACT, activated clotting time; APC-R, activated protein C resistance; CI, confidence interval; HA, hemophilia A; HAWI, hemophilia A with inhibitors; IV, intravenous; rFVIIa, recombinant activated factor VII; SC, subcutaneous

3.1. Review Issue List

3.1.1. Key Efficacy Review Issues

3.1.1.1. Determination If the Pause in Study 4311 Due to Thrombotic Events Impacted the Benefit (ABR)

3.1.2. Key Safety Review Issues

3.1.2.1. Risk of Thrombosis

3.1.2.2. Pharmacokinetic Fluctuations Leading to Subtherapeutic Concentrations During Concizumab Treatment

3.1.2.3. Patient Fatality Due to Bleeding and Subtherapeutic Concizumab Levels

3.2. Approach to the Clinical Review

This is a joint review. Xiaoyu Cai and Yeh-Fong Chen focused on the efficacy data. The Clinical Data Scientist team (Adam Horin and Qunshu Zhang) focused on the supportive safety and efficacy data. Andrew Dmytrijuk and Carrie Diamond focused on the supportive safety and efficacy data. Jeffrey Quinn and Pedro DelValle reviewed the nonclinical toxicology studies, and Li and Sudarshan Hariharan reviewed the clinical pharmacology data. The table [below](#) provides an overview of the clinical studies submitted in support of the efficacy and/or safety determinations for concizumab.

Table 4. Clinical Studies/Trials Submitted in Support of Efficacy and/or Safety Determinations¹ for Concizumab

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Enrolled²	Number of Centers and Countries
Study 4311	HAwI and HBwI	Control type: Active control with on-demand therapy with bypassing agent Randomization: 2:1 (concizumab PPX: On-demand) Blinding: open-label Biomarkers: TFPI (exploratory) Innovative design features: None	Drug: Concizumab Dosage: Day 1: Single SC loading dose of 1 mg/kg. Day 2 and onwards: Initial daily SC dose of 0.20 mg/kg. Individual maintenance dose set to 0.15, 0.20 or 0.25 mg/kg based on concizumab exposure after 4 weeks of treatment Number treated: 127 Duration (quantity and units): 160 wk	Primary: The number of treated spontaneous and traumatic bleeding episodes Secondary: Change in SF-36v2 bodily pain Change in SF-36v2 physical functioning	136 planned/133 enrolled 52 randomized	27 countries
Study 4310	HAwI and HBwI	Control type: active control with eptacog alfa Randomization: 2:1 (concizumab PPX: eptacog alfa) Blinding: open-label Biomarkers: TFPI (exploratory) Innovative design features: None	Drug: Concizumab Dosage: Day 1: Single SC loading dose of 0.5 mg/kg Day 2 and onwards: Daily SC dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks Number treated: 25	Primary: Number of bleeding episodes during at least 24 weeks of treatment Secondary: The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset	26 randomized	12 countries, 17 sites

Study/Trial Identifier (NCT#)	Study/Trial Population	Study/Trial Design	Regimen (Number Treated), Duration	Primary and Key Secondary Endpoints	Number of Subjects Planned; Actual Enrolled ²	Number of Centers and Countries
			Duration (quantity and units): >76 wk			
Study 4255	HA	Control type: single-arm Randomization: none Blinding: open-label Biomarkers: TFPI (exploratory) Innovative design features: none	Drug: Concizumab Dosage: Concizumab daily SC dose of 0.15 mg/kg with potential dose escalation to 0.20 mg/kg and subsequently to 0.25 mg/kg based on number of spontaneous bleeding episodes within a period of 12 weeks Number treated: 36 Duration (quantity and units): >76 wk	Primary: The number of bleeding episodes during at least 24 weeks from treatment onset. Secondary: The number of spontaneous bleeding episodes during at least 24 weeks from treatment onset	36 enrolled	26 sites, 11 countries

Source: Reviewer.

¹ Includes all submitted clinical studies, even if not reviewed in-depth, except for Phase 1 and pharmacokinetic studies.

² If no randomization, then replace with "Actual Enrolled."

Abbreviations: BID, twice daily; d, day; DB, double-blind; h, hour; HA, hemophilia A; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; LTE, long-term extension; MC, multicenter; mo, month(s); N, number of subjects; NCT, national clinical trial; OL, open-label; PC, placebo-controlled; PG, parallel group; PPX, prophylaxis; R, randomized; SC, subcutaneous; SF-36v2, short form health survey version 2; TFPI, tissue factor pathway inhibitor; wk, week(s); y, year(s)

4. Patient Experience Data

In the Phase 3 study, Study 4311, patient-reported outcomes (PROs) were assessed. Two patient-reported outcome (PRO) endpoints were included as key secondary endpoints:

- Change in SF-36v2 bodily pain from start of treatment (Week 0) until Week 24
- Change in SF-36v2 physical functioning from start of treatment (Week 0) until Week 24

Other exploratory PRO endpoints were included by the Applicant but not assessed by the review team because they were not included in the statistical testing hierarchy. Of note, all PRO endpoints are challenging to interpret given the open-label design of the study.

Table 5. Patient Experience Data Submitted or Considered

Data Submitted in the Application		
Check if Submitted	Type of Data	Section Where Discussed, if Applicable
Clinical Outcome Assessment Data Submitted in the Application		
☒	Patient-reported outcome	Section 6.2.1
☐	Observer-reported outcome	
☐	Clinician-reported outcome	
☐	Performance outcome	
Other Patient Experience Data Submitted in the Application		
☐	Patient-focused drug development meeting summary	
☐	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel)	
☐	Observational survey studies	
☐	Natural history studies	
☐	Patient preference studies	
☐	Other: (please specify)	
☐	If no patient experience data were submitted by Applicant, indicate here.	
Data Considered in the Assessment (But Not Submitted by Applicant)		
Check if Considered	Type of Data	Section Where Discussed, if Applicable
☐	Perspectives shared at patient stakeholder meeting	
☐	Patient-focused drug development meeting summary report	
☐	Other stakeholder meeting summary report	
☐	Observational survey studies	
☐	Other: (please specify)	

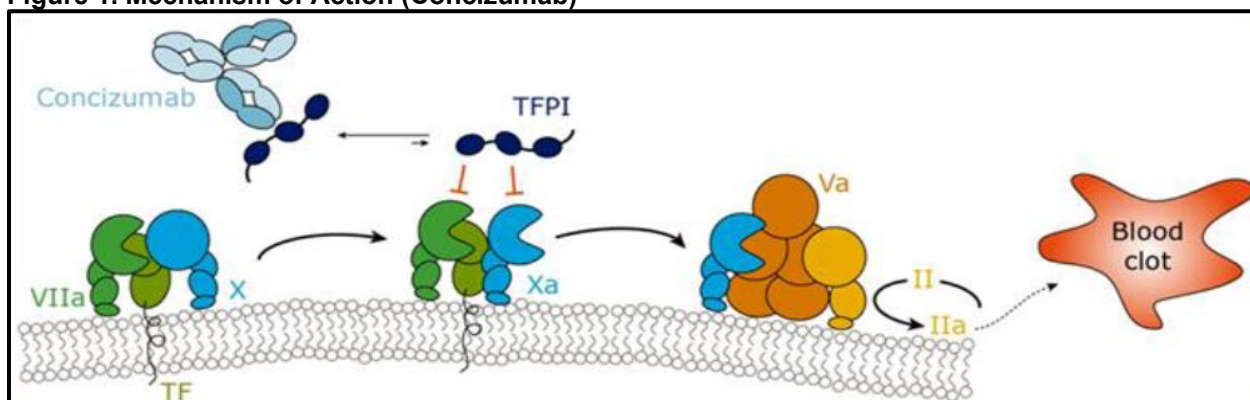
5. Pharmacologic Activity, Pharmacokinetics, and Clinical Pharmacology

5.1. Nonclinical Assessment of Potential Effectiveness

5.1.1. Primary Pharmacology

Concizumab is a humanized recombinant monoclonal antibody (mAb) that inhibits the function of TFPI α and TFPI β , that represent the two major TFPI-1 isoforms (splice variants) involved in the down regulation of the coagulation cascade in humans. Concizumab binds specifically to the Kunitz-domain-2 (K2) of the TFPI and prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (Fxa). When the TFPI inhibitory activity is reduced, the Fxa produced by the coagulation factor VIIa (FVIIa)/tissue factor (TF) complex results in sufficient generation of thrombin to achieve hemostasis. The mechanism of action of concizumab is independent of the presence or absence of FVIII or FIX, and would exert pharmacodynamic activity in both hemophilia A and B patients, regardless of their inhibitor status. Concizumab does not bind to the human TFPI-2 protein.

Figure 1. Mechanism of Action (Concizumab)



Source: Applicant's Figure Nonclinical Overview

Abbreviations: a, activated; TF, tissue factor; TFPI, tissue factor pathway inhibitor

The pharmacological activity of concizumab was confirmed by thromboelastography (TEG), that measures the shear elasticity and the dynamics of clot formation and the strength and stability of clot formation, using blood derived from humans and cynomolgus monkeys. Concizumab reduced clotting times and improved clot development in a concentration-dependent manner in both human and cynomolgus monkey whole blood. Thromboelastography (TEG) conducted using human whole blood under antibody-induced hemophilia A-like conditions resulted in half maximal effective concentration (EC₅₀) values of 0.43nM (clot time) and 2.2nM (clot development), and under antibody-induced hemophilia B-like conditions resulted in EC₅₀ values of 0.44nM (clot time) and 2.6nM (clot development). Comparable results were observed in whole blood derived from normal cynomolgus monkeys under antibody-induced hemophilia A-

like conditions where the EC₅₀ values were 0.38nM (clot time) and 0.54nM (clot development). The in vitro, ex vivo and in vivo pharmacology studies are discussed in further detail under Section [13.1.1.1](#).

Concizumab neutralized TFPI-mediated inhibition of Fxa and the FVIIa/TF/Fxa complex (in vitro) with EC₅₀ values of 0.8nM and 1.1nM, respectively. Neutralization of plasma TFPI was further quantified by measuring TFPI activity in human plasma and assessing FX activation in vitro (EC₅₀ value, 6nM). These effects occurred at clinically relevant exposures based on the steady state concizumab concentrations (maximum plasma concentration (C_{max}), mean) observed in hemophilia patients during the Explorer7 study (1167 ng/mL = 7.83nM). Concizumab was effective at neutralizing TFPI present on the surface of endothelial cells (the predominate form of TFPI on the cell surface of endothelial cells is TFPIβ). Concizumab associated with the cell surface (K_D values, 0.1nM to 0.4nM) of endothelial cells (HUVEC) and endothelial-like cells (ECV304), and promoted activation of FX (EC₅₀ values were below 0.5nM for both cell lines).

Based on the pharmacology data and the lack of cross reactivity to rodent species, the rabbit was selected as the nonclinical efficacy species (hemophilia animal models). The cynomolgus monkey was selected as the non-rodent nonclinical safety species for repeat-dose toxicology and both species were used in pharmacokinetic/pharmacodynamic (PD) assessments.

5.1.2. Animal Model Data Showing Proof of Concept

In vivo proof-of-concept studies were conducted in a cuticle bleeding model in New Zealand White (NZW) rabbits where hemophilia A-like conditions were simulated by administration of a neutralizing FVIII antibody. When administered intravenously (IV) prior to induction of bleeding, concizumab reduced blood loss in a dose-dependent manner in rabbits with a half maximal effective dose (ED₅₀) of 0.23 mg/kg (0.074 mg/kg, human equivalent dose (HED)) over the 1-hour observation period. The antihemorrhagic effect was maintained for up to 7 days after a single IV dose of 20 mg/kg (6.5 mg/kg, HED) followed by treatment (on Day 4, 7 or 10) with a neutralizing FVIII antibody to induce pseudo hemophilia. The absence of a notable PD effect on Day 10 corresponded to a significant decline in plasma concizumab exposure at the same timepoint. Procoagulant effects were not observed when concizumab was administered (IV) after an extended bleed induction period (15-30 min), indicating that concizumab needs to be administered prior to or relatively soon after (≤5 minutes) injury to be efficacious in this rabbit model of HA. Concizumab was also effective after subcutaneous (SC) administration (24 hours prior to induction of bleeding using the clinical ROA) in the rabbit cuticle bleeding model at a dose of 10 mg/kg (3.2 mg/kg, HED).

Table 6. Concizumab Effects on Clinically Relevant Endpoints in Animal Models of Hemophilia A (HA)

Parameter	Rabbit Cuticle Bleeding Models					
	HA (Anti-FVIII)	HA (Anti-FVIII)	HA (Anti-FVIII)	HA (Anti-FVIII)	HA (Anti-FVIII)	HA (Anti-FVIII)
Treatment method modeled (relative to bleed induction)	Pretreatment 35 min pre	On-Demand 5 min post	Durability 96-240 hrs pre	Extended Bleed 15-30 min post	LD Pretreatment 45 min pre	SC ROA 24 hrs pre
Concizumab dose (mg/kg)	8 (IV)	2 (IV)	20 (IV)	2 (IV)	0.25 (IV)	10 (SC)
HED (mg/kg)	2.6 (IV)	0.65 (IV)	6.5 (IV)	0.65 (IV)	0.08 (IV)	3.2 (SC)
Effective duration (hrs)	1	1	96-168	1	1	1
Clinically relevant endpoints*						
Blood loss	✓ (A)	✓ (A)	✓ (A)	✓ (N)	✓ (A)	✓ (A)
Bleeding time	✓ (A)	✓ (A)	✓ (A)	NA	NA	✓ (A)

Source: Reviewer constructed summary table of rabbit model studies submitted to the biologic license application.

ü indicates the clinically relevant endpoint was present/assessed in the rabbit model

(A) indicates the clinically relevant endpoint was alleviated by concizumab

(N) indicates the clinically relevant endpoint was not alleviated by concizumab

The neutralizing (anti-FVIII) antibody (employed to induce pseudo hemophilia) was administered 25 to 45 minutes prior to bleed induction and the initiation of clinical endpoint assessments.

*The assessment of clinically relevant endpoints was limited to a 1-hour observation period.

Abbreviations: FVIII, coagulation factor VIII; HA, hemophilia A; HED, human equivalent dose; hrs, hours; IV, intravenous; LD, low dose; NA, not applicable; ROA, route of administration; SC, subcutaneous

The effects of concizumab on local clot formation and general coagulation activation were assessed in a venous stasis model conducted in non-hemophilic NZW rabbits. There were no notable differences in the number of clots or clot size in ligated facial vein segments, and no significant differences in platelet counts, prothrombin time (PT), thrombin-anti-thrombin (TAT), and fibrinogen levels found in the absence or presence of concizumab (2 mg/kg, IV). Lung thrombi were noted microscopically in 50% of the rabbits administered concizumab and in the heart of a single control rabbit (25%). The relationship of distal clot formation in the lung and heart to the clot formation in the ligated facial vein segments could not be definitively determined, and while the Applicant argues that the formation of lung thrombi may be related to the experimental procedures, a potential relationship to the administration of concizumab cannot be excluded.

In a second study, the effect of a low molecular weight heparin (LMWH) in combination with concizumab was evaluated in a modified venous injury model in non-hemophilic NZW rabbits to assess the ability of LMWH to interfere with concizumab-induced clot formation. Intravenous injection (2 mg/kg) of concizumab was followed by a standardized crush injury and eventual ligation of the facial veins. Local clot formation following crush injury was significantly increased by the presence of concizumab; however, when followed 5 minutes later by the administration of LMWH prior to the initiation of the crush injury, local clot formation was prevented. Activated Partial Thromboplastin Time (APTT) declined minimally in concizumab-only dosed rabbits and APTT clotting time could not be established in the presence of LMWH. No other notable changes in coagulation parameters (platelet counts, PT, and fibrinogen) were observed with concizumab dosing, and these results suggest that LMWH can prevent the

procoagulant effects of concizumab in normal (non-hemophilic) NZW rabbits. These studies are discussed in detail under Section [13.1.1.3](#).

Table 7. Concizumab Effects on Clinically Relevant Endpoints in Animal Models of Venous Stasis

Parameter	Rabbit (Non-Hemophilic) Venous Stasis Models	
	Venous Clamp and Ligation	Venous Crush and Ligation
Treatment method modeled (relative to facial vein injury initiation)	Pretreatment 10 min prior to clamp	LMWH (Anti-Fxa) Rescue 10 min prior to crush
Concizumab dose (mg/kg)	2 (IV)	2 (IV)
Treatment duration (hrs)	5	0.7
Clinically relevant endpoints		
Platelet counts	ü (NO)	ü (NO)
Leukocyte (WBC) counts	NA	ü (NO)
Prothrombin time (PT)	ü (NO)	ü (NO)
Thrombin-antithrombin time (TAT)	ü (NO)	NA
Fibrinogen	ü (NO)	ü (NO)
Fibrinogen degradation products	ü (O)	NA
Activated partial thromboplastin time (APTT)	ü (O)	ü (O)
Thrombosis (local)	ü (O)	ü (O)
Thrombosis (distal)	ü (O)	NA
LMWH rescue	NA	ü (O)

Source: Reviewer constructed summary table of rabbit model studies submitted to the biologic license application.

ü indicates the clinically relevant endpoint was present/assessed in the rabbit model.

(O) indicates the clinically relevant endpoint was observed to be affected by concizumab or maintained functionality in the case of LMWH rescue.

(NO) indicates the clinically relevant endpoint was not observed to be affected by concizumab.

Abbreviations: APTT, activated partial thromboplastin time; Fxa, activated blood coagulation factor X; IV, intravenous; LMWH, low molecular weight heparin; NA, not applicable; PT, prothrombin time; TAT, thrombin-antithrombin time; WBC, leukocyte (white blood cells)

5.2. Clinical Pharmacology/Pharmacokinetics

Table 8. Summary of Clinical Pharmacology and Pharmacokinetics

Characteristic	Drug Information
	<i>Pharmacologic Activity</i>
Established pharmacologic class (EPC)	Concizumab is a tissue factor pathway inhibitor (TFPI) antagonist.
Mechanism of action	Concizumab is a humanized recombinant monoclonal antibody (IgG4) antagonist of human tissue factor pathway inhibitor 1 (TFPI-1), including TFPI α and TFPI β , that represent the two major TFPI-1 isoforms found in humans. Concizumab specifically targets the Kunitz 2 (K2) domain of TFPI and prevents TFPI from interacting with the active site of the Stuart–Prower factor [i.e., activated blood coagulation factor X (Fxa)]. In the presence of reduced TFPI inhibitory activity, the Fxa produced by the activated factor VII (FVIIa)/tissue factor (TF) complex (extrinsic tenase) results in generation of thrombin. As the mechanism of action of concizumab does not require the presence of FVIII or FIX, concizumab has the potential to elicit hemostatic activity in patients with either hemophilia A (congenital FVIII deficiency) or hemophilia B (congenital FIX deficiency), regardless of their inhibitor (anti-clotting factor antibody) status.
Active moieties	The active moiety is the (b) (4) humanized Immunoglobulin G (IgG) 4 monoclonal antibody (mAb).
QT prolongation	A thorough QT study was not conducted in humans. QT prolongation was not observed during ECG assessments in cynomolgus monkeys administered repeat doses of concizumab up to 200 mg/kg/once weekly (IV), 70000x MRHD (AUC) and 10000X MRHD (C _{max}), or 50 mg/kg/day (SC), 14000x MRHD (AUC) and 12600X MRHD (C _{max}), for up to 13 weeks. In addition, QT prolongation was not observed during ECG assessments in cynomolgus monkeys administered repeat doses of concizumab up to 9 mg/kg/day (SC), 4300x MRHD (AUC) and 4400X MRHD (C _{max}), for up to 52 weeks.
Bioanalysis	Total plasma concizumab (bound and unbound) concentration in the Phase 3 study was quantified using a validated ELISA.
Healthy subjects versus patients	Based on the popPK analysis, steady-state average concizumab plasma concentrations in healthy subjects are 55% higher (90% CI: 0%, 183%) than that in hemophilia A patients with inhibitors following subcutaneous (SC) administration of 0.20 mg/kg concizumab.
Drug exposure at steady state following the therapeutic dosing regimen (or single dose, if more relevant for the drug)	In Study 4311, the steady-state geometric mean (CV%) C _{max,ss} and C _{trough,ss} of concizumab were 1167 (130%) ng/mL and 665 (220%) ng/mL at Week 24.
Range of effective dose(s) or exposure	Based on PK/PD (free TFPI, peak thrombin) and exposure-response (ABR) relationships, concizumab steady-state trough concentrations above 200 ng/mL are effective.
Maximally tolerated dose or exposure	Based on concizumab concentrations observed in the 3 patients with thrombotic events from the Phase 3 studies, maintenance doses are adjusted to keep concizumab trough concentrations less than 4000 ng/mL.
Dose proportionality	Concizumab concentrations increased with increasing dose in a greater-than-dose-proportional manner following SC administration. Relative to the 0.25 mg/kg dose, geometric mean AUC _T values were 3-fold higher in the 0.50 mg/kg dose and nearly 11-fold higher in the 0.80 mg/kg dose.

Characteristic	Drug Information
Accumulation	Due to a loading dose on Day 1, the exact magnitude of drug accumulation upon once daily dosing was not determined. In the absence of a loading dose, simulated drug exposure at steady-state may be 10-fold higher than on Day 1 following a daily dose of 0.25 mg/kg concizumab
Time to achieve steady-state	Following a single concizumab loading dose of 1 mg/kg, the geometric mean concizumab plasma concentrations reached steady-state levels by the end of Day 1. Without a loading dose, it may take more than a week to reach to steady state exposures.
Bridge between to-be-marketed and clinical study formulations	N/A as the to-me-marketed formulation and pen injector were used in the registration study.
<i>Absorption</i>	
Bioavailability	Cannot be estimated with available data
T _{max}	Following SC administration of concizumab at 0.25 mg/kg, the median T _{max} ranges from 12 to 24 hours.
Food effect (fed/fasted) Geometric least square mean and 90% CI	N/A as concizumab is administered via SC injection.
<i>Distribution</i>	
Volume of distribution	The volume of distribution of concizumab for a typical 70 kg patient was 2.96 L.
Plasma protein binding	N/A
Drug as substrate of transporters	N/A as concizumab is a monoclonal antibody
<i>Elimination</i>	
Mass balance results	N/A
Clearance	Both linear and non-linear pathways contribute to the elimination of concizumab. This non-linear pharmacokinetic behavior 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. Non-linear PK via TMDD plays an important role in concizumab elimination at the clinically relevant concentrations.
Half-life	Concizumab terminal half-life increased with increasing dosage and ranged from 1.6 days to 8.1 days in healthy and hemophilia subjects receiving a single SC dosing of 0.25 to 3 mg/kg. In the target exposure range of 200 to 4000 ng/mL, the effective half-life is about 1-2 days.
Metabolic pathway(s)	Concizumab is expected to be metabolized into small peptides by catabolic pathways.
Primary excretion pathways (% dose)	N/A

Characteristic	Drug Information
<i>Intrinsic Factors and Specific Populations</i>	
Body weight	The apparent clearance and volume of distribution of concizumab increased with increasing body weight (27 kg to 130.7 kg). Nonetheless, after 4 weeks of treatment, patients with low or high exposure should adjust dose to 0.25 or 0.15 mg/kg, respectively. No further adjustment to dose based on body weight is warranted beyond the recommended adjustment by Week 8.
Age	No clinically significant differences in the PK of concizumab were observed based on age (12 year to 67 years).
Renal impairment	No dedicated studies have been conducted to evaluate the impact of renal impairment. As concizumab is a monoclonal antibody, there is no expectation for concizumab exposures to be different in patients with renal impairment.
Hepatic impairment	No dedicated studies have been conducted to evaluate the impact of hepatic impairment. As concizumab is a monoclonal antibody, there is no expectation for concizumab exposures to be different in patients with hepatic impairment.
<i>Drug Interaction Liability (Drug as Perpetrator)</i>	
Inhibition/induction of metabolism	N/A as concizumab is a monoclonal antibody
Inhibition/induction of transporter systems	N/A as concizumab is a monoclonal antibody
<i>Immunogenicity</i>	
Bioanalysis	Anti-concizumab antibody assay and in vitro neutralizing antibody assay have been reviewed by Dr. Scott Walsh and were considered as not fully validated (see comments in the CR letter for details)
Incidence	In concizumab clinical program, 47 out of 185 of treated patients (25%) developed anti-concizumab antibodies. Twelve (12) patients (6.5%) tested positive for anti-concizumab antibodies with in vitro-neutralizing effects.
Clinical impact	Binding anti-concizumab antibody titers were generally low. In 1 of 47 patients who developed ADAs with a high titer level, plasma concizumab concentrations cannot be measured, likely due to ADA interference in the PK. In addition, free TFPI levels returned to the baseline, indicating a loss of treatment effect. For the rest of 46 ADA positive patients, there was no identified clinically significant effect of the antibodies on PK, PD, safety, or effectiveness of concizumab.

Source: Reviewers created table

Abbreviations: ABR, annualized bleeding rate; ADA, anti-drug antibody; AUC, area under the time-concentration curve; CI, confidence interval; C_{max}, maximum plasma concentration; CR, complete response; C_{trough}, trough concentration; ECG, electrocardiogram; CV, coefficient of variation; ELISA, enzyme-linked immunoassay; EPC, established pharmacologic class; FVIIa, activated factor VII; Fxa, coagulation factor Xa; IgG4, immunoglobulin G4; IV, intravenous; mAb, monoclonal antibody; MRHD, maximum recommended human dose; N/A, not applicable; PD, pharmacodynamic; PK, pharmacokinetic; popPK, population pharmacokinetics; SC, subcutaneous; ss, steady state; TF, tissue factor; TFPI, tissue factor pathway inhibitor; T_{max}, time to maximum concentration; TMDD, target mediated drug disposition

6. Efficacy (Evaluation of Benefit)

6.1. Assessment of Dose and Potential Effectiveness

The proposed dosing regimen of concizumab is a loading dose of 1 mg/kg via SC administration on Day 1 followed by once daily dose of 0.20 mg/kg starting from Day 2 until individuation of maintenance dose is determined:

- Four weeks after initiation of treatment: For dose optimization measure concizumab plasma concentration once by concizumab enzyme-linked immunoassay (ELISA) prior to administration of next scheduled dose.
- After concizumab plasma concentration result is available, but recommended no later than 8 weeks after initiation of treatment: Individualize maintenance dose of concizumab once based on the following concizumab plasma concentrations:
 - <200 ng/mL: adjust to a once-daily dose of 0.25 mg/kg
 - 200 to 4000 ng/mL: continue once-daily dose of 0.20 mg/kg
 - >4000 ng/mL: adjust to a once-daily dose of 0.15 mg/kg

The proposed PK-guided dosing with one time PK collection and dose adjustment between weeks 4 to 8 was implemented in Study 4311 (after restart) and is considered acceptable based on favorable efficacy and safety results, aided by pharmacokinetic/pharmacodynamic (PK/PD) and exposure-response relationships in patients with hemophilia. Large fluctuations in concizumab plasma concentrations were noted in certain patients in Study 4311 (after restart) which may be due to an interplay of concizumab's target mediated drug disposition (TMDD) and patient noncompliance. It is critical that patients are compliant with administering concizumab daily (See Section [7.2](#) for more details).

Selection of Concizumab Target Exposure of 200 ng/mL to 4000 ng/mL

The Applicant proposes that concizumab dose be adjusted once to achieve target trough concentration between 200 and 4000 ng/mL. The selection of lower exposure limit of 200 ng/mL is based on exposure-response analysis using data from main part of Studies 4255 and 4310. As shown in [Table 9](#), at concentrations above 200 ng/mL, there was a trend towards a lower bleeding rate.

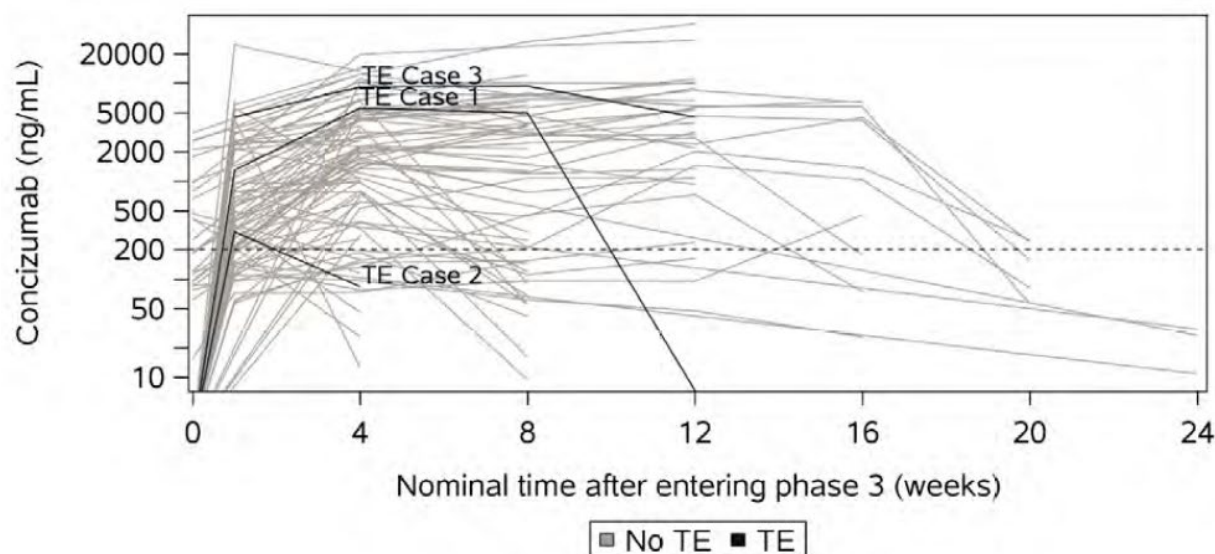
The upper exposure limit of 4000 ng/mL has been set as a measure to avoid patients persistently reaching very high concentrations of concizumab. Before the pause of Study 4311, 2 of the 3 patients with thrombotic events in phase 3 studies showed exposure levels above 5000 ng/mL ([Figure 2](#)). Despite the lack of data showing that high exposure per se is causative of thrombotic events, the observation suggests that the concizumab exposure in combination with other risk factors could contribute to thrombosis. Therefore, to avoid patients reaching very high concizumab exposure levels, the Applicant proposed a cut-off of 4000 ng/mL at Week 4. The selected target exposure of 200 to 4000 ng/mL was agreed by the Agency and implemented in Study 4311 after the trial was restarted.

Table 9. Predicted Annualized Bleeding Rates for Different Concizumab Exposure Intervals Based on Results From Main Parts of Studies 4255 and 4310

Concizumab exposure (ng/mL)	Number of subjects	Subjects with bleeds	Number of bleeds	Total exposure years	ABR
0–100	53	30	71	6.64	10.7
100–200	47	29	88	8.96	9.82
200–500	25	11	19	5.05	3.77
500–1000	13	5	9	2.32	3.88
>1000	8	3	5	1.04	4.81

Source: Table 19 of Type A meeting package dated on May 14th, 2020.
Abbreviation: ABR, annualized bleeding rate

Figure 2. Observed Exposure of Concizumab After a Loading Dose of 1 mg/kg and a Daily Maintenance Dose of 0.25 mg/kg Concizumab for Patients With Thrombotic Events Versus Those Without, Studies 4311 and 4307



Source: Type A meeting package dated on May 14th, 2020, Figure 17.
Abbreviation: TE, thrombotic event

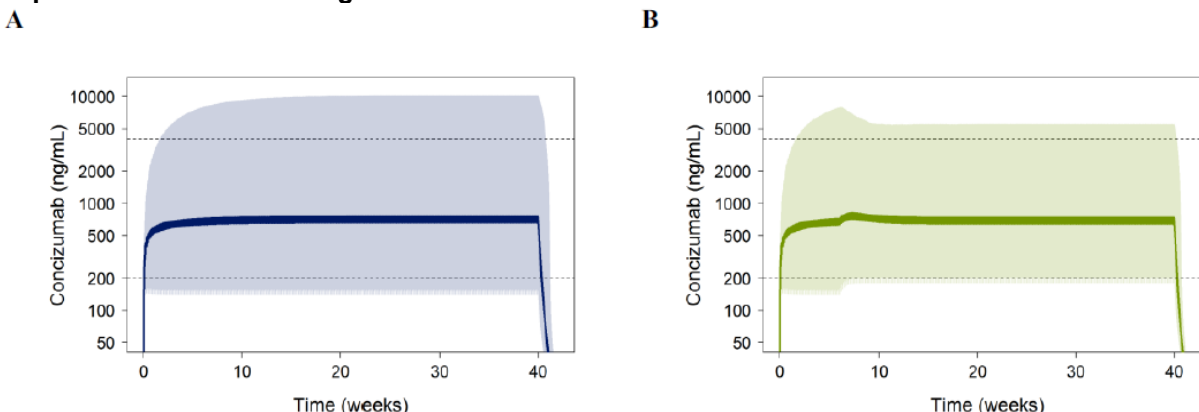
Necessity of PK-Guided Dosing for Concizumab

Both linear and non-linear clearance pathways contribute to the elimination of concizumab. At concentrations of approximately 10000 ng/mL or above, the linear clearance pathway is dominant, and the estimated half-life is approximately 22 days for a 75 kg patient based on population PK modeling analysis. Over concizumab's target exposure range of 200 to 4000 ng/mL, the non-linear clearance pathway via TMDD is dominant and the effective half-life of concizumab is much shorter, about 1 to 2 days. As a result, large between-subject variations in concizumab exposure are expected due to variability in target pool (i.e., membrane bound TFPI in the endothelium) among individual patients.

Population PK simulations suggest that a dose increase to 0.25 mg/kg or decrease to 0.15 mg/kg can reduce the population-level variability and ensure that majority of patients have concizumab trough concentrations within the target range of 200 to 4000 ng/mL ([Figure 3](#)). In Study 4311,

out of the 97 patients with maintenance dosing based on PK concentrations at visit 4, 72 patients (74.2%) remained on the 0.20 mg/kg dose level, 24 patients (24.7%) increased to 0.25 mg/kg and 1 patient (1.0%) decreased to 0.15 mg/kg. Based on data from Study 4311 (after restart), concizumab when administered according to the proposed dosing regimen was effective in reducing the ABR compared to no prophylaxis (PPX) in patients with HAWI and HBWI across all bleed-related efficacy endpoints and assessments (See [Table 13](#) under Section [6.2.1.5](#)). No thrombotic events occurred with PK-guided dosing.

Figure 3. Simulated Concizumab Exposure Following a Loading Dose of 1 mg/kg and Initial Daily Dose of 0.2 mg/kg Without (A) and With (B) One-time Dose Adjustment at Week 6 According to the Proposed PK-Guided Dosing Criteria

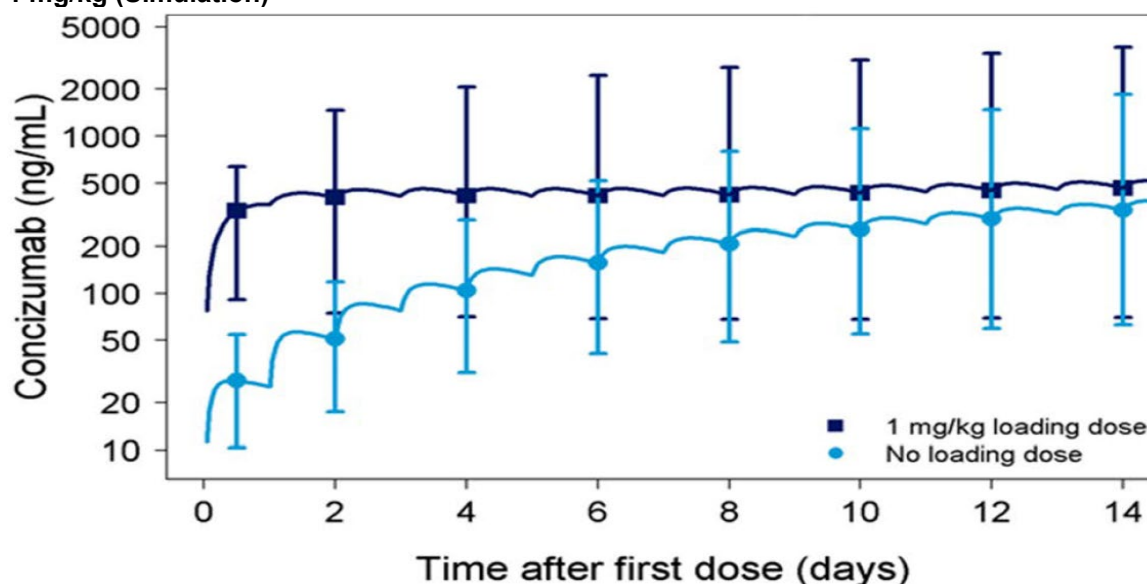


Source: Population PK and exposure-response meta-analysis of Phase 1, 2 and 3 data Figure 1-2. Simulated based on the final model (10,000 subjects simulated). Shaded area represents the 90% prediction interval, and dark line represents the median exposure levels. Dotted lines indicate the exposure range used for maintenance dose setting in Study 4311. Maintenance dose setting was implemented as a dose increase or decrease at Week 6, based on C_{trough} values occurring at Week 4.
Abbreviations: C_{trough} , trough concentration; PK, pharmacokinetics

Rationale for Loading Dose

Following a single loading dose of 1 mg/kg, the geometric mean concizumab plasma concentrations reached steady-state levels by end of Day 1 and stayed within the target exposure range with daily maintenance doses. This observation was further supported by population PK predicted concizumab plasma concentration-time profile with a loading dose of 1 mg/kg on Day 1 ([Figure 3](#) and [Figure 4](#)).

Figure 4. Concizumab PK Following 0.25 mg/kg Daily Dose With or Without a Loading Dose of 1 mg/kg (Simulation)



Source: Figure 20 of EOP2 meeting package dated 01 February 2019
Abbreviation: PK, pharmacokinetics

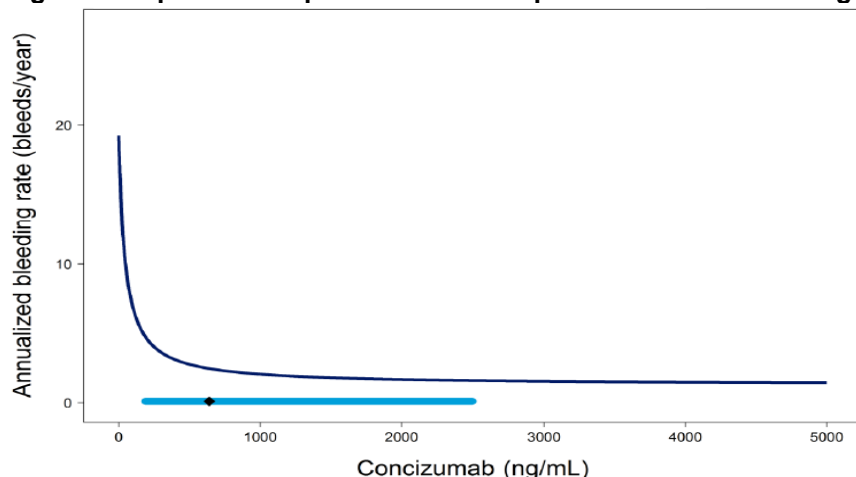
Rationale for Once-Daily Dosing

Study 4159 assessed the PK and PD of concizumab following SC administration of 0.25 mg/kg, 0.5 mg/kg and 0.8 mg/kg doses given every 3 days. This is equivalent to 0.83, 0.17 and 0.27 mg/kg/day. Because clearance is much faster in the target range (as stated earlier), a once-in-3-day dosing is expected to result in larger peak-to-trough fluctuations than desired. Combined with high inter-subject variability (as noted in the study), this regimen may put some patients at risk of going below or above the target range. Therefore, in order to reduce peak-to-trough fluctuations and maintain exposures within the target range in majority of the patients, a once-daily dosing was implemented.

Exposure-Response and PK/PD Analysis Supporting the Proposed Dosing Regimen

An exposure-response analysis of bleeding episodes shows that the concizumab dosing regimen maintains plasma concentrations at or near the plateau of effect ([Figure 5](#)). The maximum drug effect (E_{max}) was predicted to be a 93% reduction in ABR with an EC_{50} around 45.2 ng/mL. In addition, the correlation between pre-dose free TFPI and concizumab plasma concentration confirms that the most prominent effect is observed at concizumab plasma levels >200 ng/mL with free TFPI approaching the lower limit of quantification (9.6 ng/mL, [Figure 6](#)). Similarly, PK/PD analysis of thrombin peak shows that the concizumab dosing regimen maintains plasma concentrations at the plateau of effect.

Figure 5. Exposure-Response Relationship of Annualized Bleeding Rate

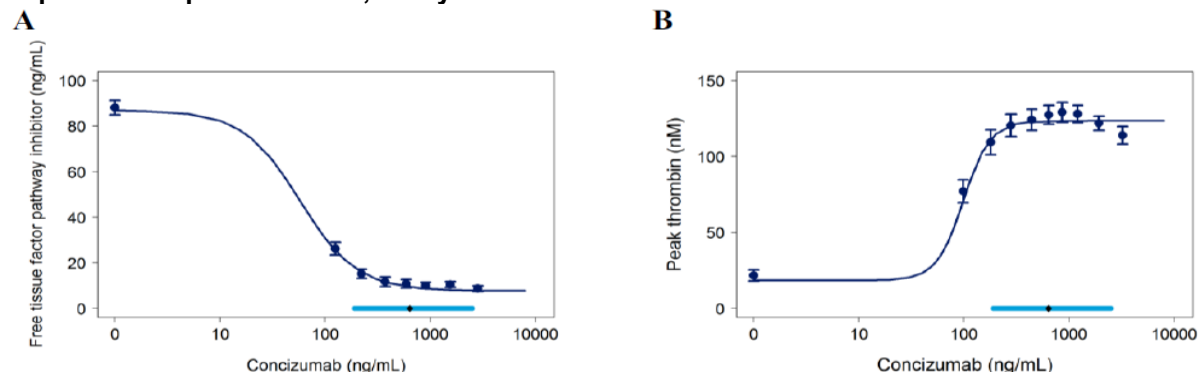


Source: Population PK and exposure-response meta-analysis of Phase 1, 2 and 3 data Figure 7-1.

The line is the mean model-based prediction. The horizontal light blue line at the bottom represents the median (diamond) and the 5-95% range of the individual average exposure predicted across the study duration (only including data after restart of Trial 4311), using C_{avg} , study estimated from the BOV PK model.

Abbreviation: BOV, between-occasion (within-subject) variability; C_{avg} , average plasma concentration; PK, pharmacokinetics

Figure 6. Exposure-response Relationships for Free TFPI and Thrombin Peak as Determined by Exposure-Response Models, Study 4311



Data Source: Modelling report (M5.3.3.5), Figure 1-3

Points with bars are mean and 95% CI of observed free TFPI plasma concentrations (A) or observed thrombin peak levels (B) versus concizumab concentrations. The dark blue line is the mean model prediction based on population predictions. The horizontal light blue line at the bottom represents the median (diamond) and the 5-95% range of the individual average exposure predicted across the study duration (only including data after restart of Study 4311), using average steady-state concizumab exposure estimated from the between-occasion variability PK model.

Abbreviations: CI, confidence interval; PK, pharmacokinetics; TFPI, tissue factor pathway inhibitor

6.2. Clinical Studies Intended to Demonstrate Efficacy

6.2.1. Study 4311

6.2.1.1. Study Design, Study 4311

Study Overview

Study 4311 was a Phase 3 prospective, multicenter, open-label, randomized-controlled study in patients with HAwI and HBwI. The primary objective of the study was to compare concizumab prophylaxis to no prophylaxis on top of standard of care (on demand therapy) in preventing bleeding episodes in patients with HAwI and HBwI.

The schema for Study 4311 is shown in [Figure 7](#) below and included 4 study arms. Patients were randomized to concizumab PPX (arm 2), no PPX (arm 1), or assigned to non-randomized concizumab PPX treatment (arms 3 or 4), based on their treatment regimen for hemophilia before entering the study. Patients included in the no PPX arm (arm 1) of the study continued the same on-demand treatment regimens with bypassing agents that they received before entering the clinical study, reflecting local standards of care. Patients randomized to the concizumab arm were permitted to use on demand treatment(s) (i.e., bypassing agents and factor) as needed for breakthrough bleeding. Arm 3 included patients who were previously enrolled in the concizumab Phase 2 study (NN7415-4310 (explorer4)). Arm 4 included patients previously on prophylaxis with bypassing agents as well as any patients receiving on-demand therapy who were screened at a timepoint where the required number of patients in arms 1 and 2 had been randomized.

The study consisted of a 3-week screening period, a main part (study period between Weeks 24-32), an extension part (study period between Weeks 128-136), and a 7-week follow-up period. The main part of the study was considered completed for a patient when at least 24 weeks of participation (screening period not included) had been completed for patients on no PPX (arm 1), or 32 weeks of participation (screening period not included) for patients on concizumab PPX (arms 2, 3 and 4). The longer duration of the study's main part for arms 2, 3 and 4 was due to the dose adjustment period in these. After the main part of the study, all patients were offered opportunities to continue in the extension part of the study and receive treatment with concizumab for up to an additional 128 weeks (arms 2-4) or 136 weeks (arm 1). A primary analysis cut-off (PACO) was defined as when all patients on no PPX (arm 1) had completed visit 9/9a (or withdrawn), and all patients on concizumab PPX (arm 2) had completed visit 10a (or withdrawn). Furthermore, a 56-week cut-off was defined as when all patients on concizumab PPX (arms 2, 3 and 4) had completed visit 13a (or permanently discontinued treatment). At this 56-week cut-off, an additional evaluation was planned to assess bleed-related endpoints and safety.

The randomization between treatment arms 1 and 2 was stratified according to hemophilia subtype (HAwI, HBwI) and bleeding frequency during the 24 weeks prior to screening (<9 bleeding episodes, ≥9 bleeding episodes).

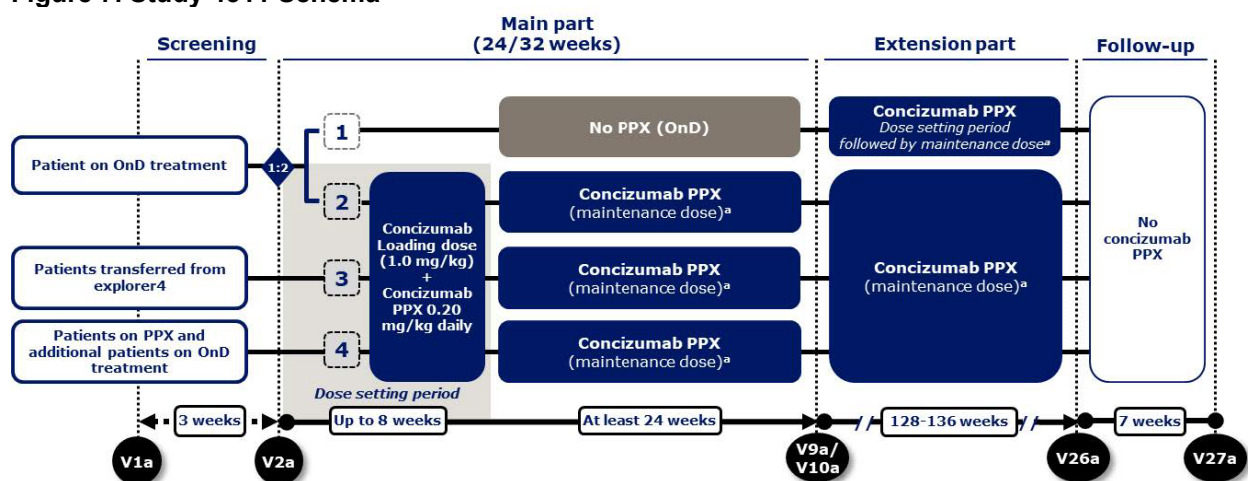
Treatment Pause

Study 4311 was initiated in October 2019. Concizumab treatment was paused in March 2020, and clinical studies were subsequently put on clinical hold due to the occurrence of 5 non-fatal thromboembolic events in 3 patients (see Section 7.7.1 for further details). Patients who were randomized to arm 1 before the treatment pause were instructed to continue their on-demand treatment during the pause. Patients who were randomized to arm 2 were instructed to discontinue concizumab treatment, and these patients received available standard of care treatment during the pause.

In order to mitigate the risk for thromboembolic events the Applicant initiated a new guidance for treatment of mild and moderate breakthrough bleeding episodes with specific guidance for use of the lowest dose of rescue factor product or bypassing agent while on concizumab PPX. The Applicant also revised the concizumab dosing regimen, consisting of a loading dose of 1.0 mg/kg (unchanged from the initial dosing regimen), and an initial daily dose of 0.20 mg/kg concizumab (instead of 0.25 mg/kg). The Applicant also revised the criteria for an increase or decrease in the daily maintenance dose to 0.25 mg/kg or 0.15 mg/kg, respectively, based on concizumab exposure level at the Week 4 visit after initiating treatment. After the restart of the study, patients continued in the treatment arm to which they were initially randomized or assigned. Newly eligible patients were randomized to concizumab PPX (arm 2), no PPX (arm 1), or assigned to arm 4.

The study visit schedule is shown in Figure 62 and the study schedule of events are shown in Table 119. Drug stopping criteria included clinical or laboratory evidence of thrombosis, microangiopathy, disseminated intravascular coagulopathy, or hypersensitivity reactions to concizumab.

Figure 7. Study 4311 Schema



Source: Study NN7415-4311 Clinical Study Report, Figure 9-1 (p.42)

Note: the individual maintenance dose was either 0.15, 0.20 or 0.25 mg/kg concizumab.

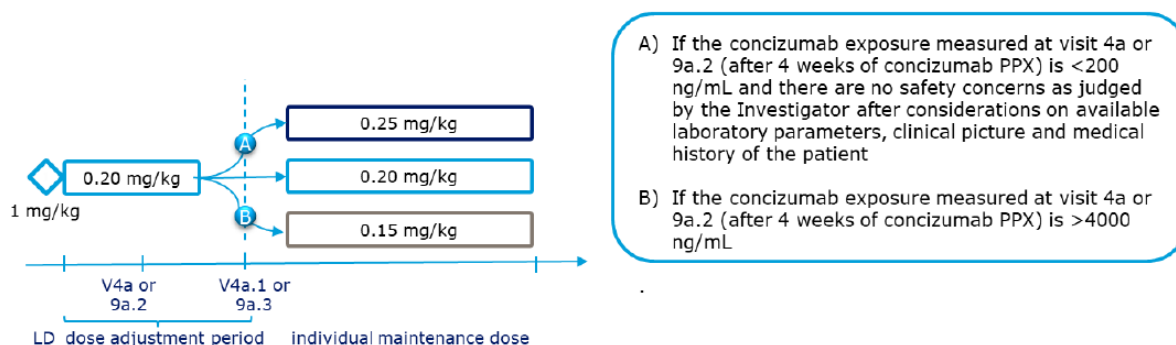
Abbreviations: OnD, on demand; PPX, prophylaxis; V, visit

Concizumab Dosing

Initially, patients randomized or allocated to the concizumab prophylaxis received a loading dose of 1.0 mg/kg concizumab SC on the first day of treatment, followed by a maintenance dose of

0.25 mg/kg concizumab given as a daily SC injection from the second day onwards. After the concizumab treatment pause and restart, the dosing regimen was as follows: When patients were randomized/allocated to concizumab prophylaxis they received a loading dose of 1.0 mg/kg concizumab at visit 2a (arm 2, 3 and 4) or visit 9a (arm 1) followed by an initial daily dose of 0.20 mg/kg concizumab from treatment Day 2. Within an initial 5 to 8-week maintenance dose setting period on 0.20 mg/kg concizumab, the patients could be increased or decreased in dose to 0.25 mg/kg or 0.15 mg/kg concizumab or remain at 0.20 mg/kg based on concizumab exposure level of <200ng/mL, >4000ng/mL or between 200-4000ng/mL, respectively. The study drug dosing schematic is shown in the figure [below](#).

Figure 8. Concizumab Dosing



Source: Applicant figure Protocol 4311

Notes: Concizumab exposure level is measured at V4a/9a.2; Potential maintenance dose setting will take place at V4a.1/9a.3.

Abbreviations: LD, loading dose; PPX, prophylaxis; V, visit

Clinical Reviewer Comment: The open-label study design of comparing concizumab PPX to on demand treatment with bypassing agents is acceptable, as it would be unethical to include a placebo control arm. This approach is consistent with other drugs approved for hemophilia (e.g., emicizumab). See Section 7 for further discussion regarding the potential impact of the study pause on the study results.

6.2.1.2. Eligibility Criteria, Study 4311

The key inclusion criteria for Study 4311 are as follows:

- Informed consent obtained before any study-related activities
- Male aged ≥ 12 years at the time of signing informed consent
- Body weight >25 kg at screening
- Congenital Hemophilia A or B of any severity with documented history of inhibitor (≥ 0.6 Bethesda Units)
- Patient has been prescribed, or needs treatment with bypassing agents in the last 24 weeks prior to screening (for patients not previously enrolled in NN7415-4310)

The key exclusion criteria for Study 4311 are as follows:

- Known or suspected hypersensitivity to any constituent of the study product or related products

- Previous participation in this study due to pause. However, this is not applicable for patients who were screen failed at Applicant's decision due to the treatment pause
- Participation in any clinical study of an approved or non-approved investigational medicinal product within 5 half-lives or 30 days from screening, whichever is longer (not applicable for patients from Study 4310)
- Platelets $\leq 100,000/\mu\text{L}$ at screening
- Fibrinogen below laboratory lower normal limit at screening
- Hepatic dysfunction defined as serum aspartate aminotransferase (AST) and/or serum alanine aminotransferase (ALT) >3 times the upper limit of normal (ULN), combined with serum total bilirubin (Tbili) >1.5 times the ULN at screening.
- Renal impairment defined as estimated Glomerular Filtration Rate (eGFR) $\leq 30 \text{ mL/min/1.73 m}^2$ for serum creatinine measured at screening
- Known inherited or acquired coagulation disorder other than congenital hemophilia
- History of thromboembolic disease, current clinical signs of or treatment for thromboembolic disease, and patients who, in the judgement of the investigator, are considered at high risk of thromboembolic event
- A known systemic inflammatory condition requiring systemic treatment at screening
- Treatment with emicizumab within 180 days before screening
- Ongoing or planned Immune Tolerance Induction treatment

6.2.1.3. Endpoints, Study 4311

Primary Endpoint

The number of treated spontaneous and traumatic bleeding episodes:

- On demand (arm 1): From randomization (Week 0) up until start of concizumab treatment (at least 24 weeks)
- Concizumab PPX (arm 2): From start of the new concizumab dosing regimen (Week 0) up until the primary analysis cut-off (at least 32 weeks)

Key Secondary Endpoints

- Change in SF-36v2 bodily pain, from start of treatment (Week 0) until Week 24
- Change in SF-36v2 physical functioning, from start of treatment (Week 0) until Week 24

Other Efficacy Endpoints

- Number of treated spontaneous bleeding episodes

- Number of treated spontaneous and traumatic joint bleeds
- Number of treated spontaneous and traumatic target joint bleeds

Clinical Reviewer Comment: While not prespecified as an endpoint the Applicant also described the number of patients with bleeding episodes. This endpoint is clinically meaningful, as having zero patients with bleeds is the ultimate goal to hemophilia prophylaxis.

6.2.1.4. Statistical Analysis Plan, Study 4311

Key information regarding statistical analysis from the clinical study report, protocol, and statistical analysis plan (SAP) are summarized in this section.

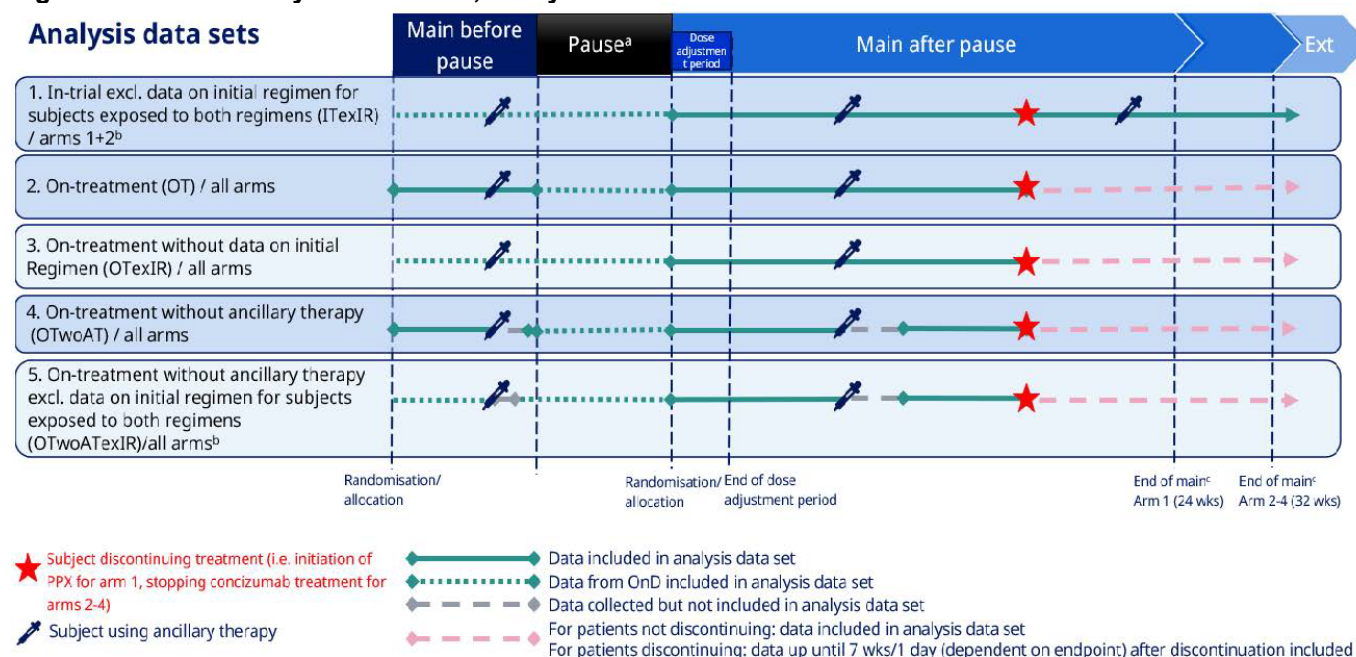
Analysis Population

The following analysis sets were defined for the statistical analysis:

- Full analysis set (FAS): All patients randomized to concizumab PPX or no PPX or allocated to arm 3 or 4. Patients from arms 1 and 2 will contribute to the evaluation ‘as randomized’.
- Safety analysis set (SAS): All patients exposed to concizumab PPX or randomized to no PPX. All patients will contribute to the evaluation ‘as treated’.

The defined analysis data sets for the main part of the study are included in [Figure 9](#).

Figure 9. Defined Analysis Data Sets, Study 4311



Source: Study NN7415-4311 Clinical Study Report, Figure 9-4 (p.86).

^a For data sets 2 and 4: concizumab data up until 7 weeks after start of pause was included

^b In case a patient from arm 2 did not re-start concizumab treatment after the pause, the data from before the pause was to be included

^c End-of-period was defined as the first of 1) death, 2) withdrawal date, 3) last contact for LTFU patients, 4) start of concizumab (only arm 1, On demand), 5) primary analysis cut-off

Abbreviations: ext, extension; LTFU, long-term follow-up; OnD, on-demand; OT, on-treatment; OtxIR, initial regimen for subjects exposed to both treatments; OtwoAT, on-treatment without ancillary therapy; OtwoATexIR, on-treatment without ancillary therapy excluding data on initial regimen for subjects exposed to both regimens; wks, weeks

The primary analysis for the primary efficacy endpoint was based on the FAS using the OtwoATexIR (the 5th analysis data set defined in [Figure 9](#)) analysis data set. The primary analysis for the key secondary efficacy endpoints was based on the FAS using the OtxIR (the 3rd analysis data set defined in [Figure 9](#)) analysis data set.

Analysis of the Primary Endpoint

The estimand associated with the primary endpoint is presented in [Table 10](#).

Table 10. Estimand Associated With the Primary Endpoint, Study 4311

Estimand Attribute	Content
Population	HAwI and HBwI patients treated on demand prior to entering Trial NN7415-4311.
Endpoint	On demand (arm 1): The number of treated spontaneous and traumatic bleeding episodes from randomization (Week 0) up until start of concizumab treatment (at least 24 weeks) Concizumab (arm 2): The number of treated spontaneous and traumatic bleeding episodes from start of the new concizumab dosing regimen (Week 0) up until the primary analysis cut-off (at least 32 weeks)

Estimand Attribute	Content
Intercurrent event strategy	<u>Permanent treatment discontinuation.</u> For this intercurrent event, the data from the period after permanent discontinuation of study treatment were not included. It is to be noted that for patients in the on-demand arm, permanent treatment discontinuation means initiation of PPX. <u>Temporary treatment discontinuation after restart of the study.</u> For this intercurrent event the 'treatment policy' strategy was used meaning that the data from this period were included. <u>Use of factor products not related to treatment of a bleed.</u> For this intercurrent event, the data during this period were not included^a. <u>Minor surgery.</u> For this intercurrent event the 'treatment policy' strategy was used.
Population-level summary	The treatment ratio of the ABRs between the two treatment regimens

Source: Study NN7415-4311 Clinical Study Report, Figure 8-2 (p.41)

^a Use of factor products for surgery and medical procedures was exempted

Abbreviations: ABR, annualized bleeding rate; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; PPX, prophylaxis

The comparison of the number of treated bleeds between the randomized arms 1 and 2 was based on the FAS and the on-treatment without ancillary therapy exclude data on initial regimen for patients exposed to both regimens (OtwoATexIR) analysis data set using negative binomial regression with the patient's number of bleeds analyzed as a function of the randomized treatment regimen, type of hemophilia (HAWI or HBwI) and bleeding frequency (<9 or ≥9 bleeding episodes during the past 24 weeks prior to screening) and the logarithm of the length of the observation period included as an offset in the model.

From the statistical model, an estimate of the rate ratio of the annualized bleeding rate (ABR) between the treatment regimens (concizumab prophylaxis and no prophylaxis) with corresponding 95% confidence interval and a p-value for the test for superiority were provided. Estimates of the actual ABRs with corresponding 95% confidence intervals were also provided for arms 1 and 2.

Analysis of Key Secondary Endpoints

The two key secondary endpoints included in the statistical testing hierarchy were:

- Change in SF-36v2 bodily pain from start of treatment (Week 0) until Week 24
- Change in SF-36v2 physical functioning from start of treatment (Week 0) until Week 24

The Week 0 is defined as time of randomization to on-demand administration or time of start of the new concizumab dosing regimen.

The two key secondary endpoints based on SF-36v2 were analyzed including all patients in the FAS using the on-treatment without data on initial regimen (OtexIR) analysis dataset.

Due to the low number of patients in arms 1 and 2 contributing data both at baseline and post-baseline, the pre-planned multiple imputation (MI) analyses for key secondary endpoint based on SF-36 could not be performed as planned due to non-convergence. Instead of using MI, a post hoc mixed model for repeated measurements (MMRM) was used in the following way:

The changes in SF-36v2 scores from Week 0 to Weeks 4, 8, 16 and 24 were analyzed using a MMRM, with treatment, type of hemophilia (HAWI or HBwI) and bleeding frequency (<9 or ≥9 bleeding episodes during the 24 weeks prior to screening) as factors, and baseline SF-36v2 as a covariate, all nested within week (Week 4, Week 8, Week 16 and Week 24). An unstructured covariance matrix was used to describe the variability for the repeated measurements for a patient. From the MMRM model, the treatment difference at Week 24 was estimated and the corresponding 95% confidence interval and p-value were presented. Change from baseline estimate and 95% CI for each arm was also obtained, in addition to the estimated mean score at Week 24 and corresponding 95% CI for each arm.

Statistical Reviewer's Comments: Because of the low number of patients in arms 1 and 2 and the following two reasons, the program for the MI analysis could not converge:

- *Large amount of the imputes values lied outside the range with unrealistic imputed values, (e.g., lower than -200 or higher than 300) which exceed the range of allowed values for the given PROs*
- *Not enough observations to fit regression models with a monotone regression method.*

The Applicant discussed the issue with the Agency during the pre-BLA meeting and proposed to use MMRM as an alternative model. The proposed alternative model was determined to be reasonable. However, the PRO endpoints were conducted in open-label studies, thus the Applicant's results should be interpreted with caution. As discussed in the FDA guidance for industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims¹, "Open-label clinical studies, where patients and investigators are aware of assigned therapy, are rarely adequate to support labeling claims based on PRO instruments. Patients who know they are in an active treatment group may overestimate benefit whereas patients who know they are not receiving active treatment may under-report the improvement they experienced."

Multiple Testing Strategy

The type I error was controlled at 5% significance level (two-sided) using a hierarchical (fixed sequence) testing procedure. This was based on a priority ordering of the null hypotheses for major efficacy endpoints. If a hypothesis was rejected (superiority confirmed), the significance level was to be reallocated to the next hypothesis in the hierarchy and then that hypothesis was to be tested at the 5% significance level. This process was repeated sequentially until no further hypotheses can be confirmed.

The steps in the hierarchical testing procedure were as follows:

- Step 1: Superiority in number of treated spontaneous and traumatic bleeding episodes
- Step 2: Superiority in change from baseline in SF-36v2 bodily pain
- Step 3: Superiority in change from baseline in SF-36v2 physical functioning

¹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-reported-outcome-measures-use-medical-product-development-support-labeling-claims>

Handling of Intercurrent Event or Missing Data

- The primary endpoint: refer to intercurrent event strategy in [Table 10](#).
- Key secondary endpoints: MMRM method handles missing data under the missing at random (MAR) assumption

6.2.1.5. Results of Analyses, Study 4311

In total, 141 patients were screened and 133 patients were enrolled in Study 4311 ([Table 11](#)). Reasons for screen failure for three patients was failed inclusion/exclusion criteria and patient consent was withdrawn by parent/guardian or 'other reasons' before randomization for an additional five patients.

Table 11. Patient Screening and Enrollment, Study 4311

Disposition	Study 4311
Patients screened	141
Screening failures	8
Patients enrolled	133
Patients randomized (arm 1 and arm 2)/allocated (arm 3 and arm 4)	52/81

Source: ds.xpt and Clinical Study Report; Software: R

Patient Disposition

Patient disposition is described in [Table 12](#) below. In total, 6 patients (31.6%) discontinued the study from arm 1 compared to 6 patients (18.2%) in arm 2. The most common reason for study discontinuation was withdrawal by the subject in arm 1. The most common reason for study discontinuation was death in arm 2, see Section [7.6.1.2](#) for further details.

Table 12. Patient Disposition, Study 4311

Disposition Outcome	Previous OnD Treatment		Concizumab Non-naïve	Concizumab Naïve	Total Arms 1-4 n (%)
	No PPX Arm 1 Randomized n (%)	Concizumab PPX Arm 2 Randomized n (%)	Concizumab PPX Arm 3 Non-randomized n (%)	Concizumab PPX Arm 4 Non-randomized n (%)	
Safety analysis set	19 (100)	33 (100)	21 (100)	60 (100)	133 (100.0)
Randomized	19 (100)	33 (100)	NA (NA)	NA (NA)	52 (39.1 ²)
Exposed		33 (100)	21 (100)	60 (100)	114 (100.0 ³)
Completed treatment at 24/32 weeks	14 (73.7)	28 (84.8)	15 (71.4)	53 (88.3)	110 (82.7 ²)
Discontinued study drug		6 (18.2)	6 (28.6)	7 (11.7)	19 (16.7 ³)
Adverse event		2 (6.1)	2 (9.5)	1 (1.7)	5 (4.4)
Discretion of investigator		1 (3)	2 (9.5)	0 (0)	3 (2.6)
Other		3 (9.1)	2 (9.5)	6 (10)	11 (9.6)

Disposition Outcome	Previous OnD Treatment		Concizumab Non-naive	Concizumab Naive	Total Arms 1-4 n (%)
	No PPX Arm 1 Randomized n (%)	Concizumab PPX Arm 2 Randomized n (%)	Concizumab PPX Arm 3 Non- randomized n (%)	Concizumab PPX Arm 4 Non- randomized n (%)	
Discontinued study	6 (31.6)	6 (18.2)	6 (28.6)	7 (11.7)	25 (18.8 ²)
Withdrawal by parent/guardian	0 (0)	0 (0)	0 (0)	2 (3.3)	2 (1.5)
Withdrawal by subject	5 (26.3)	2 (6.1)	3 (14.3)	5 (8.3)	15 (11.3)
Investigator decision	0 (0)	1 (3)	2 (9.5)	0 (0)	3 (2.3)
Death	1 (5.3)	3 (9.1)	1 (4.8)	0 (0)	5 (3.8)

Source: Study NN7415-4311 Clinical Study Report, Table 10-1 (p.102); FDA statistical reviewer's analysis.

¹ Duration: Primary analysis cutoff reached; extension part ongoing; main part (24-32 weeks treatment period); extension part (128-136 weeks treatment period)

² Percentage calculated based on the number of patients randomized/allocated to arm 1-4

³ Percentage calculated based on the number of patients randomized/allocated to concizumab PPX arms 2-4

Abbreviations: n, number of patients in specified population or group; OnD, on demand; PPX, prophylaxis

Patient Demographics

The median age of patients enrolled in arm 1 of the study was slightly older than in arm 2 (i.e., 27 years (range 15, 67 years) in arm 1 and 17 years (range 12, 61 years) in arm 2. Only 1 patient was enrolled age ≥ 65 years (arm 1 only), and no patients age ≥ 75 years were enrolled in either treatment arm. The majority of patients enrolled were white in arm 1 (47%) and Asian (42%) in arm 2. The table [below](#) shows the demographics for Study 4311.

Table 13. Baseline Demographic and Clinical Characteristics, Safety Population, Study 4311

Characteristic	No PPX Arm 1 Main N=19	Concizumab PPX Arm 2 Main N=33	Concizumab PPX				
			Arm 1 Extension N=13	Arm 2 Overall N=33	Arm 3 Overall N=21	Arm 4 Overall N=60	Arms 2-4 Overall N=114
Sex, n (%)							
Male	19 (100)	33 (100)	13 (100)	33 (100)	21 (100)	60 (100)	114 (100)
Age, years							
Mean (SD)	32.3 (17.6)	24.9 (14.3)	26.2 (15.5)	24.9 (14.3)	37.9 (12)	27.6 (13.2)	28.7 (13.9)
Median (min, max)	27 (15, 67)	17 (12, 61)	19 (15, 60)	17 (12, 61)	35 (20, 61)	25.5 (12, 79)	26.5 (12, 79)
Age group, years, n (%)							
≥12 to <18 years	6 (31.6)	18 (54.5)	6 (46.2)	18 (54.5)	0	18 (30.0)	36 (31.6)
≥18 to <65 years	12 (63.2)	15 (45.5)	7 (53.8)	15 (45.5)	21 (100)	41 (68.3)	77 (67.5)
≥65 to <85 years	1 (5.3)	0	0	0	0	1 (1.7)	1 (0.9)
Age group ≥65, years, n (%)							
≥65	1 (5.3)	0	0	0	0	1 (1.7)	1 (0.9)
Age group ≥75, years, n (%)							
≥75	0	0	0	0	0	1 (1.7)	1 (0.9)
Race, n (%)							
American Indian or Alaska Native	1 (5.3)	1 (3.0)	1 (7.7)	1 (3.0)	0	1 (1.7)	2 (1.8)
Asian	6 (31.6)	14 (42.4)	3 (23.1)	14 (42.4)	4 (19.0)	13 (21.7)	31 (27.2)
Black or African American	1 (5.3)	4 (12.1)	1 (7.7)	4 (12.1)	0	4 (6.7)	8 (7.0)
White	9 (47.4)	12 (36.4)	7 (53.8)	12 (36.4)	17 (81.0)	40 (66.7)	69 (60.5)
Not reported	2 (10.5)	2 (6.1)	1 (7.7)	2 (6.1)	0	2 (3.3)	4 (3.5)
Ethnicity, n (%)							
Hispanic or Latino	1 (5.3)	3 (9.1)	1 (7.7)	3 (9.1)	0	2 (3.3)	5 (4.4)
Not Hispanic or Latino	16 (84.2)	29 (87.9)	11 (84.6)	29 (87.9)	21 (100)	56 (93.3)	106 (93.0)
Not reported	2 (10.5)	1 (3.0)	1 (7.7)	1 (3.0)	0	2 (3.3)	3 (2.6)

Characteristic	No PPX Arm 1 Main N=19	Concizumab PPX Arm 2 Main N=33	Concizumab PPX				
			Arm 1 Extension N=13	Arm 2 Overall N=33	Arm 3 Overall N=21	Arm 4 Overall N=60	Arms 2-4 Overall N=114
Region of participation, n (%)							
Africa	1 (5.3)	4 (12.1)	1 (7.7)	4 (12.1)	0	11 (18.3)	15 (13.2)
Asia	5 (26.3)	14 (42.4)	3 (23.1)	14 (42.4)	4 (19.0)	17 (28.3)	35 (30.7)
Europe	11 (57.9)	10 (30.3)	8 (61.5)	10 (30.3)	16 (76.2)	26 (43.3)	52 (45.6)
North America	2 (10.5)	4 (12.1)	1 (7.7)	4 (12.1)	1 (4.8)	3 (5.0)	8 (7.0)
Oceania	0	1 (3.0)	0	1 (3.0)	0	3 (5.0)	4 (3.5)
Region group of participation, n (%)							
Non-USA	18 (94.7)	30 (90.9)	13 (100)	30 (90.9)	20 (95.2)	58 (96.7)	108 (94.7)
USA	1 (5.3)	3 (9.1)	0	3 (9.1)	1 (4.8)	2 (3.3)	6 (5.3)

Source: adsl.xpt; Software: R

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Trial 4310. Arm 4 consists of patients previously treated on PPX or on demand.

The On-treatment analysis dataset was used for this analysis.

Abbreviations: N, number of patients in treatment group; max, maximum, min, minimum; n, number of patients with given characteristic; PPX, prophylaxis; SD, standard deviation

Per the protocol for Study 4311, randomization between the treatment arms 1 and 2 was stratified according to hemophilia subtype (HAWI versus HBWI) and bleeding frequency (<9 bleeding episodes, ≥9 bleeding episodes) during the 24 weeks prior to screening of patients. This stratification did not apply to treatment arms 3 and 4. In treatment arm 1 there were 7/19 (36.8%) patients with <9 bleeding episodes and 12/19 (63.2%) patients with ≥9 bleeding episodes during the 24 weeks prior to screening, respectively. In treatment arm 2, there were 10/33 (30.3%) patients with <9 bleeding episodes and 23/33 (69.7%) with ≥9 bleeding episodes during the 24 weeks prior to screening, respectively. The table [below](#) summarizes the key baseline disease characteristics for patients in Study 4311.

Table 14. Additional Patient Characteristics, Study 4311

Characteristic	No PPX Arm 1 Main N=19 n, (%)	Concizumab PPX Arm 2 Main N=33 n, (%)	Concizumab PPX Arm 3 Overall N=21 n, (%)	Concizumab PPX Arm 4 Overall N=60 n, (%)	Total Overall N=133 n, (%)
Hemophilia type					
HAWI	9 (47.4)	18 (54.5)	13 (61.9)	40 (66.7)	80 (60.2)
HBWI	10 (52.6)	15 (45.5)	8 (38.1)	20 (33.3)	53 (39.8)
Inhibitor test results					
< 0.6 BU	3 (15.8)	3 (9.1)	2 (9.5)	9 (15.0)	17 (12.8)
≥ 0.6 and < 5 BU	4 (21.1)	13 (39.4)	6 (28.6)	19 (31.7)	42 (31.6)
≥ 5 BU	10 (52.6)	16 (48.5)	13 (61.9)	32 (53.3)	71 (53.4)
Not reported	2 (10.5)	1 (3.0)	0 (0)	0 (0)	3 (2.3)
Baseline bleeding 24 weeks before					
<9 bleeds	7 (36.8)	10 (30.3)	NA	NA	NA
>9 bleeds	12 (63.2)	23 (69.7)	NA	NA	NA
History of target joint bleed ^a					
Any target joint bleed ^b	10 (52.6)	12 (36.4)	8 (38.1)	30 (50.0)	60 (45.1)
Median number target joint bleeds within 12 months (range)	5 (3-22)	6 (3, 10)	4 (3, 7)	6 (3, 30)	6 (3, 30)

Source: Reviewer's table derived from CSR 4311.

^a Ankle, elbow, hip, knee, shoulder.

^b Bleeding may be in more than 1 target.

Abbreviation: BU, Bethesda units; HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; N, number of subjects; n, number of subjects with specific characteristics; NA, not applicable; PPX, prophylaxis

Clinical Reviewer Comment: In an information request sent on January 13, 2021, the clinical reviewer asked the Applicant to provide the inhibitor levels at screening, the following information was provided.

Table 15. Inhibitor Levels at Screening Arms 1 and 2, Study 4311

Inhibitor (FVIII or FIX)	No PPX N=19	Concizumab PPX N=33
Missing	2 (11%)	2 (6%)
<0.6U	4 (21%)	11 (33%)
≥0.6U - <5BU	3 (16%)	14 (42%)
≥5BU	10 (53%)	6 (18%)

Source: Applicant's Response to IR

Abbreviations: FVIII, coagulation factor VIII; FIX, coagulation factor IX; N, number of subjects; PPX, prophylaxis

While more patients in arm 1 (no PPX) had high titer inhibitors levels at screening compared to arm 2 (concizumab PPX), the patient population remains consistent with patients with HAwI and HBwI as all patients had a documented history of an inhibitor level >0.6BU. Given the mechanism of action of concizumab, which is not impacted by FVIII or FIX, it is not expected that the titer of the inhibitor would impact the efficacy results.

The historical bleeding rate of each patient enrolled was reviewed by investigators and only documented as above or below 9 bleeds in the previous 24 weeks. The actual number of bleeds was not recorded in datasets so the baseline bleeding rate could not be reported for each patient. While not ideal, the study results are still interpretable as the Applicant did stratify randomization for above or below 9 bleeds in the previous 24 weeks therefore, the severity of hemophilia based on the previous 24 weeks is expected to be similar between study arms.

Analysis of the Primary Endpoint, Study 4311

Superiority of concizumab PPX (arm 2) over no PPX (arm 1) was confirmed for the primary endpoint number of treated spontaneous and traumatic bleeding episodes. Using a negative binomial regression model, the estimated mean ABR was 1.7 with 95% CI (1.01, 2.87) for patients on concizumab PPX (arm 2) and 11.8 with 95% CI (7.03, 19.86) for patients on no PPX (arm 1). The estimated ABR ratio between patients on concizumab PPX (arm 2) and no PPX (arm 1) was 0.14 with 95% CI (0.07, 0.29) and 2-sided p-value<0.001, corresponding to an 86% reduction in ABR for patients on concizumab PPX (arm 2) compared to no PPX (arm 1).

The Applicant's primary efficacy analysis results were confirmed by the FDA statistical reviewer. Results of the primary efficacy endpoint are summarized in [Table 16](#).

Descriptive results (e.g., median, IQR, mean, standard deviation (SD), min, max, etc.) for bleeding episodes related endpoints were also provided by the Applicant for arm 1 to 4 and summarized in Supplementary Section [16.1](#).

Table 16. Primary Analysis Results of the Primary Efficacy Endpoint: Number of Treated Spontaneous and Traumatic Bleeding Episodes (FAS and OtwoATexIR), Study 4311

The Primary Efficacy Endpoint	No PPX (Arm 1)	Concizumab PPX (Arm 2)
N in FAS	19	33
N in FAS and OtwoATexIR	19	33
Treated spontaneous and traumatic bleeding episodes		
ABR estimate ¹	11.8	1.7
95% CI	(7.03, 19.86)	(1.01, 2.87)
ABR ratio (arm 2/arm 1)		0.14
95% CI		(0.07, 0.29)
% Reduction		86
2-sided p-value ²		<0.001

Source: Study NN7415-4311 Clinical Study Report, Table 11-2 (p.117); FDA statistical reviewer's analysis.

¹ Includes bleeding episodes with missing cause.

² p-values are for two-sided tests of no difference from 1. Bleeding endpoints are analyzed using a negative binomial regression model with the logarithm of the length of the observation period included (in years) as offset with treatment, type of hemophilia and bleeding frequency prior to screening as factors.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; FAS, full analysis set; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; N, number of subjects; OtwoATexIR, on-treatment without ancillary therapy exclude data on initial regimen for subjects exposed to both regimens; PPX, prophylaxis

Statistical Reviewer's Comments: Study 4311 had a concizumab treatment pause for 6 months during the study due to thromboembolic events reported in 3 patients. After the concizumab treatment pause and subsequent restart of Study 4311, a new concizumab dosing regimen was introduced to concizumab PPX arms. The original randomization was potentially compromised because more than half of the planned sample size had already been enrolled and treated on the original regimen. There were 4 patients randomized before pause in concizumab PPX arm 2 who did not restart on the new concizumab dosing regimen. Please refer to Section 8.5.1 for further clinical and statistical evaluation and discussion regarding the determination if the pause in Study 4311 due to thrombotic events impacted the benefit (ABR).

Analysis of Key Secondary Endpoints, Study 4311

Because the primary efficacy endpoint analysis was statistically significant (2-sided p-value<0.001) in favor of concizumab PPX, the two key secondary efficacy endpoints were further tested in the prespecified hierarchical order.

For both key secondary endpoints, the low number of patients in arms 1 and 2 contributing data at both baseline and post-baseline caused a convergence issue in the pre-planned multiple imputation (MI) analyses. Instead of using MI, the Applicant conducted post hoc mixed model for repeated measurements (MMRM) for both key secondary endpoints.

SF-36v2 Bodily Pain

The first key secondary endpoint was change in SF-36 v2 bodily pain from Week 0 to Week 24. Applying a mixed model for repeated measurements (MMRM), the estimated mean change in the bodily pain score from baseline to Week 24 was 9.2 with 95% CI (5.06, 13.25) for patients on concizumab PPX (arm 2) compared to 2.2 with 95% CI (-5.14, 9.52) for patients on no PPX (arm 1), yielding a difference estimate at Week 24 of 6.96 with 95% CI (-1.64, 15.57) and 2-sided p-value=0.109. This endpoint failed to achieve statistically significant superiority in SF-36v2 bodily pain score change from baseline to Week 24 for concizumab PPX compared to no PPX. The statistical testing hierarchy for key secondary endpoints was stopped at the endpoint SF-36v2 bodily pain and the results of the endpoints after it can only be considered descriptive. The Applicant's primary efficacy analysis results were confirmed by the FDA statistical reviewer and summarized in [Table 17](#).

Table 17. Primary Analysis Results of the First Key Secondary Endpoint: SF-36v2 Bodily Pain (FAS and OtxIR), Study 4311

The First Key Secondary Efficacy Endpoint	No PPX (Arm 1)	Concizumab PPX (Arm 2)
N in FAS	19	33
N in FAS and OtxIR	19	29
N contributing to analysis	9	23
Mean score estimate at Week 24	44.2	51.2
95% CI	(36.91, 51.57)	(47.11, 55.30)
Mean change from baseline score estimate at Week 24 ¹	2.2	9.2
95% CI	(-5.14, 9.52)	(5.06, 13.25)

The First Key Secondary Efficacy Endpoint	No PPX (Arm 1)	Concizumab PPX (Arm 2)
Difference at Week 24		6.96
95% CI		(-1.64, 15.57)
2-sided p-value		0.109

Source: Study NN7415-4311 Clinical Study Report, Table 11-11 (p.140); FDA statistical reviewer's analysis.

¹ Change from baseline values have been analyzed using a mixed model for repeated measurements (MMRM), with treatment, type of hemophilia and bleeding frequency prior to screening as factors, and baseline value as a covariate, all nested within week (Week 4, 8, 16 and 24). An unstructured covariance matrix is used to describe the variability for the repeated measurements for a subject.

Abbreviations: CI, confidence interval; FAS, full analysis set; HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; N, number of subjects; OtxIR, on-treatment without data on initial regimen; PPX, prophylaxis

SF-36v2 Physical Functioning

The second key secondary endpoint was change in SF-36 v2 physical functioning from Week 0 to Week 24. Applying a mixed model for repeated measurements (MMRM), the estimated mean change in the physical functioning score from baseline to Week 24 was 4.5 with 95% CI (0.77, 8.19) for patients on concizumab PPX (arm 2) compared to 1.2 with 95% CI (-4.76, 7.10) for patients on no PPX (arm 1), yielding a difference estimate at Week 24 of 3.30 with 95% CI (-3.76, 10.36) and descriptive 2-sided p-value=0.347. The Applicant's primary efficacy analysis results were confirmed by the FDA statistical reviewer and summarized in [Table 18](#).

Table 18. Primary Analysis Results of the Second Key Secondary Endpoint: SF-36v2 Physical Functioning (FAS and OtxIR), Study 4311

The Second Key Secondary Efficacy Endpoint	No PPX (Arm 1)	Concizumab PPX (Arm 2)
N in FAS	19	33
N in FAS and OtxIR	19	29
N contributing to analysis	9	23
Mean score estimate at Week 24	37.9	41.2
95% CI	(31.95, 43.80)	(37.47, 44.89)
Mean change from baseline score estimate at Week 24 ¹	1.2	4.5
95% CI	(-4.76, 7.10)	(0.77, 8.19)
Difference at Week 24		3.30
95% CI		(-3.76, 10.36)
2-sided p-value		0.347

Source: Study NN7415-4311 Clinical Study Report, Table 11-13 (p.145); FDA statistical reviewer's analysis.

¹ Change from baseline values have been analyzed using a mixed model for repeated measurements (MMRM), with treatment, type of hemophilia and bleeding frequency prior to screening as factors, and baseline value as a covariate, all nested within week (Week 4, 8, 16 and 24). An unstructured covariance matrix is used to describe the variability for the repeated measurements for a subject.

Abbreviations: CI, confidence interval; FAS, full analysis set; HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; N, number of subjects; OtxIR, on-treatment without data on initial regimen; PPX, prophylaxis

Statistical Reviewer's Comments: This post hoc analysis using MMRM model has similar underlying assumptions to the initially planned multiple imputation (MI) model (i.e., Missing at Random), which can be a reasonable alternative model now that the pre-planned MI model cannot converge due to the low number of patients in arms 1 and 2 contributing data both at baseline and post-baseline. However, unlike the findings for the primary endpoint, both key secondary endpoints failed to achieve significant result using the MMRM model.

Subgroup Analysis of the Primary Endpoints, Study 4311

Subgroup analyses were conducted to assess potential differences in the treatment effect for various demographic and clinical characteristics groups. Because of the small size of the study, only descriptive statistics for the randomized arm 1 (no PPX) and arm 2 (concizumab PPX) by age, race, ethnicity, region, and hemophilia subtype were summarized by the FDA statistical reviewer in [Table 19](#). The sample size was imbalanced for different categories of subgroups and many subgroup analysis results were limited due to very small numbers of patients. Therefore, the subgroup analysis Results should be interpreted with caution. For those categories with relatively larger sample size, results were generally consistent with the full analysis data set results.

Exploratory Endpoint, Study 4311

The Applicant described the number of patients with treated spontaneous and traumatic bleeding episodes in the first 24 weeks of treatment. For patients on no PPX (arm 1), 17 patients (89.5%) reported at least one bleeding event during the first 24 weeks, compared to 12 patients (36.4%) on concizumab PPX (arm 2). In total, 94.7% of patients in arm 1 (no PPX) had a treated bleed or discontinued before Week 24 compared to 48.5% in arm 2 (concizumab PPX).

Clinical Reviewer Comment: A numerically lower proportion of patients in the concizumab PPX arm experienced at least one bleeding episode in the main treatment period compared to no concizumab PPX. While clinically meaningful, these results should be interpreted with caution as this endpoint was not prespecified.

Table 19. Subgroup Analysis of the Number of Treated Spontaneous and Traumatic Bleeding Episodes (Randomized Arm 1 (No PPX) and Arm 2 (Concizumab PPX)), Study 4311

Subgroup	Category	Arm	N	Median Weeks of Exposure in ADS (Min, Max)	Number of Episodes	Median ABR (IQR)	Mean ABR (SD)
Age	Adolescents	Arm 1	6	37.4 (24.4, 49.9)	66	12.7 (8.4, 20.2)	14.1 (10.7)
		Arm 2	18	40.1 (6, 56.1)	26	0.7 (0, 3.3)	1.7 (2.1)
	Adults	Arm 1	13	24 (3.9, 72.9)	100	8.6 (6.5, 14.3)	20.4 (29.2)
		Arm 2	15	40.4 (3.1, 56.3)	33	0 (0, 4.3)	6.3 (17.2)
Race	Asian	Arm 1	6	20.1 (4.1, 31.1)	38	8.5 (3.2, 10.9)	17.6 (28.1)
		Arm 2	14	40.1 (5.7, 56.3)	46	2.6 (0.9, 4.3)	3.5 (4.4)
	Black or African American	Arm 1	1	40.1 (40.1, 40.1)	11	14.3 (14.3, 14.3)	14.3 (NE)
		Arm 2	4	44.9 (32, 56.1)	2	0 (0, 1.6)	0.8 (1.6)
	White	Arm 1	9	37.4 (3.9, 53.1)	99	15.7 (9.8, 20.5)	23.9 (27.4)
		Arm 2	12	40.1 (3.1, 56.1)	11	0 (0, 0.9)	6.1 (19)
	Other	Arm 1	3	54.1 (24.4, 72.9)	18	6.7 (0, 7.9)	4.9 (4.3)
		Arm 2	3	32.3 (31.1, 40.1)	0	0 (0, 0)	0 (0)
Ethnicity	Hispanic or Latino	Arm 1	1	24.4 (24.4, 24.4)	0	0 (0, 0)	0 (NE)
		Arm 2	3	32.1 (31.1, 40.1)	0	0 (0, 0)	0 (0)
	Not Hispanic or Latino	Arm 1	16	27.6 (3.9, 53.1)	148	11.4 (7.4, 20.4)	20.9 (26.2)
		Arm 2	29	40.1 (3.1, 56.3)	59	0.9 (0, 3.3)	4.3 (12.4)
	Not Reported	Arm 1	2	63.5 (54.1, 72.9)	18	7.3 (6.7, 7.9)	7.3 (0.8)
		Arm 2	1	32.3 (32.3, 32.3)	0	0 (0, 0)	0 (NE)

Subgroup	Category	Arm	N	Median Weeks of Exposure in ADS (Min, Max)	Number of Episodes	Median ABR (IQR)	Mean ABR (SD)
Region	US	Arm 1	1	4.1 (4.1, 4.1)	0	0 (0, 0)	0 (NE)
		Arm 2	3	32.1 (3.1, 40.1)	4	0 (0, 66.4)	22.1 (38.3)
	Non-US	Arm 1	18	34.2 (3.9, 72.9)	166	10.3 (6.7, 20.2)	19.4 (25.0)
		Arm 2	30	40.1 (5.7, 56.3)	55	0 (0, 3.3)	2.0 (3.4)
Hemophilia Type	HAwI	Arm 1	9	24 (3.9, 72.9)	99	11.8 (7.9, 30.8)	29.2 (32.8)
		Arm 2	18	48 (14.9, 56.3)	35	1.6 (0, 3.9)	2.2 (2.2)
	HBwI	Arm 1	10	34.3 (4.1, 54.1)	67	8.5 (3.2, 14.3)	8.7 (6.7)
		Arm 2	15	32.3 (3.1, 55.9)	24	0 (0, 0)	5.7 (17.3)

Source: FDA statistical reviewer's analyses.

Abbreviations: ADS, analysis data set; FAS, full analysis set; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; IQR, interquartile range (the 25th/75th percentile); N, number of subjects; NE, not estimable; OtwoATeXIR, on-treatment without ancillary therapy exclude data on initial regimen for subjects exposed to both regimens; SD, standard deviation

The Applicant's subgroup results were provided using descriptive statistics for all the combined data of concizumab PPX arms 1 to 4 in [Table 20](#).

Table 20. Subgroup Analysis of the Number of Treated Spontaneous and Traumatic Bleeding Episodes (All the Combined Data of Concizumab PPX Arms 11-4), Study 4311

Subgroup	Category	N	Median Weeks of Exposure in ADS (Min; Max)	Number of Episodes	Median ABR (IQR)	Mean ABR (SD)
Age	Adolescents	42	40.1 (2.6; 64.4)	59	0 (0; 2.6)	1.5 (2.1)
	Adults	85	39.7 (2.0; 64.1)	221	0 (0; 3.9)	3.8 (9.7)
Race	Asian	34	40.1 (3.0; 64.1)	79	1.5 (0; 3.9)	2.8 (3.7)
	Black or African American	9	33.7 (6.7; 56.1)	9	0 (0; 3.3)	2.0 (2.9)
	White	76	40.1 (2.0; 64.4)	192	0 (0; 3.7)	3.6 (10.1)
	Other	8	32.1 (5.4; 40.1)	0	0 (0; 0)	0 (0)

Subgroup	Category	N	Median Weeks of Exposure in ADS (Min; Max)	Number of Episodes	Median ABR (IQR)	Mean ABR (SD)
Ethnicity	Hispanic or Latino	6	32.1 (7.9; 40.4)	0	0 (0; 0)	0 (0)
	Not Hispanic or Latino	117	40.1 (2.0; 64.4)	280	0.9 (0; 3.7)	3.3 (8.4)
	Not Reported	4	32.1 (5.4; 32.3)	0	0 (0; 0)	0 (0)
Region	US	6	36.3 (3.1; 48.1)	4	0 (0; 0)	11.1 (27.1)
	Non-US	121	40.0 (2.0; 64.4)	276	0.8 (0; 3.6)	2.7 (5.9)
Hemophilia Type	HAwI	76	37.0 (2.0; 56.9)	128	0 (0; 3.7)	2.2 (4.6)
	HBwI	51	40.1 (2.6; 64.4)	152	0 (0; 3.3)	4.3 (11.5)

Source: Study NN7415-4311 Summary of clinical efficacy

¹ Arm 1 concizumab PPX corresponds to the patients randomized to no PPX (arm 1) that started concizumab PPX before the primary analysis cut-off but after having completed the on-demand treatment in the main part

Abbreviations: ADS, analysis data set; FAS, full analysis set; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; IQR, interquartile range (the 25th/75th percentile); N, number of subjects; OtwoATexIR, on-treatment without ancillary therapy exclude data on initial regimen for subjects exposed to both regimens; SD, standard deviation

6.2.2. Study 4310

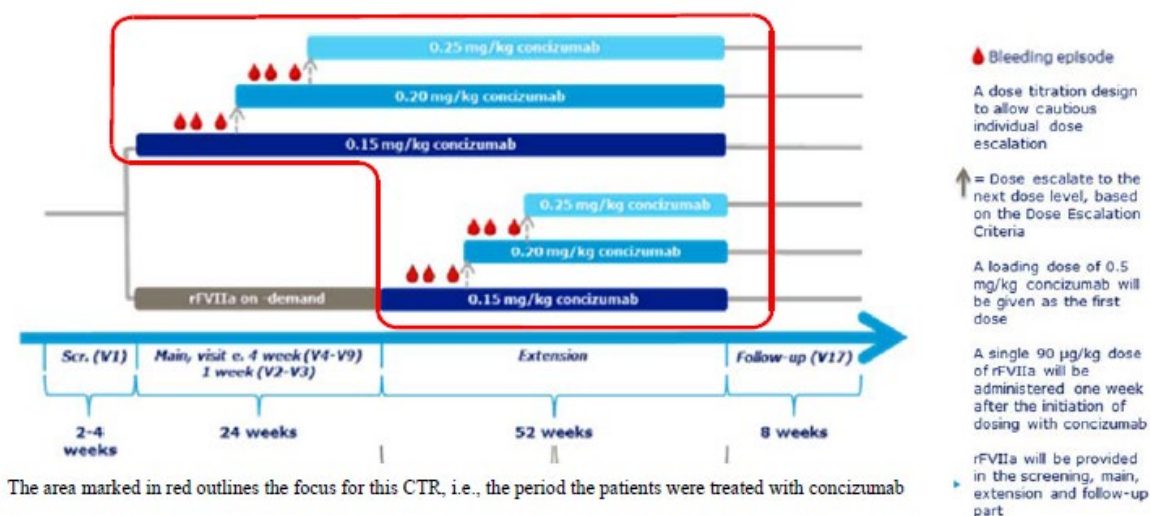
6.2.2.1. Design, Study 4310

Study 4310, EXPLORER 4, is titled, “A Multi-Centre, Randomized, Open-Label, Controlled Trial Evaluating the Efficacy and Safety of Prophylactic Administration of Concizumab in Hemophilia A and B Patients with Inhibitors.” This study is considered supportive of the safety and efficacy profile of concizumab for the treatment of patients with HAwI and HBwI.

Study 4310 is a Phase 2 interventional, multi-national, multicenter, randomized (2:1), open-label, controlled, dose escalation study of concizumab 0.15 mg/kg, 0.20 mg/kg and 0.25 mg/kg administered daily SC compared to treatment with eptacog alfa (rFVIIa) in patients with HAwI and HBwI. Only patients using on-demand therapies were eligible for the study. The study consisted of a 2-week screening period, a subsequent 76 to 118-week treatment period and an 8-week follow-up period. The 76 to 118-week treatment period consisted of a main part which lasted 24 weeks for patients randomized to eptacog alfa and at least 24 weeks for patients randomized to concizumab. The extension part lasted up to 94 weeks. The study schema is shown in the figure [below](#).

In all patients treated with concizumab, a single 90µg/kg dose of eptacog alfa was administered in a non-bleeding state one week after dosing with concizumab had been initiated. The investigator evaluated if there were any safety concerns 24 hours post eptacog alfa administration. Furthermore, the scheduled administration of eptacog alfa was staggered for the first four patients entering the study with concizumab. In the comparator arm, patients received eptacog alfa on-demand treatment during the main part of the study. After completion of the main part, the patients continued the study in the extension part being treated with prophylactic daily SC doses of 0.15 mg/kg concizumab (with potential dose escalation).

Figure 10. Trial Schema, Study 4310



Source: Applicant CSR for Study 4310

Abbreviation: CTR, clinical trial report; rFVIIa, recombinant activated factor VII; V, visit

6.2.2.2. Eligibility Criteria, Study 4310

Key Inclusion Criteria

- Informed consent obtained before any study related activities
- Male HA or HB patients with inhibitors aged ≥ 18 years at the time of signing informed consent
- Patients currently in need of treatment with bypassing agents

Key Exclusion Criteria

- Known or suspected hypersensitivity to study product(s) or related products
- Known inherited or acquired bleeding disorder other than hemophilia
- Ongoing or planned immune tolerance induction therapy or prophylaxis with FVIII or FIX

6.2.2.3. Statistical Analysis Plan, Study 4310

Key information regarding statistical analysis from the clinical study report, protocol, and statistical analysis plan (SAP) are summarized in this section.

Analysis Population

All dosed patients were included in the Full Analysis Set (FAS) as well as in Safety Analysis Set (SAS).

Statistical Reviewer's Comments: According to the Study 4310 Clinical Study Report (CSR), all the 26 subjects randomized to this study were dosed. Thus, the FAS is the same as the Intent-to-Treat, which is defined as all randomized patients.

Analysis of the Primary Endpoint

The primary endpoint for this study was the number of bleeding episodes occurring at least 24 weeks from treatment onset. All treated bleeding episodes were considered for this endpoint, including bleeding episodes recorded as post-surgical or caused by surgery or other medical or dental procedures. The reporting of the primary endpoint was produced via two Clinical Proof of Concept (CpoC) criteria that were evaluated in a hierarchical fashion:

- The primary CpoC (CpoC1) criterion aimed at evaluating the effect of concizumab at the last dose level reached for a patient. Hence, for this evaluation, only observations from the period where patients were on their last dose level at the time of analysis contributed to the analysis.
- The secondary CpoC (CpoC2) criterion aimed at evaluating the effect of concizumab when given as an escalation regimen. This analysis included all bleeding episodes (i.e., from the entire treatment period).

The primary endpoint was analyzed based on the FAS using a negative binomial regression with log of exposure time in the included observational period of the main part as offset and regimen as factor.

- The offset for first CpoC criterion of patients in concizumab arm is the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for patients on 0.15 mg/kg
- The offset for the second criterion of patients in concizumab arm is the log of the individual exposure time in the main part
- For patients in the on-demand arm regardless of criterion, the offset is the log of the exposure time in the main part

The analysis provides an estimate of the ABR ratio between regimens (concizumab prophylactic and on-demand eptacog alfa (rFVIIa)) with corresponding 95% confidence interval in addition to the actual estimate of the ABR with corresponding 95% confidence interval for each regimen.

Multiple Testing Strategy

Two CpoC criteria were evaluated in a hierarchical fashion following the aforementioned order. No secondary endpoints were included in the statistical testing hierarchy.

Handling of Intercurrent Event or Missing Data

The primary endpoint: The primary analysis method had the underlying assumption that the missing data mechanism is “missing at random”, (i.e., MAR). Only data collected prior to discontinuation of study product or initiation of alternative treatment options were used to draw inference.

6.2.2.4. Results of Analyses, Study 4310

Patient Disposition

Overall, in Study 4310 there were 26 patients randomized, 17 patients (HAWI = 9, HBWI = 8) randomized to concizumab and 9 patients (HAWI = 7, HBWI = 2) randomized to eptacog alfa. The table [below](#) shows the patient disposition in Study 4310. A total of 25 patients completed the main part and were exposed to concizumab in the extension part. Of the 25 patients, 22 (88%) patients completed the treatment, and 3 patients discontinued the treatment, 2 were discontinued due to ‘other’ reasons (1 was due to withdrawal of consent, 1 was due to suspect of no therapeutic effect due to normal TFPI level with binding antibody) and 1 was due to lack of efficacy (more than 3 treated spontaneous bleeding episodes within 12 weeks on 0.25 mg/kg concizumab).

Table 21. Patient Disposition, ISS Study 4310

	Concizumab PPX Main		Eptacog Alfa Main		Concizumab PPX Overall	
	HAWI N=9	HBWI N=8	HAWI N=7	HBWI N=2	HAWI N=15	HBWI N=10
Disposition Outcome	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Randomized	9 (100)	8 (100)	7 (100)	2 (100)	15 (100)	10 (100)
Safety population	9 (100)	8 (100)	7 (100)	2 (100)	15 (100)	10 (100)

Disposition Outcome	Concizumab PPX Main		Eptacog Alfa Main		Concizumab PPX Overall	
	HAwI	HBwI	HAwI	HBwI	HAwI	HBwI
	N=9 n (%)	N=8 n (%)	N=7 n (%)	N=2 n (%)	N=15 n (%)	N=10 n (%)
Discontinued study drug	0 (0)	0 (0)	1 (14.3)	0 (0)	1 (6.7)	2 (20)
Lack of efficacy	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.7)	0 (0)
Other	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	2 (20)
Discontinued study	0 (0)	0 (0)	1 (14.3)	0 (0)	1 (6.7)	2 (20)
Physician decision	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)
Withdrawal by subject	0 (0)	0 (0)	1 (14.3)	0 (0)	0 (0)	1 (10)
Other	0 (0)	0 (0)	0 (0)	0 (0)	1 (6.7)	0 (0)

Source: ds.xpt and adsl.xpt; Software: R

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: HA wI, hemophilia A with inhibitors; HB wI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients in specified population or group; PPX, prophylaxis

Patient Demographics and Baseline Characteristics

Table 22. Baseline Demographic and Clinical Characteristics by Hemophilia Subtype, Safety Population, ISS Study 4310

Characteristic	Concizumab PPX Main		Eptacog Alfa Main		Concizumab PPX Overall	
	HAwI	HBwI	HAwI	HBwI	HAwI	HBwI
	N=9 n (%)	N=8 n (%)	N=7 n (%)	N=2 n (%)	N=15 n (%)	N=10 n (%)
Sex, n (%)						
Male	9 (100)	8 (100)	7 (100)	2 (100)	15 (100)	10 (100)
Age, years						
Mean (SD)	38 (12.1)	29.8 (8.5)	43.1 (15.4)	34 (15.6)	38.7 (12.2)	30.6 (9.3)
Median (min, max)	38 (23, 59)	28.5 (18, 43)	46 (24, 64)	34 (23, 45)	38 (23, 59)	28.5 (18, 45)
Age group, years, n (%)						
≥18 to <65	9 (100)	8 (100)	7 (100)	2 (100)	15 (100)	10 (100)
Race, n (%)						
Asian	1 (11.1)	1 (12.5)	2 (28.6)	2 (100)	3 (20.0)	3 (30.0)
White	8 (88.9)	7 (87.5)	5 (71.4)	0	12 (80.0)	7 (70.0)
Ethnicity, n (%)						
Not Hispanic or Latino	9 (100)	8 (100)	7 (100)	2 (100)	15 (100)	10 (100)

Characteristic	Concizumab PPX Main		Eptacog Alfa Main		Concizumab PPX Overall	
	HAwI N=9	HBwI N=8	HAwI N=7	HBwI N=2	HAwI N=15	HBwI N=10
Country of participation, n (%)						
Austria	1 (11.1)	0	1 (14.3)	0	1 (6.7)	0
Denmark	1 (11.1)	1 (12.5)	0	0	1 (6.7)	1 (10.0)
Spain	0	4 (50.0)	0	0	0	4 (40.0)
Great Britain	1 (11.1)	0	0	0	1 (6.7)	0
Croatia	0	1 (12.5)	2 (28.6)	0	2 (13.3)	1 (10.0)
Israel	1 (11.1)	0	0	0	1 (6.7)	0
Italy	1 (11.1)	0	1 (14.3)	0	2 (13.3)	0
Japan	0	1 (12.5)	0	1 (50.0)	0	2 (20.0)
Malaysia	1 (11.1)	0	2 (28.6)	0	3 (20.0)	0
Sweden	0	1 (12.5)	0	0	0	1 (10.0)
Ukraine	2 (22.2)	0	1 (14.3)	0	3 (20.0)	0
United States	1 (11.1)	0	0	1 (50.0)	1 (6.7)	1 (10.0)

Source: adsl.xpt; Software: R

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; max, maximum; min, minimum; N, number of patients in treatment arm; n, number of patients in specified population or group; PPX, prophylaxis; SD, standard deviation

At baseline, 54% of patients had family history of hemophilia. The mean time from diagnosis was 33.5 years in the concizumab Arm and 40.3 years in the eptacog alfa arm. All the patients came from an on-demand treatment regimen. However, four of the patients also received prophylaxis within a year prior to screening (two patients in each study arm). At baseline, 20 out of 26 patients were reported to have at least one target joint. The target joint location for these 20 patients included ankle, elbow, hip, knee, shoulder, and wrist. The mean number of bleeds in specified joint within 1-year prior to screening was 8.1 (range 3–30 bleeds) in the concizumab Arm and 6.3 (range 3-12) in the eptacog alfa arm.

Clinical Reviewer Comment: Overall, the baseline demographic and disease characteristics were well balanced between study arms.

Analysis of the Primary Endpoint, Study 4310

The Primary CpoC (CpoC1) Criterion

The primary CpoC (CpoC1) criterion aimed at evaluating the effect of concizumab at the last dose level reached for a patient. Hence, for this evaluation, only observations from the period when patients were on their last dose level at the time of analysis contributed to the analysis.

In the concizumab arm, the estimated ABR on the last dose level for each patient was 4.5 with a 95% CI of [3.2, 6.4]. In the eptacog alfa (rFVIIa) on-demand arm, the estimated ABR was 20.4 with a 95% CI of [14.4, 29.1]. The ABR ratio was 0.22 with a 95% CI of [0.13, 0.36]. The analysis results are summarized in [Table 23](#).

Table 23. Primary Analysis Results of the Primary Endpoint: Number of Bleeding Episodes During at Least 24 Weeks From Treatment Onset – Bleeds Occurring by Last Dose Level¹ – CpoC1 (FAS), Study 4310

The Primary Endpoint, CpoC1	Eptacog Alfa	Concizumab
N in FAS	9	17
ABR estimate ²	20.4	4.5
95% CI	(14.4, 29.1)	(3.2, 6.4)
ABR ratio (concizumab/eptacog alfa) ²		0.22
95% CI		(0.13, 0.36)
2-sided p-value ³		<0.001

Source: Study NN7415-4310 Clinical Study Report, Table 11-2 (p.112); FDA statistical reviewer's analysis.

¹ Last dose level is the individual highest dose level at time of analysis and hence, previous dose levels and run-in are disregarded. Duration is the period where subjects are on their last dose at time of analysis.

² Ls-means estimates based on a negative binomial regression with treatment arm as factor and the log of the individual exposure time at the last dose level reached at the time of analysis excluding the 2 weeks run-in period for patients on 0.15 mg/kg as offset for patients in concizumab arm and the log of the exposure time in the main part as offset for patients in the on-demand arm

³ Two-sided p-value for test of ratio between arm different from 1.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; CpoC, clinical proof of concept; FAS, full analysis set; N, number of subjects

The Secondary CpoC (CpoC2) Criterion

The secondary CpoC (CpoC2) criterion aimed at evaluating the effect of concizumab when given as an escalation regimen. This analysis included all bleeding episodes (i.e., from the entire treatment period).

The estimated ABR during the entire treatment period (CpoC2) in the concizumab arm was 5.4 with a 95% CI of [3.8, 7.6]. In the eptacog alfa (rFVIIa) on-demand arm, the estimated ABR was 20.6 with a 95% CI of [13.7, 30.8]. The ABR ratio was 0.26 with a 95% CI of [0.15, 0.44]. The analysis results are summarized in [Table 24](#).

Table 24. Primary Analysis Results of the Primary Endpoint: Number of Bleeding Episodes During at Least 24 Weeks From Treatment Onset – Bleeding Episodes During Trial¹ – CpoC2 (FAS), Study 4310

The Primary Endpoint, CpoC2	Eptacog Alfa	Concizumab
N in FAS	9	17
ABR estimate ²	20.6	5.4
95% CI	(13.7, 30.8)	(3.8, 7.6)
ABR ratio (Concizumab/Eptacog Alfa) ²		0.26
95% CI		(0.15, 0.44)
2-sided p-value ³		<0.001

Source: Study NN7415-4310 Clinical Study Report, Table 11-4 (p.115); FDA statistical reviewer's analysis.

¹ All data after enrolment contribute to this analysis.

² Ls-means estimates based on a negative binomial regression with treatment arm as factor and the log of the exposure time in the main part as offset

³ Two-sided p-value for test of ratio between arm different from 1.

Abbreviations: ABR, annualized bleeding rate; CI, confidence interval; CpoC, clinical proof of concept; FAS, full analysis set; N, number of subjects

Statistical Reviewer's Comments: In Study 4310, the primary endpoint of number of bleeding episodes showed a significant result in which ABR was lower in the concizumab arm compared to the Eptacog alfa arm, which may serve as supportive evidence for the proposed indication. However, Study 4310 was a very small sized, open-label Phase 2 study, therefore the results of the study should be interpreted with caution.

Dedicated juvenile animal studies have not been conducted with concizumab as studies in neonatal and infant monkeys are technically challenging and are unlikely to identify potential reactions that were not identified from studies in fully developed (adult) animals. Notable findings in the hemostatic system and immune-related vascular toxicity were observed in adolescent (2 to 3 years of age) and sexually mature (3.5 to 6 years of age) cynomolgus monkeys. The human hemostatic system matures during the early weeks and months of life, and the concentrations of most hemostatic proteins, both in full-term and preterm infants, are comparable to adult values by 6 months of age ([Albisetti 2003](#); [Chalmers 2004](#)).

Table 25. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
Pregnancy	Dedicated reproductive and developmental toxicology studies were not conducted as concizumab is primarily indicated for use in male patients with hemophilia and the clinical development program was conducted exclusively in males. Hemophilia A is inherited in an X-linked recessive manner and the disease which occurs predominantly in males (99%) is extremely rare in females. Concizumab is also being indicated for hemophilia B (Factor IX deficiency or Christmas disease, caused by mutations in the Factor IX (FIX) gene on the X chromosome) and hence, is predominantly observed in males (some females who carry the gene may display mild or, rarely, severe symptoms of bleeding).
8.3 Females and Males of Reproductive Potential	Histopathological evaluations conducted during repeat-dose toxicology studies in adolescent (up to 13 weeks in duration) and sexually mature (up to 52 weeks in duration) male and female cynomolgus monkeys did not elicit any notable effects in reproductive organs. In mice, inactivation of the TFPI-gene has been shown to result in embryonic lethality (Huang et al. 1997; Ellery et al. 2015) and total TFPI deficiency has not been described in humans (Wood et al. 2014). As placental transfer of IgG, particularly during organogenesis, may differ between mice and humans, the clinical relevance of these findings is unknown (DeSesso et al. 2012). Recurrent pregnancy loss has been observed in women who exhibited TFPI deficiency in combination with an Activated Protein C (APC) resistance phenotype or in women with anti-TFPI antibodies in combination with antiphospholipid antibodies and suggests that TFPI may be critical to the maintenance of normal pregnancy in humans (Martinuzzo et al. 2005; Gardiner et al. 2006). The potential risk of blocking TFPI with a monoclonal IgG antibody (e.g., concizumab) in pregnant women is not clear.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Concizumab is not functional in rodents and standard carcinogenicity studies have not been conducted. Instead, the Applicant conducted a carcinogenicity risk assessment of concizumab using a weight-of-evidence (WOE) approach that considered the mode of action (MOA), a review of relevant literature and an evaluation of the nonclinical and clinical data. It was concluded that treatment with concizumab has the potential to enhance the prothrombotic conditions observed in some cancer patients (as would be expected for any procoagulant compound). However, the assessment did not identify evidence that treatment with concizumab could definitively lead to an increased risk of inducing or enhancing tumor development in humans. The Division determined that no additional nonclinical studies assessing the carcinogenic potential of concizumab were warranted for the indications of hemophilia A and hemophilia B and the CDER Executive Carcinogenicity Assessment Committee (ECAC) concurred with the Division's recommendation. Genotoxicity studies were not conducted, as concizumab consists of naturally occurring amino acids (endogenous) and is not anticipated to be genotoxic and there were no mechanistic data that suggested a mutagenic potential for concizumab. Fertility evaluations were included in the 26-week chronic toxicity study conducted in sexually mature male and female cynomolgus monkeys and there were no notable effects on the menstrual cycle duration, the length, width and volume of the testis, total sperm count, sperm motility or sperm morphology in cynomolgus monkeys administered concizumab at doses up to 9 mg/kg/day (SC).

Source: Reviewer constructed summary table of reproductive toxicology studies submitted to the BLA.
Abbreviations: APC, Activated Protein C; ECAC, Executive Carcinogenicity Assessment Committee; FIX, Factor IX; IgG, immunoglobulin G; MOA, mode of action; SC, subcutaneous; TFPI, tissue factor pathway inhibitor; WOE, weight-of-evidence.

Table 26. Reproductive Toxicity Exposure Margins/Dose Multiples

Study Duration (Sexual Maturity)	NOAEL (mg/kg/day)	Nonclinical Exposure (µg.hr/mL)	Exposure Margins* (AUC, Based)
4-Week Adolescent Reproductive Tissue Effects	9 mg/kg/day (SC)	37400 µg.hr/mL	1670x
13-Week Adolescent Reproductive Tissue Effects	50 mg/kg/day (SC)	326000 µg.hr/mL	14500x
26-Week Sexually Mature Fertility Endpoints Reproductive Tissue Effects	9 mg/kg/day (SC)	76500 µg.hr/mL	3400x
52-Week Sexually Mature Reproductive Tissue Effects	9 mg/kg/day (SC)	99300 µg.hr/mL	4400x

Source: Reviewer constructed summary table of chronic toxicology studies submitted to the BLA.

*Exposure margins were based on the concizumab plasma exposure level measured after 4 weeks of treatment (steady state) in the clinical Trial NN7415-4311 in patients with hemophilia A and B (with inhibitors) that employed a loading dose of 1 mg/kg (SC) followed by an initial once daily maintenance dose of 0.20 mg/kg (SC). The maintenance dose was adjusted to 0.15, 0.20 or 0.25 mg/kg/day (SC) and for exposure ratios, the mean across all three dose levels was used (22.4 µg.hr/mL, AUC₀₋₂₄).
Abbreviations: AUC, area under the curve (exposure); NOAEL, no observed adverse effect level

6.3. Key Efficacy Review Issues

6.3.1. Determination If the Pause in Study 4311 Due to Thrombotic Events Impacted the Benefit (ABR)

Issue

Determination if the pause in Study 4311 due to thrombotic events impacted the benefit (ABR).

Background

Study 4311 had a concizumab treatment pause for 6 months due to thromboembolic events reported in 3 patients. After the concizumab treatment pause and subsequent restart of Study 4311, a new concizumab dosing regimen was introduced to concizumab PPX arms. The original randomization could have been compromised because more than half of the planned sample size (refer to [Table 27](#)) were already enrolled and treated on the original regimen. Four patients randomized before the study pause in the concizumab PPX arm 2 did not restart on the new concizumab dosing regimen.

Table 27. Number of Subjects Randomized Before and After Pause, Study 4311

Arm 1(no PPX) N=19		Arm 2 (Concizumab PPX) N=33		All Randomized Subjects N=52	
Randomized Before Pause	Randomized After Pause	Randomized Before Pause	Randomized After Pause	Randomized Before Pause	Randomized After Pause
13 (68.4%)	6 (31.6%)	28 (84.8%)	5 (15.2%)	41 (78.8%)	11 (21.2%)

Source: Study NN7415-4311 Clinical Study Report, p.118.

Abbreviation: PPX, prophylaxis

Assessment

As recommended in previous IND meetings, the impact of potential bias introduced by the treatment pause and the robustness of the primary analysis was investigated by the Applicant with four sensitivity analyses. The results from all four sensitivity analyses in [Table 28](#) were confirmed by the FDA statistical reviewer. It was determined that the results of superiority from the primary analysis are robust.

Table 28. Sensitivity Analysis for the Primary Efficacy Endpoint: Number of Treated Spontaneous and Traumatic Bleeding Episodes, Study 4311

Purpose	Sensitivity Analysis	Result
To investigate the robustness of directly using the bleed data on the initial dosing regimen for patients who were not exposed to the new concizumab regimen	Used multiple imputation to impute the number of treated bleeds on the new concizumab dosing regimen for the 4 patients in arm 2 who did not restart	Estimated ABR ratio (arm 2/arm 1) was 0.14 with 95% CI (0.07, 0.29) and 2-sided p-value <0.001
To investigate the effect of using bleed data on the initial dosing regimen on the treatment effect of concizumab	Used all concizumab exposure data in arm 2 up until the primary analysis cut-off, irrespective of the dosing regimen	Estimated ABR ratio (arm 2/arm 1) was 0.14 with 95% CI (0.07, 0.29) and 2-sided p-value <0.001
To investigate the robustness of a potential superiority conclusion in terms of missing information for patients who were not exposed to the new concizumab regimen	Conducted tipping point analysis for patients only exposed to the initial dosing regimen. Patients only exposed to the initial dosing regimen were modelled with an increasing bleeding rate until the conclusion of superiority is changed	Tipping point was 25, means patients only exposed to the initial dosing regimen need to have 25 more bleed episodes to have non-significant result, which is considered implausible
To investigate a potential difference in treatment effects between patients randomized before and after the pause	Conducted subgroup analysis for patients randomized before and after treatment pause	Estimated ABR ratio (arm 2/arm 1) for patients randomized before the pause was 0.16 with 95% CI (0.08, 0.35) Estimated ABR ratio (arm 2/arm 1) for patients randomized after restart was 0.06 with 95% CI (0.01, 0.42)

Source: Study NN7415-4311 Clinical Study Report, Section 9.7.1.2.2 and section 11.2.2; FDA statistical reviewer's analysis.
Abbreviations: ABR, annualized bleeding rate; CI, confidence interval.

Conclusion

Study 4311 was paused due to thromboembolic events however, multiple sensitivity analysis confirmed the conclusion of superiority of concizumab PPX over on-demand therapy in reduction in ABR. Despite the study pause, Study 4311 is determined to be an adequate and well controlled study and provides substantial evidence of effectiveness of concizumab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients with HAWI and HBWI.

7. Safety (Risk and Risk Management)

7.1. Potential Risks or Safety Concerns Based on Nonclinical Data

Toxicological characterization of concizumab was assessed in cynomolgus monkeys (4 weeks, 13 weeks, 26 weeks, and 52 weeks) with normal intact coagulation systems (non-hemophilic) during repeat-dose toxicology studies. Cynomolgus monkeys were considered the most relevant

nonclinical species for toxicological evaluations based on amino acid sequence homology between humans and cynomolgus monkeys in the target epitope (K2 domain), and the observed binding and functional cross-reactivity of concizumab to human and cynomolgus monkey endogenous TFPI (Section [13.1](#)).

No definitive risks were identified during in vitro safety pharmacology assessments (human Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), complement fixation and binding to peripheral blood cells) or during in vivo safety pharmacology assessments conducted as part of the 13-week and/or 52-week repeat-dose toxicity studies in cynomolgus monkeys (cytokine release, blood pressure measurement, ECG, respiration rate, urinalysis, CNS endpoints). Furthermore, activated protein C (APC) generation and antithrombin activity (negative regulators of the coagulation cascade) were not affected by the presence of concizumab (in vitro), and these results were consistent with the absence of changes in APC and antithrombin levels in the repeat-dose toxicology studies conducted in cynomolgus monkeys. The in vitro and in vivo safety pharmacology studies are discussed in further detail under Section [13.1.1.2](#).

The results of the nonclinical toxicology studies were consistent with the expected mechanism of action of TFPI inhibition, which results in a downstream increase in thrombin generation and hemostasis. These events were reflected by an increase in markers of coagulation activation, Thrombin-Antithrombin (TAT) and D-dimers, and a decrease in fibrinogen levels in repeat-dose cynomolgus monkey studies. Minor changes in clotting parameters (prolonged APTT and PT and/or a decrease in platelet counts) were induced at supra-pharmacological exposures that exceeded 400-fold the anticipated exposure at the proposed therapeutic dose during the 26-/52-week toxicity studies. This response is likely indicative of homeostatic regulation of the coagulation system in cynomolgus monkeys in a normo-coagulative state.

Notable findings in nonclinical toxicology studies conducted in cynomolgus monkeys included thrombi and focal vascular changes. Thrombi were predominantly observed in the lungs and heart and were associated with a single early mortality (HD female presented with lung thrombi, lung parenchymal necrosis, and anemia in the 26-week study) across all of the repeat-dose toxicology studies conducted in cynomolgus monkeys. The onset of thrombi was regarded as an exaggerated pharmacological effect of administering a procoagulant to cynomolgus monkeys with normal intact coagulation systems. Focal vascular changes were primarily observed in the choroid plexus (in the cerebral ventricles of the brain), lungs, and at the injection sites and included endothelial hypertrophy, subendothelial thickening and/or inflammatory cell infiltration. Mechanistic analyses (discussed in detail under Section [13.1.2.5.3](#)) suggested that the observed vascular changes were due to an immunogenic reaction driven by the development of anti-drug antibodies (ADAs) and subsequent formation/deposition of immune-complexes (Ics). The extent of ADA-related-immune complex formation exceeded the clearance capacity for Ics in cynomolgus monkeys and the associated vascular changes were found to be reversible, consistent with the eventual clearance of the Ics. There were no notable changes observed in immunotoxicity, local tolerance, or fertility endpoints incorporated into the repeat-dose toxicity studies.

The toxicities observed in nonclinical studies occurred at exposures which were significantly higher than those anticipated at the proposed therapeutic dose and interpretation of these safety margins should also take into consideration that the toxicology studies were conducted in normal, healthy cynomolgus monkeys with intact coagulation systems. This clearly shifted the

toxicological exposure/response curve leftward, and the exaggerated pharmacological effects and immunogenic responses observed in cynomolgus monkeys were not recapitulated in clinical studies (albeit at significantly lower exposures). Thus, the results from the toxicology studies more accurately represent the consequences of excessive procoagulant effects in normal (non-disease state) animals and, presumably, what may occur in human subjects who do not harbor a clotting disorder, such as hemophilia. Additionally, patients with hemophilia would be expected to have a reduced immunogenic response towards a humanized mAb like concizumab, and the risk of IC formation exceeding the clearance capacity in humans is considered low. The repeat-dose toxicity studies in cynomolgus monkeys are discussed in further detail under Section [13.1.2](#).

Table 29. Exposure Margins (Cynomolgus Monkey Toxicology Studies, Pivotal)

Study Duration (Sexual Maturity)	NOAEL¹ (mg/kg/day)	Nonclinical Exposure (µg.hr/mL)	Exposure Margins² (AUC, Based)
4-Week Adolescent	9 mg/kg/day (SC)	37400 µg.hr/mL	1670x
13-Week Adolescent	1 mg/kg/day (SC)	5930 µg.hr/mL	265x
26-Week Sexually Mature	< 3 mg/kg/day (SC)	< 21400 µg.hr/mL	955x (LOAEL@)
52-Week Sexually Mature	0.5 mg/kg/day (SC)	1660 µg.hr/mL	74x

Source: Reviewer constructed summary table of chronic toxicology studies submitted to the BLA.

¹ A NOAEL was not established in the 26-Week study due to thrombotic changes at all dose levels.

² Exposure margins were based on the concizumab plasma exposure level measured after 4 weeks of treatment (steady state) in the clinical Trial NN7415-4311 (Explorer7) in patients with hemophilia A and B (with inhibitors) that employed a loading dose of 1 mg/kg (SC) followed by an initial once daily maintenance dose of 0.20 mg/kg (SC). The maintenance dose was adjusted to 0.15, 0.20 or 0.25 mg/kg/day (SC) and for exposure ratios, the mean across all three dose levels was used (22.4 µg.hr/mL, AUC₀₋₂₄). Abbreviations: AUC, area under the curve (exposure); NOAEL/LOAEL, no/lowest observed adverse effect level

7.2. Potential Risks or Safety Concerns Based on Drug Class or Other Drug-Specific Factors

Concizumab elicited a minimal release of TFPI from the surface of endothelial cells (compared to heparin) and is consistent with the mechanism required for TFPI-release that involves association with the C-terminal region (not the K2 domain) of the TFPI α form. This result suggests that the potential risk of concizumab-mediated release of TFPI from the surface endothelial cells (an anticoagulant effect) is low.

In certain pathological situations (e.g., severe generalized infections and/or sepsis) increased expression of tissue factor (TF) can occur. Because TFPI is involved in regulation of the TF-related response, it is a theoretical concern that inhibition of TFPI in situations with increased TF expression may lead to increased thrombogenicity, and thereby complicate and/or aggravate these clinical conditions. Situations with increased expression of TF have not been specifically investigated in nonclinical studies conducted with concizumab, and based on the literature, a theoretical concern of thrombotic events cannot be excluded if concizumab is used in patients with increased TF expression.

Issue

PK fluctuations leading to subtherapeutic concentrations during concizumab treatment

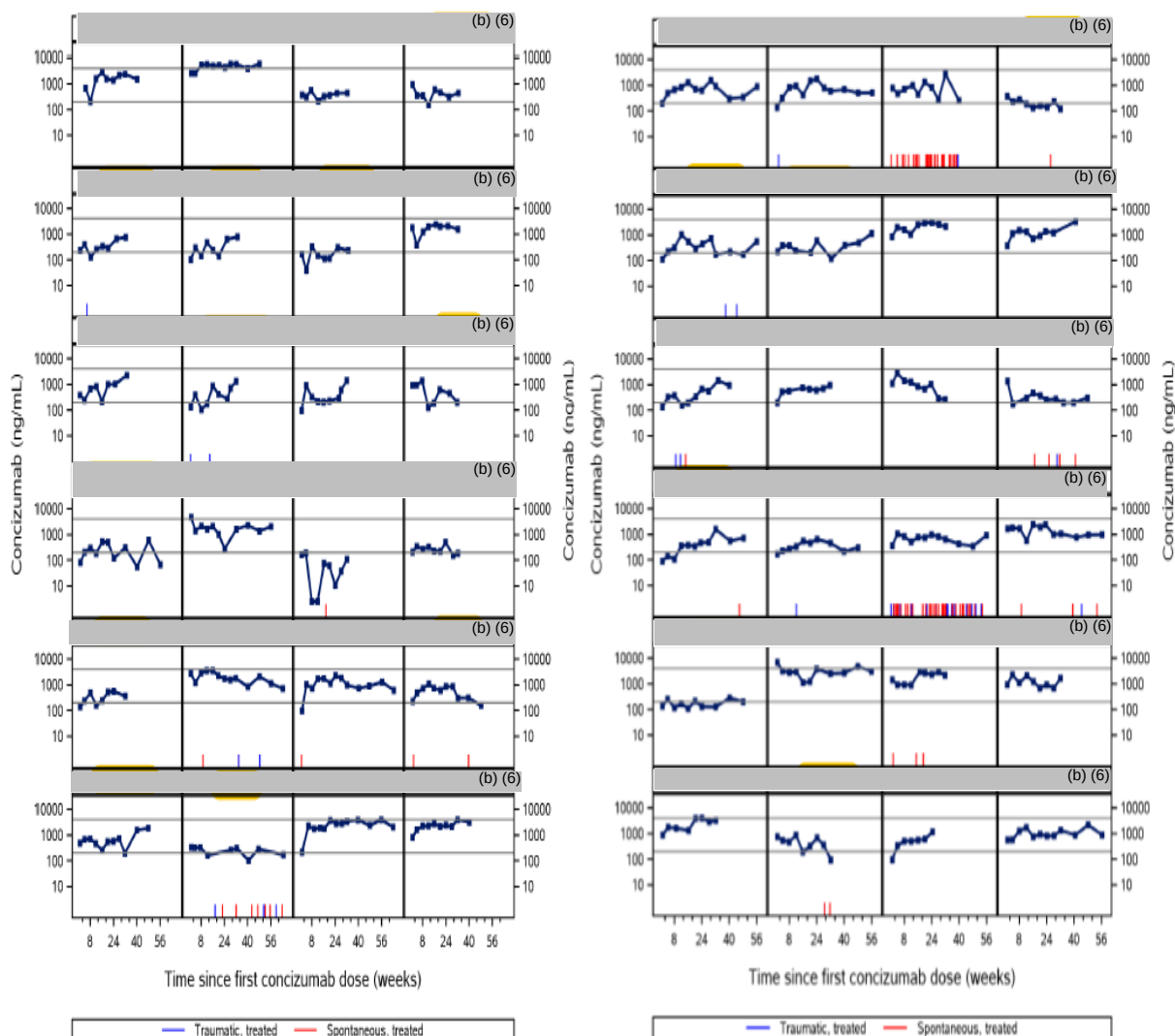
Background

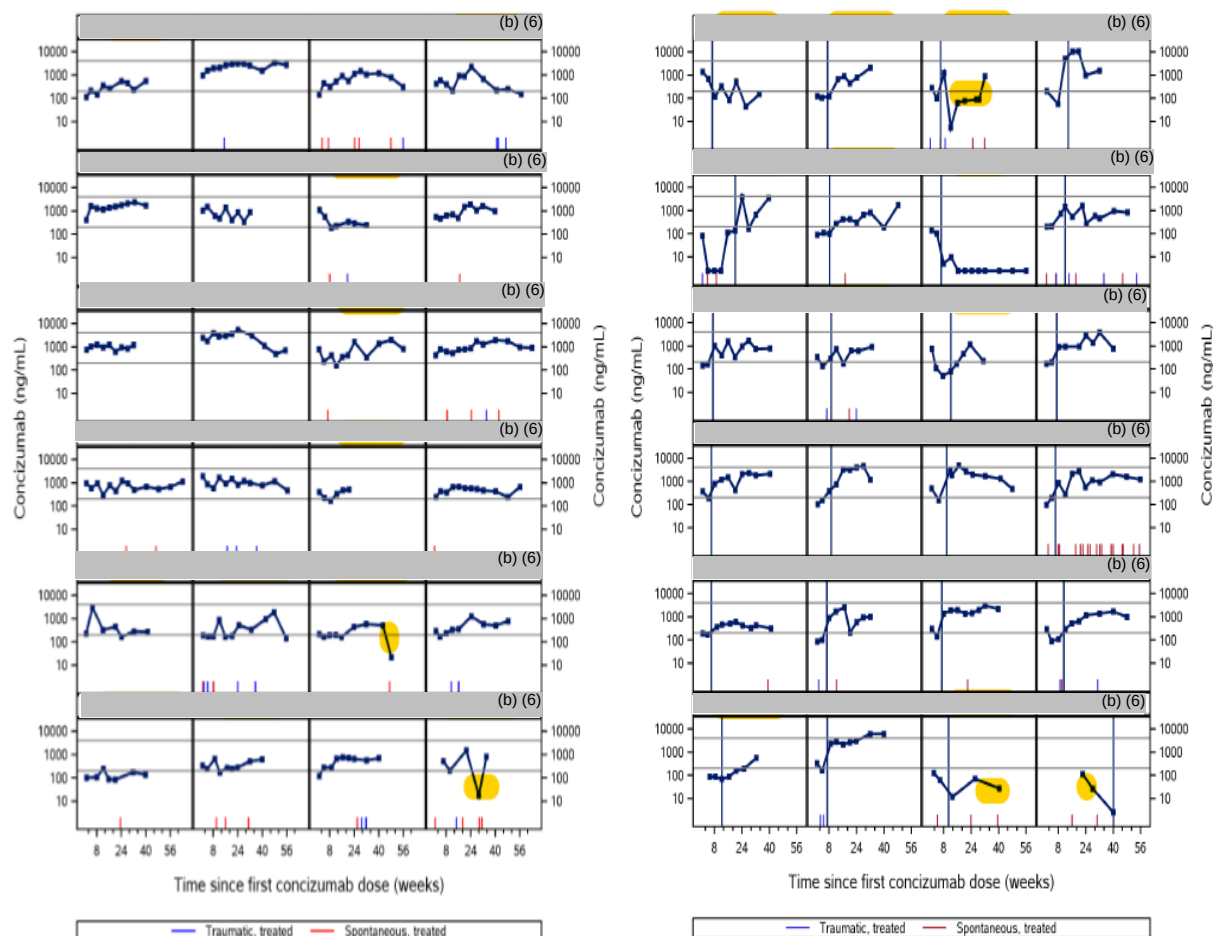
As stated earlier, concizumab's clearance through TMDD is predominant in the target exposure of 200 to 4000 ng/mL. The effective half-life in the target exposure range is estimated to be only one to two days which necessitates once-daily dosing of concizumab to reduce peak-to-trough fluctuations. Additionally, due to variability in target pool (membrane bound TFPI) between patients, PK guided dosing is necessary to maintain concizumab exposures within the target range. Despite these measures, significant fluctuations in plasma PK profiles were observed in individual patients.

In Study 4311, PK samples for measuring concizumab concentrations were collected at each study visit throughout the study, which allows for review of the observed PK profile over the course of concizumab treatment in each individual patient ([Figure 11](#)). For example, patient ID (b) (6) had an 87-fold higher concizumab concentration at Week 12 compared to Week 8 at the dose of 0.2 mg/kg. Following the dose increase to 0.25 mg/kg between Week 12 and Week 16, the concizumab concentrations at Week 20 was 10500 ng/mL but decreased to 970 ng/mL (approximately 90% decrease) at Week 24, while the dose was not changed. In another example, patient ID (b) (6) exhibited an increase in concizumab concentration to 1200 ng/mL after the dose increase to 0.25 mg/kg, but during subsequent visits the levels decreased to 5 ng/mL (99% decrease in exposure) while on the same maintenance dose. These patients PK profiles prompted the review team to look systematically into patients whose concentrations during concizumab treatment either went below or exceeded the target exposure range. The review team noted that 42 (43%) out of 97 patients had concizumab exposure levels below 200 ng/mL at some point during the maintenance dose setting and up until primary analysis cut-off (PACO). Upon further review, the team identified a small proportion of patients (e.g., patient ID (b) (6) (b) (6)) who had concizumab concentrations far below the therapeutic range for a prolonged period.

It should be noted that the lower end of the target exposure range for efficacy i.e., 200 ng/mL, is adequately supported by exposure-response (E-R) and PK/PD data from Study 4311 (See [Section 6.1](#)). An increased risk for bleeding is expected when concentrations fall below 200 ng/mL. That said, concizumab exposures occasionally dropping below 200 ng/mL probably does not pose a significant risk, as the previously identified 42 patients have ABR that was significantly lower than in patients without concizumab treatment. However, it is the few patients whose exposure falls below 200 ng/mL for prolonged periods that is of concern. This is reflected in patient ID (b) (6), who had concizumab concentrations near or below the subtherapeutic levels for prolonged periods before the fatal bleeding event (intracranial hemorrhage). A 100-fold change in concizumab levels were observed in Patient ID (b) (6), where the trough concentration was about 3000 ng/mL at Week 24 when concizumab was dosed at the study site and 28 ng/mL at Week 48, 8 days before the fatal bleeding event occurred (See [Table 30](#)). Therefore, the review team is mainly concerned that consistently lower concentrations of concizumab far below 200 ng/mL for a prolonged period of time may put the patient at risk for bleeding, sometimes even a serious/fatal bleeding event.

Figure 11. Pre-dose Trough Concizumab Plasma Concentration (ng/mL) – Patients Ending on Maintenance Dose 0.20 mg/kg (Top Panels and Left Bottom Panel) and 0.25 mg/kg (Right Bottom Panel) – Individual Plots – HAwI + HBwI – OtxeIR – Safety Analysis Set of Study 4311





Source: Applicant's response to the FDA's Information Request on March 2nd, 2023

Note: horizontal lines represent concentration levels of 200 ng/mL and 4000 ng/mL. Subjects in arm 2, 3 and 4 on concizumab PPX are included. Treated bleeding episodes from OtwoATeXIR are included as vertical markers at the bottom of each plot. Yellow highlight represents patients who had at least one measured concizumab concentration below 200 ng/mL during the maintenance dose setting till PACO.

Abbreviations: HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; OtexIR, on-treatment without data on initial regimen; OtwoATeXIR, on-treatment without ancillary therapy excluding data on initial regimen for subjects exposed to both regimens

Table 30. Concizumab Concentrations of Patient ID (b) (6) During Treatment

Treatment Week	Concizumab Concentration (ng/mL)				
	0 Hours*	3 Hours*	6 Hours*	9 Hours*	24 Hours
Week 1 (Day 1)	0	145	664	979	1280
Week 2	749				
Week 4	110				
Week 8	51				
Week 12	78				
Week 16	167				
Week 20	452				
Week 24	1130	1360	1710	2110	2890
Week 32	223				
Week 40	212				
Week 48	28				

Source: Reviewer created table

* hours post-dose, 0 hr and 24 hr represent pre-dose or trough concentrations for daily dosing

Assessment

The issue of significant PK fluctuation in few individual patients was communicated to the Applicant. The Applicant associates the high degree of inter- and intra-subject variability to concizumab's TMDD. While a high inter-subject PK variability of concizumab can be expected based on varying target pool between patients, the magnitude of within-subject PK changes, as noted in few individuals, is unlikely to be completely explained by TMDD alone. Therefore, the review team considered other factors that may play a role in these observations. These are discussed in detail below:

- ADAs: A total of 16 out of the 42 patients with concizumab exposure levels below 200 ng/mL tested positive for binding ADAs at some point during maintenance dose setting and up until PACO. Most occurrences were transient, and titers were very low. Three patients had in vitro neutralizing antibodies at one or a few visits (Subjects [REDACTED] (b) (6) [REDACTED]); however, binding titers were very low, and no increased bleeding were observed in these patients. In general, there was no association between occurrence of ADAs and bleeding episodes (if any) for patients testing positive for ADAs. The immunogenicity analysis based on comparison between ADA positive and negative patients also supports a lack of impact on concizumab PK and PD due to ADAs (See Section 14.4).
- PK assay: ELISA that was used in the clinical study was adequately validated and accepted by the Agency as fit-for-purpose to determine concizumab plasma concentrations. During the study, PK and PD samples were collected in a time-matched manner. Considering that the concentration of free TFPI (PD marker) was determined using a commercial assay and which mostly shows an inverse relationship with PK, it suggests that the large fluctuation in concizumab concentration is unlikely to be due to any imprecision with the PK assay.
- Membrane-bound TFPI: Concizumab clearance is mainly mediated by TMDD, where concizumab binds to endothelial cell-anchored TFPI (the target) with subsequent endocytosis and degradation (target-mediated clearance). It is not clear if the expression of membrane bound TFPI could increase during concizumab treatment and lead to increased drug clearance. However, the mean C_{ave} of concizumab in all patients receiving concizumab was relatively stable over the treatment period, which suggests that increased target synthesis may be unlikely and cannot explain the large PK variability observed in a small portion of patients.

Lastly, one plausible explanation for significant changes in drug levels during treatment could be due to lack of patient adherence to daily SC injection of concizumab. As noted earlier, based on concizumab's PK characteristics, administration once-daily is critical to avoid large peak-to-trough fluctuations. The assessment of the review team related to patient compliance is discussed below:

- The impact of missed doses on concizumab concentrations was demonstrated in Study 4159. In this study, concizumab was dosed at 0.25, 0.5 and 0.8 mg/kg on Day 1, Day 2, and every 3 days thereafter. As all concizumab SC injections were administered at the study site, the dosing records were reliable and complete, which allows for the analysis on the impact of missing doses on concizumab PK. Table 31 shows the pre-dose concizumab concentrations at each visit in the 6 subjects who were assigned to the 0.8 mg/kg group (equivalent to

0.27 mg/kg/day). Although there is some degree of concentration fluctuation at each visit, a more than 10-fold change in PK concentration within individual patients is primarily associated with missing doses. For example, subject ID (b) (6) (represented by the blue line) had a big drop in concentration from 3140 ng/mL on Day 5 to 346 ng/mL on Day 11 due to one missed dose on Day 8. Similar trends for larger drops in concentration with a missed dose were also observed in other patients (highlighted in red).

- For patient ID (b) (6), at the two study visits where drug dosing was done on site and when rich PK samples were collected, concizumab concentrations were 1280 ng/mL at the end of Day 1 and 2890 ng/mL at Week 24. However, at other visits where only pre-dose PK samples were collected, concizumab levels were mostly below the target level of 200 ng/mL (Table 30). The reason for such a pattern is hard to explain for anything other than patient noncompliance. To corroborate this inference, the patient's e-Diary shows multiple incidences of missing dose for more than four consecutive days (See Section 7.7.3). As per the Applicant, the trend for lower concentrations coincided with large number of missing doses in this patient. In addition, protocol violation for missing doses were also reported in other patients.
- The significant impact of missed dosing on concizumab concentration is also consistent with the PK characteristics of this drug. As a monoclonal antibody, the PK of concizumab is characterized by a combination of saturable non-linear TMDD and nonspecific linear elimination processes. At the target concentration range, TMDD plays a dominant role in the clearance of concizumab leading to a rapid clearance and a short half-life. As illustrated in Figure 12, following administration of a single SC dose of 1 mg/kg, concizumab concentrations drop steeply from a C_{max} of around 2000 ng/mL to <200 ng/mL within a couple of days without subsequent dosing. When concentrations drop to low subtherapeutic levels due to missed doses, in the absence of a loading dose, it may take several days of consecutive dosing to gradually return to target concentrations of >200 ng/mL (light blue line in Figure 13).

Taken together, these assessments strongly suggests that patient compliance to daily administration of concizumab is critical to maintain therapeutic concentrations.

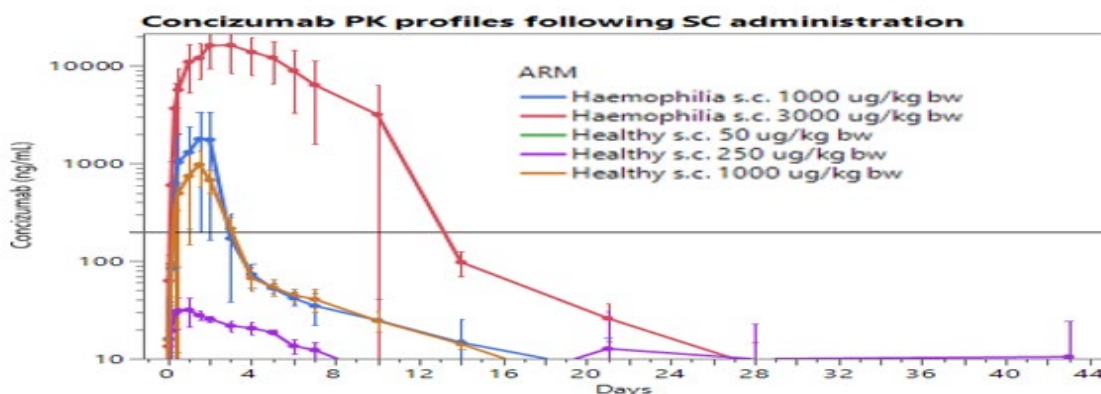
Table 31. Concizumab Trough Concentrations Following Subcutaneous Administration of 0.8 mg/kg on Day 1, Day 2 and Every Fourth Day Afterward

Subject		Subject		Subject		Subject		Subject		Subject	
										(b) (6)	
Day	Conc.	Day	Conc.	Day	Conc.	Day	Conc.	Day	Conc.	Day	Conc.
1	2.5	1	2.5	1	2.5	1	2.5	1	2.5	1	2.5
2	2090	2	406	2	122	2	40	2	106	2	795
5	3140	5	2240	7	95.2	7	35	6	109	5	151
11	346	9	663	9	1540	10	69	9	170	10	69
15	1060	15	123	15	98	15	93	14	130	15	31
18	2580	19	124	18	213	18	104	16	555	18	56
22	3570	22	108	23	81	22	154	22	125	22	69
26	2780	26	495	25	1160	25	106	27	108	26	83
30	4600	29	744	31	93	30	96	30	222	29	96
33	4630	33	662	35	123	35	89	34	210	33	84

Subject		Subject		Subject		Subject		Subject		Subject	
(b) (6)											
Day	Conc.	Day	Conc.	Day	Conc.	Day	Conc.	Day	Conc.	Day	Conc.
38	2580	37	192	37	447	38	88	38	325	37	81
43	628	40	1180	43	551	43	90	42	324	40	155

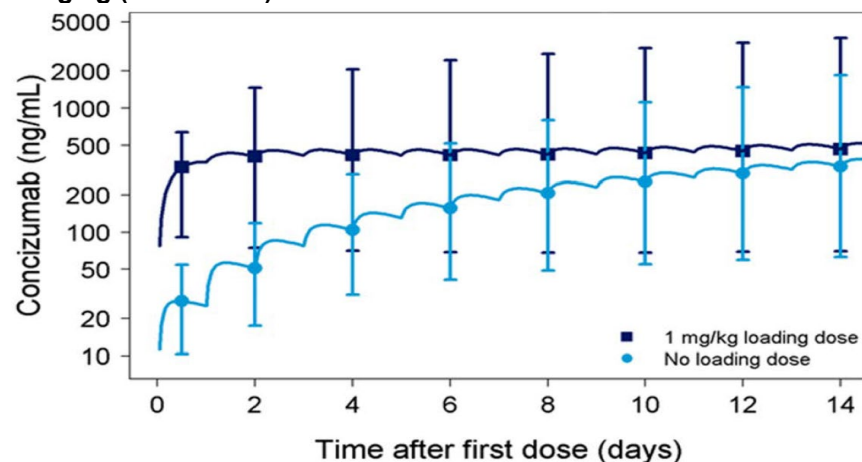
Source: Reviewer created table
Actual dosing and PK sampling day
LLOQ= 2.5 ng/mL
Abbreviations: Conc., concentration; LLOQ, lower level of quantification

Figure 12. Concizumab Geometric Mean (SE) Concentration-time Profile Following a Single Subcutaneous Dose of 0.05, 0.25 and 1.0 mg/kg in Healthy Subjects and 1.0, 3.0 mg/kg in Patient With Hemophilia A, Study 3813)



Source: Reviewer's plot based on data from Study 3813
Abbreviation: bw, body weight; SC, subcutaneous; SE, standard error

Figure 13. Concizumab PK Following 0.25 mg/kg Daily Dose With or Without a Loading Dose of 1 mg/kg (Simulation)



Source: Figure 20 of EOP2 meeting package dated 01 February 2019
Abbreviation: PK, pharmacokinetics

Conclusion

Overall, based on the PK characteristics of concizumab and observation in Study 4159, patient compliance to daily administration is critical to maintain therapeutic concentrations. Therefore,

the Applicant should propose labeling language that clearly informs of the risks of missed doses, the importance of adherence prior to the measurement of concizumab concentrations after four weeks of treatment, and a proposal for how to initiate the next dose after missed dose(s) (e.g., repeat loading dose?). The Applicant should also enhance patient education on adherence to therapy, likely by including a Medication Guide in FDA labeling.

7.3. Potential Risks or Safety Concerns Identified Through Postmarket Experience

Concizumab is not currently approved or marketed in the United States or elsewhere.

7.4. FDA Approach to the Safety Review

The safety review focuses on the Phase 3 Study 4311. Supportive safety information was obtained from the Phase 2 dose escalation Study 4310. Studies were analyzed separately due to differences in study design and concizumab dosing regimen.

The safety database of Study 4311 included a total of 133 adolescent or adult patients with HAwI or HBwI, of which 127 patients were exposed to concizumab PPX in either the main treatment period or the extension period. In total, there were 19 patients in the no PPX arm 1 in the main treatment portion (randomized portion consisting of 24 weeks of study drug therapy) of the study and 13 patients continued the study to receive concizumab prophylaxis (PPX) in the extension portion of the study. In arm 2 (concizumab PPX arm) of the study, 33 patients were evaluated in the main treatment portion of the study. In total, there were 81 patients in arms 3 to 4 who received concizumab PPX, which includes patients who were enrolled in the main treatment portion of the study, the extension portion, and follow-up parts of the study.

Support for the safety database included 26 adult patients with HAwI or HBwI from Study 4310, of which 25 patients were exposed to concizumab in either main treatment period or the extension period.

The data cutoff date for the safety assessments submitted in the BLA was March 10, 2022. The 120-Day safety update provided additional safety data collected from ongoing clinical studies, including Study 4311 through July 11, 2022.

Review of safety was based upon:

- Clinical Study Report (CSR) for studies
- Protocol for studies
- Data sets for the populations described above
- Summary of clinical safety
- 120-day safety update
- Patient narratives
- Case report forms

Case report forms and narratives were provided and reviewed for adverse events (AEs) of interest, serious adverse events (SAEs), and deaths. Treatment-emergent adverse events (TEAEs) of interest were thromboembolic events.

No major issues were identified with the respect to recoding, coding, and categorizing AEs. The analysis dataset for adverse events data file was reviewed for accuracy of translation of the verbatim to preferred term by manual review.

7.5. Adequacy of the Clinical Safety Database

The Applicant reported that a total of 185 unique patients with HAwI and HBwI and HA have been exposed to concizumab, corresponding to a total of 228.6 patient-years exposed (PYE) in the overall concizumab clinical development program. Across the concizumab clinical development program, 148 (80%) patients of the pooled population were exposed to concizumab for at least 6 months, corresponding to the duration of the main part in Study 4311 and Study 4310.

In Study 4311, the median duration of the main treatment period was 31.1 weeks (range 3.9, 72.9 weeks) in arm 1 (No PPX) compared to a longer duration of therapy of 45.0 weeks (range 10.0, 58.3 weeks) in arm 2 (concizumab PPX). The proportion of patients who completed between 32 and 52 weeks of therapy was 6/19 (32%) patients in arm 1 and 22/33 (66.7%) patients in arm 2. Median duration based on the main treatment and extension period for arms 2 to 4 was 40.7 weeks (range 32.1, 68.2 weeks).

Overall, the duration of therapy was adequate to evaluate the safety of concizumab compared to no PPX. The reviewer table [below](#) summarizes the duration of exposure in the safety population in Study 4311.

In Study 4310 only patients on previous on-demand therapy were enrolled. The median duration of treatment in study 4310 was 39.3 weeks (range 23.3, 48.1 weeks) in the concizumab arm and 23.9 weeks (range 10, 24.7 weeks) in the eptacog alfa arm before the data cut-off for the main part of the study. The median duration of therapy in the 24 week main treatment period and extension portions of the study was 30.3 weeks (21.3, 46.1 weeks) in the concizumab arm and 2.4 weeks (range 1.0, 5.0 weeks) in the eptacog alfa arm in the main portion of the study. After 24 weeks patients in the eptacog alfa arm crossed over to concizumab treatment. There were 16 out of 17 patients in the concizumab arm in Study 4310 who were treated with concizumab for at least 24 weeks. No patients randomized to the eptacog alfa arm received eptacog alfa beyond 24 weeks.

Table 32. Duration of Exposure, Safety Population, Study 4311

Parameter	No PPX Concizumab PPX		Concizumab PPX				
	Arm 1 Main N=19 n (%)	Arm 2 Main N=33 n (%)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Duration of treatment, weeks							
Mean (SD)	32.9 (19.9)	40.2 (12.9)	37.5 (21.5)	50.2 (20.1)	60.5 (28.7)	40.4 (18.7)	46.9 (22.4)
Median (Q1, Q3)	31.1 (20.1, 42.1)	45 (32.1, 49.1)	49.4 (13.3, 56)	55.3 (32.1, 65.6)	70.4 (21.3, 80.4)	33.1 (32.1, 43)	40.7 (32.1, 68.2)
Min, Max	3.9, 72.9	10, 58.3	3, 56.6	10, 81.9	10.4, 89.3	4.1, 87.6	4.1, 89.3
Total exposure (person years)	12	25	9	32	24	46	102
Patients treated, by duration, n (%)							
<12 weeks	3 (15.8)	1 (3.0)	2 (15.4)	1 (3.0)	2 (9.5)	3 (5.0)	6 (5.3)
≥12 to <24 weeks	3 (15.8)	4 (12.1)	2 (15.4)	4 (12.1)	4 (19.0)	3 (5.0)	11 (9.6)
≥24 to <32 weeks	4 (21.1)	2 (6.1)	0	2 (6.1)	0	1 (1.7)	3 (2.6)
≥32 to <52 weeks	6 (31.6)	22 (66.7)	3 (23.1)	7 (21.2)	0	42 (70.0)	49 (43.0)
≥52 to <100 weeks	3 (15.8)	4 (12.1)	6 (46.2)	19 (57.6)	15 (71.4)	11 (18.3)	45 (39.5)
≥100 weeks	0	0	0	0	0	0	0

Source: adex.xpt and adsl.xpt; Software: R

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (Arm 3 Overall), and 33.1 weeks (Arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Trial 4310. Arm 4 consists of patients previously treated on PPX or on demand.

The On-treatment analysis dataset was used for this analysis.

Abbreviations: N, number of subjects in treatment arm; n, number of subjects with given treatment duration; PPX, prophylaxis; Q1, first quartile; Q3, third quartile; SD, standard deviation

Reviewer Comment: The duration of concizumab therapy in Study 4311 and Study 4310 appears to be adequate to evaluate the safety and efficacy of concizumab for the prophylaxis of bleeding in patients with HAwI and HBwI.

7.6. Safety Results

7.6.1. Safety Results, Study 4311

7.6.1.1. Overview of Treatment-Emergent Adverse Events Summary, Study 4311

In Study 4311, more patients in the concizumab PPX arm 2 experienced TEAEs compared to the no PPX arm 1, 60.6% versus 42.1%, respectively. AEs in either treatment arm were primarily reported as mild severity. A similar proportion of patients in arms 1 and 2 reported SAEs in the main part of the study, although more patients reported adverse events (AEs) leading to study drug dose modification in arm 2 compared to arm 1, 15.2% versus 0%, respectively. AEs leading to treatment dose modification in arm 2 were headache, dizziness, melena, each reported in one patient and COVID-19 infection reported two patients. The reviewer's table below shows an overview of adverse events in Study 4311.

Table 33. Overview of Adverse Events, Safety Population, Study 4311

Event Category	Concizumab PPX			Concizumab PPX				
	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
SAE	3 (15.8)	5 (15.2)	-0.6 (-21.1, 19.8)	0	6 (18.2)	1 (4.8)	7 (11.7)	14 (12.3)
SAEs with fatal outcome	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	2 (6.1)	0	0	2 (1.8)
Life-threatening SAEs	1 (5.3)	2 (6.1)	0.8 (-12.1, 13.7)	0	3 (9.1)	0	0	3 (2.6)
AE leading to permanent discontinuation of study drug	0	1 (3.0)	3.0 (-2.8, 8.9)	0	2 (6.1)	1 (4.8)	1 (1.7)	4 (3.5)
AE leading to dose modification of study drug	0	5 (15.2)	15.2 (2.9, 27.4) *	0	5 (15.2)	0	4 (6.7)	9 (7.9)
AE leading to interruption of study drug	0	4 (12.1)	12.1 (1.0, 23.3) *	0	4 (12.1)	0	4 (6.7)	8 (7.0)
AE leading to reduction of study drug	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
AE leading to dose delay of study drug	0	0	0 (0, 0)	0	0	0	0	0
Other	1 (5.3)	2 (6.1)	0.8 (-12.1, 13.7)	0	3 (9.1)	0	0	3 (2.6)
Any AE	8 (42.1)	20 (60.6)	18.5 (-9.3, 46.3)	5 (38.5)	20 (60.6)	16 (76.2)	39 (65.0)	75 (65.8)
Severe and worse	3 (15.8)	5 (15.2)	-0.6 (-21.1, 19.8)	0	6 (18.2)	1 (4.8)	6 (10.0)	13 (11.4)
Moderate	0	5 (15.2)	15.2 (2.9, 27.4) *	1 (7.7)	4 (12.1)	5 (23.8)	10 (16.7)	19 (16.7)
Mild	5 (26.3)	10 (30.3)	4.0 (-21.3, 29.2)	4 (30.8)	10 (30.3)	10 (47.6)	23 (38.3)	43 (37.7)

Source: adae.xpt; Software: R

Other represents patients who had AEs considered to be possible bleeding in which the reported outcome was 'dose increased'. However, based on available dosing information, no increases in dose appears to have occurred due to AEs.

Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Severity as assessed by the investigator.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Trial 4310. Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with at least one event; PPX, prophylaxis; SAE, serious adverse event

7.6.1.2. Deaths, Study 4311

Deaths were reported infrequently in Study 4311. The reviewer's table [below](#) summarizes the reported deaths in Study 4311 and causes of death. There was one death reported in arm 1 of the study and 2 deaths reported in arm 2 of the study while on study treatment at the time of the primary data cut-off ([Table 34](#)). An additional two deaths were reported in patients during the treatment pause and are described below. Two additional deaths occurred in the 120-safety update and are described below.

Table 34. Listing of All Individual Patient Deaths, Safety Population, Study 4311

Study Arm	Patient ID	Age	Sex	Dosage	Dosing Duration (Days)	Study Day of Death	Cause of Death	
							Preferred Term	Verbatim Term
Concizumab PPX Arm 2 Overall	(b) (6)	34	M	Maintenance dose up to 0.25 mg/kg	144	560	Humerus fracture	Humerus fracture
							Femur fracture	Femur fracture
							Road traffic accident	Road traffic accident
Concizumab PPX Arm 2 Overall		41	M	Maintenance dose up to 0.25 mg/kg	383	574	COVID-19	Covid-19 infection
No PPX Arm 1 Main		67	M	NA	75	75	Pneumonitis	Pneumonitis

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX Arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310.

Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; ID, identifier; M, male; NA, not applicable; PPX, prophylaxis

Clinical Reviewer Comment: The case of death related to COVID-19 does not appear to be related to concizumab therapy. One patient died due to multiple fractures from a motor vehicle accident (MVA). While the details are limited in this case narrative, it is possible the patient died to bleeding related complications. As a recent concizumab level was not reported, it is not clear if the patient had a subtherapeutic level at the time of the event, increasing the risk of fatal bleeding. .

Fatal Cases Reported in the 120-Safety Update Period

- Patient ID (b) (6). This patient was a male age 44 years, with HBwI. The patient was treated in arm 2 of the study (concizumab PPX) for 375 days. The patient had an alcohol related

coma with respiratory arrest. Three days later the patient died due to hypoxic cardiorespiratory arrest.

- Patient ID (b) (6). This patient was a male age 13 years with HBwI. In the 24 weeks prior to study enrollment, 3 bleeding episodes and 5 spontaneous bleeding episodes (<9 bleeding episodes) were reported. The patient was randomized to treatment arm 2. Concizumab doses were administered at the site at visit 2a and 9a. The patient was treated in arm 2 with concizumab. He had his individual maintenance dose set at visit 6a, in which the dose of concizumab was increased to 0.25 mg/kg due to a subtherapeutic level. All other injections were to be administered at home by the patient or caregiver. On study day 345, the patient developed an intense headache and repeated vomiting and was instructed by the investigator to go to the nearest emergency room (ER). The following day, the mother took the patient to the ER. A CT scan was performed and showed an intracranial hemorrhage that required surgical intervention with hematoma drainage. Surgery was performed the same day. Six days following the surgery, the patient died after presenting tachycardia with hypotension and subsequently cardio-respiratory arrest (death diagnosis: brain death). According to the Applicant, the patient's mother confirmed that the bleeding event was spontaneous and there was no recent history of trauma. There was no family or personal history of intracerebral hemorrhage or aneurysms.

The Applicant reported that the patient had no bleeding events prior to the fatal bleeding event while on study. The Applicant reported that, "missing doses for more than 4 consecutive days were identified for this subject in the following periods: 30 Sep 2021–5 Oct 2021 (6 missing doses); 28 Oct 2021–26 Dec 2022 (59 missing doses); 4 Jan 2022–26 Jan 2022 (6 doses); 16 Feb 2022–13 Mar 2022 (28 missing doses); 2 Mar 2022–07 Apr 2022 (missing 15 doses)." In addition, "According to the medical note, it was confirmed that doses were taken but not documented in the eDiary by the study subject." The Applicant reported that the patient's concizumab levels during the last 6 months prior to the fatal event (onset date (b) (6)) peaked at 1130 ng/mL in end (b) (6) (visit 9a) and declined to 223 ng/mL end (b) (6) (visit 10a), to 212 ng/mL (b) (6) (visit 11a) and to 28.1 ng/mL mid- (b) (6) (visit 12a). There was inverse relationship between concizumab exposure and free TFPI levels over time according to the Applicant after concizumab was administered on site. No neutralizing antibody was reported.

Clinical Reviewer Comment: The fatal case of patient (b) (6) is concerning because it appears the patient was likely non-compliant with concizumab PPX, which may have caused, or at least contributed, to the fatal event. This clinical reviewer recommends that the Applicant submit a Medication Guide to address the need for good patient education about compliance with treatment.

7.6.1.3. Serious Treatment-Emergent Adverse Events, Study 4311

Overall, in the randomized treatment part of Study 4311, few SAEs were reported in either treatment arm (approximately 15% patients arm 1 and 2, respectively). No SAE was reported in ≥2 patients as shown in the table [below](#).

The only TEAE that occurred in more than one patient exposed to concizumab at any timepoint during the study (main and extension parts) was COVID-19, which occurred in 2 patients (1.8%) in arms 2 to 4.

Table 35. Patients With Serious Adverse Events by System Organ Class and Preferred Term, Safety Population, Study 4311

System Organ Class Preferred Term	Concizumab PPX			Concizumab PPX				
	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Any SAE	3 (15.8)	5 (15.2)	-0.6 (-21.1, 19.8)	0	6 (18.2)	1 (4.8)	7 (11.7)	14 (12.3)
Gastrointestinal disorders (SOC)	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Hematemesis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Melena	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Immune system disorders (SOC)	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Hypersensitivity	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Infections and infestations (SOC)	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	2 (6.1)	0	2 (3.3)	4 (3.5)
Encephalitis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Catheter site infection	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
COVID-19	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Injury, poisoning and procedural complications (SOC)	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Femur fracture	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Humerus fracture	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Ligament sprain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Road traffic accident	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	0	0	1 (0.9)
Lower limb fracture	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Investigations (SOC)	0	0	0 (0, 0)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Fibrin D dimer increased	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Hemoglobin decreased	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Prothrombin fragment 1.2 increased	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Musculoskeletal and connective tissue disorders (SOC)	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Hemarthrosis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Muscle hemorrhage	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Nervous system disorders (SOC)	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Dizziness	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Renal and urinary disorders (SOC)	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Renal infarct	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders (SOC)	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Pneumonitis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0

System Organ Class Preferred Term	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Concizumab PPX Arm 2 Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Concizumab PPX				
				Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Vascular disorders (SOC)	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Hematoma	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX Arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310. Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis; SAE, serious adverse event; SOC, system organ class

The table below shows the SAEs by narrow FDA Medical Query (FMQ). No SAE was reported in ≥ 2 patients in the main treatment period as shown in the table [below](#).

TEAEs which occurred in more than one patient exposed to concizumab at any timepoint (main and extension portions) included viral infection (N=2, 1.8%) and hemorrhage (N=3, 2.6%) in arms 2 to 4.

Table 36. Patients With Serious Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 4311

System Organ Class FMQ (Narrow)	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Concizumab PPX Arm 2 Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Concizumab PPX				
				Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Blood and lymphatic system disorders (SOC)								
Anemia	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Gastrointestinal disorders (SOC)								
Vomiting	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
General disorders and administration site conditions (SOC)								
Dizziness	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Immune system disorders (SOC)								
Hypersensitivity	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Infections and infestations (SOC)								
Bacterial Infection	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Viral Infection	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Musculoskeletal and connective tissue disorders (SOC)								
Fracture	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	0	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders (SOC)								
Pneumonitis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0

System Organ Class FMQ (Narrow)	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Concizumab PPX Arm 2 Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Concizumab PPX				
				Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Vascular disorders (SOC)								
Thrombosis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Thrombosis Arterial	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Hemorrhage	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	0	2 (3.3)	3 (2.6)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX Arm 1 Main), 45 weeks (Concizumab PPX Arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (Arm 2 Overall), 70.4 weeks (Arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

Some preferred terms are not included in any FDA medical query. Those preferred terms are not shown or counted in this table.

For specific preferred terms under each FMQ, see the table "Serious Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310. Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis; SOC, system organ class

Clinical Reviewer Comment: SAEs occurred infrequently in Study 4311, the most common serious adverse reaction in the entire study was viral infection, which occurred in 2 patients. Hemorrhage was not considered related to concizumab, as it is likely due to the underlying disease. Thrombotic events are discussed in Section 7.7.1. Of note, one patient in arm 2 of the clinical study experienced a serious hypersensitivity reaction 12 hours after exposure to concizumab. Symptoms included generalized erythema and pruritus with skin rash, persistent dry cough, and abdominal pain, leading to hospitalization. Concizumab was temporarily discontinued and symptoms improved with antihistamines and steroids. As this event was likely related to study drug, if approved, the product label should include a warning for hypersensitivity reactions.

7.6.1.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study 4311

Adverse events (AEs) leading to treatment discontinuation were uncommon in Study 4311. In arm 2 there was 1 patient who had an adverse event (AE) leading to treatment discontinuation (i.e., renal infarct (reported as arterial thrombosis by narrow FDA medical query) during the randomized treatment portion of the study as shown in the table [below](#).

In total, 4 patients (3.5%) discontinued concizumab due to a TEAE during the entire study (main and extension portion).

Table 37. Patients With Adverse Events Leading to Treatment Discontinuation by System Organ Class and Preferred Term, Safety Population, Study 4311

System Organ Class Preferred Term	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Concizumab PPX Arm 2 Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Concizumab PPX				
				Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Any AE leading to Discontinuation	0	1 (3.0)	3.0 (-2.8, 8.9)	0	2 (6.1)	1 (4.8)	1 (1.7)	4 (3.5)
Cardiac disorders (SOC)	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Congestive cardiomyopathy	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Immune system disorders (SOC)	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Hypersensitivity	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Infections and infestations (SOC)	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
COVID-19	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Renal and urinary disorders (SOC)	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Renal infarct	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX Arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310. Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis; SOC, system organ class

Clinical Reviewer Comment: Drug discontinuation rates were low, supporting the tolerability of concizumab. Thrombotic events, including the case of renal infarct are discussed in Section [7.7.1](#).

One patient discontinued due to a TEAE of congestive cardiomyopathy on study Day 4. Of note, the patient had pre-existing congestive cardiomyopathy, which worsened during the study. Due to the AE, the patient prematurely discontinued treatment on study Day 24 and later recovered. This case is confounded by pre-existing heart failure; therefore, attribution is difficult.

One patient discontinued due to a hypersensitivity reaction. On study Day 14 (1 day after SC administration of concizumab in the abdomen), the patient had a non-serious event of injection site rash with burning and itching. Concizumab was temporarily discontinued for 7 days. After restarting concizumab the patient experienced a headache and fatigue which was treated with antihistamines. Following this, concizumab was permanently discontinued. Given the event was due to concizumab, along with another patient experiencing a serious hypersensitivity reaction following concizumab treatment (see Section [7.6.1.3](#) for further details), if approved, hypersensitivity reactions should be included as a warning in the product label.

7.6.1.5. Treatment-Emergent Adverse Events, Study 4311

TEAEs were reported in 60% of patients in arm 2 compared to 42% patients in arm 1 in the randomized treatment portion of Study 4311. With the exception of 2 patients in arm 2 reporting arthralgia, no AE was reported in ≥ 2 patients in either treatment arm in the randomized treatment portion of Study 4311 as shown in the table [below](#).

Overall, in arms 2-4, 75 patients (65.8%) experienced a TEAE after exposure to concizumab. The most common TEAEs which occurred at any timepoint in the study (main and extension parts) were arthralgia (11.4%), injection site erythema (7.9%), upper respiratory tract infection (7%), prothrombin fragment 1.2 increased (6.1%), fibrin d-dimer increased (5.3%), headache (5.3%), COVID-19 (5.3%), nasopharyngitis (5.3%), and pyrexia (5.3%).

Table 38. Patients With Adverse Events, Safety Population, Study 4311

Preferred Term	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Concizumab PPX Arm 2 Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Concizumab PPX				
				Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Any AE	8 (42.1)	20 (60.6)	18.5 (-9.3, 46.3)	5 (38.5)	20 (60.6)	16 (76.2)	39 (65.0)	75 (65.8)
Arthralgia	0	2 (6.1)	6.1 (-2.1, 14.2)	0	2 (6.1)	4 (19.0)	7 (11.7)	13 (11.4)
Anxiety	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Bronchitis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Diarrhea	0	1 (3.0)	3.0 (-2.8, 8.9)	0	2 (6.1)	1 (4.8)	0	3 (2.6)
Encephalitis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Epilepsy	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Face oedema	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Facial pain	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Femur fracture	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Fibrin D dimer increased	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	5 (8.3)	6 (5.3)
Gastroenteritis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	2 (9.5)	0	3 (2.6)
Hematemesis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Headache	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	4 (6.7)	6 (5.3)
Humerus fracture	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Hypersensitivity	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	2 (3.3)	3 (2.6)
Hypertension	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	2 (3.3)	4 (3.5)
Injection site bruising	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	2 (3.3)	4 (3.5)
Injection site erythema	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	7 (11.7)	9 (7.9)
Injection site hematoma	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	1 (1.7)	3 (2.6)
Injection site hemorrhage	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	2 (3.3)	3 (2.6)
Injection site reaction	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Injection site urticaria	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	2 (3.3)	3 (2.6)
Joint injury	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Melaena	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Musculoskeletal stiffness	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Nasal septum deviation	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	0	2 (1.8)
Overdose	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	2 (3.3)	3 (2.6)
Patella fracture	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Prothrombin fragment 1.2 increased	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	5 (8.3)	7 (6.1)
Renal colic	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)

Preferred Term	Concizumab PPX			Concizumab PPX				
	No PPX	Concizumab PPX	Main vs. No PPX					
	Arm 1	Arm 2	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4
	Main N=19 n (%)	Main N=33 n (%)	Main Risk Difference (%) (95% CI)	Extension N=13 n (%)	Overall N=33 n (%)	Overall N=21 n (%)	Overall N=60 n (%)	Overall N=114 n (%)
Renal infarct	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Rhinitis allergic	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Rib fracture	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
SARS-CoV-2 test positive	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Seizure	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Sinusitis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Urticaria	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	1 (1.7)	2 (1.8)
Vitreous floaters	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Abdominal pain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Alanine aminotransferase increased	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Alopecia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Angina pectoris	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Animal bite	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Arthropathy	0	0	0 (0, 0)	1 (7.7)	0	0	0	0
Asthenia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Aura	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Blood creatinine increased	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Blood fibrinogen decreased	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Bone pain	0	0	0 (0, 0)	1 (7.7)	0	0	0	0
C-reactive protein increased	0	0	0 (0, 0)	1 (7.7)	0	0	1 (1.7)	1 (0.9)
Catheter site infection	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Congestive cardiomyopathy	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Contusion	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Cough	0	0	0 (0, 0)	1 (7.7)	0	1 (4.8)	1 (1.7)	2 (1.8)
Deafness	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Dermatitis contact	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Disturbance in attention	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Dizziness	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Dry skin	0	0	0 (0, 0)	0	0	2 (9.5)	1 (1.7)	3 (2.6)
Dyspepsia	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Dysphagia	0	0	0 (0, 0)	0	0	2 (9.5)	0	2 (1.8)
Dysuria	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)

Preferred Term	Concizumab PPX			Concizumab PPX				
	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Ear pain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Ecchymosis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Eczema	0	0	0 (0, 0)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Erythromelalgia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Fall	0	0	0 (0, 0)	0	0	0	3 (5.0)	3 (2.6)
Fatigue	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Fibrinolysis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Gastric polyps	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Gastritis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Gastroesophageal reflux disease	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
General physical health deterioration	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Gilbert's syndrome	0	0	0 (0, 0)	1 (7.7)	0	0	1 (1.7)	1 (0.9)
Glomerular filtration rate decreased	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Hemarthrosis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Hematoma infection	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Hemoglobin decreased	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Hepatic steatosis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Hypercholesterolemia	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Hyperuricemia	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Hypoesthesia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Injection site hypoesthesia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Injection site induration	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Injection site pain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Injection site pruritus	0	0	0 (0, 0)	1 (7.7)	0	0	2 (3.3)	2 (1.8)
Injection site rash	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Injection site swelling	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Intraocular pressure increased	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Iron deficiency	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Joint range of motion decreased	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Joint swelling	0	0	0 (0, 0)	0	0	0	3 (5.0)	3 (2.6)
Ligament sprain	0	0	0 (0, 0)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Limb injury	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)

Preferred Term	Concizumab PPX			Concizumab PPX				
	No PPX	Concizumab PPX	Main vs. No PPX	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4
	Arm 1	Arm 2	Arm 1	Extension	Overall	Overall	Overall	Overall
	Main N=19 n (%)	Main N=33 n (%)	Main Risk Difference (%) (95% CI)	N=13 n (%)	N=33 n (%)	N=21 n (%)	N=60 n (%)	N=114 n (%)
Lip swelling	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Lipoprotein increased	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Liver function test decreased	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Localized infection	0	0	0 (0, 0)	1 (7.7)	0	0	1 (1.7)	1 (0.9)
Migraine	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Migraine with aura	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Muscle atrophy	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Muscle contracture	0	0	0 (0, 0)	1 (7.7)	0	0	0	0
Muscle hemorrhage	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Musculoskeletal chest pain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Myalgia	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Nasal congestion	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Nasal obstruction	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Nausea	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Neck pain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Oedema peripheral	0	0	0 (0, 0)	1 (7.7)	0	1 (4.8)	0	1 (0.9)
Oral herpes	0	0	0 (0, 0)	1 (7.7)	0	0	0	0
Oral mucosal blistering	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Oropharyngeal pain	0	0	0 (0, 0)	1 (7.7)	0	1 (4.8)	0	1 (0.9)
Orthostatic hypotension	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Osteoarthritis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Osteoporosis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Pain	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Pain in extremity	0	0	0 (0, 0)	0	0	0	4 (6.7)	4 (3.5)
Palpitations	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Periarthritis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Periodontitis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Peripheral swelling	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Pharyngitis	0	0	0 (0, 0)	0	0	1 (4.8)	2 (3.3)	3 (2.6)
Phimosis	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Pulpitis dental	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Radiculopathy	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)

Preferred Term	Concizumab PPX			Concizumab PPX				
	No PPX	Concizumab PPX	Main vs. No PPX	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4
	Arm 1	Arm 2	Arm 1	Extension	Overall	Overall	Overall	Overall
	Main N=19 n (%)	Main N=33 n (%)	Risk Difference (%) (95% CI)	N=13 n (%)	N=33 n (%)	N=21 n (%)	N=60 n (%)	N=114 n (%)
Rash	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Respiratory disorder	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Scoliosis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Scrotal ulcer	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Shunt thrombosis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Skin papilloma	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Sleep disorder	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Spinal osteoarthritis	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Synovial cyst	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Synovitis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Tendon calcification	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Tendonitis	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Tonsillitis	0	0	0 (0, 0)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Toothache	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Underdose	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Urinary tract infection	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Vaccination complication	0	0	0 (0, 0)	0	0	1 (4.8)	3 (5.0)	4 (3.5)
Vaccination site pain	0	0	0 (0, 0)	0	0	2 (9.5)	0	2 (1.8)
Viral upper respiratory tract infection	0	0	0 (0, 0)	2 (15.4)	0	0	0	0
Visual field defect	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Vitamin D deficiency	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Vomiting	0	0	0 (0, 0)	0	0	1 (4.8)	2 (3.3)	3 (2.6)
Weight decreased	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
COVID-19	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	2 (6.1)	3 (14.3)	1 (1.7)	6 (5.3)
Nasopharyngitis	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	3 (14.3)	2 (3.3)	6 (5.3)
Pyrexia	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	2 (6.1)	2 (9.5)	2 (3.3)	6 (5.3)
Road traffic accident	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	0	0	1 (0.9)
Upper respiratory tract infection	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	2 (6.1)	4 (19.0)	2 (3.3)	8 (7.0)
Acrodermatitis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Arthritis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	2 (9.5)	0	2 (1.8)
Back pain	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Blood alkaline phosphatase increased	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0

Preferred Term	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Concizumab PPX Arm 2 Main vs. No PPX Main Risk Difference (%) (95% CI)	Concizumab PPX				
				Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Blood pressure increased	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Conjunctival hyperemia	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Constipation	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Erythema	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Fibroma	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Hematoma	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Hematuria	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Lower limb fracture	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Pneumonitis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Pruritus	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	1 (1.7)	1 (0.9)
Respiratory tract infection viral	1 (5.3)	0	-5.3 (-15.3, 4.8)	1 (7.7)	0	0	0	0
Rhinitis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	2 (9.5)	0	2 (1.8)
Skin abrasion	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Subcutaneous abscess	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Thermal burn	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Tibia fracture	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0

Source: adae.xpt; Software: R

One patient was reported to have a seizure in arm 2 of the study. The patient is a male age 16 with a history of epilepsy who had a seizure event. The event is not considered related to concizumab therapy. Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (Arm 1 Extension), 55.3 weeks (Arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Coded as Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310. Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; CI, confidence interval; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis

The table [below](#) shows the AEs by System Organ Class (SOC) and narrow FMQ. AEs by narrow FMQ reported in at least three patients in the randomized portion of Study 4311 are local administration reaction (arm 2 n = 6 (18%) patients compared to arm 1 n = 0 (0%) patients), nasopharyngitis (arm 2 n = 3 (9%) patients compared to arm 1 n = 3 (16%) patients) and hemorrhage (arm 2 n = 4 (12%) patients compared to arm 1 n = 2 (11%) patients).

The most common TEAEs (by narrow FMQ) at any timepoint after exposure to concizumab in arms 2-4, were local administration reaction (23.7%), nasopharyngitis (14.9%), hemorrhage (13.2%), viral infection (7%), erythema (7.9%), pyrexia (5.3%), arthritis (5.3%), headache (5.3%), and rash (5.3%).

Table 39. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow), Safety Population, Study 4311

System Organ Class FMQ (Narrow)	Concizumab PPX			Concizumab PPX				
	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Blood and lymphatic system disorders (SOC)								
Anemia	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Cardiac disorders (SOC)								
Heart failure	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Myocardial ischemia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Palpitations	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Systemic hypertension	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	1 (4.8)	2 (3.3)	4 (3.5)
Gastrointestinal disorders (SOC)								
Diarrhea	0	1 (3.0)	3.0 (-2.8, 8.9)	0	2 (6.1)	1 (4.8)	0	3 (2.6)
Vomiting	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	2 (3.3)	4 (3.5)
Abdominal pain	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Dyspepsia	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Nausea	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Constipation	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
General disorders and administration site conditions (SOC)								
Local administration reaction	0	6 (18.2)	18.2 (5.0, 31.3) *	1 (7.7)	6 (18.2)	4 (19.0)	17 (28.3)	27 (23.7)
Dizziness	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Fall	0	0	0 (0, 0)	0	0	0	3 (5.0)	3 (2.6)
Fatigue	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Peripheral edema	0	0	0 (0, 0)	1 (7.7)	0	1 (4.8)	2 (3.3)	3 (2.6)
Pyrexia	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	2 (6.1)	2 (9.5)	2 (3.3)	6 (5.3)
Hepatobiliary disorders (SOC)								
Hepatic injury	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Immune system disorders (SOC)								
Hypersensitivity	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	2 (3.3)	3 (2.6)
Infections and infestations (SOC)								
Viral infection	2 (10.5)	2 (6.1)	-4.5 (-20.5, 11.6)	3 (23.1)	3 (9.1)	3 (14.3)	2 (3.3)	8 (7.0)
Bacterial infection	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	1 (3.0)	1 (4.8)	1 (1.7)	3 (2.6)
Purulent material	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Nasopharyngitis	3 (15.8)	3 (9.1)	-6.7 (-25.8, 12.4)	0	4 (12.1)	7 (33.3)	6 (10.0)	17 (14.9)

System Organ Class FMQ (Narrow)	Concizumab PPX Arm 2			Concizumab PPX				
	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Metabolism and nutrition disorders (SOC)								
Lipid disorder	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Musculoskeletal and connective tissue disorders (SOC)								
Arthralgia	0	2 (6.1)	6.1 (-2.1, 14.2)	0	2 (6.1)	4 (19.0)	7 (11.7)	13 (11.4)
Myalgia	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Osteoporosis	0	0	0 (0, 0)	0	0	1 (4.8)	0	1 (0.9)
Tendinopathy	0	0	0 (0, 0)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Fracture	2 (10.5)	2 (6.1)	-4.5 (-20.5, 11.6)	0	2 (6.1)	0	0	2 (1.8)
Arthritis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	1 (3.0)	4 (19.0)	1 (1.7)	6 (5.3)
Back pain	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	1 (4.8)	1 (1.7)	2 (1.8)
Nervous system disorders (SOC)								
Seizure	0	2 (6.1)	6.1 (-2.1, 14.2)	0	2 (6.1)	0	0	2 (1.8)
Headache	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	4 (6.7)	6 (5.3)
Paresthesia	0	0	0 (0, 0)	0	0	0	2 (3.3)	2 (1.8)
Psychiatric disorders (SOC)								
Anxiety	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Renal and urinary disorders (SOC)								
Renal & urinary tract infection	0	0	0 (0, 0)	0	1 (3.0)	0	0	1 (0.9)
Respiratory, thoracic and mediastinal disorders (SOC)								
Cough	0	0	0 (0, 0)	1 (7.7)	0	1 (4.8)	1 (1.7)	2 (1.8)
Pneumonitis	1 (5.3)	0	-5.3 (-15.3, 4.8)	0	0	0	0	0
Skin and subcutaneous tissue disorders (SOC)								
Urticaria	0	2 (6.1)	6.1 (-2.1, 14.2)	0	2 (6.1)	0	2 (3.3)	4 (3.5)
Rash	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	5 (8.3)	6 (5.3)
Alopecia	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)
Erythema	1 (5.3)	1 (3.0)	-2.2 (-13.9, 9.4)	0	1 (3.0)	1 (4.8)	7 (11.7)	9 (7.9)
Pruritus	1 (5.3)	0	-5.3 (-15.3, 4.8)	1 (7.7)	0	0	2 (3.3)	2 (1.8)

System Organ Class FMQ (Narrow)	Concizumab PPX Arm 2			Concizumab PPX				
	No PPX Arm 1 Main N=19 n (%)	Concizumab PPX Arm 2 Main N=33 n (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n (%)	Arm 2 Overall N=33 n (%)	Arm 3 Overall N=21 n (%)	Arm 4 Overall N=60 n (%)	Arms 2-4 Overall N=114 n (%)
Vascular disorders (SOC)								
Thrombosis	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	1 (4.8)	0	2 (1.8)
Thrombosis arterial	0	1 (3.0)	3.0 (-2.8, 8.9)	0	1 (3.0)	0	0	1 (0.9)
Hemorrhage	2 (10.5)	4 (12.1)	1.6 (-16.1, 19.3)	0	4 (12.1)	3 (14.3)	8 (13.3)	15 (13.2)
Hypotension	0	0	0 (0, 0)	0	0	0	1 (1.7)	1 (0.9)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as AEs that occurred in the On-treatment observation period.

The On-treatment observation period was used for assessment of AEs and is defined as the time period where subjects are considered to be affected by on demand treatment or concizumab treatment. Thus, for concizumab treated patients, On-treatment includes data before the treatment pause (including 7 weeks follow-up from the last dose of concizumab) as well as after concizumab treatment restart.

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (Arm 1 Extension), 55.3 weeks (Arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310. Arm 4 consists of patients previously treated on PPX or on demand.

Abbreviations: AE, adverse event; CI, confidence interval; FMQ, FDA medical query; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis; SOC, system organ class

Clinical Reviewer Comment: The most common TEAEs (>10%) in the main treatment period and occurred in a higher proportion of patients in the concizumab arm compared to no PPX was local administration reactions. The preferred terms encompassed under this FMQ were injection site bruising, injection site erythema, injection site hemorrhage, injection site hematoma, injection site reaction, injection site urticaria, injection site induration, injection site pain, injection site pruritis, injection site rash, injection site swelling, and injection site hypoesthesia.

The most common TEAEs (>10%) at any timepoint (main and extension parts) after exposure to concizumab were local administration reaction (23.7%), nasopharyngitis (14.9%), hemorrhage (13.2%), and arthralgia (11.4%). Hemorrhage is not considered an adverse reaction as it is most likely related to the underlying disease.

In total, 6% of patients had elevated prothrombin fragment and 5.3% had an elevated d-dimer in arms 2-4. No patients in the arm 1 (no concizumab PPX) had elevated prothrombin fragment or d-dimer. Elevated prothrombin fragment and d-dimer are associated with an increased risk of thrombosis therefore, if approved, the product label should include a warning for elevated prothrombin fragment and elevated d-dimer.

7.6.1.6. Laboratory Findings, Study 4311

There were no significant clinical laboratory changes in serum albumin (Alb), creatinine (Cr), alkaline phosphatase (AlkP), total bilirubin (Tbili), estimated glomerular filtration rate (eGFR, Cockcroft-Gault), reported in Study 4311. There were three patients reported with elevation in serum AST, ALT (>3x, >5x and >10x ULN, respectively). However, no patients reported elevations in serum Tbili in the randomized portion of the study. In the extension portion of the study there were 3 patients who had reported >3x ULN serum Tbili, 1 patient with >5x ULN and 1 patient with >10x ULN. However, there were no patients who reported corresponding significant changes in serum AST or ALT.

Table 40. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels, Safety Population, Study 4311

Study 4511								
Laboratory Parameter	Concizumab PPX			Concizumab PPX				
	No PPX	Concizumab PPX	Main vs. No PPX					
	Arm 1	Arm 2	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4
	Main	Main	Main	Extension	Overall	Overall	Overall	Overall
	N=19	N=33	Risk Difference	N=13	N=33	N=21	N=60	N=114
	n/N _w (%)	n/N _w (%)	(%) (95% CI)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
Albumin, low (g/dL)								
Level 1 (<3.1)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	1/60 (1.7)	1/114 (0.9)
Level 2 (<2.5)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	1/60 (1.7)	1/114 (0.9)
Level 3 (<2)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Baseline for Concizumab PPX Arm 1 Extension is the last valid value collected on or before Week 24.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Study 4310. Arm 4 consists of patients previously treated on PPX or on demand.

The On-treatment (OT) analysis dataset was used for this analysis.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; OT, On-treatment; PPX, prophylaxis

Table 41. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels, Safety Population, Study 4311

Laboratory Parameter	Concizumab PPX			Concizumab PPX				
	No PPX	Concizumab PPX	Main vs. No PPX	Arm 1 Extension N=13 n/N _w (%)	Arm 2 Overall N=33 n/N _w (%)	Arm 3 Overall N=21 n/N _w (%)	Arm 4 Overall N=60 n/N _w (%)	Arms 2-4 Overall N=114 n/N _w (%)
	Arm 1	Arm 2	Arm 1					
	Main	Main	Main					
	N=19	N=33	Risk Difference					
n/N _w (%)	n/N _w (%)	(%) (95% CI)						
Alkaline phosphatase, high (U/L)								
Level 1 (>1.5X ULN)	1/17 (5.9)	0/33 (0)	-5.9 (-17.1, 5.3)	1/13 (7.7)	0/33 (0)	0/21 (0)	1/60 (1.7)	1/114 (0.9)
Level 2 (>2X ULN)	0/17 (0)	0/33 (0)	0 (0, 0)	1/13 (7.7)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)
Level 3 (>3X ULN)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)

Laboratory Parameter	Concizumab PPX			Concizumab PPX				
	No PPX Arm 1 Main N=19 n/N _w (%)	Concizumab PPX Arm 2 Main N=33 n/N _w (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 1 Extension N=13 n/N _w (%)	Arm 2 Overall N=33 n/N _w (%)	Arm 3 Overall N=21 n/N _w (%)	Arm 4 Overall N=60 n/N _w (%)	Arms 2-4 Overall N=114 n/N _w (%)
Alanine aminotransferase, high (U/L)								
Level 1 (>3X ULN)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	0/60 (0)	1/114 (0.9)
Level 2 (>5X ULN)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	0/60 (0)	1/114 (0.9)
Level 3 (>10X ULN)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	0/60 (0)	1/114 (0.9)
Aspartate aminotransferase, high (U/L)								
Level 1 (>3X ULN)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	2/60 (3.3)	3/114 (2.6)
Level 2 (>5X ULN)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	1/60 (1.7)	2/114 (1.8)
Level 3 (>10X ULN)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	0/60 (0)	1/114 (0.9)
Bilirubin, total, high (mg/dL)								
Level 1 (>1.5X ULN)	1/17 (5.9)	0/33 (0)	-5.9 (-17.1, 5.3)	3/13 (23.1)	1/33 (3.0)	0/21 (0)	3/60 (5.0)	4/114 (3.5)
Level 2 (>2X ULN)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	1/60 (1.7)	1/114 (0.9)
Level 3 (>3X ULN)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	1/60 (1.7)	1/114 (0.9)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is at least 24 weeks (Arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (Arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Baseline for Concizumab PPX Arm 1 Extension is the last valid value collected on or before Week 24.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Trial 4310. Arm 4 consists of patients previously treated on PPX or on demand.

The On-treatment (OT) analysis dataset was used for this analysis.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; OT, On-treatment; PPX, prophylaxis

Overall, in Study 4311, there were no clinically significant risk differences among patients in arm 1 or arm 2 of the study in terms of clinical hematology laboratory parameters.

Table 42. Patients With One or More Hematology Analyte Values Exceeding Specified Levels, Safety Population, Study 4311

Laboratory Parameter	Concizumab PPX				Concizumab PPX				
	No PPX Arm 1 Main N=19 n/N _w (%)	Concizumab PPX Arm 2 Main N=33 n/N _w (%)	Main vs. No PPX Arm 1 Main Risk Difference (%) (95% CI)	Arm 2					
				Arm 1 Extension N=13 n/N _w (%)	Arm 2 Overall N=33 n/N _w (%)	Arm 3 Overall N=21 n/N _w (%)	Arm 4 Overall N=60 n/N _w (%)	Arms 2-4 Overall N=114 n/N _w (%)	
Complete Blood Count									
WBC, low (cells/uL)									
Level 1 (<3500)	0/17 (0)	5/33 (15.2)	15.2 (2.9, 27.4)	2/13 (15.4)	5/33 (15.2)	5/21 (23.8)	6/60 (10.0)	16/114 (14.0)	
Level 2 (<3000)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	2/13 (15.4)	2/33 (6.1)	1/21 (4.8)	3/60 (5.0)	6/114 (5.3)	
Level 3 (<1000)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)	
WBC, high (cells/uL)									
Level 1 (>10800)	1/17 (5.9)	5/33 (15.2)	9.3 (-7.3, 25.8)	1/13 (7.7)	5/33 (15.2)	1/21 (4.8)	4/60 (6.7)	10/114 (8.8)	
Level 2 (>13000)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	0/13 (0)	2/33 (6.1)	0/21 (0)	3/60 (5.0)	5/114 (4.4)	
Level 3 (>15000)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	1/60 (1.7)	1/114 (0.9)	
Hemoglobin, low (g/dL)									
Level 2 (>1.5 g/dL dec. from baseline)	0/17 (0)	3/33 (9.1)	9.1 (-0.7, 18.9)	0/13 (0)	3/33 (9.1)	6/21 (28.6)	5/57 (8.8)	14/111 (12.6)	
Level 3 (>2 g/dL dec. from baseline)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	0/13 (0)	3/33 (9.1)	5/21 (23.8)	0/57 (0)	8/111 (7.2)	
Hemoglobin, high (g/dL)									
Level 2 (>2 g/dL inc. from baseline)	1/17 (5.9)	8/33 (24.2)	18.4 (-0.0, 36.8)	6/13 (46.2)	8/33 (24.2)	4/21 (19.0)	6/57 (10.5)	18/111 (16.2)	
Level 3 (>3 g/dL inc. from baseline)	0/17 (0)	3/33 (9.1)	9.1 (-0.7, 18.9)	3/13 (23.1)	3/33 (9.1)	1/21 (4.8)	0/57 (0)	4/111 (3.6)	
Platelets, low (cells/uL)									
Level 1 (<140000)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	1/13 (7.7)	2/33 (6.1)	2/21 (9.5)	1/60 (1.7)	5/114 (4.4)	
Level 2 (<125000)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	1/13 (7.7)	2/33 (6.1)	2/21 (9.5)	0/60 (0)	4/114 (3.5)	
Level 3 (<100000)	0/17 (0)	1/33 (3.0)	3.0 (-2.8, 8.9)	0/13 (0)	1/33 (3.0)	0/21 (0)	0/60 (0)	1/114 (0.9)	
WBC Differential									
Lymphocytes, low (cells/uL)									
Level 1 (<1000)	0/17 (0)	4/33 (12.1)	12.1 (1.0, 23.3)	3/13 (23.1)	4/33 (12.1)	4/21 (19.0)	5/60 (8.3)	13/114 (11.4)	
Level 2 (<750)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	3/21 (14.3)	1/60 (1.7)	4/114 (3.5)	
Level 3 (<500)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)	

Laboratory Parameter	Concizumab PPX							
	Concizumab PPX Arm 2				Main vs. No PPX Arm 1			
	No PPX Arm 1	Concizumab PPX Arm 2	Main vs. No PPX Arm 1	Main vs. No PPX Arm 1				
	Main N=19	Main N=33						
	n/N _w (%)	n/N _w (%)	Risk Difference (%) (95% CI)	Arm 1 Extension N=13	Arm 2 Overall N=33	Arm 3 Overall N=21	Arm 4 Overall N=60	Arms 2-4 Overall N=114
				n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)	n/N _w (%)
Lymphocytes, high (cells/uL)								
Level 1 (>4000)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	0/13 (0)	2/33 (6.1)	1/21 (4.8)	0/60 (0)	3/114 (2.6)
Level 2 (>10000)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)
Level 3 (>20000)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)
Neutrophils, low (cells/uL)								
Level 1 (<2000)	1/17 (5.9)	11/33 (33.3)	27.5 (7.9, 47.0)	4/13 (30.8)	11/33 (33.3)	6/21 (28.6)	13/60 (21.7)	30/114 (26.3)
Level 2 (<1000)	0/17 (0)	2/33 (6.1)	6.1 (-2.1, 14.2)	0/13 (0)	2/33 (6.1)	1/21 (4.8)	1/60 (1.7)	4/114 (3.5)
Level 3 (<500)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)
Eosinophils, high (cells/uL)								
Level 1 (>650)	1/17 (5.9)	3/33 (9.1)	3.2 (-11.7, 18.1)	1/13 (7.7)	3/33 (9.1)	0/21 (0)	3/60 (5.0)	6/114 (5.3)
Level 2 (>1500)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)
Level 3 (>5000)	0/17 (0)	0/33 (0)	0 (0, 0)	0/13 (0)	0/33 (0)	0/21 (0)	0/60 (0)	0/114 (0)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is at least 24 weeks (arm 1) or 32 weeks (arms 2-4) for the main part, 128-136 weeks for the extension part, and 7 weeks for the follow-up part of the study.

Median analysis duration based on the data are 31.1 weeks (No PPX arm 1 Main), 45 weeks (Concizumab PPX arm 2 Main), 49.4 weeks (arm 1 Extension), 55.3 weeks (arm 2 Overall), 70.4 weeks (arm 3 Overall), and 33.1 weeks (arm 4 Overall).

Overall includes the main, extension, and follow-up parts of the study. Arm 1 Extension includes the extension and follow-up parts of the study.

Baseline for Concizumab PPX Arm 1 Extension is the last valid value collected on or before Week 24.

Risk difference (with 95% confidence interval) is shown between treatment and comparator. An asterisk (*) indicates the 95% confidence interval excludes zero.

Arm 1 and arm 2 consist of patients previously treated on demand. Arm 3 consists of patients transferred from Phase 2 Trial 4310. Arm 4 consists of patients previously treated on PPX or on demand.

The On-treatment (OT) analysis dataset was used for this analysis.

Abbreviations: CI, confidence interval; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; OT, On-treatment; PPX, prophylaxis

Reviewer Comment: There were three patients reported with elevation in serum AST and ALT (>3x, >5x and >10x ULN, respectively) in the extension portion of the study. Of note, none of the patients had concurrent elevation in bilirubin at the time of transaminitis. One of the three patients reported with elevated hepatic enzyme elevations had ALT>5 UNL (519 U/L) and AST >5 UNL (612 U/L) at Week 32 of concizumab therapy. The event was reported 1 day after the patient had an AE of COVID-19 (the AE of COVID-19 was fatal), therefore it is unlikely the elevated liver enzymes were related to concizumab. The remaining 2 cases appear to be potentially related to concizumab therapy as no other etiology for liver enzyme elevation was identified (no patient narratives provided).

In addition, in the extension portion of the study there were 3 patients who had reported >3x ULN serum Tbili, 1 patient with >5x ULN and 1 patient with >10x ULN. An etiology for hyperbilirubinemia was not identified (no patient narratives were provided). There were no patients who reported corresponding significant changes in serum AST or ALT.

The elevated liver enzymes and hyperbilirubinemia is concerning, although with the exception of the patient with the fatal event due to COVID-19, none of the events of liver enzyme increase of bilirubin increase led to concizumab interruption or discontinuation. Further investigation is required to assess the hepatotoxicity risk, including a request for patient narratives which describes any concurrent illness and medications.

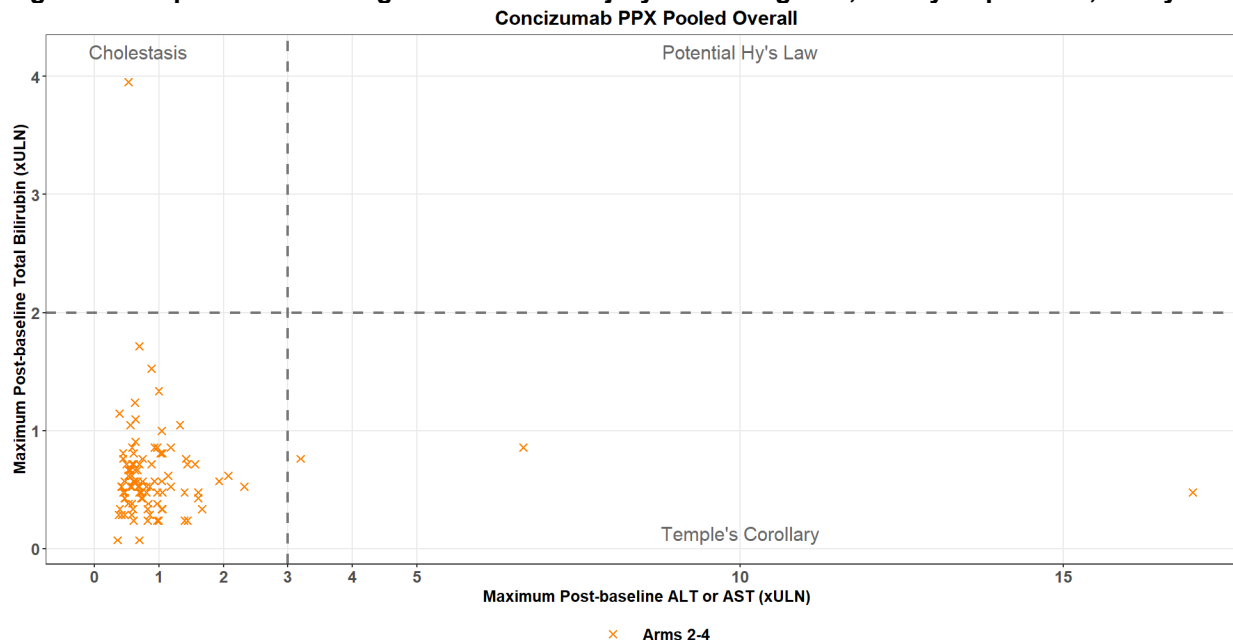
There were two patients in Study 4311 in arm 1 (ID# (b) (6)) who did not have clinical laboratory postbaseline laboratory data during the randomized portion of the study. These patients were discontinued from the study for the following reasons.

- (b) (6): withdrawal by subject. This patient withdrew consent after discussing temporary closure of study due to the reported SAE of thromboembolism.*
- (b) (6): death. This case is summarized in Section [7.6.1.2 Deaths, Study 4311](#).*

7.6.1.7. Assessment of Drug-Induced Liver Injury, Study 4311

The figure [below](#) shows a screening assessment for potential cases of serious drug-induced liver injury (DILI). No potential cases met Hy's Law criteria. One patient (as shown in [Figure 14](#)) had evidence of cholestasis (maximum Tbili (3.95xULN), without elevated liver enzymes. This patient had an elevated bilirubin at baseline.

Figure 14. Hepatocellular Drug-Induced Liver Injury Screening Plot, Safety Population, Study 4311



Source: adlb.xpt; Software: R

Each data point represents a patient plotted by their maximum ALT or AST versus their maximum total bilirubin values in the post-baseline period.

All patients with at least one post-baseline ALT or AST and bilirubin are plotted.

The On-treatment excluding initial regimen (OTeXIR) analysis dataset was used for this analysis.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PPX, prophylaxis; ULN, upper limit of normal, ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; OTeXIR, On-treatment excluding initial regimen; PPX, prophylaxis; ULN, upper limit of normal

7.6.1.8. Vital Signs' Analyses, Study 4311

No clinically significant risk differences in vital signs were reported among patients in arm 1 compared to arm 2 in Study 4311. In the randomized portion of the study after 24 weeks the median systolic/diastolic blood pressure was 119/77 mm Hg (range 102-191/62-118 mm Hg) in arm 1 and 122/80 mm Hg (range 101-150/53-103 mm Hg) in Arm 2 in the randomized portion of the study. The median systolic/diastolic change from baseline was 3/1 mm Hg (range -16-23/-9-22 mm Hg) in arm 1 and 2/1 mm Hg (range -26-33/-17-32 mm Hg) in arm 2. Overall, the median heart rate was similar in both treatment arms after 24 weeks of therapy during the randomized portion of the study, i.e., 73-76 beats/min (range 55-129 beats/min). Overall, the median change in heart rate from baseline to Week 24 was -1 beats/min (range -29-50 beats/min) in both treatment arms.

7.6.1.9. Subgroup Analyses, Study 4311

Overall, no significant differences in serious adverse events were reported between patients in treatment arms 1 and 2 based on race. However, most patients (67 of 118 (57%) enrolled in Study 4311 were white. Only 8 of 118 (7%) of patients enrolled in Study 4311 were black. There were 3 of 118 (3%) patients enrolled in Study 4311 were American Indian or Alaska Native. There were 5 of 118 (4%) of patients who did not have a race reported in Study 4311.

Clinical Reviewer Comment: No conclusions should be made based on subgroup analysis based on limited sample size.

7.6.2. Safety Results, Study 4310

7.6.2.1. Overview of Treatment-Emergent Adverse Events Summary, Study 4310

In Study 4310, there were 17 patients who were treated with concizumab PPX and 9 patients who were randomized to the no PPX arm. In total, there was 1 of 17 (6%) patients and 3 of 9 (33%) patients in the concizumab PPX and no PXX arms, respectively, who had a SAE reported. Overall, 13 of 17 (76%) patients in the concizumab PPX arm and 8 of 9 (89%) patients in the No PPX arm who had any AE reported. Most AEs were mild.

Table 43. Overview of Adverse Events by Hemophilia Subtype, Safety Population, Study 4310

Event Category	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
SAE	0	1 (12.5)	2 (28.6)	1 (50.0)	0	5 (50.0)
SAEs with fatal outcome	0	0	0	0	0	0
Life-threatening SAEs	0	0	0	0	0	1 (10.0)
AE leading to permanent discontinuation of study drug	0	0	0	0	0	0
AE leading to dose modification of study drug	1 (11.1)	0	0	0	1 (6.7)	1 (10.0)
AE leading to interruption of study drug	1 (11.1)	0	0	0	1 (6.7)	1 (10.0)
AE leading to reduction of study drug	0	0	0	0	0	0
AE leading to dose delay of study drug	0	0	0	0	0	0
Other	0	0	0	0	0	1 (10.0)
Any AE	7 (77.8)	6 (75.0)	6 (85.7)	2 (100)	13 (86.7)	9 (90.0)
Severe and worse	0	0	0	0	0	2 (20.0)
Moderate	3 (33.3)	2 (25.0)	5 (71.4)	1 (50.0)	8 (53.3)	4 (40.0)
Mild	4 (44.4)	4 (50.0)	1 (14.3)	1 (50.0)	5 (33.3)	3 (30.0)

Source: адае.хpt; Software: R

Treatment-emergent adverse events defined as Treatment-emergent adverse events defined as adverse events with onset from randomization and until the last planned visit in the study (i.e., end of the post-treatment follow-up period 8 weeks after the last dose of concizumab).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Severity as assessed by the investigator.

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: AE, adverse event; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with at least one event; PPX, prophylaxis; SAE, serious adverse event

7.6.2.2. Deaths, Study 4310

No deaths were reported in Study 4310.

7.6.2.3. Serious Treatment-Emergent Adverse Events, Study 4310

One SAE was reported among patients in the concizumab PPX arm, i.e., requirement for removal of a central venous catheter. SAEs reported in the no PPX arm included anemia, congestive cardiomyopathy and hordeolum in the randomized portion of the study, as shown in the table [below](#).

In patients exposed to concizumab at any time (randomized and extension periods), 20% of patients experienced an SAE. Of note, the same patient experienced SAEs of hemorrhagic shock (after femoral artery puncture), muscle hemorrhage (after fall), puncture site hemorrhage, and subdural hemorrhage (after fall), the patient narrative is below.

Table 44. Patients With Serious Adverse Events by System Organ Class and Preferred Term by Hemophilia Subtype, Safety Population, Study 4310

System Organ Class Preferred Term	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
Any SAE	0	1 (12.5)	2 (28.6)	1 (50.0)	0	5 (50.0)
Blood and lymphatic system disorders (SOC)	0	0	0	1 (50.0)	0	0
Anemia	0	0	0	1 (50.0)	0	0
Cardiac disorders (SOC)	0	0	1 (14.3)	0	0	0
Congestive cardiomyopathy	0	0	1 (14.3)	0	0	0
General disorders and administration site conditions (SOC)	0	0	0	0	0	1 (10.0)
Puncture site hemorrhage	0	0	0	0	0	1 (10.0)
Infections and infestations (SOC)	0	0	1 (14.3)	0	0	0
Hordeolum	0	0	1 (14.3)	0	0	0
Injury, poisoning and procedural complications (SOC)	0	0	0	0	0	1 (10.0)
Hand fracture	0	0	0	0	0	1 (10.0)
Subdural hemorrhage	0	0	0	0	0	1 (10.0)
Musculoskeletal and connective tissue disorders (SOC)	0	0	0	0	0	2 (20.0)
Arthropathy	0	0	0	0	0	1 (10.0)
Muscle hemorrhage	0	0	0	0	0	1 (10.0)
Nervous system disorders (SOC)	0	0	0	0	0	1 (10.0)
Loss of consciousness	0	0	0	0	0	1 (10.0)
Respiratory, thoracic and mediastinal disorders (SOC)	0	0	0	0	0	1 (10.0)
Sleep apnea syndrome	0	0	0	0	0	1 (10.0)

System Organ Class Preferred Term	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
Surgical and medical procedures (SOC)	0	1 (12.5)	0	0	0	1 (10.0)
Central venous catheter removal	0	1 (12.5)	0	0	0	1 (10.0)
Vascular disorders (SOC)	0	0	0	0	0	1 (10.0)
Shock hemorrhagic	0	0	0	0	0	1 (10.0)

Source: adae.xpt; Software: R

Central venous catheter removal was due to line infection. Treatment-emergent adverse events defined as Treatment-emergent adverse events defined as adverse events with onset from randomization and until the last planned visit in the study (i.e., end of the post-treatment follow-up period 8 weeks after the last dose of concizumab).

Serious adverse events defined as any untoward medical occurrence that, at any dose that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent incapacity or substantial disruption of the ability to conduct normal life functions, or is a congenital anomaly or birth defect.

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis; SOC, system organ class

Patient (b) (6) was a 34-year-old male with HBwI and baseline ABR of 45. He was receiving concizumab at 0.15 mg/kg. The patient had an accident at Week 32 resulting in bone fractures and required surgery. Concizumab was stopped and the patient developed hemorrhagic shock a week later after a femoral artery puncture. Concizumab was restarted at Week 40. The patient developed a medium ADA titer with neutralizing antibodies, and the TFPI level returned to baseline. The ADA titer further increased to very high levels starting at Week 48. Per the Applicant, the patient's "bleeding pattern" did not change. The patient also had worsening liver function which was a pre-existing condition due to alcoholic fatty liver disease. At Week 72 the patient fell and developed a muscle and subdural hemorrhage. The patient was hospitalized and treatment was discontinued due to lack of therapeutic effect due to neutralizing antibody.

Clinical Reviewer Comment: One SAE occurred during the randomized treatment period, which was central line removal. This was an elective procedure and not related to concizumab treatment.

One patient had multiple SAEs related to hemorrhage. While each AE was due to a traumatic event, the lack of therapeutic effect of concizumab due to neutralizing antibodies likely contributed. If concizumab is approved, the risk of neutralizing antibodies should be noted in the product label. See Section 14.4 for further details regarding immunogenicity.

7.6.2.4. Adverse Events and FDA Medical Queries Leading to Treatment Discontinuation, Study 4310

No adverse events (AEs) leading to treatment discontinuation were reported in Study 4310.

7.6.2.5. Treatment-Emergent Adverse Events, Study 4310

The treatment-emergent adverse events reported in Study 4310 are shown in the table [below](#). In the main treatment period, the most common TEAEs in the concizumab PPX arm were injection site hematoma (17.6%), nasopharyngitis (17.6%), headache (11.8%) and prothrombin level increased (11.8%). The most common TEAEs in the no PPX arm was contusion (22.2%).

The most common TEAEs (>10%) in patients exposed to concizumab in the main and extension periods of the study included diarrhea (16%), upper respiratory tract infection (16%), arthralgia (12%), and injection site hematoma (12%).

Table 45. Patients With Adverse Events by Hemophilia Subtype, Safety Population, Study 4310

Preferred Term	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
Any AE	7 (77.8)	6 (75.0)	6 (85.7)	2 (100)	13 (86.7)	9 (90.0)
Prothrombin level increased	2 (22.2)	0	0	0	2 (13.3)	0
Arthralgia	1 (11.1)	0	0	0	3 (20.0)	0
Carpal tunnel syndrome	1 (11.1)	0	0	0	1 (6.7)	0
Diarrhea	1 (11.1)	0	1 (14.3)	0	3 (20.0)	1 (10.0)
Fibrin D dimer increased	1 (11.1)	0	0	0	1 (6.7)	1 (10.0)
Groin pain	1 (11.1)	0	0	0	1 (6.7)	0
Hemorrhoids	1 (11.1)	0	0	0	1 (6.7)	0
Headache	1 (11.1)	1 (12.5)	0	0	1 (6.7)	1 (10.0)
Injection site erythema	1 (11.1)	0	0	0	1 (6.7)	0
Injection site hematoma	1 (11.1)	2 (25.0)	0	0	1 (6.7)	2 (20.0)
Osteoarthritis	1 (11.1)	0	0	0	1 (6.7)	0
Overdose	1 (11.1)	0	0	0	1 (6.7)	0
Pharyngitis	1 (11.1)	0	0	0	1 (6.7)	0
Post-traumatic pain	1 (11.1)	0	0	0	1 (6.7)	0
Sinusitis	1 (11.1)	0	0	0	1 (6.7)	0
Skin infection	1 (11.1)	0	0	0	1 (6.7)	0
Upper respiratory tract infection	1 (11.1)	0	1 (14.3)	0	2 (13.3)	2 (20.0)
Vitamin D deficiency	1 (11.1)	0	0	0	1 (6.7)	0
Abdominal pain	0	1 (12.5)	0	0	0	1 (10.0)
Abdominal pain lower	0	0	0	0	0	1 (10.0)
Anemia	0	0	0	1 (50.0)	1 (6.7)	1 (10.0)
Arthropathy	0	0	0	0	0	1 (10.0)
Blood loss anemia	0	0	0	0	1 (6.7)	0
Bursitis	0	0	0	0	1 (6.7)	0
Catarrh	0	0	0	0	1 (6.7)	0
Cellulitis	0	0	1 (14.3)	0	1 (6.7)	0
Central venous catheter removal	0	1 (12.5)	0	0	0	1 (10.0)
Chest pain	0	0	0	0	1 (6.7)	0
Congestive cardiomyopathy	0	0	1 (14.3)	0	1 (6.7)	0
Constipation	0	0	1 (14.3)	0	1 (6.7)	0
Contusion	0	0	0	2 (100)	0	0
Dental caries	0	0	0	0	0	1 (10.0)
Dry eye	0	0	0	0	1 (6.7)	0
Ear infection	0	0	0	0	1 (6.7)	0
Eosinophil count increased	0	0	0	0	0	1 (10.0)
Fatty liver alcoholic	0	0	0	0	0	1 (10.0)

Preferred Term	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI	HBwI	HAwI	HBwI	HAwI	HBwI
	N=9 n (%)	N=8 n (%)	N=7 n (%)	N=2 n (%)	N=15 n (%)	N=10 n (%)
Flatulence	0	0	1 (14.3)	0	1 (6.7)	0
Food poisoning	0	0	0	0	0	1 (10.0)
Gastritis	0	0	0	0	2 (13.3)	0
Gastroenteritis	0	0	0	1 (50.0)	0	0
Gastroenteritis bacterial	0	0	0	0	1 (6.7)	0
Gastroenteritis viral	0	1 (12.5)	0	0	0	2 (20.0)
Gastrointestinal infection	0	0	0	0	1 (6.7)	0
Gingivitis	0	0	0	0	1 (6.7)	0
Hemophilic arthropathy	0	1 (12.5)	0	0	0	1 (10.0)
Hand fracture	0	0	0	0	0	1 (10.0)
Hepatic cyst	0	0	1 (14.3)	0	0	0
Hepatic enzyme increased	0	0	0	0	0	1 (10.0)
Hordeolum	0	0	1 (14.3)	0	1 (6.7)	0
Hypertension	0	0	0	0	1 (6.7)	0
Influenza	0	0	1 (14.3)	0	1 (6.7)	0
Injection site bruising	0	0	0	0	1 (6.7)	1 (10.0)
Injection site hemorrhage	0	1 (12.5)	0	0	0	1 (10.0)
Insomnia	0	0	0	0	1 (6.7)	1 (10.0)
Joint swelling	0	0	0	0	0	1 (10.0)
Loss of consciousness	0	0	0	0	0	1 (10.0)
Lower respiratory tract infection	0	0	0	0	1 (6.7)	0
Muscle hemorrhage	0	0	0	0	0	1 (10.0)
Myalgia	0	0	0	0	1 (6.7)	0
Nasal congestion	0	0	0	0	0	1 (10.0)
Nasopharyngitis	0	3 (37.5)	0	0	0	3 (30.0)
Nausea	0	0	0	0	0	1 (10.0)
Osteoporosis	0	1 (12.5)	0	0	0	1 (10.0)
Paresthesia	0	0	0	0	1 (6.7)	0
Platelet count increased	0	0	0	0	1 (6.7)	0
Postoperative wound infection	0	0	0	0	0	1 (10.0)
Prothrombin fragment 1.2 increased	0	0	0	0	0	1 (10.0)
Pulpitis dental	0	0	0	0	1 (6.7)	0
Puncture site hemorrhage	0	0	0	0	0	1 (10.0)
Pyrexia	0	0	0	0	2 (13.3)	0
Respiratory tract infection	0	1 (12.5)	1 (14.3)	0	1 (6.7)	1 (10.0)
Rhinitis	0	0	0	0	2 (13.3)	0
Rhinorrhea	0	0	0	0	1 (6.7)	0
Shock hemorrhagic	0	0	0	0	0	1 (10.0)
Skin hemorrhage	0	0	0	0	0	1 (10.0)
Skin ulcer	0	1 (12.5)	0	0	0	1 (10.0)
Sleep apnea syndrome	0	0	0	0	0	1 (10.0)
Subdural hemorrhage	0	0	0	0	0	1 (10.0)
Synovitis	0	0	0	1 (50.0)	0	0
Tachycardia	0	0	0	0	1 (6.7)	0
Tendonitis	0	0	0	0	1 (6.7)	0
Tooth fracture	0	0	0	0	1 (6.7)	0
Toothache	0	1 (12.5)	0	0	1 (6.7)	1 (10.0)
Ulnar nerve palsy	0	0	0	1 (50.0)	0	0
Ureterocele	0	0	0	0	0	1 (10.0)

	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
Preferred Term						
Urinary tract infection	0	0	0	0	1 (6.7)	0
Vomiting	0	1 (12.5)	0	0	0	2 (20.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as Treatment-emergent adverse events defined as adverse events with onset from randomization and until the last planned visit in the study (i.e., end of the post-treatment follow-up period 8 weeks after the last dose of concizumab).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Coded as Medical Dictionary for Regulatory Activities preferred terms.

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: AE, adverse event; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis

The most common TEAEs by FMQ (>15%) which occurred in a higher proportion of patients in the concizumab PPX arm compared to the no PPX arm were nasopharyngitis (29% versus 11.1%), local administration reaction (23.5% versus 0%), and hemorrhage (23.5% versus 22.2%), respectively.

In the main and extension parts, the most common TEAEs (>10%) were nasopharyngitis (32%), hemorrhage (32%), local administration reaction (24%), bacterial infection (16%), diarrhea (16%), anemia (12%), viral infection (12%), and arthralgia (12%).

Table 46. Patients With Adverse Events by System Organ Class and FDA Medical Query (Narrow) by Hemophilia Subtype, Safety Population, Trial 4310

System Organ Class FMQ (Narrow)	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
Blood and lymphatic system disorders (SOC)						
Anemia	0	0	0	1 (50.0)	2 (13.3)	1 (10.0)
Cardiac disorders (SOC)						
Arrhythmia	0	0	0	0	1 (6.7)	0
Heart Failure	0	0	1 (14.3)	0	1 (6.7)	0
Systemic Hypertension	0	0	0	0	1 (6.7)	0
Tachycardia	0	0	0	0	1 (6.7)	0
Gastrointestinal disorders (SOC)						
Diarrhea	1 (11.1)	0	1 (14.3)	0	3 (20.0)	1 (10.0)
Abdominal Pain	0	1 (12.5)	0	0	0	2 (20.0)
Constipation	0	0	1 (14.3)	0	1 (6.7)	0
Nausea	0	0	0	0	0	1 (10.0)
Vomiting	0	1 (12.5)	0	0	0	2 (20.0)
General disorders and administration site conditions (SOC)						
Local Administration Reaction	1 (11.1)	3 (37.5)	0	0	2 (13.3)	4 (40.0)
Pyrexia	0	0	0	0	2 (13.3)	0
Hepatobiliary disorders (SOC)						
Hepatic Injury	0	0	0	0	0	1 (10.0)
Infections and infestations (SOC)						
Nasopharyngitis	2 (22.2)	3 (37.5)	1 (14.3)	0	4 (26.7)	4 (40.0)
Bacterial Infection	1 (11.1)	0	2 (28.6)	0	3 (20.0)	1 (10.0)
Viral Infection	0	1 (12.5)	1 (14.3)	0	1 (6.7)	2 (20.0)
Musculoskeletal and connective tissue disorders (SOC)						
Arthralgia	1 (11.1)	0	0	0	3 (20.0)	0
Arthritis	1 (11.1)	0	0	1 (50.0)	1 (6.7)	0
Fracture	0	0	0	0	1 (6.7)	1 (10.0)
Myalgia	0	0	0	0	1 (6.7)	0
Osteoporosis	0	1 (12.5)	0	0	0	1 (10.0)
Tendinopathy	0	0	0	0	1 (6.7)	0
Nervous system disorders (SOC)						
Headache	1 (11.1)	1 (12.5)	0	0	1 (6.7)	1 (10.0)
Paresthesia	0	0	0	0	1 (6.7)	0
Psychiatric disorders (SOC)						
Insomnia	0	0	0	0	1 (6.7)	1 (10.0)
Renal and urinary disorders (SOC)						
Renal & Urinary Tract Infection	0	0	0	0	1 (6.7)	0
Respiratory, thoracic and mediastinal disorders (SOC)						
Respiratory Failure	0	0	0	0	0	1 (10.0)
Skin and subcutaneous tissue disorders (SOC)						
Erythema	1 (11.1)	0	0	0	1 (6.7)	0

System Organ Class FMQ (Narrow)	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n (%)	HBwI N=8 n (%)	HAwI N=7 n (%)	HBwI N=2 n (%)	HAwI N=15 n (%)	HBwI N=10 n (%)
Vascular disorders (SOC) Hemorrhage	1 (11.1)	3 (37.5)	0	2 (100)	3 (20.0)	5 (50.0)

Source: adae.xpt; Software: R

Treatment-emergent adverse events defined as Treatment-emergent adverse events defined as adverse events with onset from randomization and until the last planned visit in the study (i.e., end of the post-treatment follow-up period 8 weeks after the last dose of concizumab).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Each FMQ is aligned to a single SOC based on clinical judgment. However, please be aware that some FMQs may contain PTs from more than one SOC.

For specific preferred terms under each FMQ, see the table "Adverse Events by System Organ Class, FDA Medical Query (Narrow) and Preferred Term..."

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: FMQ, FDA medical query; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients with adverse event; PPX, prophylaxis; SOC, system organ class

Clinical Reviewer Comment: The most common TEAEs in the concizumab arm (main and extension period), which occurred in a higher proportion of patients compared to the no PPX arm included nasopharyngitis (32%), local administration reaction (24%), diarrhea (16%), anemia (12%), viral infection (12%), and arthralgia (12%). Hemorrhage was considered related to the underlying disease and not a TEAE related to concizumab.

7.6.2.6. Laboratory Findings, Study 4310

No clinically relevant differences in clinical laboratory testing results (i.e., serum albumin, serum creatinine, eGFR, alkaline phosphatase, ALT, AST, and total bilirubin, respectively, were observed between treatment arms in Study 4310, as shown in the tables below. A higher proportion of patients reported lymphopenia (<1000 cells/μL) in the concizumab PPX arm (3 of 17 (18% patients)) compared to the No PPX arm (0 of 9 (0%) patients)) in Study 4310, as shown below. Overall, there were 6 patients with mild (>4000 cells/μL) increase. The mild changes lymphocyte counts or other minor blood cell count changes during concizumab therapy are of unclear clinical significance.

Table 47. Patients With One or More Chemistry Analyte Values With Elevated or Low Values Meeting Specified Levels by Hemophilia Subtype, Safety Population, ISS Study 4310

Laboratory Parameter	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI	HBwI	HAwI	HBwI	HAwI	HBwI
	N=9 n/N _w (%)	N=8 n/N _w (%)	N=7 n/N _w (%)	N=2 n/N _w (%)	N=15 n/N _w (%)	N=10 n/N _w (%)
Albumin, low (g/dL)						
Level 1 (<3.1)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 2 (<2.5)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (<2)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)

Source: adlb.xpt; Software: R

Note that glucose values for hyperglycemia do not follow a nested format like the other labs. Level 1 corresponds to the diagnosis of prediabetes and is not inclusive of Level 2 and 3. Level 2 corresponds to the diagnosis of diabetes. Level 3 represents significant hyperglycemia that may indicate need for insulin or increased risk for diabetic ketoacidosis or other complications.

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PPX, prophylaxis

Table 48. Patients With One or More Kidney Function Analyte Values Exceeding Specified Levels by Hemophilia Subtype, Safety Population, ISS Study 4310

Laboratory Parameter	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI	HBwI	HAwI	HBwI	HAwI	HBwI
	N=9 n/N _w (%)	N=8 n/N _w (%)	N=7 n/N _w (%)	N=2 n/N _w (%)	N=15 n/N _w (%)	N=10 n/N _w (%)
Creatinine, high (mg/dL)						
Level 1 (≥1.5X baseline)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 2 (≥2X baseline)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (≥3X baseline)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
eGFR, low (ml/min/1.73 m ²)						
Level 1 (≥25% decrease)	1/9 (11.1)	0/8 (0)	0/7 (0)	0/2 (0)	1/15 (6.7)	0/10 (0)
Level 2 (≥50% decrease)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (≥75% decrease)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: eGFR, estimated glomerular filtration rate; HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PPX, prophylaxis

Table 49. Patients With One or More Liver Biochemistry Analyte Values Exceeding Specified Levels by Hemophilia Subtype, Safety Population, ISS Study 4310

Laboratory Parameter	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n/N _w (%)	HBwI N=8 n/N _w (%)	HAwI N=7 n/N _w (%)	HBwI N=2 n/N _w (%)	HAwI N=15 n/N _w (%)	HBwI N=10 n/N _w (%)
Alkaline phosphatase, high (U/L)						
Level 1 (>1.5X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 2 (>2X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (>3X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Alanine aminotransferase, high (U/L)						
Level 1 (>3X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 2 (>5X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (>10X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Aspartate aminotransferase, high (U/L)						
Level 1 (>3X ULN)	0/9 (0)	1/8 (12.5)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 2 (>5X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 3 (>10X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Bilirubin, total, high (mg/dL)						
Level 1 (>1.5X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 2 (>2X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (>3X ULN)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

For specific evaluation of drug-induced liver injury (DILI), see the figures "Hepatocellular Drug-Induced Liver Injury Screening Plot..." and "Cholestatic Drug-Induced Liver Injury Screening Plot..." and the tables "Patients in Each Quadrant for Potential Hepatocellular DILI Screening Plot..." and "Patients in Each Quadrant for Cholestatic DILI Screening Plot..."

Overall includes the main, extension, and follow-up parts of the trial.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PPX, prophylaxis; ULN, upper limit of normal

Table 50. Patients With One or More Hematology Analyte Values Exceeding Specified Levels by Hemophilia Subtype, Safety Population, ISS Study 4310

Laboratory Parameter	Concizumab PPX Main		No PPX Main		Concizumab PPX Overall	
	HAwI N=9 n/N _w (%)	HBwI N=8 n/N _w (%)	HAwI N=7 n/N _w (%)	HBwI N=2 n/N _w (%)	HAwI N=15 n/N _w (%)	HBwI N=10 n/N _w (%)
Complete Blood Count						
WBC, low (cells/uL)						
Level 1 (<3500)	0/9 (0)	1/8 (12.5)	0/7 (0)	0/2 (0)	1/15 (6.7)	4/10 (40.0)
Level 2 (<3000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	1/10 (10.0)
Level 3 (<1000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
WBC, high (cells/uL)						
Level 1 (>10800)	3/9 (33.3)	2/8 (25.0)	1/7 (14.3)	0/2 (0)	4/15 (26.7)	2/10 (20.0)
Level 2 (>13000)	0/9 (0)	2/8 (25.0)	0/7 (0)	0/2 (0)	0/15 (0)	2/10 (20.0)
Level 3 (>15000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Hemoglobin, low (g/dL)						
Level 2 (>1.5 g/dL dec. from baseline)	3/9 (33.3)	4/8 (50.0)	1/7 (14.3)	1/2 (50.0)	6/15 (40.0)	6/10 (60.0)
Level 3 (>2 g/dL dec. from baseline)	1/9 (11.1)	2/8 (25.0)	1/7 (14.3)	1/2 (50.0)	4/15 (26.7)	2/10 (20.0)
Hemoglobin, high (g/dL)						
Level 2 (>2 g/dL inc. from baseline)	0/9 (0)	1/8 (12.5)	0/7 (0)	0/2 (0)	1/15 (6.7)	1/10 (10.0)
Level 3 (>3 g/dL inc. from baseline)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	1/15 (6.7)	0/10 (0)
WBC Differential						
Lymphocytes, low (cells/uL)						
Level 1 (<1000)	2/9 (22.2)	4/8 (50.0)	0/7 (0)	0/2 (0)	2/15 (13.3)	4/10 (40.0)
Level 2 (<750)	1/9 (11.1)	2/8 (25.0)	0/7 (0)	0/2 (0)	1/15 (6.7)	2/10 (20.0)
Level 3 (<500)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Lymphocytes, high (cells/uL)						
Level 1 (>4000)	1/9 (11.1)	2/8 (25.0)	0/7 (0)	0/2 (0)	4/15 (26.7)	2/10 (20.0)
Level 2 (>10000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (>20000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Neutrophils, low (cells/uL)						
Level 1 (<2000)	0/9 (0)	2/8 (25.0)	0/7 (0)	0/2 (0)	2/15 (13.3)	6/10 (60.0)
Level 2 (<1000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (<500)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Eosinophils, high (cells/uL)						
Level 1 (>650)	1/9 (11.1)	0/8 (0)	0/7 (0)	0/2 (0)	1/15 (6.7)	0/10 (0)
Level 2 (>1500)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)
Level 3 (>5000)	0/9 (0)	0/8 (0)	0/7 (0)	0/2 (0)	0/15 (0)	0/10 (0)

Source: adlb.xpt; Software: R

Threshold levels 1, 2, and 3 as defined by the [Standard Safety Tables & Figures Integrated Guide](#).

Duration is 24 weeks (Main part), 52 weeks (Extension part), and 8 weeks (Follow-up part).

Overall includes the main, extension, and follow-up parts of the study.

The Concizumab PPX Main and No PPX Main study arms contain patients who were randomized. The Concizumab PPX Overall study arm contains patients from the Concizumab PPX Main study arms and patients from the No PPX Main study arms after they switched to Concizumab PPX at the start of the extension part of the study (excluding one patient from the No PPX Main study arm who discontinued before the end of the main part of the study).

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; ISS, integrated summary of safety; N, number of patients in treatment arm; n, number of patients meeting criteria; N_w, number of patients with data; PPX, prophylaxis

7.6.2.7. Assessment of Drug-Induced Liver Injury, Study 4310

No cases of drug-induced liver injury were identified in Study 4310.

7.6.2.8. Vital Signs' Analyses, Study 4310

No clinically relevant differences in vital signs were identified in Study 4310.

7.7. Key Safety Review Issues

7.7.1. Risk of Thrombosis

Issue Thrombosis

Three patients experienced non-fatal thrombotic events while receiving concizumab in clinical studies. The clinical reviewer assessed the safety data surrounding these events.

Background

Concizumab acts by enhancing the initiation phase of coagulation through increased activated coagulation factor X (Fxa) production, allowing sufficient thrombin generation and thus formation of clots. As a pro-coagulant, there is a risk of thrombosis with exaggerated pharmacology. Thrombosis formation was observed in non-clinical studies.

In clinical trials, three patients experienced thrombotic TEAEs while receiving concizumab. The clinical development program was subsequently put on a full clinical hold due to the potential for increased risk of thrombosis among patients treated with concizumab. The full clinical hold was removed after risk mitigation strategies were put in place as described below.

- Included a new guidance for treatment of breakthrough bleeds, with specific guidance for use of the lowest labeled dose of factor product or bypassing agent while on concizumab prophylaxis (PPX).
- Patients must contact the site when they have a suspected bleed.
- Continuation of previous PPX for up to two weeks after initiation of concizumab dosing was no longer allowed (Study 4307).
- A new concizumab dosing regimen including an initial daily dose of 0.20 mg/kg concizumab (instead of 0.25 mg/kg) was put in place. Criteria for an increase or decrease in the daily maintenance dose to 0.25 mg/kg or 0.15 mg/kg, respectively (based on concizumab exposure levels at the Week 4 visit 200 ng/mL-4000 ng/mL) were provided. The loading dose remained 1.0 mg/kg.
- Elective major surgery was no longer allowed in clinical studies.
- Trial stopping rule requiring urgent evaluation by the Novo Nordisk Safety Committee and consultation with the data monitoring committee (DMC) in case of one (instead of two)

significant thromboembolic event, disseminated intravascular coagulation (DIC), thrombotic microangiopathy (TMA) or death of study patient which may be related to the study product put in place.

Assessment

A summary of the three patients with thrombotic events while receiving concizumab is described in the table [below](#). It is notable that both arterial and venous thrombotic events were reported 21 to 86 days after starting concizumab. In addition, all patients had additional risk factors for thrombosis including smoking, history of hypertension (HTN) and/or obesity. Two of the three patients had elevated concizumab levels >4000ng/mL. Concizumab levels for each patient is described in the figure [below](#). Lastly, all patients had received factor or a bypassing agent at the time of the thrombotic event. No patient had ADAs at the time of the event.

Table 51. Summary of Thrombotic Events in Clinical Trials

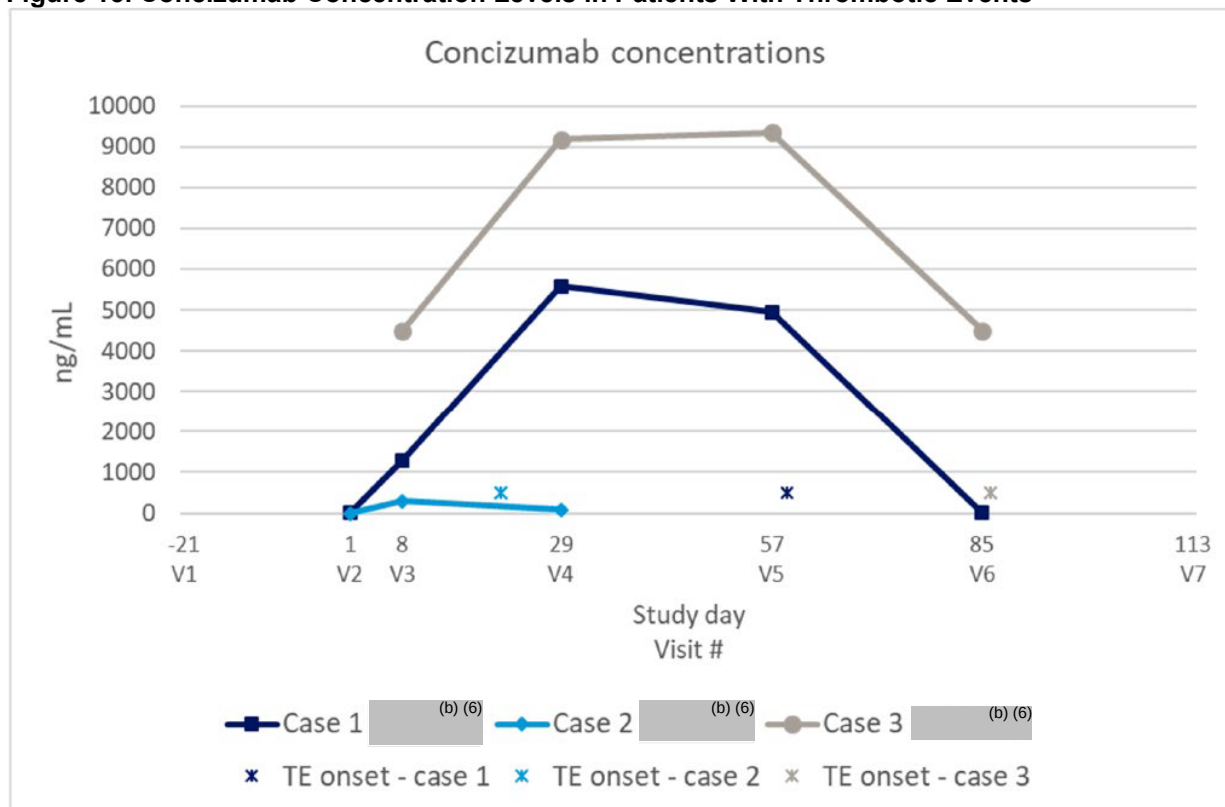
Patient/ Trial	Diagnosis/ Age (years)	Risk Factors for Thrombosis	Concomitant Therapy	Concizumab Level	Thrombotic Event	FDA Reviewer Interpretation
(b) (6) NN7415-4307	HA/46	11-year smoking history Hx of intermittent chest pain, use of ACE-inhibitor, and nitroglycerin at home Elevated BP at screening	FVIII (Advate) at 67 IU/kg for joint bleed the night prior to the thrombotic event. FVIII (Advate) at 60IU/kg for tooth removal a few weeks before the event The FVIII doses were all higher than local guidelines (50 IU/kg)	>4000ng/mL	MI 59 days after starting concizumab.	Concizumab could have caused the event of thrombosis as elevated concizumab levels were reported. Although, additional administration of FVIII at higher doses possibly contributed to the event of thrombosis, along with risk factors at baseline for thrombosis (i.e., likely underlying CAD, smoking history, and HTN).
(b) (6) NN7415-4311	HBwl/28	Obesity	Eptacog alfa (Novoseven) 89-130 µg/kg/8 hours starting day 18-21 for wrist bleed	<4000ng/mL	Acute right abdominal pain and renal infarct 21 days after start concizumab. CT /Nuclear scan old infarct in same area as a potential smaller infarct on US (reported by external independent review panel).	The timing of the renal infarct is unclear, as imaging was not completed prior to study entry, while it is possible that concizumab contributed to the event it appears less likely given low concizumab levels and imaging consistent with an older renal infarct.

Patient/ Trial	Diagnosis/ Age (years)	Risk Factors for Thrombosis	Concomitant Therapy	Concizumab Level	Thrombotic Event	FDA Reviewer Interpretation
(b) (6) NN7415-4307	HA/44	Obesity High cholesterol HTN during the study	FVIII 35 IU/kg (Advate) every day during study for bilateral ankle joint bleeds	>4000ng/mL	Leg DVT 86 days after start Concizumab. Concizumab and FVIII continued. PE and superficial vein thrombosis Day 92.	Concizumab could have caused the event of thrombosis as elevated concizumab levels were reported. Additional administration of FVIII possibly contributing, along with risk factors for thrombosis at baseline (i.e., obesity, high cholesterol and HTN).

Source: Patient narratives, Applicant's Investigations During Treatment Pause Document.

Abbreviations: HB, hemophilia B; HBwI, hemophilia B with inhibitors; Hx, history; HTN, hypertension; BP, blood pressure; MI, myocardial infarction; DVT, deep vein thrombosis; US, ultrasound; CAD, coronary artery disease

Figure 15. Concizumab Concentration Levels in Patients With Thrombotic Events



Source: Applicant's Document Investigations During Treatment Pause
Abbreviation: TE, thrombotic event; V, visit

One additional patient (Patient (b) (6)) age 42 years male with HAWI was treated with concizumab PPX at 0.25 mg/kg in the main part of the study prior to the treatment pause. Due to the treatment pause, the patient discontinued treatment with concizumab PPX on study Day 92. The patient did not re-initiate treatment with concizumab PPX after study restart and withdrew from the study on study Day 364. On study Day 106 (15 days after discontinuation of concizumab PPX), the patient had a non-serious event of infection in his left forearm following a shunt puncture. An ultrasound showed partial shunt stenosis. The patient had started treatment with eptacog alfa (activated) on study Day 104 (2 days prior to the event of shunt thrombosis) and initiated treatment with emicizumab (240 mg SC once weekly) on study Day 106 after which a complete shunt stenosis was reported. The thrombotic event for patient (b) (6) is not clearly related to concizumab therapy due to infection and treatment with additional coagulant factor and emicizumab.

After the clinical hold was removed and clinical studies were restarted, there were no thrombotic events.

Conclusion

Patients exposed to supratherapeutic doses of concizumab are at increased risk of thrombosis likely due to exaggerated pharmacologic effect. While the sample size is small, this risk appears to be increased in the setting of additional thrombotic risk factors, receiving concomitant factor

or bypassing agent, and concizumab levels >4000ng/mL. The risk for thrombosis among patients undergoing concizumab therapy appears to have decreased once the Applicant included PK monitoring in the clinical development program, providing specific guidance for use of the lowest labeled dose of factor product or bypassing agent while on concizumab prophylaxis (PPX), and a new concizumab dosing regimen which targets concizumab levels <4000ng/mL. If the product were to be approved, thromboembolic events should be included in the Warnings and Precautions section of the USPI. The new dosing regimen used after the treatment pause should be included in the USPI along with a statement to use the lowest effective dose of factor or bypassing agent to decrease the risk of thrombotic events. The frequency of PK monitoring is still unresolved at the time of this review and will be deferred to the next review cycle.

7.7.2. Pharmacokinetic Fluctuations Leading to Subtherapeutic Concentrations During Concizumab Treatment

Issue: PK Fluctuations Leading to Subtherapeutic Concentrations During Concizumab Treatment

Due to PK fluctuations, there were patients with concizumab levels <200ng/mL. Patients with concizumab levels <200 ng/mL are at increased risk of bleeding.

Background

Bleeding is inextricably linked with hemophilia and is commonly observed among the subset of patients with inhibitors. A concern for concizumab is the potential increase for bleeding if patients do not maintain the recommended concizumab plasma concentration of 200 ng/mL-4000 ng/mL, in particular a level over 200ng/mL (see Section [6.1](#) for further details). Significant fluctuations in plasma PK profiles were observed in individual patients. The review team (clinical pharmacology and clinical) investigated why PK fluctuations occurred and the potential impact on bleeding.

Assessment

The review team noted that 42 out of 97 patients (43%) had concizumab exposure levels below 200 ng/mL at some point during the maintenance dose setting and up until primary analysis cut-off (PACO). In total, 7 out of 42 patients (16.7%) with subtherapeutic levels of concizumab (<200ng/mL) had 11 AEs of bleeding in Study 4311. Nine out of 11 bleeding adverse events appear to be related to injection site reactions and were mild in severity. The remaining 2 events, occurring simultaneously in 1 patient, were severe and serious events related to muscle hemorrhage. No other bleeding episodes were reported for this patient. An additional patient reported in the 120-day safety update had a fatal bleeding event with a subtherapeutic level (28.1ng/mL) of concizumab. This patient is discussed further in Section [7.7.3](#).

A total of 16 patients out of the 42 patients with concizumab exposure levels below 200 ng/mL at some point in time from maintenance dose to the end of data closure tested positive for binding ADAs. Most occurrences were transient, and titers were very low. Three patients had in

vitro neutralizing antibodies at 1 or a few visits (Subjects (b) (6)); however, binding titers were very low, and no clinical impact of ADAs was observed in these patients. Based on further analysis (see Section 14.4) immunogenicity does not appear to have impacted PK.

The Applicant believes the significant PK variability observed in some patients was due to TMDD. The review team believes this certainly contributed to PK fluctuations but could not solely explain the large PK fluctuations. As described in detail in Section 7.2, the most plausible explanation is the issue of compliance. Study 4159 demonstrated subtherapeutic concizumab levels within a few days of missed doses. In addition, when concentrations drop to low subtherapeutic levels due to missed doses, in the absence of a loading dose, it may take several days of consecutive dosing to gradually return to target concentrations of >200 ng/mL.

Conclusion

While most bleeds that occurred when patients had subtherapeutic concizumab levels were minor, the potential remains for a moderate or severe or fatal bleeding events as observed in clinical studies. Outside of a controlled clinical study, risk of poor compliance to concizumab PPX will be greater and could pose a serious risk for the patient by increasing the potential for serious and fatal bleeding events. Given that a concizumab concentration above 200ng/mL is key to the therapeutic effect, the Applicant needs to provide a plan for a missed dose or multiple missed doses in labeling. This may include a plan for additional concizumab laboratory monitoring and/or a loading dose. In addition, given patients can become subtherapeutic quickly with missed doses, the Applicant should include a Medication Guide and address the need for good patient education and compliance with treatment.

7.7.3. Patient Fatality Due to Bleeding and Subtherapeutic Concizumab Levels

Issue: Fatal Bleeding Event With Subtherapeutic Levels

A 13-year-old male with HBwI had a fatal intracranial hemorrhage while receiving concizumab PPX.

Background

Patient (b) (6) is summarized in Section 7.6.1.2 Deaths, Study 4311 in this review. Briefly, this patient was a male age 13 years with HBwI who developed a fatal intracranial bleed after 345 days of concizumab treatment. The patient had subtherapeutic concizumab levels at the time of the fatal event.

Assessment

The etiology of the fatal intracranial hemorrhage was investigated by the clinical reviewer.. Based on the eDiary, the patient had multiple periods of 4 or more missed doses and missed doses corresponded to the subtherapeutic concizumab levels at visit 9a and 11a, see Table 30 during treatment.

The patient did not have ADAs near the time of the fatal event, so it is not likely that this contributed. During visits in which the patient received concizumab at the study site enhanced PK monitoring was conducted. The patient was therapeutic at those visits and there was inverse relationship between concizumab exposure and free TFPI levels over time.

Given the information gathered by the FDA reviewer the most likely explanation for the subtherapeutic concizumab level at the time of the fatal intracranial hemorrhage was non-compliance, as the patient did have therapeutic levels when administered concizumab on site and eDiary had documentation of missing doses which resulted in a protocol violation. No other patients had fatal bleeding events while utilizing concizumab.

Conclusion

In summary, patient (b) (6) was likely non-compliant with concizumab, and therefore was subtherapeutic and vulnerable to fatal bleeding. This case highlights the need for strict compliance, which can be difficult with a daily medication. Please refer to Section [7.7.2](#) regarding recommendations to improve patient compliance.

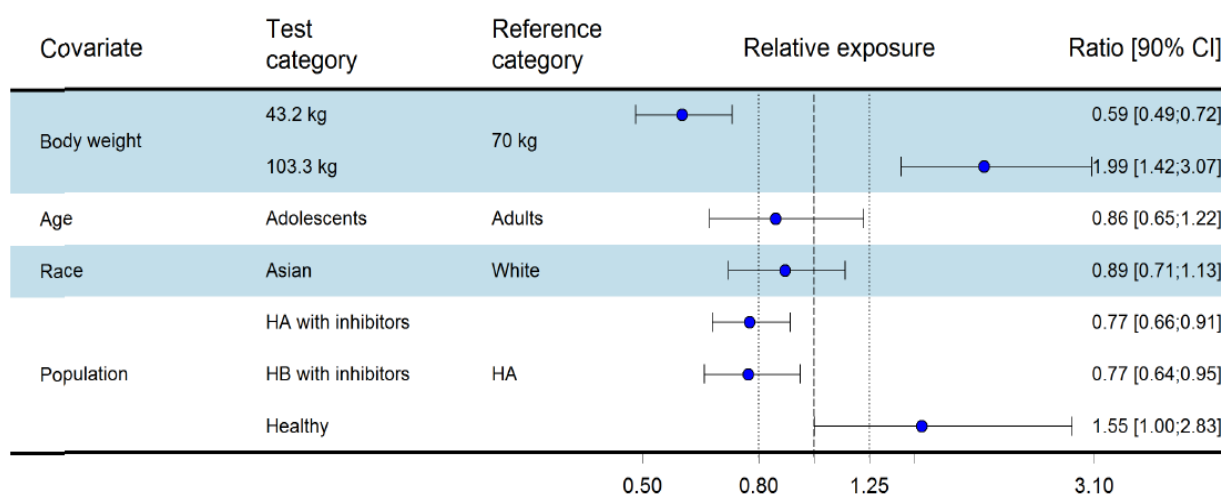
8. Therapeutic Individualization

8.1. Intrinsic Factors

The PK of concizumab is not influenced by age (12 to 79 years), race (White 62.9%, Asian 25.0%, Black 6.0%), hemophilia type (A versus B). Concizumab exposures are generally higher in healthy subjects compared to patients with hemophilia. The apparent clearance and volume of distribution of concizumab increased with increasing body weight (27 kg to 130.7 kg). See figure [below](#) for concizumab trough plasma concentration as a function of body weight following administration of concizumab 0.2 mg/kg. Nonetheless, after 4 weeks of treatment, patients with low or high exposure should adjust dose to 0.25 or 0.15 mg/kg, respectively, resulting in more similar exposure across patients.

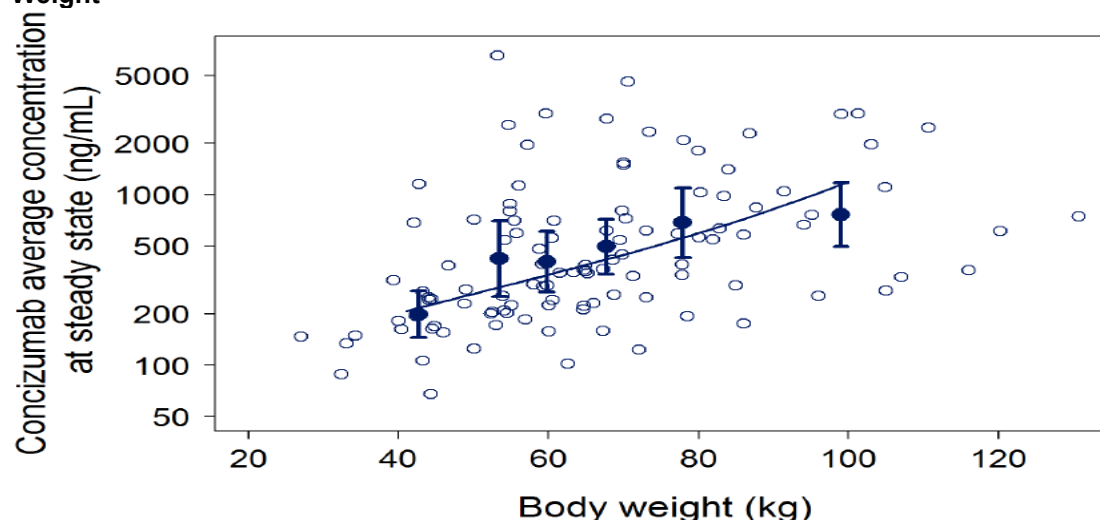
No dedicated studies have been conducted to evaluate the impact of renal or hepatic impairment. As concizumab is a monoclonal antibody, there is no expectation for concizumab exposures to be different in patients with renal or hepatic impairment.

Figure 16. Forest Plot of Covariate Effects on Concizumab Exposure (0.20 mg/kg)



Source: Modelling Report on Population PK and exposure-response meta-analysis Phase 1, 2 and 3 data Figure 1-1
Data are expressed as steady-state average concizumab plasma concentrations (C_{avg}) following administration of 0.20 mg/kg relative to the reference subject profile, based on the full population PK model. The reference subject profile was non-Hispanic or Latino, White, adult male (≥ 18 years), with a body weight of 70 kg not enrolled in Trial 4311. The points and bars (the column on the right) show point estimates (based on the maximum likelihood estimates) and 90% confidence intervals based on SIR relative to the reference subject. The reference body weight of 70 kg corresponds to the approximate median in the population. Body weight test categories (43.2 and 103.3 kg) represent the 5% and 95% percentiles, respectively, in the data set. Vertical dotted lines indicate the [0.80;1.25]-limits.
Abbreviations: CI, confidence interval; HA, hemophilia A

Figure 17. Individually Predicted Average Exposure at Steady State of 0.20 mg/kg Versus Body Weight



Source: Modelling Report on Population PK and exposure-response meta-analysis Phase 1, 2 and 3 data Figure 6-3

8.2. Extrinsic Factors

No clinical drug-drug interaction (DDI) study was conducted with concizumab. Considering concizumab is a monoclonal antibody, the likelihood of PK-based drug interaction is low.

In vitro and ex vivo DDI studies were performed with factor products or bypassing agents including rFVIIa, activated prothrombin complex concentrate (aPCC), rFVIII or rFIX in plasma

from hemophilia patients who were on prophylactic treatment with concizumab. The studies show that thrombin peak is increased in an additive and sometimes synergistic manner with concomitant factor product or bypass agents, indicating pharmacodynamic interaction. While these factor products or bypassing agents can be used in cases of breakthrough bleeds, the following dosing strategies should be implemented as was done in the Phase 3 study by the Applicant:

- Discontinue treatment with rFVIIa at least 12 hours before starting concizumab
- Discontinue treatment with aPCC at least 48 hours before starting concizumab
- Healthcare providers should discuss with patients receiving concizumab and/or their caregivers the dose and schedule of bypassing agents, if required, while receiving concizumab prophylaxis

“Treatment with bypassing agents (e.g., rFVIIa or aPCC) can be used for breakthrough bleeds, and the dose and duration will depend on the location and severity of the bleed. For mild and moderate bleeds that require additional treatment with bypassing agents (e.g., rFVIIa or aPCC), the lowest-approved dose in the approved product labeling is recommended. For aPCC, a maximum dose of 100 U/kg body weight within 24 hours is recommended. For severe bleeds, follow the dosing instructions provided in the approved labeling for the specific product based on clinical judgement.”

8.3. Plans for Pediatric Drug Development

Animal Data

Dedicated juvenile animal studies have not been conducted with concizumab as studies in neonatal and infant monkeys are technically challenging and are unlikely to identify potential reactions that were not identified from studies in fully developed (adult) animals. Notable findings in the hemostatic system and immune-related vascular toxicity were observed in adolescent (2 to 3 years of age) and sexually mature (3.5 to 6 years of age) cynomolgus monkeys. The human hemostatic system matures during the early weeks and months of life, and the concentrations of most hemostatic proteins, both in full-term and preterm infants, are comparable to adult values by 6 months of age ([Albisetti 2003](#); [Chalmers 2004](#)).

Clinical Data

Clinical Study 4311, 42 pediatric patients ages 12 to <18 years old, with HAwI or HBwI, were exposed to concizumab either in the main or extension treatment periods. Concizumab has been provided for compassionate use (expanded access) to a total of 14 children and adolescents ages 1 month to <17 years with HBwI up to the cut-off date for the compassionate use report (10 March 2022). Exposure from the compassionate use program has ranged from 1 month to 3 years. (b) (4)

8.4. Pregnancy, Lactation, and Females/Males of Reproductive Potential

Animal Data

The following nonclinical information was used in support of the indicated labeling sections and final labeling discussed in Section [23](#).

Table 52. Nonclinical Data Supporting Labeling on Pregnancy and Lactation

Labeling Section	Nonclinical Data
Pregnancy	Dedicated reproductive and developmental toxicology studies were not conducted as concizumab is primarily indicated for use in male patients with hemophilia and the clinical development program was conducted exclusively in males. Hemophilia A is inherited in an X-linked recessive manner and the disease which occurs predominantly in males (99%) is extremely rare in females. Concizumab is also being indicated for hemophilia B (Factor IX deficiency or Christmas disease, caused by mutations in the Factor IX (FIX) gene on the X chromosome) and hence, is predominantly observed in males (some females who carry the gene may display mild or, rarely, severe symptoms of bleeding).
8.3 Females and Males of Reproductive Potential	Histopathological evaluations conducted during repeat-dose toxicology studies in adolescent (up to 13 weeks in duration) and sexually mature (up to 52 weeks in duration) male and female cynomolgus monkeys did not elicit any notable effects in reproductive organs. In mice, inactivation of the TFPI-gene has been shown to result in embryonic lethality (Huang et al. 1997; Ellery et al. 2015) and total TFPI deficiency has not been described in humans (Wood et al. 2014). As placental transfer of IgG, particularly during organogenesis, may differ between mice and humans, the clinical relevance of these findings is unknown (DeSesso et al. 2012). Recurrent pregnancy loss has been observed in women who exhibited TFPI deficiency in combination with an Activated Protein C (APC) resistance phenotype or in women with anti-TFPI antibodies in combination with antiphospholipid antibodies and suggests that TFPI may be critical to the maintenance of normal pregnancy in humans (Martinuzzo et al. 2005; Gardiner et al. 2006). The potential risk of blocking TFPI with a monoclonal IgG antibody (e.g., concizumab) in pregnant women is not clear.

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility	Concizumab is not functional in rodents and standard carcinogenicity studies have not been conducted. Instead, the Applicant conducted a carcinogenicity risk assessment of concizumab using a weight-of-evidence (WOE) approach that considered the mode of action (MOA), a review of relevant literature and an evaluation of the nonclinical and clinical data. It was concluded that treatment with concizumab has the potential to enhance the prothrombotic conditions observed in some cancer patients (as would be expected for any procoagulant compound). However, the assessment did not identify evidence that treatment with concizumab could definitively lead to an increased risk of inducing or enhancing tumor development in humans. The Division determined that no additional nonclinical studies assessing the carcinogenic potential of concizumab were warranted for the indications of hemophilia A and hemophilia B and the CDER Executive Carcinogenicity Assessment Committee (ECAC) concurred with the Division's recommendation. Genotoxicity studies were not conducted, as concizumab consists of naturally occurring amino acids (endogenous) and is not anticipated to be genotoxic and there were no mechanistic data that suggested a mutagenic potential for concizumab. Fertility evaluations were included in the 26-week chronic toxicity study conducted in sexually mature male and female cynomolgus monkeys and there were no notable effects on the menstrual cycle duration, the length, width and volume of the testis, total sperm count, sperm motility or sperm morphology in cynomolgus monkeys administered concizumab at doses up to 9 mg/kg/day (SC).

Source: Reviewer constructed summary table of reproductive toxicology studies submitted to the BLA.
Abbreviations: APC, Activated Protein C; ECAC, Executive Carcinogenicity Assessment Committee; FIX, Factor IX; IgG, immunoglobulin G; MOA, mode of action; SC, subcutaneous; TFPI, tissue factor pathway inhibitor; WOE, weight-of-evidence.

Table 53. Reproductive Toxicity Exposure Margins/Dose Multiples

Study Duration (Sexual Maturity)	NOAEL (mg/kg/day)	Nonclinical Exposure (µg.hr/mL)	Exposure Margins* (AUC, Based)
4-Week Adolescent Reproductive Tissue Effects	9 mg/kg/day (SC)	37400 µg.hr/mL	1670x
13-Week Adolescent Reproductive Tissue Effects	50 mg/kg/day (SC)	326000 µg.hr/mL	14500x
26-Week Sexually Mature Fertility Endpoints Reproductive Tissue Effects	9 mg/kg/day (SC)	76500 µg.hr/mL	3400x
52-Week Sexually Mature Reproductive Tissue Effects	9 mg/kg/day (SC)	99300 µg.hr/mL	4400x

Source: Reviewer constructed summary table of chronic toxicology studies submitted to the BLA.

*Exposure margins were based on the concizumab plasma exposure level measured after 4 weeks of treatment (steady state) in the clinical Trial NN7415-4311 in patients with hemophilia A and B (with inhibitors) that employed a loading dose of 1 mg/kg (SC) followed by an initial once daily maintenance dose of 0.20 mg/kg (SC). The maintenance dose was adjusted to 0.15, 0.20 or 0.25 mg/kg/day (SC) and for exposure ratios, the mean across all three dose levels was used (22.4 µg.hr/mL, AUC₀₋₂₄).
Abbreviations: AUC, area under the curve (exposure); NOAEL, no observed adverse effect level

8.5. Key Efficacy Review Issues

8.5.1. Determination If the Pause in Study 4311 Due to Thrombotic Events Impacted the Benefit (ABR)

Issue

Determination if the pause in Study 4311 due to thrombotic events impacted the benefit (ABR).

Background

Study 4311 had a concizumab treatment pause for 6 months due to thromboembolic events reported in 3 patients. After the concizumab treatment pause and subsequent restart of Study 4311, a new concizumab dosing regimen was introduced to concizumab PPX arms. The original randomization could have been compromised because more than half of the planned sample size (refer to [Table 54](#)) were already enrolled and treated on the original regimen. Four patients randomized before the study pause in the concizumab PPX arm 2 did not restart on the new concizumab dosing regimen.

Table 54. Number of Subjects Randomized Before and After Pause, Study 4311

Arm 1(no PPX) N=19		Arm 2 (Concizumab PPX) N=33		All Randomized Subjects N=52	
Randomized Before Pause	Randomized After Pause	Randomized Before Pause	Randomized After Pause	Randomized Before Pause	Randomized After Pause
13 (68.4%)	6 (31.6%)	28 (84.8%)	5 (15.2%)	41 (78.8%)	11 (21.2%)

Source: Study NN7415-4311 Clinical Study Report, p.118.

Abbreviation: PPX, prophylaxis

Assessment

As recommended in previous IND meetings, the impact of potential bias introduced by the treatment pause and the robustness of the primary analysis was investigated by the Applicant with four sensitivity analyses. The results from all four sensitivity analyses in [Table 55](#) were confirmed by the FDA statistical reviewer. It was determined that the results of superiority from the primary analysis are robust.

Table 55. Sensitivity Analysis for the Primary Efficacy Endpoint: Number of Treated Spontaneous and Traumatic Bleeding Episodes, Study 4311

Purpose	Sensitivity Analysis	Result
To investigate the robustness of directly using the bleed data on the initial dosing regimen for patients who were not exposed to the new concizumab regimen	Used multiple imputation to impute the number of treated bleeds on the new concizumab dosing regimen for the 4 patients in arm 2 who did not restart	Estimated ABR ratio (arm 2/arm 1) was 0.14 with 95% CI (0.07, 0.29) and 2-sided p-value <0.001
To investigate the effect of using bleed data on the initial dosing regimen on the treatment effect of concizumab	Used all concizumab exposure data in arm 2 up until the primary analysis cut-off, irrespective of the dosing regimen	Estimated ABR ratio (arm 2/arm 1) was 0.14 with 95% CI (0.07, 0.29) and 2-sided p-value <0.001
To investigate the robustness of a potential superiority conclusion in terms of missing information for patients who were not exposed to the new concizumab regimen	Conducted tipping point analysis for patients only exposed to the initial dosing regimen. Patients only exposed to the initial dosing regimen were modelled with an increasing bleeding rate until the conclusion of superiority is changed	Tipping point was 25, means patients only exposed to the initial dosing regimen need to have 25 more bleed episodes to have non-significant result, which is considered implausible
To investigate a potential difference in treatment effects between patients randomized before and after the pause	Conducted subgroup analysis for patients randomized before and after treatment pause	Estimated ABR ratio (arm 2/arm 1) for patients randomized before the pause was 0.16 with 95% CI (0.08, 0.35) Estimated ABR ratio (arm 2/arm 1) for patients randomized after restart was 0.06 with 95% CI (0.01, 0.42)

Source: Study NN7415-4311 Clinical Study Report, Section 9.7.1.2.2 and section 11.2.2; FDA statistical reviewer's analysis. Abbreviations: ABR, annualized bleeding rate; CI, confidence interval.

Conclusion

Study 4311 was paused due to thromboembolic events. However, multiple sensitivity analysis confirmed the conclusion of superiority of concizumab PPX over on-demand therapy in reduction in ABR. Despite the study pause, Study 4311 is determined to be an adequate and well controlled study and provides substantial evidence of effectiveness of concizumab for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in adult and adolescent patients with HAWI and HBWI.

9. Product Quality

Complete Response (CR) With Quality Issues

Although the Office of Pharmaceutical Quality (OPQ) Review team has assessed BLA 761315 with respect to microbiology and immunogenicity assays and has determined that it meets all of those applicable standards to support the identity, strength, quality, and purity that it purports, the drug substance (DS), drug product (DP) (including device constituent), and facilities disciplines have unresolved quality issues. The deficiencies include inadequate characterization and control

strategy for (b) (4) inadequate cell bank stability protocols, inadequate reference material stability protocols, inadequate DS and DP release and stability specifications, and inadequate DS and DP post-approval annual stability protocols. In addition, during the inspection of the (b) (4) DS manufacturing facility for this application, investigators conveyed deficiencies to the representative of the facility. Therefore, from an OPQ perspective, this BLA is not deemed ready for approval in its present form until the above-mentioned issues are satisfactorily resolved. As such, OPQ recommends a CR action from a product quality perspective.

9.1. Device or Combination Product Considerations

CDRH was consulted to assess the proposed concizumab ELISA which is intended for the quantitative measurement of concizumab concentration at a single time point after four weeks from the initiation of treatment with concizumab. The measurement of concizumab concentration is used for a one-time dose adjustment decision based on the Concizumab-ELISA result. CDRH has identified multiple issues with the concizumab ELISA and has determined it is inadequate for postmarket use. See Consult Memo by Dr. Yan Cai for further details.

CDRH reviewed studies that (b) (4) conducted to support validation of the (b) (4) Concizumab ELISA kit for post market sample analysis (b) (4). The (b) (4) ELISA will be used for a limited period for post market sample analysis. (b) (4)

The following comments were communicated to the Applicant at the late cycle meeting on March 15, 2023,

(b) (4)

The Applicant's comments at the late cycle meeting did not adequately address the concerns stated above. CDRH has thus recommended the following comment to be included in the complete response letter (CRL):

As stated in the Late-cycle meeting package on March 9, 2023, the validation of the (b) (4) Concizumab ELISA was found inadequate to support the use of the assay in testing clinical specimens. Specifically, for the correlation/cross-validation study, you should include evaluation of a sufficient number of native patient samples to include samples that cover the medical decision levels in order to demonstrate safe use of the (b) (4) Concizumab ELISA as it will be used clinically/for patients. In the precision study, you should include an assessment of instrument-to-instrument and lot-to-lot precision, as multiple instruments and reagent lots will be used clinically and an estimate of device imprecision including these components of precision should be understood prior to device use. For the assay specificity/interference study, you should conduct a dose-response study to determine at which concentrations these substances (hemoglobin, cholesterol, triglyceride, Factor VII (NovoSeven), biotin, Ledipasvir and acetaminophen) no longer interfere with the (b) (4) Concizumab ELISA. You should provide the sample stability data using (b) (4) Concizumab ELISA (b) (4)

inally, you should provide a root-cause analysis to address the underestimation of concizumab concentrations for contrived samples by the (b) (4) Concizumab ELISA as was seen for specific validation studies (interference, carryover, dilution scheme and sample stability studies).

10. Human Subjects Protections/Clinical Site and Other Good Clinical Practice Inspections/Financial Disclosure Review

The Studies 4310 and 4311 were conducted in accordance with the principles of the Declaration of Helsinki, and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. An Independent Ethics Committee (IEC) and Institutional Review Board (IRB) reviewed and monitored the studies. Signed written informed consent forms (ICFs) were required for study enrollment. A Clinical Site Inspection consult review was completed by Dr. Anthony Orencia in the Office of Scientific Investigations and is summarized below in Section [22](#) in this review below. A Financial Disclosure summary review is located in Section [25](#) in this review below.

11. Advisory Committee Summary

An Advisory Committee meeting was not convened to discuss this application. No issues were identified that might have benefitted from a public discussion.

III. Additional Analyses and Information

12. Summary of Regulatory History

The Applicant received orphan drug designation for patients with hemophilia A (HA) and hemophilia B (HB) with or without inhibitors. In addition, the Applicant was granted breakthrough therapy designation in HBwI. Key regulatory history is described in the table [below](#).

Table 56. Summary of Regulatory History

Action	Date	Comments
Meeting request	Mar 10, 2011	Type B, Pre-IND Meeting Face-to-Face meeting held Aug 10, 2011
Meeting request	Feb 28, 2014	Type B, Pre-IND Meeting Face-to-Face meeting held Jun 10, 2014
New IND submission	May 19, 2015	
Study may proceed	Jun 18, 2015	Advice given with non-hold comments
Meeting request	Mar 02, 2016	Type C, Guidance Meeting Teleconference held May 12, 2016 Notable meeting comments included: dose selection strategies

Action	Date	Comments
Meeting request	Aug 31, 2017	Type C, Guidance Meeting Face-to-Face meeting held Nov 30, 2017 Notable meeting recommendations included: - A request for representative patient population in terms of demographics and clinical characteristics for the proposed qualitative research to support patient reported outcome (PRO) measurements. - A reanalysis of the Phase 2 study PRO data and the proposed qualitative research results that inform PRO measurement strategies for the Phase 3 clinical development program.
Breakthrough therapy request	Jan 10, 2019	Granted on Mar 11, 2019 Indication: for routine prophylaxis to prevent or reduce the frequency of bleeding episodes in hemophilia B patients with inhibitors
Meeting request	Jan 16, 2019	Type B, End-of-Phase 2 Meeting Teleconference held on Mar 19, 2019 Meeting purpose: Chemistry, Manufacturing, and Controls
Meeting request	Jan 16, 2019	Type B, End-of-Phase 2 Meeting Face-to-Face meeting held Mar 27, 2019
Meeting request	Jul 05, 2019	Type C, Guidance Meeting Face-to-Face meeting held Sep 11, 2019
Meeting request	Jul 05, 2019	Type C, Guidance Meeting Teleconference held Sep 04, 2019 Notable meeting recommendations included: A shorter recall period to minimize any recall error, as well as strengthen the PRO data due to the open-label study design.
Proprietary name granted	Sep 19, 2019	ALHEMO® was conditionally approved as the proprietary name
Meeting request	Dec 16, 2019	Type B, Guidance Meeting Written Response Only
Meeting request	Feb 18, 2020	Type B, Guidance Meeting Teleconference held Apr 22, 2020 Sponsor requested this meeting to be cancelled, preliminary comments were sufficient
Meeting request	Feb 28, 2020	Sponsor requested this meeting to be cancelled, clinical studies were paused.
Full clinical hold	Mar 20, 2020	21 CFR 312.42(b)(2)(i): Unreasonable and significant risk of illness or injury to human subjects Protocols associated include: NN7415-4311, NN7415-4307 and NN7415-4255 were placed on hold after 3 patients experienced non-fatal treatment-emergent adverse events (TEAEs) of thrombosis.
Meeting request	May 15, 2020	Type A, Guidance Meeting Teleconference meeting held on Jun 16, 2020 Meeting objective: discuss clinical hold issues
Remove full clinical hold	Aug 11, 2020	
Meeting request	Jul 13, 2021	Type B, Pre-BLA Teleconference held on Sep 23, 2021

Action	Date	Comments
Meeting request	Oct 05, 2021	Sponsor requested this meeting to be cancelled, because the Agency's comments on the ligand binding assay for detection of neutral antibodies provided on Oct 12, 2021, were sufficient.
Rolling review	Feb 02, 2022	Granted on May 05, 2022
Meeting request	Feb 15, 2022	Type C, Guidance Teleconference held on Apr 25, 2022
Meeting request	Mar 07, 2022	Type B, Guidance Teleconference held on May 05, 2022

Source: Reviewer Analysis

Abbreviations: BLA, biologics license application; CFR, Code of Federal Regulations; IND, investigational new drug application; PRO, patient reported outcome; TEAE, treatment-emergent adverse event

13. Pharmacology Toxicology

13.1. Summary Review of Studies Submitted With the Investigational New Drug Application

13.1.1. Concizumab Pharmacology

Concizumab binds to an epitope in the K2 domain of tissue factor pathway inhibitor (TFPI) that overlaps with the interface of Fxa binding. The results of in vitro and in vivo nonclinical pharmacology studies are consistent with the proposed mechanism of action of TFPI neutralization, whereby the Fxa produced by the activated coagulation factor VII (FVIIa)/tissue factor (TF) complex (normally downregulated by TFPI activity) results in increased thrombin generation leading to increased clot formation and theoretically hemostasis.

The rabbit and cynomolgus monkey were identified as relevant nonclinical species. No other nonclinical species were identified that expressed Kunitz domain sequences that contained the amino acid residues in the epitope of concizumab on the human K2 domain. The cynomolgus monkey and rabbit K2 domains have a 96% and 93% sequence homology to the human K2 domain, respectively.

The binding constants (K_D) of concizumab to rabbit, cynomolgus monkey and human TFPI are 0.22nM, 0.06nM, and 0.04nM, respectively (determined by surface plasmon resonance, SPR). The TFPI association constants (k_a) for concizumab were 1.3×10^6 , 4.2×10^6 , and 1.7×10^6 ($M^{-1} \times s^{-1}$) and the TFPI disassociation constants (k_d) for concizumab were 2.8×10^6 , 2.3×10^6 , and 6.3×10^6 (s^{-1}) in rabbits, cynomolgus monkeys and humans, respectively. These data suggest that concizumab binds to TFPI with high affinity and to a comparable extent in humans, cynomolgus monkeys and rabbits. Functional cross-reactivity was evaluated in a modified prothrombin time (PT) clot assay and concizumab was found to be functionally active against TFPI in plasmas derived from rabbits, cynomolgus monkeys, healthy humans, and FVIII-deficient humans (half maximal effective concentration (EC_{50}) values were 0.49nM, 0.41nM, 0.56nM, and 0.62nM, respectively).

Other names used for concizumab in this review include: NNC0172-2021, NNC0172-0000-2021, mAb 2021 and HzTFPI4F36.

13.1.1.1. In Vitro, Ex Vivo, and In Vivo Pharmacodynamic Activity

Table 57. Pharmacodynamic Studies

Study Details	Findings
Study No: 209161 Study Title: Epitope Mapping of the Murine Anti-TFPI Antibody TFPI4F36 by X-ray crystallography Species: Recombinantly produced K2 subdomain of human TFPI and the Fab fragment of murine TFPI4F36 were co-crystallized and the structure of the complex was solved by X-ray crystallography. Control: N/A	The murine TFPI4F36 and concizumab antibodies share the same K2 binding mode of action and the complementarity determining region (CDR) loops governing the binding to the K2 region of TFPI were reported to be identical between TFPI4F36 and concizumab. Barring the K2 domains of TFPI in rabbits, monkeys (cynomolgus, orangutang and rhesus) and humans, no additional Kunitz domain epitopes were identified for TFPI4F36 and concizumab. The epitope (binding surface on K2) and the paratope (binding surface on the antibody) are identical for the murine and the humanized antibodies and suggests that data derived with the murine antibody in this study is applicable to concizumab. These results support the premise that the rabbit and the cynomolgus monkey are relevant nonclinical species. The binding epitope for TFPI4F36 to the second Kunitz domain (K2) exhibits an extensive overlap with the Factor Xa binding surface on K2, accounting for (on a structural basis) the neutralizing action of TFPI4F36 (and by extension concizumab) on TFPI.

Study Details	Findings
Study No: 210179 Study Title: Binding Affinity of Concizumab (NNC 0172-2021) for Recombinant TFPI derived from Human, Cynomolgus Monkey and Rabbit Protein Sequences assessed using a CM5 chip (carrying a matrix of carboxymethylated dextran covalently attached to a gold surface). Species: Recombinant TFPI proteins derived from rabbits, monkeys, and human protein sequences. Control: Assay Buffer	The binding constants (K_D) for recombinant TFPI were 0.04nM (human), 0.06nM (monkey) and 0.22nM (rabbits) and were considered comparable. This data are consistent with the findings that the epitope of the human Kunitz 2 domain (mapped by X-ray crystallography) is also found with TFPI derived from cynomolgus monkeys and rabbits. Based on the binding affinities to recombinant TFPI, the rabbit and cynomolgus monkey are considered relevant species for the nonclinical assessment of concizumab.
Study No: 209168 Study Title: Neutralization of Plasma TFPI by Concizumab (HzTFPI4F36) or its Murine Precursor (MuTFPI4F36) in an In Vitro Dilute Prothrombin Time (dPT) Assay conducted with Plasma derived from Humans (Healthy or FVIII-Deficient) or Various Nonclinical Animal Species. Species: Mouse, Rat, Guinea Pig, Rabbit (NZW), Dog, Cynomolgus Monkey, Pig, and Human. Concentrations: 0.02nM to 20nM Control: Plasma spiked with either buffer or a goat polyclonal anti-TFPI antibody or recombinant FVIIa.	Concizumab is capable of neutralizing endogenous TFPI (shortening dilute prothrombin time (dPT) clotting times) in plasma derived from humans (healthy or FVIII-deficient), cynomolgus monkeys and rabbits with similar potency. The murine precursor of concizumab (MuTFPI4F36) elicited no effect on dPT in mouse, rat, dog, and pig plasma, and concizumab had no effect on dPT in guinea pig plasma. These results support the premise that the rabbit and cynomolgus monkey are relevant nonclinical species.
Study No.: 209169 Study Title: Thromboelastography following Concizumab (HzTFPI4F36) Exposure in Hemophilia A-like (anti-FVIII antibody treated) Human Blood Derived from Healthy Male Donors Concentrations: 0.01nM to 50nM Control: Buffer and huFVIIa (10nM)	Concizumab elicited hemostatic activity with a half-maximal effect in the low nM range (0.4nM and 1nM for reduced clotting time and improved clot development, respectively) in human blood derived from healthy male donors that was treated (ex vivo) with a neutralizing anti-FVIII antibody to mimic the hemophilia A condition. The thromboelastography results indicate that concizumab has a pro-hemostatic effect on (male) human blood (in vitro) and may elicit hemostatic effects in patients with hemophilia A.

Study Details	Findings
Study No.: BBSN100201 Study Title: Thromboelastography following Concizumab (NNC 0172-2021) exposure in Hemophilia A-like (anti-FVIII antibody treated) and Hemophilia B-like (anti-FIX antibody treated) Human Blood Derived from Healthy Male Donors. Concentrations: 0.01nM to 50nM Controls: Normal Blood and Buffer	Concizumab elicited a comparable level of hemostatic activity with regards to reduced clotting times (0.4nM, EC₅₀) and improved clot development (2.2nM to 2.6nM, EC₅₀) in human blood derived from healthy male donors that was treated (ex vivo) with either a neutralizing anti-FVIII antibody or a neutralizing anti-FIX antibody to mimic the hemophilia A and hemophilia B conditions, respectively. The thromboelastography results indicate that concizumab has a pro-hemostatic effect in (male) human blood (in vitro) and suggests that concizumab may elicit similar hemostatic effects in patients with hemophilia A or hemophilia B.
Study No.: BBSN091002 Study Title: Thromboelastography Analysis of Concizumab (NNC 0172-2021) in Hemophilia A-like (anti-FVIII antibody treated) Blood Derived from Healthy Male Cynomolgus Monkeys. Concentrations: 0.01nM to 50nM Controls: Normal Blood and Buffer	Concizumab elicited a comparable level (versus humans) of hemostatic activity with regards to reduced clotting times (0.4nM, EC₅₀) and improved clot development (0.5nM, EC₅₀) in blood derived from healthy male cynomolgus monkeys that was treated (ex vivo) with a neutralizing anti-FVIII antibody to mimic the hemophilia A condition. The thromboelastography results indicate that concizumab has a pro-hemostatic effect in (male) cynomolgus monkey blood (in vitro) and supports the premise that the cynomolgus monkey is a pharmacologically relevant animal species.
Study No.: 209144 Study Title: Neutralization of TFPI Activity in a Fxa Activity Assay (In Vitro) by Concizumab (HzTFPI4F36). Concentrations: 0.24nM to 15nM Controls: Assay buffer that included all FX activation assay components (minimum activity) or assay buffer with all components but excluding TFPI (maximum activity).	Concizumab neutralized (EC₅₀, 0.8nM) a fixed concentration of human TFPI (6nM) that in the absence of concizumab would be expected to achieve a 60% to 90% reduction in Fxa activity. Concizumab increased human Fxa activity in a concentration dependent manner and at concentrations exceeding 1.8nM the Fxa activity was increased above the maximum anticipated level of Fxa activity (> 100%). No explanation for the observed super-activity was provided however the result is consistent with the findings that neutralization of TFPI may result in increased and/or more sustained activity of FVIIa/Fxa (in vitro). The mean plasma TFPI concentration in healthy humans ranges from 1.6nM to 2.5nM and suggests that concizumab may completely neutralize the TFPI activity (facilitating unrestricted Fxa activity) in human plasma at circulating antibody concentrations in the low nM range.

Study Details	Findings
Study No.: 210180 Study Title: Neutralization of TFPI Activity in a FVIIa/TF/Fxa Activity Assay (In Vitro) by Concizumab (NNC 0172-2021). Concentrations: 0.16nM to 30nM Controls: Assay buffer that included all FX activation assay components (minimum activity) or assay buffer with all components but excluding TFPI (maximum activity).	Concizumab neutralized (EC₅₀, 2.8nM) a fixed concentration of human TFPI (1nM) that in the absence of concizumab elicited a 70% to 90% reduction in the FVIIa/TF/Fxa complex activity. Concizumab increased human FVIIa/TF/Fxa complex activity in a concentration dependent manner and as concizumab was not preincubated with TFPI this assay reflects the direct competition between Fxa and concizumab for the TFPI target substrate. The mean plasma TFPI concentration in healthy humans ranges from 1.6nM to 2.5nM and suggests that concizumab may completely neutralize the TFPI activity (facilitating unrestricted FVIIa/TF/Fxa complex activity) in human plasma at circulating antibody concentrations in the low nM range.
Study No.: LCP080802 Study Title: Functional In Vitro Characterization of Concizumab (NNC 0172-0000-2021-1A) Neutralization of Endothelial Cell Associated TFPI Activity (Inhibition of TF/FVIIa-mediated activation of FX) Measured in a FX Activation Assay. Cell Lines: Human Cell Line and Primary Cells: ECV304 cells and TNFα/IL1β-stimulated HUVECs, respectively. Concentrations: 0.04nM to 5nM Concentrations: 0.3nM to 20nM Control: Assay buffer that included all FX activation assay components (minimum activity).	Concizumab neutralized cell associated TFPI activity (the inhibition of TF/FVIIa-mediated activation of FX) in a concentration dependent manner (EC₅₀, less than 0.5nM) in TNFα / IL1β stimulated (to induce TF expression) HUVEC cells and in ECV304 cells (constitutively express low levels of TF). The murine precursor of concizumab (MuTFPI4F36) elicited a comparable result in ECV304 cells. These data indicate that concizumab is capable of neutralizing the activity (inhibition of TF/FVIIa-mediated FX activation) of the cell-associated (glycosylphosphatidylinositol (GPI) anchored) form of TFPI that specifically inhibits TF-mediated activity when TF is expressed on the same cell as the TFPI protein.
Study No.: MTBH100403 Study Title: Residual TFPI Functionality Measured in Human Plasma Spiked with Concizumab Species: NZW Rabbit, Cynomolgus Monkey and Human Concentrations: 0.63nM to 630nM Control: Actichrome TFPI activity assay buffer and components (minimum activity).	Concizumab neutralized TFPI activity (the inhibition of the catalytic activity of Fxa) in a concentration dependent manner (EC₅₀, 6nM) in pooled human plasma (10-fold diluted samples). Note: As dilution linearity was not evaluated, the EC₅₀ could vary if other dilution factors are employed. The EC₅₀ values for concizumab inhibition of TFPI activity were estimated using FVIII-inhibited rabbit plasma (5.8nM) and monkey plasma (1.6nM) and were comparable to the human EC₅₀ value. The optimal dilution factors with respect to the best Fxa response were found to be a 10-fold dilution for rabbit samples and a 5-fold dilution for monkey samples in human TFPI depleted plasma. Dilution linearity was not observed with either rabbit plasma or monkey plasma and as the EC₅₀s varied widely when applying different dilution factors in these species similar variability would be expected with human samples.

Study Details	Findings
Study No.: LCP080102 Study Title: In Vitro Characterization of the Mouse Monoclonal Antibody 4F36 including the Neutralization of TFPI in the presence of various concentrations of rFVIII in Tissue Factor-Induced Thrombin Generation and Fibrin Clot Formation in FVIII-depleted Plasma supplemented with phospholipids or platelets Measured by Endogenous Thrombin Potential (ETP), Thromboelastography (TEG) and Calibrated Automated Thrombin (CAT) Generation. Species: Human Concentration: 10nM (4F36) Concentrations: 0.005-1 IU/mL (rFVIII) Control: Assay buffer that included all of the CAT generation components and increasing concentrations (0 to 1.5 U/mL) of FVIII replenishment. Control: Assay buffer that included TEG components and increasing concentrations (0 to 1 U/mL) of recombinant FVIII.	The murine precursor of concizumab (MuTFPI4F36) promoted coagulation (thrombin generation and TEG) in the presence of low concentrations of FVIII (consistent with the conditions present in severe and moderate hemophilia A plasma). The extent of coagulation was comparable to that achieved when normal levels of FVIII were restored (1 IU/mL) and the effect of MuTFPI4F36 was more pronounced at subtherapeutic levels of FVIII with only a minimal effect at the highest concentration. The thrombin generation pattern of 4F36 was distinctly different from the pattern obtained by replenishment of FVIII-depleted plasma with rFVIII and indicated that the thrombin formed in patients with hemophilia under the influence of concizumab may be more susceptible to fibrinolysis than thrombin formed under normal conditions or with FVIII supplementation. These results suggest that concizumab can promote thrombin burst formation in the presence of low concentrations of FVIII (in vitro). Concizumab is also being indicated for hemophilia B (Factor IX deficiency) where patients maintain normal levels of functional FVIII. Normal levels of FVIII may result in diminished coagulation and are consistent with the results observed with pooled plasma from patients with HB that showed a negative DDI effect when concizumab was combined with rFIX (321538).
Study No.: 215093 Study Title: Evaluation of TFPI Binding and Release from Endothelial Cells using Concizumab via Flow Cytometry and ELISA. Cell Lines: Human ECV304 and EA.hy926 endothelial cells Concentrations: 10, 100, or 1000nM Controls: Assay buffer, Heparin (5 U/mL, positive control), TFPI Kunitz domain 3 specific mAb (positive control mAb) and a trinitrophenol specific mAb (negative control)	Concizumab (up to 1000nM) bound to TFPI on the cell surface of endothelial cells (EC₅₀ of 0.1nM) and elicited a concentration dependent release of TFPI that was significantly lower than the level of release achieved with heparin (5 U/mL) or a mAb directed against the Kunitz domain 3 (C-terminus) of TFPI. The predominant form of TFPI on the endothelial cell surface is TFPIβ, that lacks a portion in the C-terminal region and instead is comprised of an alternative carboxy terminus with a glycosyl phosphatidyl inositol (GPI) anchor. These results are consistent with the mechanism required for the release of cell surface bound TFPI that involves association with the C-terminal region (not the K2 domain) of the TFPIα form (that exhibits reduced surface expression) of the protein and suggests that the extent of concizumab-mediated release of TFPI from the endothelial cell surface (an anticoagulant effect) will be minimal.

Study Details	Findings
Study No.: BLZ100301 Study Title: Effect of Concizumab (HzTFPI4F36) on Cuticle Bleeding in Pseudo/Transient (Anti FVIII-Treated) Hemophilia A Female NZW Rabbits Species: NZW Rabbit (Female) Doses: 1 to 8 mg/kg (IV) Control: Buffer with isotype control (IgG) antibody (4 mg/kg)	Concizumab (administered (IV) 35 minutes before induction of cuticle bleeding) dose-dependently reduced bleeding time (statistically significant only at the HD) and reduced blood loss (statistically significant at doses greater than or equal to 4 mg/kg) in transient hemophilic female NZW rabbits (administered a neutralizing anti-FVIII antibody 45 minutes prior to bleed induction) over a 1-hr observation period. No signs of adverse effects (e.g., decrease in platelet numbers) were present. The maximum efficacious dose with regards to reduced bleeding time in pseudo-HA female NZW rabbits was 8 mg/kg (HD).
Study No.: BLZ110403/ BLZ110701 Study Title: Dose (IV) Response of Concizumab (mAb 2021) on Cuticle Bleeding in Pseudo/Transient (Anti FVIII-Treated) Hemophilia A Female NZW Rabbits Species: NZW Rabbit (Female) Doses: 0.125 to 1 mg/kg (IV) Control: Buffer with isotype control (IgG) antibody (1 mg/kg)	Blood loss was reduced dose-dependently when concizumab was administered (IV) 35 minutes prior to induction of cuticle bleeding in transient hemophilic female NZW rabbits (administered a neutralizing anti-FVIII antibody 45 minutes prior to bleed induction) over a 1-hour observation period. The maximum efficacious dose (MED) was reached at 0.375 mg/kg (statistical significance was not achieved at any dose level) and the ED₅₀ was 0.23 mg/kg. The maximum effect achieved In this study was not significantly different from the maximum effect achieved at higher doses (up to 8 mg/kg) in prior studies and indicates that doses exceeding 0.375 mg/kg are not required to achieve maximal efficacy in the NZW rabbit cuticle bleed model.
Study No.: BLZ090801 Study Title: Effect of "On-Demand" Treatment (IV) with Concizumab (HzTFPI4F36) on Cuticle Bleeding (Ongoing Bleeding Model) in Pseudo/Transient (Anti FVIII-Treated) Hemophilia A Female NZW Rabbits Species: NZW Rabbit (Female) Doses: 2 mg/kg (IV) Control: Buffer with isotype control (IgG) antibody (2 mg/kg) or rFVIIa (9 mg/kg)	"On-Demand" treatment (initiated 5 minutes after bleed induction) with concizumab (2 mg/kg, IV) significantly reduced blood loss from an ongoing cuticle bleeding event in transient hemophilic female NZW rabbits (administered a neutralizing anti-FVIII antibody 45 minutes prior to bleed induction). The extent of reduced blood loss and bleeding time (over the 1-hour observation period) were comparable between concizumab and rFVIIa (9 mg/kg, IV) and the reduction in bleeding time was not statistically significant for either compound. The results indicate that the procoagulant effects of concizumab can be achieved when administered shortly after injury induction (within 5 minutes) in the NZW rabbit cuticle bleed model.

Study Details	Findings
Study No.: BLZ100602 Study Title: Effect of "On-Demand" Treatment (IV) with Concizumab (NNC 0172-0000-2021) on Cuticle Bleeding (Ongoing Bleeding Model) in Pseudo/Transient (Anti FVIII-Treated) Hemophilia A Female NZW Rabbits Species: NZW Rabbit (Female) Doses: 0.5 to 4 mg/kg (IV) Control: Buffer with isotype control (IgG) antibody (4 mg/kg)	"On-Demand" treatment (initiated 5 minutes after bleed induction) with concizumab significantly reduced blood loss from an ongoing cuticle bleeding event in transient hemophilic female NZW rabbits (administered a neutralizing anti-FVIII antibody 45 minutes prior to bleed induction) at doses greater than or equal to 1 mg/kg (IV) over a 1-hour observation period. The effect at the LD (0.5 mg/kg) was not statistical significance and a significant reduction in bleeding time was present only at the MD (2 mg/kg). The results indicate that the procoagulant effects of concizumab can be achieved at doses of 1 mg/kg or higher when administered (IV) shortly after injury induction (within 5 minutes) in the NZW rabbit cuticle bleed model.
Study No.: 209164 (BLZ090101) Study Title: Effect of (IV) Concizumab (HzTFPI4F36) on Cuticle Bleeding in Pseudo/Transient (Anti FVIII-Treated) Hemophilia A Female NZW Rabbits (PK/PD Study) Note: Duration of Action Study Species: NZW Rabbit (Female) Doses: 20 mg/kg (IV) Control: Buffer with isotype control (IgG) antibody (20 mg/kg, reduced to 2 mg/kg in some control rabbits due to a lack of antibody availability)	A single (IV) dose (20 mg/kg) of concizumab (followed by treatment (on Day 4, 7 or 10) with a neutralizing anti-FVIII mAb to induce pseudo hemophilia before the induction of cuticle bleeding 45 minutes later) reduced bleeding (blood loss and bleeding time) in transient hemophilic female NZW rabbits over a 1-hour observation period on Day 4 and Day 7. No hemostatic effects were observed on Day 10 when concizumab levels were found to be significantly reduced in the plasma. No signs of adverse effects (e.g., decrease in platelet numbers) were observed. The results indicate that the procoagulant effects of concizumab are durable for up to 7 days after a single (IV) dose of 20 mg/kg (administered prior to injury induction) in the NZW rabbit cuticle bleed model. The observed pharmacokinetic profile indicated that concizumab was cleared by target mediated mechanisms after 10 days and the decline in plasma concentrations corresponded to a loss in pharmacodynamic activity.
Study No.: BLZ090501 Study Title: Effect of Treatment (SC) with Concizumab on Cuticle Bleeding in Pseudo/Transient (Anti FVIII-Treated) Hemophilia A Female NZW Rabbits. Species: NZW Rabbit (Female) Doses: 10 mg/kg (SC) Control: Buffer with isotype control (IgG) antibody (10 mg/kg)	A single subcutaneous (SC) dose (10 mg/kg) of concizumab reduced bleeding time and blood loss significantly (over a 1-hour observation period) when administered 24 hrs prior to induction of bleeding in transient hemophilic female NZW rabbits. No signs of adverse effects (e.g., decrease in platelet numbers) were observed. The results indicate that the procoagulant effects of concizumab can be achieved after a single (SC) dose (the clinical ROA) of 10 mg/kg when administered 24 hrs prior to injury induction in the NZW rabbit cuticle bleed model. The observed pharmacokinetic profile indicated that plasma concizumab levels (40 µg/mL) were relatively stable in rabbits over the 1-hour observation period and corresponded to the observed pharmacodynamic activity.

Study Details	Findings
Study No.: PJOH090201 Study Title: Acute Effects of (IV) Concizumab (NNC 0172-0000-2021) a humanized anti-TFPI antibody on Clot Formation and Coagulation Markers in a Venous Stasis Model in Normal (non-hemophilic) Female NZW Rabbits Species: NZW Rabbit (Female) Doses: 2 mg/kg (IV) Control: Buffer with isotype control (IgG) antibody (2 mg/kg)	The frequency of distal clot formation and the size of clots present locally in the ligated facial veins of normal female NZW rabbits were comparable between the animals administered concizumab or an isotype control antibody (10 minute prior to clamp ligation). There were no statistically significant differences in platelet counts, PT, TAT, and fibrinogen levels. A minimal decrease in APTT and fibrinogen degradation products (relative to control) was observed with concizumab. Lungs thrombi (noted microscopically) were present only in concizumab-dosed rabbits (50%) and were considered potentially related to the administration of concizumab.
Study No.: PJOH090802 Study Title: Acute Effects of (IV) Concizumab (NNC 0172-0000-2021) a humanized anti-TFPI antibody on Local Clot Formation in a Venous Stasis Model in Female NZW Rabbits Following Vessel Wall Injury and Prevention with a Low Molecular Weight Heparin (LMWH). Species: NZW Rabbit (Female) Dose: 2 mg/kg (IV) Concizumab Dose: 500 IU/kg (IV) LMWH Control: Saline buffer with isotype control (IgG) antibody (2 mg/kg)	Prophylactic treatment with concizumab significantly increased local clot formation in healthy female NZW rabbits when facial veins were crushed and then ligated 30 minutes later. When concizumab dosing was followed by (5 minutes later) the administration of LMWH (before injury) local clot formation was prevented. No changes in coagulation parameters were observed (platelet counts, WBC counts, PT, and fibrinogen). A minimal decrease in APTT was observed after concizumab (only) dosing. These results indicate that LMWH can prevent the procoagulant effects of concizumab in non-hemophilic rabbits and suggest that LMWH may be used as a preventive treatment option if complications caused by exaggerated pharmacology arise.

Study Details	Findings
Secondary Pharmacodynamics	
Study No.: HHBP100601 Study Title: In Vitro Effects of Concizumab on Protein C Activation and Antithrombin Activity using Human Umbilical Vein Endothelial Cells (HUVECs) Cell Line: HUVECs Concentrations: 350nM (50µg/mL) to 1.75µM (250µg/mL). Controls: Assay buffer with all components (positive control). Anti-Thrombomodulin Antibody, No Thrombin, No Protein C, and No HUVECs (negative controls).	Concizumab bound to (0.42nM or 0.06µg/mL, K_D) surface expressed TFPI on HUVEC cells (ELISA) and indicated that surface associated TFPI would be saturated at the concentrations employed in the subsequent coagulation activity assessments (≥ 350nM or 5 µg/mL). After incubating (30 min) HUVECs with thrombin and protein C (with or without antithrombin), concizumab did not affect thrombin mediated protein C activation or antithrombin inhibition of thrombin. However, effects on the initial rate (0 to 30 min) of antithrombin-mediated thrombin inhibition were not assessed. These results indicate that two independent negative regulators (activated protein C and antithrombin) of the coagulation cascade (which function downstream and independent of TFPI) remained functional in the presence of concizumab and its saturation of cell associated TFPI (in vitro).

Source: Reviewer constructed summary table of pharmacodynamic studies submitted to the BLA.

Abbreviations: APTT, activated partial thromboplastin time; CAT, calibrated automated thrombin; CDR, complementarity determining region; DDI, drug-drug interaction; dPT, dilute prothrombin time; EC50, half maximal effective concentration; ELISA, enzyme-linked immunoassay; ETP, endogenous thrombin potential; FIX, factor IX; FVIIa, factor VIIa; Fxa, factor Xa; GPI, glycosylphosphatidylinositol; HB, hemophilia B; HD, high dose; hrs, hours; HUVEC, human umbilical vein endothelial cell; IV, intravenous; K2, second Kunitz domain; KD, dissociation constant; LMWH, low molecular weight heparin; mAb, monoclonal antibodies; MD, mid dose; MED, maximum efficacious dose; N/A, not applicable; NZW, New Zealand White; PT, prothrombin time; rFIX, recombinant factor IX; rFVIII, recombinant factor VIII; ROA, routes of administration; SC, subcutaneous; TAT, thrombin-anti-thrombin; TEG, thromboelastography; TF, tissue factor; TFPI, tissue factor pathway inhibitor; WBC, white blood cell

13.1.1.2. Safety Pharmacology

Safety pharmacology studies were conducted as part of the pivotal 13-week toxicity study with an 11-week recovery in cynomolgus monkeys (See Study 209206 for a summarized report of findings in Section [13.1.2.1](#)). In brief, neurobehavioral observations which included extended clinical signs (CNS endpoints), respiratory evaluations (visual appraisal of respiratory rate/depth) and a cytokine release assessment (IL-2, IL-4, IL-5, IL-6, TNF-α, IFN-γ) were all unremarkable.

Cardiovascular assessments (blood pressure, heart rates, electrocardiogram (ECG) intervals, and the morphology of the ECG waveform) and urinalysis were conducted during the pivotal 13-week and 52-week repeat-dose toxicity studies in cynomolgus monkeys, and no effects of concizumab were observed up to the highest doses assessed (200 mg/kg/QW, intravenous (IV) and 50 mg/kg/day, SC).

Safety pharmacology assessments conducted in vitro consisted of human Fc receptor binding, antibody-dependent cell-mediated cytotoxicity (ADCC), complement fixation and binding to peripheral blood cells and are described in detail below.

Table 58. Safety Pharmacology Studies (In Vitro)

Study Details	Findings
Study No: 210178 Study Title: In Vitro Binding to Human Fc Gamma Receptors by Surface Plasmon Resonance (SPR) GLP Compliance Status: Non-GLP Species: Human Concentrations: 3.9 to 1000nM (FcR) Control: Assay buffer with isotype control (IgG4) mAb	FcγRI (CD64) bound to immobilized (monovalent) concizumab with a KD of 2nM. The dissociation constants (KDs) for the other Fc gamma receptors assessed: FcRn (H-274), FcγRIIa (131R and 131H variants, CD32a), FcγRIIb (CD32b), and FcγRIIIa (158V variant, CD16b, genetic polymorphism) ranged from 0.4μM to 1.7μM and negligible binding to FcγRIIIa (158F variant, CD16b, genetic polymorphism) was achieved. The FcR gamma binding constants (KD) for immobilized (monovalent) concizumab were comparable to those achieved with a human IgG4 control antibody and suggest that the specific attributes of the concizumab mAb do not alter normal FcR gamma interactions under the conditions of this assay.
Study No.: 209148 Study Title: Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) by concizumab (NNC 0172-0000-2021) GLP Compliance Status: Non-GLP Species: Human Endothelial Cell Line (EA.hy926WT) Primary HUVECs Concentrations: 0.64 ng/mL to 250μg/mL Control: Assay buffer with isotype control (IgG4) mAb or an anti-TFPI IgG1 control mAb (positive control for ADCC)	Concizumab bound to TFPI expressed on the surface of an endothelial cell line (EA.hy926WT) and on primary HUVECs (independent of the state of TNFα stimulation) to a degree that was similar to an anti-TFPI IgG1 control mAb by flow cytometry. Concizumab did not facilitate cell lysis by peripheral blood mononuclear effector cells (PBMCs) in either case and the IgG1 control antibody functioned as expected (induced cytotoxicity via PBMC effector cells). These results indicate that concizumab does not promote ADCC (via lysis of antibody-coated human endothelial cells) initiated by Fc-receptor interactions with effector cells (PBMCs) under these in vitro conditions.
Study No.: 209134 Study Title: Evaluation of the Ability of Anti-TFPI Monoclonal Antibodies to Activate the Complement Cascade (In Vitro) in a Complement Fixation ELISA Assay GLP Compliance Status: Non-GLP Species: Human Concentrations: 0.5 to 500 ng/mL Controls: Assay buffer with all components (negative control). Anti-TFPI serum from rabbit 2460A (positive control).	Concizumab (in complex with full length human TFPI) did not bind to complement component 4 (C4) or facilitate the activation of the complement cascade under the conditions of the complement fixation ELISA assay (in vitro). Binding of C4 was detected with the positive control rabbit polyclonal antibody (2460A) and was likely driven by the presence of IgG1 isotypes that preferentially bind to complement component 1q (C1q). These results are consistent with the IgG4 isotype of concizumab which (in general) does not bind to C1q and is therefore not expected to initiate activation of the complement system and the subsequent recruitment and cleavage of C4.

Study Details	Findings
Study No.: 209137	Flow cytometric analysis revealed that concizumab does not significantly bind to human peripheral blood cell subsets (granulocytes, monocytes, lymphocytes, thrombocytes, or erythrocytes) that do not express significant levels of TFPI on their cell surface.
Study Title: Flow Cytometric Evaluation of Binding of Concizumab to Human Peripheral Blood Cells and Human Endothelial Cell Lines	
GLP Compliance Status: Non-GLP	These findings are consistent with the results that showed that concizumab selectively binds to the TFPI expressing endothelial cell line (EAHy926WT) but not to the TFPI negative cell line (EAHy926AR).
Species: Human	
Concentrations: 6pg/mL to 300µg/mL	
Control: human IgG4 control anti-trinitrophenyl mAb antibody (hzATNP)	

Source: Reviewer constructed summary table of safety pharmacology studies (in vitro) submitted to the BLA.
Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; C1q, component 1q; C4, component 4; CD64, cluster of differentiation 64; ELISA, enzyme-linked immunoassay; FcR, Fc Receptor; FcRn, neonatal Fc Receptor; FcγRI, Fc Gamma Receptor 1; FcγRIIa, Fc gamma Receptor IIa; FcγRIIIa, Fc gamma Receptor IIIa; GLP, good laboratory practices; HUVEC, human umbilical vein endothelial cell; hzATNP, human IgG4 control anti-trinitrophenyl mAb antibody; IgG1, Immunoglobulin G1; IgG4, Immunoglobulin G4; K_D, equilibrium dissociation constant; K_{DS}, equilibrium dissociation constants; mAb, monoclonal antibodies; SPR, surface plasmon resonance; TFPI, tissue factor pathway inhibitor.

13.1.1.3. Pharmacodynamic Drug Interactions

Table 59. Pharmacodynamic Drug Interaction Studies

Study Details	Findings
Study No.: 300077 Sub Studies: BLz120302, BLz120304, BLz120601 and BLz120901. Study Title: Effect Studies with the Combination of Concizumab and rFVIIa in a Cuticle Bleeding Model in Rabbits with Transient (Anti FVIII-Antibody-Induced) Hemophilia A. Note: Extended Bleed Induction Species: NZW Rabbit (Female) Doses: Concizumab: 0.25 to 2 mg/kg Doses: rFVIIa: 1 to 9 mg/kg Controls: Assay buffer with isotype control (IgG) antibody (2 mg/kg)	Co-administration (IV) of concizumab and rFVIIa in a cuticle bleeding model in NZW rabbits (administered a neutralizing anti-FVIII antibody 25 minutes prior to bleed induction to transiently induce Hemophilia A) did not result in any clear additive or synergistic effects across 4 different sub-studies. BLz120302 (dosed 2 mg/kg concizumab + 9 mg/kg rFVIIa, 15 min after bleed induction) BLz120304 (dosed 1 mg/kg concizumab + 9 mg/kg rFVIIa, 5 min prior to bleed induction) BLz120601 (dosed 0.25 mg/kg concizumab + 1 mg/kg rFVIIa, 5 min prior to bleed induction) BLz120901 (dosed 2 mg/kg concizumab + 1 to 9 mg/kg rFVIIa, 30 min after bleed induction) Procoagulant effects were not observed when concizumab was administered after an extended bleed induction (15-30 min). In addition, there were no signs of adverse effects (e.g., decreases in platelet counts (up to 1-hour post-dose) and suggests that the degree of coagulation activation and consumption (e.g., associated with disseminated intravascular coagulation, DIC) was minimal in rabbits. Due to the nature and design of these rabbit studies, it is not possible to fully exclude an additive or synergistic effect of rFVIIa and concizumab and precautions should be taken when patients receiving concizumab prophylaxis experience break-through bleeding events and require treatment with rFVIIa (or another bypassing agent).

Source: Reviewer constructed summary table of the (in vitro) pharmacodynamic drug interaction studies submitted to the BLA.
Note: The clinical pharmacodynamic drug interaction (in vitro/ex vivo) studies (319076 and 321538) have been reviewed separately by the clinical pharmacology discipline.
Abbreviations: DIC, disseminated intravascular coagulation; FVIII, factor VIII; IgG, Immunoglobulin G; IV, intravenous; NZW, New Zealand White; rFVIIa, recombinant factor VIIa; rFVIIIa, recombinant factor VIIIa.

28-Day (Pharmacokinetic/Pharmacodynamic) Drug-Drug Interaction (Concizumab and rFVIIa) Toxicity Study in Cynomolgus Monkeys (Study 215431, GLP)

Key Study Findings:

- Administration of rFVIIa (IV) to cynomolgus monkeys at doses ≤ 1 mg/kg (three times with two-hour intervals) on Day 28 in the presence or absence of steady state concentrations of concizumab was well tolerated, with no dose-related pathological findings (e.g., no thrombi)
- Concizumab and rFVIIa were pharmacologically active in cynomolgus monkeys as indicated by the observed reduction in plasma fibrinogen, free TFPI, and residual TFPI functionality and the shortening of prothrombin times (PT), respectively.
- Thrombin/anti-thrombin (TAT) complex and D-dimer concentrations in the plasma tended to increase in cynomolgus monkeys administered concizumab or rFVIIa alone and the effects of

rFVIIa in the presence of steady state concentrations of concizumab were shown to be additive with respect to these markers of coagulation

Reviewer Comments: The pharmacological effects of concizumab (SC) and rFVIIa (IV) tended to be additive (when combined) with respect to clotting parameters and steady state concentrations of concizumab and did not adversely impact the safety profile of rFVIIa in cynomolgus monkeys.

Table 60. Study Information, Study 215431, GLP

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	<u>Concizumab</u> Initial loading dose: 9 mg/kg/day (Days 1 to 4, SC) Maintenance dose: 1 mg/kg/day (Days 5 to 28, SC) <u>Recombinant FVIIa</u> Three doses at 2-hr intervals at dose levels of 0.25, 0.5 or 1 mg/kg (Day 28 only, IV bolus).
Route of administration	SC (concizumab) / IV (rFVIIa)
Formulation/Vehicle	5.12 mg/mL L-histidine, 51.3 mg/mL sucrose, 0.01 mg/mL Polysorbate 80, 5.27 mg/mL arginine HCl, 1.46 mg/mL NaCl, pH 6.
Control	A control group (3/sex) received vehicle on Days 1 to 28 and three doses (1 mg/kg/dose) of rFVIIa on Day 28 for comparison of potential effects excluding the steady state concentration of NNC0172-2021.
Species/Strain	Cynomolgus monkey
Number/Sex/Group	3
Age	2 to 2.5 years of age / adolescent (sexually immature)
Satellite groups/unique design	Drug-drug interaction study Anti-drug antibody (ADA) analysis included No recovery No ophthalmometry
Deviations from study protocol	None that affected the interpretation of the results.

Source: Reviewer constructed summary table of Study 215431 submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; GLP, good laboratory practices; IV, intravenous; NaCl, sodium chloride; rFVIIa, recombinant factor VIIa; SC, subcutaneous

Table 61. Observations and Results, Study 215431, GLP

Parameters	Major Findings
Mortality	There were no unscheduled deaths in cynomolgus monkeys administered concizumab for 4 weeks at 1 mg/kg/day (SC) followed by 3 doses of rFVIIa at 2-hour intervals of 0.25, 0.5 or 1 mg/kg (Day 28 Only, IV Bolus).
Clinical signs	Transient reddening of the SC injection site on the upper back of a single male (#10) was noted on Day 8 only (non-adverse) and clinical signs were otherwise unremarkable.
Body weights and food consumption	Unremarkable
Hematology	To evaluate the effect of rFVIIa in the presence of a steady state concentration of concizumab compared to rFVIIa alone, data from Day 26 was compared with data from after rFVIIa dosing (Day 28 2 hours post first rFVIIa dose; Day 28 two hours post third rFVIIa dose; Day 29 - necropsy).

Parameters	Major Findings
	(RBC Parameter): Erythroid parameters (hemoglobin, red blood cells, packed cell volumes and mean cell volumes) tended to decline with repeat blood sampling (Day 28 and Day 29) and mean values on Day 26 were similar to pretreatment. The decline in RBC parameters was considered driven by the frequent blood sampling (not test article related). (WBC Parameters): A similar decline was observed in platelet counts in all dosing groups (including controls).
Coagulation	Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT): There were no notable changes in PT and APTT in cynomolgus monkeys administered concizumab (only) for 4 weeks at 1 mg/kg/day (SC). A shortening of PT was observed in both sexes at 2 hours after the third dose of rFVIIa (only) and rebounded thereafter. Prothrombin Time (independent of dose level of rFVIIa) was shortened in both sexes in the presence of concizumab at 2 hours after the first rFVIIa administration and persisted after the third administration at the HD (1 mg/kg) only. Prothrombin time reductions at the HD (1 mg/kg, rFVIIa) in the presence of steady state concizumab were comparable to those seen with rFVIIa only and normalized on Day 29 (slightly exceeding baseline values). Fibrinogen: A reduction in fibrinogen was present in monkeys administered concizumab for 4 weeks at 1 mg/kg/day (SC). (Thrombin Antithrombin (TAT) Complex): Thrombin antithrombin complex is a protein complex of thrombin and antithrombin and is a marker of net activation of coagulation. Thrombin antithrombin complex (TAT) concentrations (in general) increased in cynomolgus monkeys administered concizumab (only) for 4 weeks at 1 mg/kg/day (SC). On Day 28, after treatment with rFVIIa (2-hrs after first and third administrations) in the presence of concizumab the average TAT concentration was increased further (dose-dependently) and indicated an additive effect.

Table 62. Thrombin Antithrombin (TAT) Complex

		Ratio D.26		D.28	Ratio		D.28	Ratio D.28		Ratio D.29	
TAT (µg/L)	Pre-treatment	D.26	vs pre-treatment	2h+1st rFVIIa	D.28 (1) vs D.26	2h+3rd rFVIIa	(3) vs D.26	D.29	vs D.26		
M+F											
Gp 1	47.0	7.9	0.17	*11.6	1.5	49.6	6.3	13.6	1.7		
Gp 2	17.6	36.9	2.1	46.7	1.3	40.1	1.1	80.6	2.2		
Gp 3	35.5	34.1	1.0	56.7	1.7	55.9	1.6	27.6	0.8		
Gp 4	14.5	31.4	2.2	63.8	2.0	73.1	2.3	24.2	0.8		
[Gp 4 vs Gp 1]		4.0		5.5		1.5		1.8			

a Control value at this timepoint represents a further baseline value. For this group only, this was two hours after a vehicle dose and before exposure to rFVIIa (see deviations Section 3). Calculated ratios comparing post-rFVIIa dose values with pre-rFVIIa dose values on Day 26 are based on unrounded group means.

a Control value at this timepoint represents a further baseline value. For this group only, this was two hours after a vehicle dose and before exposure to rFVIIa (see deviations Section 3). Calculated ratios comparing post-rFVIIa dose values with pre-rFVIIa dose values on Day 26 are based on unrounded group means.

Source: Study Report 215431

GP1 (rFVIIa Only: 1 mg/kg), GP2, GP3, GP4 (Concizumab: Initial loading dose: 9 mg/kg/day (Days 1-4, SC), Maintenance dose: 1 mg/kg/day (Days 5-28, SC) + rFVIIa 0.25, 0.5 or 1 mg/kg, respectively, administered three times on Day 28 only. Two hours between doses).

(D-dimer Biomarker): The concentrations of D-dimer (in general) increased in cynomolgus monkeys administered concizumab (only) for 4 weeks at 1 mg/kg/day (SC) and in cynomolgus monkeys administered rFVIIa (alone). On Day 28, after treatment with rFVIIa in the presence of concizumab, the mean D-dimer

Parameters

Major Findings

concentration was increased further and indicated an additive effect.

Table 63. D-Dimer (MDDM) Biomarker

MDDM (mg/L)	Pre-treatment	D.26	Ratio D.26 vs pre-treatment	D.28 2h +1st rFVIIa	Ratio D.28 (1) vs D.26	D.28 2h +3rd rFVIIa	Ratio D.28 (3) vs D.26	D.29	Ratio D.29 vs D.26
M+F									
Gp 1	2.1	0.7	0.3	*1.0	1.5	2.3	3.2	1.2	1.8
Gp 2	0.7	4.0	5.8	5.1	1.3	5.4	1.4	4.1	1.0
Gp 3	1.1	4.9	4.6	6.6	1.4	7.5	1.5	5.5	1.1
Gp 4	0.6	3.8	6.5	6.1	1.6	7.0	1.9	4.7	1.2
[Gp 4 vs Gp 1]		5.4		5.9		3.1		3.8	

a Control value at this timepoint represents a further baseline value. For this group only, this was two hours after a vehicle dose and before exposure to rFVIIa (see deviations Section 3). Calculated ratios comparing post-rFVIIa dose values with pre-rFVIIa dose values on Day 26 are based on unrounded group means.

Source: Study Report 215431

GP1 (rFVIIa Only: 1 mg/kg), GP2, GP3, GP4 (Concizumab: Initial loading dose: 9 mg/kg/day (Days 1-4, SC), Maintenance dose: 1 mg/kg/day (Days 5-28, SC) + rFVIIa 0.25, 0.5 or 1 mg/kg, respectively, administered three times on Day 28 only. Two hours between doses).

Thrombin Antithrombin (TAT) and D-dimer concentrations were notably reduced in a single male (#8) that was shown to be ADA positive, exhibited reduced concizumab exposures and elevated TFPI activity. After administration of rFVIIa, this male was capable of generating increases in TAT and D-dimers suggesting that the ADAs to concizumab did not interfere with the activity of rFVIIa.

(Anti-Thrombin (AT) Concentrations): AT concentrations were generally unaffected by treatment with concizumab and declined minimally after the 1st/3rd doses of rFVIIa on Day 28 and through Day 29 (independent of dose). There were no notable effects on AT after dosing with rFVIIa in the absence of concizumab.

Table 64. Anti-Thrombin Concentrations

AT (%)	Pre-treatment	D.26	Ratio D.26 vs pre-treatment	D.28 2h +1st rFVIIa	Ratio D.28 (1) vs D.26	D.28 2h +3rd rFVIIa	Ratio D.28 (3) vs D.26	D.29	Ratio D.29 vs D.26
M+F									
Gp 1	94.2	113.3	1.2	*116.3	1.0	98.2	0.9	97.0	0.9
Gp 2	99.7	94.5	0.9	96.0	1.0	89.5	0.9	81.3	0.9
Gp 3	101.8	100.3	1.0	101.2	1.0	92.3	0.9	85.7	0.9
Gp 4	97.7	96.2	1.0	94.0	1.0	84.0	0.9	79.3	0.8
[Gp 4 vs Gp 1]		0.8		0.8		0.9		0.8	

a Control value at this timepoint represents a further baseline value. For this group only this was two hours after a vehicle dose and before exposure to rFVIIa (see deviations Section 3). Calculated ratios comparing post-rFVIIa dose values with pre-rFVIIa dose values on Day 26 are based on unrounded group means.

Source: Study Report 215431

GP1 (rFVIIa Only: 1 mg/kg), GP2, GP3, GP4 (Concizumab: Initial loading dose: 9 mg/kg/day (Days 1-4, SC), Maintenance dose: 1 mg/kg/day (Days 5-28, SC) + rFVIIa 0.25, 0.5 or 1 mg/kg, respectively, administered three times on Day 28 only. Two hours between doses).

(Free Tissue Factor Pathway Inhibitor [TFPI] Concentrations): Detectable levels of free TFPI were present in all cynomolgus monkeys at pre-treatment and in controls on Days 26 and 29, with no apparent influence of dosing with rFVIIa (Day 29). On Days 26 and 29, free TFPI values were below the lower limit of detection for all concizumab-dosed cynomolgus monkeys barring the ADA positive male (#8) where quantifiable levels were present.

(Residual TFPI Functionality [Chromogenic] assay): Residual TFPI functionality was measured in all cynomolgus monkeys during pre-treatment, and the residual TFPI functionality decreased in cynomolgus monkeys administered concizumab from Day 2 forward (often below the lower limit of quantification), particularly in males. The residual TFPI functionality was not altered significantly by rFVIIa treatment.

Parameters	Major Findings
	(Protein C and Protein S): Plasma protein C/S concentrations were unaffected by treatment with concizumab and/or rFVIIa.
Clinical chemistry	There were no notable changes in clinical chemistry parameters in cynomolgus monkeys administered concizumab for 4 weeks at 1 mg/kg/day (SC) followed by 3 doses of rFVIIa at 2-hour intervals of 0.25, 0.5 or 1 mg/kg (Day 28 Only, IV Bolus).
Anti-drug antibody (ADA) analysis	Low levels of ADAs (close to the assay cut point), were detected at pre-treatment (#109 and #9) without explanation and on Day 29 (#9). Anti-drug antibodies (ADAs) detected in male #8 on Day 29, were deemed related to concizumab dosing and the Optical Density (OD) value in the ADA assay in male #8 exceeded the assay cut point by 10-fold. No ADAs were detected in the other cynomolgus monkeys in this study however the negative results may be due to interference from high concentrations of concizumab in plasma samples (leading to false negative results).
Toxicokinetics	(Concizumab) The plasma exposure to concizumab tended to be lower in females than in males and the median t_{max} was 24 hours (Day 1) and ranged from 4 hours to 6 hours on Day 27. Concizumab exposures were reduced in one male (#8) that developed ADAs. (rFVIIa) The mean terminal half-life ranged from 1.4 hours to 1.8 hours and there was no apparent difference in exposure to rFVIIa between the sexes. The FVIIa clot activity increased with ascending dose of rFVIIa (dose-proportional). There was no apparent difference in the toxicokinetics of 1 mg/kg rFVIIa administered in the presence or absence of steady state concizumab.
Gross pathology	Subcutaneous and intravenous injection sites (saphenous vein) and sampling sites (foreleg and inguinal areas) were found to be red and corresponded with the microscopic finding of hemorrhage at these sites. These findings were considered consistent with the injection procedures and venipuncture.
Organ weights	Organ weight changes in the testis, epididymis, prostate, seminal vesicles, ovary, and uterus were deemed to reflect the different stages of sexual maturity in the adolescent cynomolgus monkeys used on study rather than a direct effect of concizumab.

Parameters	Major Findings
Histopathology	(Subcutaneous Injection Site): Inflammatory cells (lymphocytic, plasmacytic cell infiltration) at the concizumab (SC) injection site were increased (dose independent) in both sexes and the infiltration was minimal at the HD (1 mg/kg) of rFVIIa when administered in the presence of steady state concizumab. These findings were present to some extent in rFVIIa only and vehicle controls and were therefore considered related to the injection procedure rather than a direct effect of either test-article.
Adequate battery: yes	(Thrombi): There were no thrombi observed in cynomolgus monkeys administered concizumab for 4 weeks at 1 mg/kg/day (SC) followed by 3 doses of rFVIIa at 2-hr intervals of 0.25, 0.5 or 1 mg/kg (Day 28 Only, IV Bolus).

Source: Reviewer constructed summary table of the toxicology Study (215431) submitted to the BLA.
Abbreviations: ADA, anti-drug antibody; APTT, activated partial thromboplastin time; AT, anti-thrombin; IV, intravenous; MDDM, D-Dimer; OD, optical density; PT, prothrombin time; RBC, red blood cell; rFVIIa, recombinant factor VIIa; SC, subcutaneous; TAT, thrombin antithrombin; TFPI, tissue factor pathway inhibitor; tmax, time to reach maximum concentration; WBC, white blood cell

13.1.1.4. ADME/Pharmacokinetics

Overall, the nonclinical data characterizing the absorption, distribution, metabolism, and elimination of concizumab supported to use of the selected nonclinical species (New Zealand White (NZW) rabbits and cynomolgus monkeys), allowed for interspecies exposure comparisons and provided relevant information to determine clinical dose selection.

Absorption

The pharmacokinetics of concizumab was evaluated in NZW rabbits and cynomolgus monkeys after single intravenous (IV) and subcutaneous (SC) administration. Repeat-dose pharmacokinetics and toxicokinetics were assessed in cynomolgus monkeys.

Table 65. Pharmacokinetic Parameters of Concizumab (Single Dose (SD) Intravenous (IV) Administration)

Species	Dose (mg/kg)	AUC _{inf} (µg.hr/mL)	Clearance (mL/kg/hr)	Volume of Distribution (mL/kg, V _z)	t _{1/2} (hour)	Study Reference
NZW Rabbit	2	1210	1.7	44	NR	209176
	2	1080	1.9	171	NR	LEEHO81102
	20	39400	0.5	123	NR	
	20	33000	0.6	52	86	209305
Cynomolgus Monkey	2	747	2.7	61	NR	LEEHO81101
	20	46600	0.4	130	210	
	0.1	1	102	3610	NR	210156
	0.5	70	7.7	1110	NR	
	1	418	2.5	205	NR	
	20	66000	0.31	NR	198	208250

Source: Reviewer constructed summary table of single dose (IV) Pharmacokinetics submitted to the BLA.
Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; NR, not reported; NZW, New Zealand White; t_{1/2}, terminal half-life

The clearance and volume of distribution of concizumab decreased with increasing (IV) dose in NZW rabbits and cynomolgus monkeys indicating non-linear pharmacokinetics. There were no

notable differences in the single dose pharmacokinetics between the sexes in cynomolgus monkeys (210156).

Lower doses of concizumab were cleared more rapidly from the circulation in cynomolgus monkeys, while at higher doses the plasma concentration profile became flat until a concentration of 10-20 µg/mL, at which the elimination rate increased. This pattern is consistent with target-mediated drug disposition (TMDD) where a compound is cleared from the circulation when binding to its target (typically a cell-bound target) in this case most likely the TFPI bound to the surface of endothelial cells. At higher concentrations, the TMDD of concizumab is saturated, resulting in a slower clearance and a flat plasma concentration profile with a half-life of 200 hours in the cynomolgus monkey, which is consistent with the pharmacokinetic characteristics of monoclonal antibodies. At lower concentrations, the target-mediated clearance of concizumab accelerates and plasma concentrations decrease rapidly.

Exposure increased with ascending dose level in NZW rabbits and cynomolgus monkeys when concizumab was administered as a single subcutaneous (SC) dose. The t_{max} increased with ascending dose from 36 hours (2 mg/kg) to 120 hours (20 mg/kg) in NZW rabbits and supports the premise of TMDD. Bioavailability was found to be 80% in NZW rabbits and cynomolgus monkeys.

Table 66. Pharmacokinetic Parameters of Concizumab (Single Subcutaneous Administration)

Species	Dose (mg/kg)	C _{max} (µg/mL)	t _{max} (hr)	AUC _{inf} (µg.hr/mL)	t _{1/2} (hr)	F (%)	Study Reference
NZW Rabbit	2	9	NR	868	NR	80	LEE081102
	2	3	36	144	NR	NR	209305
	5	19.5	48	1451	NR	NR	
	10	63	60	7490	NR	NR	
	20	175	120	27400	NR	83	
Cynomolgus Monkey	20	145	168	50700	183	77	208250

Source: Reviewer constructed summary table of single dose (SC) pharmacokinetics submitted to the BLA.

Abbreviations: AUC_{inf}, area under the concentration-time curve from time zero to infinity; C_{max}, maximum plasma concentration; F, bioavailability; NR, not reported; NZW, New Zealand White; t_{1/2}, terminal half-life; t_{max}, time to reach maximum concentration

Repeat-Dose Toxicokinetics

The toxicokinetics of concizumab was assessed as a part of a Dose Range Finding (DRF) study (SC) and the five repeat-dose toxicity studies (SC/IV) of 4, 13, 26, or 52 weeks in duration conducted in cynomolgus monkeys at dose levels ranging from 0.5 mg/kg to 200 mg/kg. Daily administration (SC) of concizumab was employed in repeat-dose toxicology studies in an attempt to overcome the effects of TMDD (particularly at low doses) and maintain target (TFPI) saturation.

Table 67. Toxicokinetic Parameters of Concizumab (SC/IV) in Cynomolgus Monkeys (GLP)

Duration	Dose (mg/kg)	Route (Frequency)	C _{max} (µg/mL)	AUC _{tau} (µg.hr/mL)	Rac	Study Reference
4 weeks	3	SC (QD)	638	14100	162	210130
	9	SC (QD)	1730	37400	73	
	30	IV (QW)	1290	154000	2.7	
13 weeks	1	SC (QD)	282	5930	385	209206
	10	SC (QD)	4200	83600	108	
	50	SC (QD)	14700	326000	58	

Duration	Dose (mg/kg)	Route (Frequency)	C _{max} (µg/mL)	AUC _{tau} (µg.hr/mL)	Rac	Study Reference
	200	IV (QW)	11800	1580000	2.8	
26 weeks	3	SC (QD)	992	21400	130	211087
	9	SC (QD)	3310	76500	58	
	30	IV (QW)	2650	307000	3.8	
52 weeks	0.5	SC (QD)	83	1660	ND	213542
	1	SC (QD)	309	6890	232	
	9	SC (QD)	5070	99300	88	
4 weeks (DDI)	(9) 1*	SC (QD)	210	4545	ND	215431

Source: Reviewer constructed summary table of repeat dose toxicokinetics (SC/IV) submitted to the BLA.

*Initial loading dose: 9 mg/kg/day (Days 1-4, SC) Maintenance dose: 1 mg/kg/day (Days 5-28, SC).

Abbreviations: AUC, area under the concentration-time curve; AUC_{0-24hr}, area under the concentration-time curve from time zero to 24 hours; AUC_{0-168hr}, area under the concentration-time curve from time zero to 168 hours; AUC_{tau}, area under the concentration-time curve for a dosing interval; C_{max}, maximum plasma concentration; DDI, drug-drug interaction; IV, intravenous; ND, not determined; QD, once daily; Rac, ratio of accumulation; SC, subcutaneous

Distribution

No dedicated distribution studies were conducted with concizumab. The distribution of concizumab was evaluated by immunohistochemistry in rabbits ([Hansen et al. 2014](#)), tissue cross-reactivity studies (human and monkey), and immunohistochemistry in cynomolgus monkeys. In general, concizumab was found to be present in the blood and associated with the vascular endothelium, with only minor differences between humans and cynomolgus monkeys.

Pilot Tissue Cross-Reactivity (TCR) Study of Concizumab with Limited Normal Human and Cynomolgus Monkey Tissues (Study 209125, Non-GLP)

Key Study Findings

- The concizumab staining pattern was (in general) similar between the human and cynomolgus monkey tissues examined and corresponded to known sites of TFPI tissue expression.
- The noted differences observed between humans and cynomolgus monkeys with regards to concizumab tissue staining patterns (e.g., cynomolgus monkey islet cells and acinar epithelium in the pancreas) may represent individual variations and/or differences in age, disease status, artifacts of the process of dying, or true species differences. As these sites in the pancreas are not known to express TFPI the observed staining in these tissue elements might represent either previously unrecognized sites of TFPI expression or true tissue cross-reactivity.

Reviewer Comments: Tissue cross-reactivity of concizumab was similar between tissue cryosections derived from healthy humans and cynomolgus monkeys.

Table 68. Study Information, Study 209125, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The objective of this study was to evaluate the potential tissue cross reactivity (TCR) of concizumab.

Study Features and Methods	Details
Methods	Concizumab was used to stain cryosections of limited normal human and cynomolgus monkey tissues (3 donors per tissue) at concentrations of 1 µg/mL or 10 µg/mL using an indirect precomplexing immunoperoxidase procedure. Positive controls consisted of cryosections of HEK cells expressing human TFPI and HEK cells expressing cynomolgus monkey TFPI. Negative controls consisted of cryosections of HEK cells expressing human interferon alpha and HEK cells expressing cynomolgus monkey interferon alpha. The specific reactivity of concizumab with the positive controls and the lack of specific reactivity with the negative controls, as well as the lack of reactivity of the control IgG with the positive and negative controls, indicated that the assay was sensitive and specific.
Results	(Human) Human tissues staining by concizumab was present in the endothelium of small to medium sized vessels in cerebellum, esophagus, small intestine, heart, kidney, liver, lung, lymph node, pancreas, spleen, and thymus. In mononuclear cells in the esophagus, small intestine, kidney, liver, lung, lymph node, spleen, and thymus. In spindle cells in the cerebellum, esophagus, small intestine, heart, kidney, liver, lung, lymph node, pancreas, spleen, and thymus. In the extracellular proteinaceous material in cerebellum, esophagus, small intestine, heart, kidney, liver, lung, lymph node, pancreas, spleen, and thymus. (Cynomolgus Monkey) In cynomolgus monkeys, concizumab tissue staining of the same cell types was present in the corresponding tissues with the addition of the cerebrum (endothelium, spindle cells, and extracellular proteinaceous material) and pancreas (mononuclear cells). Staining of islet cells and acinar epithelium in the pancreas and mesothelium in the spleen was observed only in the cynomolgus monkey tissue panel (not in the human tissue panel).

Source: Reviewer constructed summary table of Study 209125 submitted to the BLA.
Abbreviations: GLP, good laboratory practices; HEK, human embryonic kidney; IgG, immunoglobulin G; TCR, tissue cross reactivity; TFPI, tissue factor pathway inhibitor

Tissue Cross-Reactivity (TCR) Study of Concizumab with Normal Human and Cynomolgus Monkey Tissues (Study 209280, GLP)

Key Study Findings

- The concizumab staining pattern was (in general) similar between the human and cynomolgus monkey tissues examined and corresponded to known sites of TFPI tissue expression.
- The noted differences observed between humans and cynomolgus monkeys with regards to concizumab tissue staining patterns (e.g., human decidual cell staining in the placenta and

testicular spermatogenic cells, placental Hofbauer cells and trophoblastic epithelium in the cynomolgus monkey) may represent either sites with novel TFPI expression or true tissue cross reactivity.

Reviewer Comments: With the exception of the positive control HEK-293 cells that overexpressed membrane associated TFPI (either human or cynomolgus monkey), all of the cellular staining observed in this TCR study was localized to the cytoplasm or cytoplasmic structures and these cellular locations are unlikely to be accessible to concizumab under in vivo conditions.

Table 69. Study Information, Study 209280, GLP

Study Features and Methods	Details
GLP compliance	Yes
Objective	The objective of this study was to evaluate the potential tissue cross reactivity (TCR) of concizumab with cryosections of normal healthy human and cynomolgus monkey tissues.
Methods	Concizumab was used to stain cryosections of normal human and cynomolgus monkey tissues (3 donors per tissue) at concentrations of 1 µg/mL or 10 µg/mL using an indirect precomplexing immune-peroxidase procedure. Positive controls consisted of cryosections of HEK cells expressing human TFPI and HEK cells expressing cynomolgus monkey TFPI. The negative control consisted of cryosections of non-transfected HEK cells. The specific reactivity of concizumab with the positive controls and the lack of specific reactivity with the negative control, as well as the lack of reactivity of a control IgG with the positive and negative controls, indicated that the assay was sensitive and specific.
Results	(Human) Human tissues staining by concizumab was present in the endothelium of small to medium sized vessels, in hematopoietic precursor cells and mononuclear cells, in spindle cells, in extracellular proteinaceous material, and in placental decidual cells. (Cynomolgus Monkey) In cynomolgus monkeys, concizumab tissue staining of the same cell types was present with the exception of placental decidual cells. Staining of testicular spermatogenic cells, placental Hofbauer cells (placental villous macrophages) and trophoblastic epithelium was observed only in the cynomolgus monkey tissue panel (not observed in the human tissue panel).

Source: Reviewer constructed summary table of Study 209280 submitted to the BLA.

Abbreviations: GLP, good laboratory practices; HEK, human embryonic kidney; IgG, immunoglobulin G; TCR, tissue cross reactivity; TFPI, tissue factor pathway inhibitor

Concizumab Biodistribution and Immunohistochemistry (IHC) for Endogenous TFPI in the Cynomolgus Monkey Choroid Plexus (Study KAHL130402, non-GLP)

Key Study Findings

- The intensity of IHC staining for concizumab increased (in a dose-dependent manner) in the choroid plexus of cynomolgus monkeys (more intense staining at higher doses of concizumab)
- Immunohistochemical reactivity for concizumab was predominantly observed in the lumen of blood vessels (suggesting its presence in the blood plasma) and the endothelium
- Immunohistochemical reactivity for concizumab in a sample of inflamed choroid plexus tissue derived from the 26-week cynomolgus monkey study displayed a punctate staining pattern that likely represented granular tissue deposits of concizumab
- Immunohistochemical reactivity for endogenous TFPI was predominantly associated with the endothelium and the intensity of the endothelial TFPI staining was stronger (versus controls) in tissues derived from concizumab-dosed cynomolgus monkeys
- A minimal amount of TFPI staining was observed in the lumen of blood vessels derived from concizumab-dosed cynomolgus monkeys only (not present in controls)

Reviewer Comments: Concizumab was predominantly distributed to the plasma and endothelium in tissues derived from the 26-week cynomolgus monkey study. Staining of TFPI was enhanced in tissues derived from concizumab-dosed cynomolgus monkeys and suggests feedback from the coagulation system to increase TFPI levels in response to the loss in TFPI activity in normal cynomolgus monkeys.

Table 70. Study Information, Study KAHL130402, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The objective of this study was to analyze the biodistribution of concizumab and the expression of endogenous TFPI in the choroid plexus of cynomolgus monkeys treated for 26 weeks.
Methods	An immunohistochemical (IHC) stain for detecting concizumab in cynomolgus monkey tissue was established using a monoclonal mouse anti-human IgG4 antibody on paraffin-embedded samples. An IHC stain for detecting endogenous TFPI in cynomolgus monkey tissue was established using a monoclonal mouse anti-human TFPI antibody on paraffin embedded tissues. These IHC stains were applied to tissue samples of choroid plexus from the 26-week toxicity study conducted in cynomolgus monkeys (Study 211087 Section 13.1.2.1).

Source: Reviewer constructed summary table of Study KAHL130402 submitted to the BLA

Abbreviations: GLP, good laboratory practices; IHC, immunohistochemical; TFPI, tissue factor pathway inhibitor

Metabolism

Concizumab is a monoclonal antibody (mAb) consisting of naturally occurring (endogenous) amino acids. Hence the metabolism of concizumab is expected to involve the proteolytic digestion of the antibody into peptides and its constituent amino acids. Prototypical biotransformation studies are therefore not considered relevant for concizumab.

Excretion

No dedicated excretion studies were conducted as concizumab is expected to be proteolytically broken down into individual amino acids that will either be repurposed or excreted in vivo.

Pharmacokinetic Drug Interactions

The potential for pharmacokinetic drug-drug interactions between concizumab and rFVIIa was investigated in a 28 Day (PK/PD) Drug-Drug Interaction (Concizumab and rFVIIa) Toxicity Study in Cynomolgus Monkeys (Study 215431). There were no notable differences in rFVIIa exposures (Day 28) in the presence or absence of steady state concizumab and the pharmacokinetics of concizumab was not assessed after the administration of rFVIIa (Day 28). This study was thoroughly reviewed under the PD drug interactions section above (Study 215431 Section [13.1.1.3](#)).

Table 71. Toxicokinetic Data from Repeat Dose Toxicology Studies

Study Details	Major Findings
General toxicology studies	
Study no: 210130	
Study title: 4-week (SC/IV) toxicity study in cynomolgus monkeys	
Sample collection times: pre-dose, 2, 6, 24, 72, 120 and 168 hours post-dose (all groups, Day 1). Pre-dose, 2, 6, 24, 72, 120 and 168 hours post-dose (Groups 1/4, Day 22). Pre-dose, 2, 6 and 24 hours post-dose (Groups 2/3, Day 28).	
Accumulation: extensive (SC/IV).	
Dose proportionality: generally, greater than dose proportional.	
NOAEL (SC): 9 mg/kg/day (HD)	
NOAEL (IV): 30 mg/kg/day	
Exposure margin: 1670x MRHD (sex-averaged AUC at the SC NOAEL) to the MRHD (22.4 µg.hr/mL, AUC ₀₋₂₄)*	

Table 72. Mean Toxicokinetic Parameters (Week 1 and Week 4) After Subcutaneous (QD) or Intravenous (QW) Administration of Concizumab to Cynomolgus Monkeys

Mean Toxicokinetic parameters (Week 1 and Week 4) after Subcutaneous (QD) or Intravenous (QW) Administration of Concizumab to Cynomolgus Monkeys							
Week	Dose (mg/kg/day)	Route	Sex	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg.hr/mL)	RaCobs
1	3	SC	F	7.2	24	106	-
			M	6.3	24	83.4	-
	9	SC	F	34.5	24	408	-
			M	48.6	24	685	-
4	3	SC	F	542	8.7	12400	122
			M	733	24	15700	201
	9	SC	F	1580	16	34300	83.9
			M	1870	4	40500	61.8
Week	Dose (mg/kg/week)	Route	Sex	C _{2hr} (µg/mL)	AUC _{0-168hr} (µg.hr/mL)	AUC _{0-inf} (µg.hr/mL)	RaCobs
1	30	IV	F	684	53900	-	-
			M	657	65800	-	-
4	30	IV	F	1250	137000	-	2.55
			M	1310	170000	@	2.74

Source: Reviewer Generated Table from Sponsor's data

@AUC_{0-inf} in male #11 was 29900 µg.hr/mL (Suspected neutralizing ADAs)

Source: Reviewer constructed table from study report (210130) data submitted to BLA

Study Details

Study no: 209206

Study title: 13-week (SC/IV) toxicity study in cynomolgus monkeys

Sample collection times: predose, 2, 6, and 24 hours postdose (Day 1 and Day 91, SC). Predose, 0.5, 2, 6, 24, 72, 120 and 168 hours postdose (Day 1 and Day 85, IV).

Accumulation: extensive (SC) and mild (IV).

Dose proportionality: generally, greater than dose proportional.

NOAEL (SC): 1 mg/kg/day (LD)

NOAEL (IV): not determined

Exposure margin: 264x MRHD (sex-averaged AUC at the SC NOAEL) to the MRHD (22.4 µg.hr/mL, AUC₀₋₂₄)*

Major Findings

Table 73. Mean Toxicokinetic Parameters (Day 1 and Day 91) after Subcutaneous (QD) or Intravenous (QW) Administration of Concizumab to Cynomolgus Monkeys

Mean Toxicokinetic Parameters (Day 1 and Day 91) after Subcutaneous Administration (QD) of Concizumab to Cynomolgus Monkeys								
Day	Dose (mg/kg/day)	Route	Sex	C _{max} (µg/mL)	t _{max} (hr)	AUC _{0-24hr} (µg.hr/mL)	AUC _{0-inf} (µg.hr/mL)	RaC _{obs}
1	1	SC	F	1.34	6-24	17.5	-	-
			M	1.28	6-24	20.1	-	-
	10	SC	F	69.5	24	967	-	-
			M	44.5	24	695	-	-
91	50	SC	F	444	24	5840	-	-
			M	365	24	5610	-	-
	1	SC	F	270	0-24	5950	73900	390
			M	291	0-24	5895	91700	380
	10	SC	F	4340	0-24	79000	2260000	86
			M	4060	2-6	88200	875000	130
	50	SC	F	13500	0-24	297000	7850000	52
			M	15800	2-24	354000	9630000	93

Source: Reviewer Generated Table from Sponsor's data

Mean Toxicokinetic Parameters (Day 1 and Day 85) after Intravenous Administration (QW) of Concizumab to Cynomolgus Monkeys

Day	Dose (mg/kg/Week)	Route	Sex	C _{2hrs} (µg/mL)	AUC _{0-168hr} (µg.hr/mL)	AUC _{0-inf} (µg.hr/mL)	RaC _{obs}
1	200	IV	F	5040	451000	-	-
			M	4580	446000	-	-
85	200	IV	F	12200	1630000	6340000	2.8
			M	11300	1520000	6040000	2.7

Source: Reviewer Generated Table from Sponsor's data

Source: Reviewer constructed table from study report (209206) data submitted to BLA

Study no: 211087

Study title: 26-week (SC/IV) toxicity study in cynomolgus monkeys

Sample collection times: predose, 2, 6, 24, 72, 120 and 168 hours postdose (Day 1 and Week 26, SC/IV).

Accumulation: extensive (SC) and mild (IV).

Dose proportionality: generally, greater than dose proportional.

NOAEL (SC/IV): not determined

LOAEL (SC): 3 mg/kg/day

LOAEL (IV): 30 mg/kg/week

Exposure Margin: 953x MRHD (sex-averaged AUC at the SC LOAEL) to the MRHD (22.4 µg.hr/mL, AUC₀₋₂₄)*

Table 74. Mean Toxicokinetic Parameters (Day 1 and Week 26) After Subcutaneous (QD) or Intravenous (QW) Administration of Concizumab to Cynomolgus Monkeys

Toxicokinetic Parameters (Mean) in Cynomolgus Monkeys Administered (SC, QD) Concizumab for 26 Weeks (Day 1 and Week 26)							
Time point	Dose (mg/kg)	Sex	t _{max} * (h)	C _{max} (ng/mL)	AUC _{0-24h} (h*ng/mL)	AUC _{0-24h} /Dose	RaC _{obs}
Day 1	3	M	24	13500±4120	219000±48000	73000±16000	-
		F	24	10500±4550	180000±99700	59900±33200	-
		M	24	102000±44900	1640000±748000	183000±83100	-
		F	24	79600±13200	1220000±231000	135000±25700	-
Week 26	3	M	6	1070000±291000	23500000±8290000	7830000±2760000	110±42.2
		F	4	914000±278000	19200000±4300000	6400000±1430000	150±54.0
		M	6	3730000±516000	86000000±11900000	9550000±1320000	63.0±32.0
		F	6	2890000±381000	67000000±9150000	7440000±1020000	52.8±10.1

Source: 211087 Study Report (*T_{max} = Median Value)

Toxicokinetic Parameters (Mean) in Cynomolgus Monkeys Administered (IV, QW) Concizumab for 26 Weeks (Week 1 and Week 26)

Time point	Dose (mg/kg)	Sex	C ₀ (ng/mL)	T _{max} * (h)	C _{max} (ng/mL)	AUC _{0-168h} (h*ng/mL)	RaC _{obs}
Week 1	30	M	1120000±210000	2	1050000±105000	92100000±5540000	-
		F	1080000±307000	2	883000±69100	76000000±7510000	-
Week 26	30	M	1110000±497000	2	2270000±711000	238000000±74200000	2.6±0.78
		F	1880000±441000	15	3030000±163000	376000000±38600000	4.9±0.70

Source: 211087 Study Report (*T_{max} = Median Value)

Source: Applicant constructed table from study report (211087) submitted to BLA.

Study Details

Study no: 213542

Study title: 52-week (SC) toxicity study in cynomolgus monkeys

Sample collection times: predose, 2, 6, 24 hours postdose (Day 1, Week 13, Week 26, and Week 52).

Accumulation: extensive (particularly and the LD/MD)

Dose proportionality: generally, greater than dose proportional.

NOAEL (SC): 0.5 mg/kg/day

Exposure margin: 74x MRHD (sex-averaged AUC at the NOAEL) to the MRHD (22.4 µg.hr/mL, AUC₀₋₂₄)*

Major Findings

Table 75. Toxicokinetic Parameters in Cynomolgus Monkeys Administered (QD) Concizumab for 52 Weeks (Excludes Data from ADA-positive Individuals)

Week	Sex	Group/Dose Level (mg/kg/day)	C _{max} (ng/mL)	t _{max} ^a (h)	AUC _{0-24h} (h·ng/mL)	Rac _{obs}
1	M	2 (0.5)	207 ^{nm4}	6 ^{nm4}	5400 ^{nm1}	-
		3 (1)	2290 ^{nm9}	24 ^{nm9}	40000 ^{nm9}	-
	F	2 (0.5)	78500 ^{nm13}	24 ^{nm13}	1140000 ^{nm13}	-
		3 (1)	139 ^{nm1}	6 ^{nm1}	416 ^{nm1}	-
13	M	2 (0.5)	2000 ^{nm9}	6 ^{nm9}	32100 ^{nm8}	-
		3 (1)	79400 ^{nm13}	24 ^{nm13}	1140000 ^{nm13}	-
	F	2 (0.5)	94500 ^{nm2}	3 ^{nm2}	2040000 ^{nm2}	NR
		3 (1)	257000 ^{nm6}	2 ^{nm6}	5590000 ^{nm6}	119 ^{nm6}
26	M	2 (0.5)	328000 ^{nm13}	6 ^{nm13}	7190000 ^{nm13}	72.7 ^{nm13}
		3 (1)	NR	NR	NR	NR
	F	2 (0.5)	231000 ^{nm7}	2 ^{nm7}	4980000 ^{nm7}	204 ^{nm7}
		3 (1)	2980000 ^{nm13}	6 ^{nm13}	6380000 ^{nm13}	65.4 ^{nm13}
52	M	2 (0.5)	83100 ^{nm2}	13 ^{nm2}	1900000 ^{nm2}	323 ^{nm1}
		3 (1)	280000 ^{nm6}	4 ^{nm6}	6040000 ^{nm6}	128 ^{nm6}
	F	2 (0.5)	4120000 ^{nm9}	6 ^{nm9}	82500000 ^{nm7}	66.6 ^{nm7}
		3 (1)	NR	NR	NR	NR
52	M	2 (0.5)	252000 ^{nm7}	6 ^{nm7}	5290000 ^{nm7}	217 ^{nm7}
		3 (1)	3790000 ^{nm9}	6 ^{nm9}	74300000 ^{nm8}	91.4 ^{nm8}
	F	2 (0.5)	NR	NR	NR	NR
		3 (1)	303000 ^{nm4}	6 ^{nm4}	6790000 ^{nm4}	278 ^{nm4}
52	M	2 (0.5)	5550000 ^{nm5}	6 ^{nm5}	101000000 ^{nm5}	83.7 ^{nm5}
		3 (1)	75300 ^{nm1}	24 ^{nm1}	1660000 ^{nm1}	NR
	F	2 (0.5)	314000 ^{nm4}	2 ^{nm4}	6990000 ^{nm4}	186 ^{nm4}
		3 (1)	4590000 ^{nm4}	4 ^{nm4}	97500000 ^{nm4}	91.5 ^{nm4}

Source: 526913 Study Report (NR: No Result, ^amedian for t_{max}, ^bAUC_{last})

Source: Applicant constructed table from study report RPT112503 submitted to NDA.

Source: Reviewer constructed summary table of chronic toxicology studies submitted to the BLA.

*Exposure margins were based on the concizumab plasma exposure level measured after 4 weeks of treatment (steady state) in the clinical Trial NN7415-4311 in patients with hemophilia A and B (with inhibitors) that employed a loading dose of 1 mg/kg (SC) followed by an initial once daily maintenance dose of 0.20 mg/kg (SC). The maintenance dose was adjusted to 0.15, 0.20 or 0.25 mg/kg/day (SC) and for exposure ratios, the mean across all three dose levels was used (22.4 µg.hr/mL, AUC₀₋₂₄).

Abbreviations: AUC, area under the time-concentration curve (exposure); AUC₀₋₂₄, area under the time-concentration curve from time zero to time 24 hours; BLA, biological license application; HD, high dose; IV, intravenous; LD, low dose; MD, mid dose; MRHD, maximum recommended human dose; NOAEL/LOAEL, no/lowest observed adverse effect level; QD, once daily; QW, weekly; SC, subcutaneous;

13.1.2. Toxicology

13.1.2.1. General Toxicology

4 Week Dose Range Finding Subcutaneous Administration Toxicity Study (Including Safety Pharmacology Endpoints) and a 6 Week Subcutaneous and IV Administration Toxicokinetic Study in Cynomolgus Monkeys (Study 208250, Non-GLP)

Key Study Findings

- There were no toxicologically significant findings following subcutaneous administration of concizumab to cynomolgus monkeys at 2, 20, 80; 20, 80, 160; or 80, 160, 200 mg/kg/day over 4 weeks (3 escalating doses administered on Days 1, 15 and 29).
- Electrocardiograms and blood pressure assessed at 24 hours post-dose (Days 1, 15 and 29) were comparable to pre-treatment and pre-dose values.

- There was no evidence of pathological clotting in any tissue including the liver, lungs, and brain.
- The time to maximum concentration (T_{max}) was generally observed at 24 to 72 hours (post dose) and bioavailability following (SC) administration was 77%. Concizumab levels exceeded the tolerated amount for detection of antibodies in the anti-drug antibody (ADA) assay.
- The No-Observed Effect Level (NOEL) for a decline in fibrinogen was 2 mg/kg/day (SC) and is indicative of the recruitment of fibrinogen to sites of thrombogenesis.

Reviewer Comments: The no observed adverse effect level (NOAEL) was considered at 200 mg/kg/day (SC). Changes in coagulation parameters (consistent with the anticipated pharmacological effects of concizumab) were difficult to interpret in the absence of concurrent control data and the high degree of variability in the data.

Table 76. Study Information, Study 208250, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The objective of this study was to examine preliminary toxicity, safety pharmacology, toxicokinetics, immunogenicity and bioavailability of concizumab following three repeat subcutaneous (SC) dose administrations to cynomolgus monkeys over a 4-week period. The toxicokinetic profile of concizumab was also assessed over a 6-week period following a single subcutaneous or intravenous (IV) administration to male cynomolgus monkeys.
Methods	Assessment of toxicity was based on mortality, clinical observations, body weight, food consumption (qualitative assessment), blood pressure, electrocardiogram (ECG), and clinical and anatomical pathology investigations. Blood samples, for toxicokinetic evaluation, antibody analyses, immunophenotyping, coagulation markers and cytokine analysis were also acquired.

Source: Reviewer constructed summary table of Study 208250 submitted to the BLA.

Abbreviations: ECG, electrocardiogram; GLP, good laboratory practices; IV, intravenous; SC, subcutaneous

4 Week Subcutaneous and Intravenous Administration Toxicity Study in the Cynomolgus Monkey (Study 210130, GLP)

Key Study Findings

- Concizumab was pharmacologically active in cynomolgus monkeys as indicated by the observed reduction in circulating levels of fibrinogen (consistent with the recruitment of fibrinogen to sites of thrombogenesis) and increases in D-dimers and TAT (indicative of hemostatic activation), and are consistent with the exaggerated pro-coagulative (antihemorrhagic) effects of concizumab.
- The pro-coagulative effects of concizumab were not associated with any notable changes in PT, APTT, platelets parameters or thrombi formation in normo-coagulative cynomolgus

monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).

- Inflammatory cell foci/perivascular cuffing (minimal to moderate) around the blood vessels in the subcutis of the subcutaneous injection site were present in cynomolgus monkeys administered concizumab at ≥ 3 mg/kg/day (SC) and the severity of these findings tended to increase with dose. These findings were not observed in either sex administered 30 mg/kg/week (IV) and suggests that concizumab acts as a local irritant when administered via the SC route.

Reviewer Comments: The reviewer agreed with the Applicant proposed NOAELs for the subcutaneous (SC, 9 mg/kg/day) and the intravenous (IV, 30 mg/kg/week) routes of administration (ROA) based on the absence of systemic toxicity in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV). The SC NOAEL (9 mg/kg/day, sex-averaged, 37400 $\mu\text{g}\cdot\text{hr}/\text{mL}$, AUC_{0-24} , Week 4) represents a 1670x exposure margin to the anticipated clinical dose (0.2 mg/kg, 22.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC_{0-24}).

Table 77. Study Information, Study 210130, GLP

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	3 mg/kg or 9 mg/kg (QD, SC) 0 mg/kg or 30 mg/kg (QW, IV)
Route of administration	SC/IV
Formulation/Vehicle	34mM L-Histidine (5.3 mg/mL), 251mM sucrose (86 mg/mL), 0.03 % (b) (4), pH (b) (4)
Species/Strain	Cynomolgus Monkey
Number/Sex/Group	3
Age	2-3 Years / Adolescent (Sexually Immature)
Satellite groups/unique design	No Anti-Drug Antibody (ADA) Analysis No Recovery No Ophthalmometry D-Dimer (Fibrin Degradation Product) Assessment Thrombin/Anti-Thrombin (TAT) Assessment
Deviations from study protocol	None that affected the interpretation of the results.

Source: Reviewer constructed summary table of Study 210130 submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; GLP, good laboratory practices; IV, intravenous; QD, once daily; QW, weekly; SC, subcutaneous; TAT, thrombin/anti-thrombin

Table 78. Observations and Results, Study 210130, GLP

Parameters	Major Findings
Mortality	There were no unscheduled deaths in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).
Clinical signs	Soft and/or liquid feces were observed in cynomolgus monkeys in all groups (including IV controls) during the administration period with some individuals presenting with soft feces prior to the initiation of dosing. The cause/source of the GI distress observed in cynomolgus monkeys was not determined.

Parameters	Major Findings
Body weights and food consumption	There were no notable changes in body weights or qualitative appraisals (visual inspections) of food consumption in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).
Hematology	(WBC Parameters): White blood cell counts ($\uparrow 82\%$) and neutrophil counts ($\uparrow 91\%$) were statistically increased in females (only) administered concizumab at 9 mg/kg/day (SC) on Day 29. This effect was not observed at the lower dose (SC) or at the IV dose (30 mg/kg/week). There were no notable changes in platelet parameters in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).
Coagulation	Prothrombin Time (PT) and Activated Partial Thromboplastin Time (APTT): There were no notable changes in PT and APTT in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV). Fibrinogen, D-dimers, and Thrombin/Anti-Thrombin (TAT): A reduction in circulating levels of fibrinogen (consistent with the recruitment of fibrinogen to thrombus sites) and increases in D-dimers and TAT (indicative of hemostatic activation) were observed in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV) and are consistent with the exaggerated pro-coagulative (antihemorrhagic) pharmacological effects of concizumab. These findings were not associated with notable changes in platelet parameters or thrombi formation in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).
Clinical chemistry	There were no notable changes in clinical chemistry parameters in cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).
Toxicokinetics	The plasma exposure to concizumab tended to be lower in females relative to males with both routes of administration (not statistically significant). Accumulation after once-daily subcutaneous dosing (3 mg/kg/day and 9 mg/kg/day) was extensive (up to 275-fold) and after once-weekly intravenous dosing (30 mg/kg) plasma accumulation was 2-fold to 3-fold. The plasma terminal half-life ($t_{1/2}$) after intravenous (IV) administration ranged from 122 hrs to 340 hrs (5 days to 14 days), barring one male (#11) in which a $t_{1/2}$ of 24 hrs was observed. This male was excluded from the TK analysis due to the notable reduction in exposure on Day 22 and the minimal exposure noted on Day 29. These changes were likely driven by the formation of neutralizing anti-drug antibodies (ADAs) to concizumab (no ADA analysis was conducted) and correlated with a loss of pharmacodynamic activity in this individual.
Gross pathology	There were no notable changes in tissues derived from cynomolgus monkeys administered concizumab for 4 weeks at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV).
Organ weights	(Spleen): Spleen weight increased significantly ($\uparrow 59\%$, body weight relative) in females administered 9 mg/kg/day (SC) in the absence of microscopic changes. This finding was not observed in males (SC) or in either sex administered 30 mg/kg/week (IV) and its clinical relevance is unclear.

Parameters	Major Findings
Histopathology Adequate Battery: Yes	(Subcutaneous Injection Site): Inflammatory cell foci/perivascular cuffing were present in cynomolgus monkeys administered concizumab at ≥ 3 mg/kg/day (SC) and the severity of these changes increased with dose. This finding was characterized by the presence of perivascular inflammatory cells forming a sheath (cuff) around blood vessels in the subcutis. This finding was not observed in either sex administered 30 mg/kg/week (IV).

Source: Reviewer constructed summary table of the toxicology Study (210130) submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; APTT, activated partial thromboplastin time; GI, gastrointestinal; IV, intravenous; PT, prothrombin time; SC, subcutaneous; TAT, thrombin/anti-thrombin; WBC, white blood cells

13 Week Administration (SC/IV) Toxicity and Safety Pharmacology Study in Cynomolgus Monkeys Followed by a 11 Week Recovery Period (Study 209206, GLP)

Key Study Findings

- There was one unscheduled mortality (Day 35) of a MD male (#12) that was deemed related to a gastrointestinal tract lesion that correlated with loose feces and debility (weakness). While it's likely that these findings were unrelated to concizumab dosing it should be noted that this individual presented with a single thrombus in the liver which was considered driven by dehydration but is potentially related to concizumab exposure in view of its pharmacology.
- Concizumab was pharmacologically active in cynomolgus monkeys as indicated by the observed decreases in fibrinogen and increases in Thrombin Antithrombin Complex (TAT) and D-dimers (biomarkers of increased coagulation). Activated partial thromboplastin time (APTT) was prolonged (increased clotting time) early on (Day 16) in males only (in the absence of a decline in platelets) and may be indicative of homeostatic regulation of the coagulation system in normo-coagulative cynomolgus monkeys administered concizumab.
- Safety pharmacology endpoints (neurobehavioral, respiratory rate, blood pressure and electrocardiography), immunophenotyping data and a cytokine assessment were all unremarkable in cynomolgus monkeys administered concizumab at ≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV) for 13-weeks. Safety pharmacology endpoints were not assessed post-recovery and there was no indication of delayed toxicity in immunophenotyping or cytokine values.
- Antibodies to concizumab (ADAs) were detected in 90% of control cynomolgus monkeys; however, measurable levels of drug exposure were not observed, and the Applicant did not provide an explanation for the presence of ADAs in the control group. The Applicant's anti-drug antibody (ADA) assessment was likely insufficient to assess the extent of ADA production in the presence of high plasma concentrations of concizumab (due to assay interference). When ADAs were detected, their presence correlated with a decline in pharmacodynamic activity (e.g., fibrinogen, TAT, and D-dimers) and a reduction in systemic exposure, indicating that the ADAs produced in cynomolgus monkeys (particularly at the LD) were inhibitory in nature.
- Adverse changes in the vasculature (e.g., heart and lung thrombosis and pulmonary vascular intimal proliferation, chronic inflammation, hemorrhage, and blood vessel

necrosis/mineralization) were observed in cynomolgus monkeys administered concizumab (50 mg/kg/day, SC and/or 200 mg/kg/week, IV) and thrombosis persisted in the heart and lung following the 11-week recovery period. Thrombosis was likely the result of exaggerated pharmacology and was considered adverse in cynomolgus monkeys in a normo-coagulative state as their presence impacted local blood circulation in the individuals affected and failed to normalize post recovery.

- Chronic inflammation and subendothelial intimal proliferation in the lung were likely driven by the observed immunogenic response (deposition of immune complexes, secondary to development of ADAs) to concizumab (a humanized mAb) in cynomolgus monkeys and resolved during the 11-week recovery period.
- Inflammatory cell foci/perivascular cuffing were present in the subcutaneous injection site in all groups (including controls). However, the overall incidence and severity tended to increase in HD males (SC) and in females at all doses (≥ 1 mg/kg/day, SC). These findings were characterized by the presence of perivascular inflammatory cells (predominantly mononuclear) forming a sheath (cuff) around blood vessels in the subcutis and were trending towards resolution (minimal severity) in both sexes (MD/HD) following the 11-week recovery period.
- Cellulitis/fibrosis was noted predominantly in the subcutaneous injection site of females (dose independent) at all doses (≥ 1 mg/kg/day) and was characterized by mixed inflammatory cell infiltration into the subcutis, with varying levels of fibroblastic proliferation and collagen deposition. The extent of these findings was comparable to controls in males (SC) and this condition had completely resolved by the end of the 11-week recovery period.

Reviewer Comments: The reviewer agreed with the Applicant proposed NOAEL (1 mg/kg/day [LD], SC) based in the adverse changes in the vasculature (e.g., thrombosis) observed at the MD/HD that persisted at the HD following a 11-week recovery period in cynomolgus monkeys administered (SC) concizumab at 1, 10 and 50 mg/kg/day for 13-weeks. A NOAEL for intravenous (IV) dosing was not established as thrombosis-related histopathological findings were observed at the 200 mg/kg/week (IV) dose. The NOAEL (1 mg/kg/day, SC, 5923 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC₀₋₂₄, Day 91) represents a 264x exposure margin to the anticipated clinical dose (0.2 mg/kg, 22.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC₀₋₂₄).

Table 79. Study Information, Study 209206, GLP

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 1, 10 or 50 mg/kg (QD, SC) 200 mg/kg (QW, IV)
Route of administration	SC/IV
Formulation/Vehicle	34mM Histidine, 251mM sucrose, 0.03% (b) (4), pH (b) (4)
Species/Strain	Cynomolgus Monkey
Number/Sex/Group	5
Age	2-3 Years / Adolescent (Sexually Immature)
Satellite groups/unique design	11 Week Recovery (2/Sex/Group) Safety Pharmacology Endpoints (No Recovery) Immunophenotyping/Cytokine Assessment D-Dimer (Fibrin Degradation Product) Assessment Free TFPI Assessment ADA Analysis Conducted
Deviations from study protocol	None that affected the interpretation of the results.

Source: Reviewer constructed summary table of Study 209206 submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; GLP, good laboratory practices; IV, intravenous; QD, once daily; QW, weekly; SC, subcutaneous; TAT, thrombin/anti-thrombin

Table 80. Observations and Results, Study 209206, GLP

Parameters	Major Findings
Mortality	There was one unscheduled death at the 10 mg/kg/day (MD, SC) dose (male #12) where this individual was terminated on Day 35 due to poor condition. Prior to termination, this male presented with intermittent body weight loss (up to ↓11%, Day -7 to Day 29), diarrhea (Week 1 to Week 2) and was thin and dehydrated up until the day of its sacrifice. Predose clinical pathology samples revealed changes in kidney and liver parameters, notably low plasma electrolytes (correlating with a gastrointestinal tract lesion and loose feces) and elevated plasma urea and creatinine. Dosing in this male was intermittent, and this individual was treated with intravenous fluid therapy as well as antibiotics. The observed clinical signs were likely unrelated to the administration of concizumab as the body weight loss commenced prior to the initiation of dosing. The cause of death in this male was considered related to the gastrointestinal tract lesion, which correlated with the loose feces and debility (weakness) recorded clinically. While it's unlikely that these findings were related to concizumab dosing it should be noted that this male presented with a single thrombus in the liver which was deemed related to the dehydration but is consistent with the pharmacology of concizumab.
Clinical signs	Gastrointestinal distress (soft and/or liquid feces) was present in all groups (including controls) with some individuals displaying these signs prior to the commencement of dosing. A single LD (1 mg/kg/day, SC) female (#27) and 2 MD (10 mg/kg/day, SC) monkeys (#9, male and #33, female) were thin and/or dehydrated at various times within the first 4 weeks of the administration period. There was no clear dose-response relationship and the Applicant failed to identify the root cause of these clinical signs.

Parameters	Major Findings
	At the subcutaneous injection site there were intermittent incidences of rash/redness in all groups (including controls) and these local skin reactions were deemed to be related to the dosing procedure.
Body weights and food consumption	Minimal body weight loss (Week 8 to Week 13) was observed at the 200 mg/kg/week dose (IV) and by the end of the administration period male body weight was reduced (↓9%) relative to controls. Female body weights were comparable to controls at the end of dosing and there were no effects on body weights in cynomolgus monkeys administered concizumab subcutaneously (≤ 50 mg/kg/day). Following the 11-week recovery period, body weights were comparable to controls indicating that this condition was reversible in males and there was no indication of delayed toxicity in other groups. Qualitative assessments (visual inspections) did not reveal any corresponding changes in food consumption.
Ophthalmoscopy	Unremarkable
Hematology	There were no notable changes in RBC, WBC or platelet parameters derived from cynomolgus monkeys dosed with concizumab [≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV)] for 13 weeks and there was no evidence of delayed hematologic toxicity.
Immunophenotyping	There were no definitive changes observed during assessments of white blood cell (WBC) sub-sets (performed by flow cytometry) in the following WBC populations: total T lymphocytes (CD3 ⁺), total B lymphocytes (CD20 ⁺) and total monocytes (CD14 ⁺) derived from cynomolgus monkeys dosed with concizumab [≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV)] for 13 weeks and there was no evidence of a delayed onset of immune cell toxicity.
Coagulation	(Prothrombin Time, PT): There were no clear changes in PT values derived from cynomolgus monkeys dosed with concizumab [≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV)] for 13 weeks and there was no evidence of a delayed onset of toxicity. (Activated Partial Thromboplastin Time, APTT): Activated partial thromboplastin times were prolonged in males at 24 hrs after the administration (Day 16) of concizumab on Day 15 (↑28%, ↑44% and ↑43% at the LD, MD, and HD, respectively (SC) and ↑68% at the 200 mg/kg/week dose, IV). These changes occurred in the absence of changes in platelet parameters and there were no significant changes in APTT during the remainder of the administration period in males (Days 30, 58, 92 and 93). This effect was not observed in females at any point during the study and there was no evidence of a delayed onset of toxicity in either sex. Activated partial thromboplastin time prolongation (increased clotting time) is counterintuitive to the anticipated effects of an antihemorrhagic (that seeks to decrease the time needed to induce clotting) and may be indicative of homeostatic regulation of the coagulation system in cynomolgus monkeys in a normo-coagulative state. (Fibrinogen): Fibrinogen concentrations tended to decline independent of dose (SC and IV) level (intermittently significant) from Day 16 forward in females (≤ ↓31%) and from Day 30 forward

Parameters	Major Findings
	in males ($\leq \downarrow 30\%$) and is consistent with the recruitment of fibrinogen to sites of thrombogenesis. Fibrinogen levels tended to normalize during the recovery period (Day 169). (D-dimer Biomarker): D-dimer is a fibrin degradation product (a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis) and it is so named because it contains two D fragments of the fibrin protein joined by a cross-link, hence forming a protein dimer. D-dimers are not normally present in blood plasma and tend to manifest when the coagulation system has been activated. The concentrations of D-dimer increased (in general, dose-dependently) and were significantly higher on Day 16 (up to $\uparrow 5$-fold, females), Day 30 (up to $\uparrow 5$-fold, males), Day 58 (up to $\uparrow 6$-fold, females), and Day 92 (up to $\uparrow 7$-fold and $\uparrow 5$-fold, in males and females, respectively). Elevations in D-dimer levels tended to persist through the end of recovery (both sexes) at doses ≥ 10 mg/kg (SC and IV) indicating that the 11-week recovery period was insufficient to restore normal coagulation in cynomolgus monkeys previously administered concizumab at these levels. (Thrombin Antithrombin (TAT) Complex): Thrombin antithrombin complex is a protein complex of thrombin and antithrombin and is a marker of net activation of coagulation. Thrombin antithrombin complex (TAT) concentrations increased with dose in both sexes on Day 16 and were found to be statistically significant in males ($\leq \uparrow 2$-fold, SC). Consistent with the observed increases in D-dimer levels, elevations in TAT tended to persist through the end of recovery (both sexes) at doses ≥ 10 mg/kg (SC and IV) indicating that the 11-week recovery period was insufficient to restore normal coagulation in cynomolgus monkeys previous administered concizumab at these levels.
Clinical chemistry	There were no clear changes in clinical chemistry parameters in whole blood derived from cynomolgus monkeys dosed with concizumab [≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV)] for 13 weeks and there was no evidence of a delayed onset of toxicity.
Cytokine assessment	There were no definitive changes in cytokine (IL-2, IL-4, IL-5, IL-6, TNF-alpha and IFN-gamma) levels during assessments (bead-based flow cytometry) of serum derived from cynomolgus monkeys dosed with concizumab [≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV)] for 13 weeks and there was no evidence of a delayed onset of toxicity.
Anti-drug antibody (ADA) analysis	Antibodies to concizumab (ADAs) were detected in 9 of the 10 cynomolgus monkeys in the control group; however, measurable levels of drug exposure were not observed (based on toxicokinetic assessment). The Applicant did not provide an explanation for the antibody results in the control group. At the end of the main study period, ADAs were detected in 2 of 9 cynomolgus monkeys in the low dose group (1 mg/kg/day, SC) and at the end of the recovery period ADAs were detected in the low and intermediate dose groups (1 and 10 mg/kg/day; 4/4 and 1/3 cynomolgus monkeys, respectively). The study report stated that the ADA assay could tolerate up to 100 μg/mL concizumab in

Parameters	Major Findings
	samples and still detect 1000 ng/mL ADAs. Mean drug concentrations exceeded the ADA assay tolerance (100 µg/mL) at the 50 mg/kg/day dose (SC) on Day 1 and at all doses (SC and IV) on Day 91. Hence, the Applicant's anti-drug antibody (ADA) assessment was likely insufficient to assess the extent of ADA production in the presence of high plasma concentrations of concizumab (due to assay interference).
Toxicokinetics	The plasma terminal half-life ($t_{1/2}$) for concizumab was, in general, short at the low dose (70 hrs to 80 hrs) and was extended at doses ≥ 10 mg/kg (400 hrs to 500 hrs). Accumulation in systemic exposure to concizumab after (SC) dosing was extensive (up to 1000-fold) and after once weekly (IV) dosing at 200 mg/kg, plasma accumulation was 2-fold to 4-fold. Cynomolgus monkeys administered concizumab once daily (SC) or once weekly (IV) for 3 months were systemically exposed throughout the administration period, with the exception of two LD individuals that displayed no exposure after nearly two months of dosing (Day 58). Cynomolgus monkeys dosed at ≥ 10 mg/kg/day (SC), or 200 mg/kg/week (IV) were likely exposed throughout the 11-week recovery period
Gross pathology	There were no notable changes in tissues derived from cynomolgus monkeys dosed with concizumab [≤ 50 mg/kg/day (SC) or 200 mg/kg/week (IV)] for 13 weeks and there was no evidence of a delayed onset of toxicity.
Organ weights	Unremarkable
Histopathology Adequate battery: yes	(Heart): Histopathological evaluations revealed thrombosis in the heart (a mature thrombus was present in the right ventricle of 1 HD female (#38) administered (SC) concizumab at 50 mg/kg/day. There were no notable findings in the heart at doses ≤ 10 mg/kg/day. A mature thrombus in the left ventricle of the heart was present in 1 HD (SC) female (#40) following the 11-week recovery period suggesting non-reversibility and/or delay onset. (Lungs): Thrombus was present in the lumen of the lung (small and medium sized blood vessels) where the vessels exhibited vascular intimal proliferation in 1 HD female (#39) administered (SC) concizumab at 50 mg/kg/day. This female also presented with chronic inflammation of the lung (left posterior lobe) that was characterized as a focal area of lung with fibroblastic proliferation and hemorrhage, and blood vessels with necrotic/mineralized walls. Vascular intimal proliferation in the lung manifested at the 200 mg/kg/week (IV) dose in the posterior lung lobe in 1 male (#19) and 1 female (#42) and was characterized by multi-layering and infolding of the vascular endothelium, and endothelial cells with plump nuclei and increased levels of cytoplasm. A thrombus (medium sized artery) was present in the female (#42, IV) and there were no notable findings in the lungs at doses ≤ 10 mg/kg/day (SC). An early fibrin thrombus was present in a large artery of the posterior lung lobe in 1 HD (SC) female (#40) following the 11-week recovery period (Note: this female also presented with a mature thrombus in the left ventricle of the heart, post recovery).

Parameters	Major Findings
	The chronic inflammation and vascular intimal proliferation in the lung were not observed after the 11-week recovery period. (Injection Site): Subcutaneous inflammatory cell foci/perivascular cuffing was present in all groups (including controls). The overall incidence and severity tended to increase in HD males (SC) and in females at all doses (≥ 1 mg/kg/day, SC) and these findings were characterized by the presence of perivascular inflammatory cells (predominantly mononuclear) forming a sheath (cuff) around blood vessels in the subcutis. This finding was trending towards resolution (minimal severity) in both sexes (MD/HD) following the 11-week recovery period. Subcutaneous cellulitis/fibrosis was noted predominantly in females (dose independent) at all doses (≥ 1 mg/kg/day, SC) and was characterized by mixed inflammatory cell infiltration into the subcutis, with varying levels of fibroblastic proliferation and collagen deposition. The extent of these findings was comparable to controls in males (SC) and there were no notable findings in the intravenous injection site of either sex at the end of the administration period. This condition had completely resolved by the end of the 11-week recovery period.

Source: Reviewer constructed summary table of the toxicology Study (209206) submitted to the BLA.
Abbreviations: ADA, anti-drug antibody; APTT, activated partial thromboplastin time; AUC0-24, area under the time-concentration curve from time zero to time 24 hours; Cmax, maximum plasma concentration; ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose; QRS, Q wave, R wave and S wave complex; PR, pulse rate; PROS, protein S; PT, prothrombin time; RacObs, ; RR, heart rate; TFPI, tissue factor pathway inhibitor; TGT, thrombin generation test; tmax, time to reach maximum concentration

26 Week Toxicity Study by the Subcutaneous and Intravenous Routes of Administration in Cynomolgus Monkeys With a 13 Week Recovery Period (Study 211087, GLP)

Key Study Findings

- A NOAEL was not identified in the 26-week repeat-dose toxicity study conducted in cynomolgus monkeys due to the presence of thrombi and/or vascular changes at all doses. The material assessed in the 26-week study contained a disproportionate increase in the level of high molecular weight proteins (HMWPs) that consisted predominantly of concizumab multimers. In contrast, the material used in the 4-, 13-, and 52-week toxicity studies was comparable to the clinical material and contained significantly lower amounts of HMWPs. Evaluations were conducted to assess if the change in impurity profile could account for the increased toxicity observed in the 26-week cynomolgus monkey study. There were no significant differences noted between the monomeric and the multimeric forms of concizumab across multiple in vitro assays (See Section [13.1.2.5.3 Mechanistic Analyses](#)). The contribution of the multimeric forms of concizumab to the observed pathology/toxicity in the 26-week cynomolgus monkey study was considered driven by increased immunogenicity and the subsequent immune complex (IC) formation/deposition.
- There was one unscheduled mortality at the 9 mg/kg/day (SC) dose (HD) that was triggered by the onset of a severe adverse reaction (Day 121) to concizumab (0.5 hours post-dose) in a single female (#34) where thrombosis and subsequent massive coagulative lung necrosis precipitated the moribund condition.

- Concizumab was pharmacologically active in cynomolgus monkeys as indicated by the observed decreases in TFPI activity and fibrinogen and the increases in D-dimer and TAT (biomarkers of increased coagulation). Prothrombin time and activated partial thromboplastin time were prolonged (in the absence of a significant decline in platelets) and may be indicative of homeostatic regulation of coagulation in normo-coagulative monkeys administered an antihemorrhagic.
- The Applicant's anti-drug antibody (ADA) assessment in cynomolgus monkeys was likely insufficient to assess the extent of ADA production in the presence of high plasma concentrations of concizumab (due to assay interference). In some cases, the development of ADAs correlated with a reduction in systemic exposure and suggests that the ADAs produced in cynomolgus monkeys were likely inhibitory in nature.
- Adverse changes in the vasculature of the brain and/or choroid plexus (e.g., hypertrophy, hyperplasia, inflammation, edema and/or lymphoid foci) and the lungs (e.g., subendothelial intimal thickening and/or endothelial cell hypertrophy) were observed in cynomolgus monkeys administered concizumab at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV) for 26 weeks. These vascular changes are consistent with an immunogenic response (deposition of immune complexes, secondary to development of ADAs) to a foreign protein and the administration of an antihemorrhagic (pro-coagulant) to cynomolgus monkeys in a normo-coagulative state and tended to resolve during recovery.
- Thrombosis manifested in the lungs, liver, epididymis, and thymus of cynomolgus monkeys administered concizumab at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV) for 26 weeks. Thrombi were present in the lungs, heart, and IV injection site at the end of recovery and indicate that a duration of 13 weeks was insufficient to reverse the presence of drug-induced thrombi in normo-coagulative monkeys previously administered concizumab at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV). Thrombosis was likely the result of exaggerated pharmacology and was considered adverse at all doses in cynomolgus monkeys.
- Perivascular cellular infiltrates (consisting predominantly of plasma cells and lymphocytes, e.g., neutrophils, eosinophils, and giant cells) and endothelial hypertrophy in the local blood vessels were associated with the subcutaneous injection site and were trending towards resolution post-recovery (13 weeks) in cynomolgus monkeys previously administered concizumab at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV) for 26 weeks.

Reviewer Comments: The reviewer agreed with the Applicant that a NOAEL could not be established for this study based in the adverse changes in the vasculature and thrombosis observed in cynomolgus monkeys administered concizumab at ≤ 9 mg/kg/day (SC) and 30 mg/kg/week (IV) for 26-weeks. The lowest observed adverse effect level (LOAEL) for subcutaneous (SC) dosing was 3 mg/kg/day (21350 $\mu\text{g}\cdot\text{hr}/\text{mL}$, AUC_{0-24} , sex-averaged, Week 26) and represents a 953x exposure margin to the anticipated clinical dose (0.2 mg/kg/day, 22.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC_{0-24}).

Table 81. Study Information, Study 211087, GLP

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0 mg/kg, 3 mg/kg or 9 mg/kg (QD, SC) 30 mg/kg (QW, IV)
Route of administration	SC/IV
Formulation/Vehicle	Arginine (5.27 mg/mL), sucrose (51.3 mg/mL), L-histidine (5.12 mg/mL), sodium chloride (1.46 mg/mL), polysorbate 80 (0.01 mg/mL) at pH 6.
Species/Strain	Cynomolgus Monkey
Number/Sex/Group	5
Age	3-5 Years of Age / Sexually Mature
Satellite groups/unique design	13 Week Recovery (2/Sex/Group) No Electrocardiograms Performed Fertility Evaluations Included D-Dimer (Fibrin Degradation Product) Assessment TFPI Activity Assessment ADA Analysis Conducted
Deviations from study protocol	None that affected the interpretation of the results.

Source: Reviewer constructed summary table of the toxicology Study (211087) submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; GLP, good laboratory practices; IV, intravenous; QD, once daily; QW, once weekly; SC, subcutaneous; TFPI, tissue factor pathway inhibitor

Table 82. Observations and Results, Study 211087, GLP

Parameters	Major Findings
Mortality	There was one unscheduled death (female #34) at the 9 mg/kg/day (SC) dose (HD) where this individual was terminated on Day 121 due to the onset of a severe adverse reaction to concizumab. Clinical signs in this HD female following the administration of concizumab (Day 121) included: severe subdued behavior, paleness (gums and face), shallow breathing, slow movement, and a collapsed state (unconsciousness). Due to the moribund condition, this female was terminated at 0.5 hrs post-dose on Day 121. There were no clinical signs recorded in this female (#34) before Day 121. Hematological values (versus predose) in this female showed a marked reduction in hemoglobin concentrations, erythrocyte counts and hematocrit that corresponded to a notable increase in reticulocyte counts and elevations in total leukocyte, and neutrophil counts. Coagulation parameter values were comparable to predose and no dose controls. The Applicant indicated that (at the time of termination) this female had presented with a heavy menstrual blood flow that was observed for 9 days and may have contributed to the observed anemia. Clinical chemistry values (versus predose) in this HD female showed increases in creatine phosphokinase activity, creatinine and phosphate concentrations and reductions in sodium, chloride, total protein, albumin, and globulin concentrations.

Parameters	Major Findings
	Pale discoloration of the internal organs was observed at necropsy and a recently formed blood clot was present in the vagina that correlated clinically and histologically with menstruation. Two firm, mottled masses were present in the caudal lung lobes and upon histopathological evaluation, thrombosis and subsequent massive coagulative necrosis of the lung parenchyma were determined to be the cause of the moribund condition. In addition, subendothelial intimal thickening manifested in a number of blood vessels, and a subset of affected blood vessels showed an accumulation of foamy macrophages within the thickened intimal stroma. Endothelial hypertrophy and hyperplasia were also observed in blood vessels in the lungs and mononuclear cell infiltration (minimal) was present in the choroid plexus.
Clinical signs	Barring the adverse clinical signs observed in the HD female (#37) that was terminated early (Day 121; Week 18), there were no notable clinical signs associated with the administration of concizumab at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV) to cynomolgus monkeys for 26-weeks.
Body weights and food consumption	There were no notable differences in the observed trends in body weight changes or the qualitative measurement of food consumption in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks.
Ophthalmoscopy	Unremarkable
Hematology	Barring the hematological changes observed in the HD female (#37) that was terminated early (Day 121; Week 18), there were no notable changes in hematological parameters (including platelet parameters) in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks or following the 13-week recovery period
Coagulation	(Prothrombin Time, PT) Prothrombin time prolongation (significant) was observed in intravenously dosed males only (30 mg/kg/week, IV) from Week 6 forward and tended to normalize during the recovery period. Prothrombin time prolongation (increased clotting time) is counterintuitive to the anticipated effects of an antihemorrhagic (that seeks to decrease the time needed to induce clotting) and may be indicative of homeostatic regulation of the coagulation system in cynomolgus monkeys in a normo-coagulative state. (Activated Partial Thromboplastin Time, APTT) Activated partial thromboplastin time prolongation (significant intermittently) manifested during Week 6 in intravenously dosed males (30 mg/kg/week, IV) and in LD (3 mg/kg/day, SC) females during Week 13 and LD/HD (≤ 9 mg/kg/day, SC) females during Week 26. These findings tended to normalize during the recovery period. Activated partial thromboplastin time prolongation (increased clotting time) is also counterintuitive to the anticipated effects of an antihemorrhagic (that seeks to decrease the time needed to induce clotting) and may be indicative of homeostatic regulation of the coagulation system in cynomolgus monkeys in a normo-coagulative state.

Parameters	Major Findings
	(Fibrinogen - Prothrombin Time-Derived): Fibrinogen concentrations tended to decline independent of dose level (intermittently significant) from Week 6 forward in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks and is consistent with the recruitment of fibrinogen to sites of clot formation. Fibrinogen concentrations were comparable to pre-dose controls in recovery females but tended to remain lower (not significant) in males following the 13-week recovery period. (Fibrinogen - Clauss Assay): The Clauss fibrinogen assay is a quantitative, clot-based, functional assay that measures the ability of fibrinogen to form fibrin clot after being exposed to a high concentration of purified thrombin. Fibrinogen concentrations tended to decline (intermittently significant) from Week 6 forward in males administered concizumab (30 mg/kg/week, IV). Similar findings were observed during Week 13 in LD males (3 mg/kg/day, SC) and to a lesser extent in HD males (9 mg/kg/day, SC). Numerical decreases were noted intermittently in females (not significant) and these changes tended to normalize in both sexes during recovery. (D-dimer Biomarker): D-dimer is a fibrin degradation product (a small protein fragment present in the blood after a blood clot is degraded by fibrinolysis) that is so named because it contains two D fragments of the fibrin protein joined by a cross-link, hence forming a protein dimer. D-dimers are not normally present in blood plasma and tend to manifest when the coagulation system has been activated. The concentrations of D-dimer increased from Week 6 forward in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks and is consistent with the clot promoting effects of concizumab. This effect was persistent at the 9 mg/kg/day (SC) dose and was tending towards normalization at the 3 mg/kg/day (SC) dose and the 30 mg/kg/week (IV) dose. (Thrombin Antithrombin (TAT) Complex): Thrombin antithrombin complex (TAT) is a protein complex of thrombin and antithrombin and is a marker of net activation of coagulation. Thrombin antithrombin complex (TAT) concentrations tended to increase (intermittently) with dose during the administration period but showed a high degree of intra- and inter-group variability throughout the administration period and following recovery in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks.
Clinical chemistry	There were no notable changes in clinical chemistry parameters in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks or following the 13-week recovery period.
Residual TFPI functionality (activity)	Blood samples for the chromogenic plasma TFPI activity were collected on Day -21, Week 1, 5, 9, 13, 17, 21, 25, and 26 (predose) from cynomolgus monkeys. A high degree of variability was observed in the chromogenic activity assay that attempted to quantitate the residual TFPI functionality/activity in the plasma of cynomolgus monkeys administered concizumab. Assay values

Parameters	Major Findings
	(U/mL) tended to be lower in concizumab-dosed groups (when adjusted for individual baseline levels) and suggests that the plasma TFPI activity may have been reduced by concizumab.
Anti-drug antibody (ADA) analysis	Two males and two females administered 3 mg/kg/day (SC), 1 male (9 mg/kg/day, SC) and 1 male and 1 female dosed at 30 mg/kg/week (IV) developed anti-drug antibodies (ADAs) to concizumab.
Toxicokinetics	Exposure to concizumab was reduced in two females (#30, 3 mg/kg/day, SC and #36, 30 mg/kg/week, IV) that developed ADAs. In the subcutaneously dose female (#30), exposure was reduced from Week 5 forward and in the female (#36) administered 30 mg/kg/week (IV) the exposure was reduced from Week 13 forward indicating that the ADAs produced in these individuals were likely neutralizing. In general, lower exposures were observed in females relative to males after subcutaneous administration. Accumulation ratios (R_{acObs}) ranged from: 60 to 195 at 3 mg/kg/day (SC), 29 to 115 at 9 mg/kg/day (SC) and 1.5 to 5.8 at 30 mg/kg/week (IV).
Urinalysis	Unremarkable
Gross pathology	Irregular red foci were noted in the lungs of 1 male (#17) that was administered concizumab at 30 mg/kg/week (IV) and correlated with the presence of thrombi observed microscopically. There were no other notable findings observed grossly in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks or following the 13-week recovery period.
Organ weights	Unremarkable
Histopathology Adequate battery: yes	(Brain): Vascular changes (hypertrophy/hyperplasia, inflammation, edema and/or lymphoid foci) in the brain (choroid plexus) were observed in 1 male (#16) administered concizumab at 30 mg/kg (QW) intravenously (IV) and in 1 female (#32, 9 mg/kg/day, SC), 2 males (#7M and #8, 3 mg/kg/day, SC) and 1 female (#26, 3 mg/kg/day, SC) administered concizumab for 26-weeks. Vascular changes in the choroid plexus were not present after the 13-week recovery period. These vascular changes are consistent with an immunogenic response to a foreign protein and the administration of a pro-coagulant (antihemorrhagic) to cynomolgus monkeys in a normo-coagulative state. A granuloma was noted in the caudate nucleus of the brain of 1 female (#35, 9 mg/kg/day, SC) following the 13-week recovery period and the relationship of this finding to the administration of concizumab is unclear. (Lung): Vascular changes (subendothelial intimal thickening and/or endothelial cell hypertrophy) in the lungs were observed in 2 males (#17 and #18) administered concizumab at 30 mg/kg (QW) intravenously (IV), 1 female (#33, 9 mg/kg/day, SC) and/or 1 male (#6, 3 mg/kg/day, SC) administered concizumab for 26-weeks. These changes are consistent with those observed in the female (#34) that was euthanized early due to moribundity on Day 121. Vascular changes in the lungs were not observed after the 13-week recovery period. These vascular changes are consistent with an immunogenic response to a foreign protein and the

Parameters	Major Findings
	administration of an antihemorrhagic (pro-coagulant) to cynomolgus monkeys in a normo-coagulative state. (Thrombi): Concizumab induced thrombus formation in the lungs, liver, epididymis, and thymus after 26 weeks and was associated with coagulative necrosis of the lung in 1 female (#27, 9 mg/kg/day, SC). Thrombi were present in the lungs, heart, and injection site (IV) post-recovery and indicates that 13 weeks is insufficient to reverse and/or clear thrombi formation in normo-coagulative monkeys previously administered concizumab at $\leq$ 9 mg/kg/day (SC) or 30 mg/kg/week (IV). (Injection Site): Perivascular cellular infiltrates (comprised of plasma cells and lymphocytes, e.g., neutrophils, eosinophils, and giant cells) and endothelial hypertrophy of the blood vessels were associated with the subcutaneous injection site. The presence of plasma cells and eosinophils in the subcutaneous injection site persisted after the 13-week recovery period and a fistulous inflammatory tract in the skin was present in 1 recovery female (#39) previously administered concizumab at 30 mg/kg/week (IV). (Kidney): Kidney sclerosis and tubular degeneration (loss) were noted microscopically (unilaterally) in 1 male (#14, 9 mg/kg/day, SC) following the 13-week recovery period and the significance of this finding is unknown. (Spleen): Hyalinized germinal centers were present in the spleen of 1 male (#16) administered concizumab at 30 mg/kg/week (IV) for 26-weeks and was consistent with the heightened immune response (tissue inflammation in multiple tissues, including brain) noted in this individual.
Reproductive assessments	Menstrual Cycle Durations: Daily assessments of vaginal smears indicated that there were no notable effects on the menstrual cycle of cynomolgus monkeys administered concizumab ($\leq$ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks or following the 13-week recovery period. Testicular Size: There were no notable effects on the testicular size of cynomolgus monkeys administered concizumab ($\leq$ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks or following the 13-week recovery period. Sperm Analysis: There were no clear effects on sperm counts, morphology or motility in cynomolgus monkeys administered concizumab ($\leq$ 9 mg/kg/day, SC or 30 mg/kg/week, IV) for 26-weeks or following the 13-week recovery period

Source: Reviewer constructed summary table of the toxicology Study (211087) submitted to the BLA.
Abbreviations: ADA, anti-drug antibody; APTT, activated partial thromboplastin time; AUC₀₋₂₄, area under the time-concentration curve from time zero to time 24 hours; C_{max}, maximum plasma concentration; ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose; QRS, Q wave, R wave and S wave complex; PR, pulse rate; PROS, protein S; PT, prothrombin time; Rac_{Obs}, RR, heart rate; TFPI, tissue factor pathway inhibitor; TGT, thrombin generation test; t_{max}, time to reach maximum concentration

52-Week Toxicity Study by the Subcutaneous Route of Administration in Cynomolgus Monkeys with No Assessment of Recovery (Study 213542, GLP)

Key Study Findings

- Concizumab was pharmacologically active in cynomolgus monkeys as indicated by the observed decreases in free TFPI, fibrinogen and platelets, and the increase in D-dimer (a biomarker of increased coagulation). Prothrombin time and activated partial thromboplastin time were prolonged (increased clotting time) and may be indicative of homeostatic regulation of the coagulation system in normo-coagulative cynomolgus monkeys administered concizumab.
- The Applicant's anti-drug antibody (ADA) assessment in cynomolgus monkeys was likely insufficient to assess the extent of ADA production in the presence of high plasma concentrations of concizumab (due to assay interference). The development of ADAs correlated with a decline in pharmacodynamic activity (e.g., Protein C and platelets), an increase in chromogenic (TFPI) activity and a reduction in systemic exposure, indicating that the ADAs produced in cynomolgus monkeys were inhibitory in nature.
- Adverse changes in the vasculature (e.g., thrombosis, infarction/necrosis and subendothelial intimal thickening) of multiple organ systems were observed in cynomolgus monkeys administered concizumab (≥ 1 mg/kg/day, MD) for 13, 26 and 52 Weeks, and the reversibility of these conditions was not assessed. These findings are consistent with the administration of an antihemorrhagic (pro-coagulant) to cynomolgus monkeys in a normo-coagulative state.
- Thrombosis manifested in the lungs and liver at the HD (9 mg/kg/day) after 13, 26 and 52 weeks, and at the MD (1 mg/kg/day) after 52 weeks. Thrombosis was also present in the heart and axillary lymph nodes at the HD after 13 weeks, in the spleen at the HD after 26 and 52 weeks, in the epididymis and heart at the HD and in the mesenteric lymph nodes at the MD after 52 weeks. Thrombosis at the MD/HD were likely the result of exaggerated pharmacology and were considered adverse in cynomolgus monkeys in a normo-coagulative state as their presence impacted local blood circulation in the individuals affected.
- Subendothelial intimal thickening of the blood vessels (small to medium-sized arteries and/or veins) in the lungs was observed at the HD after 13, 26 and 52 weeks and at the MD after 52 weeks. This condition was also present in the liver at the HD after 26 weeks and was initially reported to be present in the large intestine (colon) after 13 weeks in the interim study report but, was ultimately excluded from the final study report. The subendothelial intimal thickening was likely driven by the observed immunogenic response (deposition of immune complexes, secondary to development of ADAs) to concizumab (a humanized mAb) in cynomolgus monkeys.
- In the central nervous system (CNS), minimal to marked inflammation (lymphoplasmacytic infiltration, with or without associated eosinophils and macrophages) of the choroid plexus (brain) was observed at the HD after 13 weeks and at all dose levels (≥ 0.5 mg/kg/day) after 26 and 52 weeks. and was likely related to the deposition of immune complexes (ADAs) in cynomolgus monkeys.

- Lymphoplasmacytic infiltrations were also present at the subcutaneous injection site at the HD after 13 weeks and at all dose levels (≥ 0.5 mg/kg/day) after 26 and 52 weeks, and were consistent with the findings observed in the CNS.

Reviewer Comments: The reviewer agreed with the Applicant proposed NOAEL (0.5 mg/kg/day, LD) based in the adverse changes in the vasculature (e.g., thrombosis, infarction, subendothelial intimal thickening) and the increased severity in CNS inflammation observed at the MD/HD in cynomolgus monkeys administered concizumab at 0.5, 1, or 9 mg/kg/day for 52 weeks. The reversibility of the findings in cynomolgus monkeys was not assessed and the NOAEL (0.5 mg/kg/day, 1660 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC₀₋₂₄, Week 52) represents a 74x exposure margin to the anticipated clinical dose (0.20 mg/kg, 22.4 $\mu\text{g}\cdot\text{hr}/\text{mL}$ AUC₀₋₂₄).

Table 83. Study Information, Study 213542, GLP

Study Features and Methods	Details
GLP compliance	Yes
Dose and frequency of dosing	0, 0.5, 1, or 9 mg/kg (QD)
Route of administration	SC
Formulation/Vehicle	33mM L-histidine (5.1 mg/mL), 150mM sucrose (51.3 mg/mL), 0.0076mM Polysorbate 80 (0.01 mg/mL), 25mM arginine HCl (5.3 mg/mL) and 25mM sodium chloride (1.46 mg/mL) at pH 6.
Species/Strain	Cynomolgus Monkey
Number/Sex/Group	9
Age	4-6 Years of Age / Sexually Mature
Satellite groups/unique design	No Recovery Assessment Electrocardiograms Performed D-Dimer (Fibrin Degradation Product) Assessment TFPI Activity Assessment ADA Analysis Conducted
Deviations from study protocol	None that affected the interpretation of the results.

Source: Reviewer constructed summary table of the toxicology Study (213542) submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; GLP, good laboratory practices; HCl, hydrochloride; QD, once daily; TFPI, tissue factor pathway inhibitor

Table 84. Observations and Results, Study 213532, GLP

Parameters	Major Findings
Mortality	A single LD male (#2009) was euthanized during Week 20 (Day 140) due to extensive lacerated wounds to the back sustained during a fight with cage mates. The same male had sustained fight wounds to the left side of the chest (Week 13) and to the thoracic-lumbar region of the back (Week 19) previously. There were no vascular findings or findings in the choroid plexus of the brain during necropsy and the early euthanization of this LD male was considered unrelated to the administration of concizumab.
Clinical signs	There were no notable changes in clinical signs in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day) for 52-weeks.
Body weights and food consumption	There were no differences in observed trends in body weight changes or the level of food consumption in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day) for 52-weeks.
Ophthalmoscopy	Unremarkable

Parameters	Major Findings
Electrocardiograms (ECG)	Electrocardiograms (ECG) were recorded in non-fasted, cynomolgus monkeys (unrestrained except for during the dosing procedure) via a jacketed external telemetry system (lead II ECG waveform morphology) once during pretreatment and at Week 12, 25 and 51 for 20 hrs to 24 hrs (post-dose). Measurement of RR (heart rate), PR, QRS and QT interval values were performed. A distribution-based rate-corrected QT (QTca) was calculated (Note: due to missing baseline data at the HD (9 mg/kg/day), a species-specific QT correction was applied instead of an individual animal correction; however, due to a lack of dose-relationship in the HR and QT interval the study cardiologist considered it unlikely that the QTca was affected). Significant changes in ECG parameters (Week 12, Week 25, and Week 51) were noted in males and/or females intermittently (at all doses) and in view of statistically significant changes present in some of the baseline data and the lack of a clear dose relationship, the study cardiologist considered these findings to be biologically irrelevant.
Hematology	(Platelet Parameters): A significant decline in platelet counts was observed in males at all doses, with the effect at the HD (↓44% to ↓86%) manifesting by Week 6 and continuing until the end of dosing. The decline in platelets in LD/MD males (↓67% to ↓79%) started during Week 34 and continued to the end of dosing. A similar effect was observed in HD females where platelet counts declined (↓58% to ↓62%) from Week 44 forward. A significant effect on platelet counts was not observed in MD females, however platelet counts declined significantly in LD females (↓67% to ↓73%). The decline in circulating platelet counts is consistent with the recruitment of platelets to thrombus sites.

Coagulation	(Prothrombin Time - PT): Significant prothrombin time prolongation (up to ↑17%) manifested during Week 6 at the HD in both sexes and persisted thru Week 26. This effect tended to wane by Week 30 in both sexes and PT values in HD males were comparable to controls by Week 48. Prothrombin time prolongation (increased clotting time) is counterintuitive to the anticipated effects of an antihemorrhagic (that seeks to decrease the time needed to induce clotting) and may be indicative of homeostatic regulation of the coagulation system in cynomolgus monkeys in a normo-coagulative state. (Activated Partial Thromboplastin Time - APTT): Significant activated partial thromboplastin time prolongation (up to ↑16%) manifested during Week 9 and persisted thru Week 48 in HD males. This effect was present to a lesser extent in HD females during Week 17 (up to ↑7%). Activated partial thromboplastin time prolongation (increased clotting time) is also counterintuitive to the anticipated effects of an antihemorrhagic (that seeks to decrease the time needed to induce clotting) and may be indicative of homeostatic regulation of the coagulation system in cynomolgus monkeys in a normo-coagulative state. (Fibrinogen - Prothrombin Time-Derived): Fibrinogen concentrations tended to decline independent of dose level (intermittently significant) from Week 6 forward in males (↓41% to ↓102%) and females (↓60% to ↓109%) and is consistent with the recruitment of fibrinogen to thrombus sites. (D-dimer Biomarker): The concentrations of D-dimer increased (dose-dependently) and were notably higher at Week 13, 26, 39 and 52 in MD/HD monkeys. These changes tended to be statistically significant at the HD after Week 13 (excluding females at Week 52) and at the MD during Weeks 26 and/or 39. The increase in D-dimer is consistent with the clot promoting effects of concizumab. (Protein C (Autoprothrombin IIA) Biomarker): Protein C (a natural anticoagulant) is a vitamin K-dependent glycoprotein structurally similar to other vitamin K-dependent proteins affecting blood clotting (i.e., prothrombin, Factor VII, Factor IX and Factor X). The Protein C system provides important control of blood coagulation by regulating the activities of factor VIIIa (FVIIIa) and factor Va (FVa), cofactors in the activation of factor X and prothrombin, respectively. Protein C levels in the plasma tended to be numerically lower (up to ↓14%) in concizumab-dosed groups and reached statistical significance on a few occasions prior to Week 52. During the last week of dosing (Week 52), plasma concentrations of Protein C increased significantly (↑15%) in MD females (consistent with the lack of an effect on platelet counts) and suggests a decline in pharmacodynamics activity. (Protein S (PROS) Biomarker): Protein S (a natural anticoagulant) is a vitamin K-dependent plasma glycoprotein synthesized in the liver. Protein S functions as a cofactor to Protein C in the inactivation of Factors Va and VIIIa. Protein S concentrations increased significantly in HD males (↑33%) and decreased significantly in LD males and in MD/HD females (↓14% to ↓16%) during Week 6. These results did not correspond sufficiently with

Parameters	Major Findings
Clinical chemistry	other pharmacodynamic analyses, and the significance of these findings is unclear. (Antithrombin Biomarker): Antithrombin is the primary inhibitor of thrombin, Factor Xa and Factor IXa. Antithrombin levels in the plasma tended to decline numerically (up to ↓27%) in concizumab-dosed cynomolgus monkeys (intermittently reached statistical significance) and is consistent with the pharmacology of concizumab. (Thrombin Generation Test - TGT): Plasma samples for TGT were analyzed using a non-validated methodology and the results were stated to be reported separately by the Applicant.
Free TFPI biomarker Residual TFPI functionality (activity)	Blood samples for the free TFPI were collected on Weeks -2, -1, Day 1, Week 6, 13, 26, 39 and 52. A dose-dependent reduction in the level of free TFPI (not bound to concizumab) following the administration of concizumab was observed in cynomolgus monkeys. The levels of free TFPI were below the lower limit of detection (12.6 ng/mL) for the majority of MD/HD cynomolgus monkeys from Week 6 forward. Free TFPI levels tended to be higher in males. These findings are consistent with the proposed mechanism of action, whereby concizumab binds specifically to the Kunitz-domain-2 of the TFPI and prevents TFPI from binding to and blocking the active site of the coagulation factor Xa (FXa). Blood samples for the chromogenic plasma TFPI activity were collected on Weeks -2, -1, Day 1, Week 6, 9, 13, 17, 21, 26, 30, 34, 39, 44 and 48 from cynomolgus monkeys. A high degree of variability was observed in the chromogenic activity assay (U/mL) that attempted to quantitate the residual TFPI functionality/activity in the plasma of cynomolgus monkeys administered concizumab. Assay values tended to be lower in concizumab-dosed groups (when adjusted for individual baseline levels) and suggests that the plasma TFPI activity may have been reduced by concizumab. The development of anti-drug antibodies (ADAs) tended to correspond to an increase in chromogenic (TFPI) activity and a decline in systemic exposure indicating that the ADAs produced in cynomolgus monkeys were likely inhibitory in nature. Total TFPI (free TFPI and TFPI bound to concizumab) was analyzed using a non-validated methodology and the results were stated to be reported separately by the Applicant.

Parameters	Major Findings
Anti-drug antibody (ADA) analysis	Anti-drug antibodies were detectable in LD monkeys at Week 6 (67%) and the number of ADA-positive monkeys increased by Week 13 (89%) and remained positive thru Week 26. Cynomolgus monkeys (LD) continuing after the 26-week interim sacrifice (N=9) were all ADA positive between Weeks 34 and Week 52, excluding a LD male (#2007) that was negative during Weeks 44 and 52. At the MD, ADAs were detectable at Week 6 (17%) and the number of ADA-positive monkeys increased by Week 13 (28%) and remained positive thru Week 26. Two of the cynomolgus monkeys (MD) continuing after the 26-week interim sacrifice (20%) were ADA positive thru Week 52. Anti-drug antibodies (ADAs) were not detected in HD monkeys and suggests that higher concentrations of concizumab in the plasma may interfere with the ADA assay. It's likely that the actual number of ADA positive monkeys at the MD was higher and that ADAs were present at the HD but not detectable due to deficiencies in ADA detection assay methodology.
Toxicokinetic	The toxicokinetic evaluation indicated that systemic exposure to concizumab was affected by the presence of anti-drug antibodies (ADAs) at the LD/MD. After the first administration, t_{max} (median) was reached at 6 hrs or 24 hrs (post dose). After repeat-dose administration (Weeks 13, 26 and 52), t_{max} (median) ranged from 0 hrs to 24 hrs. Concizumab exposures (C_{max} and $AUC_{0-24hrs}$) tended to be lower in females and increased in a greater than dose-proportional manner, particularly at the LD/MD (non-linear pharmacokinetics). Concizumab accumulation was observed at all doses but was particularly notable at the LD/MD where individual accumulation values (Rac_{Obs}) of up to 639 (MD Male - #3006) were observed.
Gross pathology	(Thrombi): Thrombus (dark focus on the left caudal lobe of the lung) was observed grossly in 1 HD female (#4502) at Week 13. No gross pathological findings were noted in cynomolgus monkeys after 26 weeks of dosing (≤ 9 mg/kg/day) with concizumab. Thrombus (mass) was observed grossly in the heart of 1 HD female (#4513) and in the lung of 1 MD female (#3505) at Week 52. The formation of thrombi is consistent with the pro-coagulative effects of concizumab in normal healthy cynomolgus monkeys.
Organ weights	Unremarkable.

Histopathology Adequate battery: yes	(Thrombosis): Histopathological evaluations revealed thrombosis affecting single blood vessels (small to medium sized arteries and occasional veins) in the lung, heart, axillary lymph node and liver of 3 HD cynomolgus monkeys terminated during the 13-Week interim sacrifice. Histopathological evaluations revealed thrombosis (minimal to moderate) was affecting single blood vessels (small to medium sized arteries and occasional veins) in the lung and liver of 1 HD male (#4006) and in the liver/spleen (#4505) or lungs (#4506) of 2 HD females terminated during the 26-Week interim sacrifice. There was no evidence of tissue necrosis in the lung, liver, or spleen in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day) for 26-weeks. Histopathological evaluations revealed thrombosis (minimal to marked) was affecting single blood vessels (small to medium sized arteries and occasional veins) in multiple organs systems in 3 MD and 6 HD cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day) for 52-weeks. The thrombosis correlated with gross necropsy findings of masses in the heart of 1 HD female (#4513) and in the lung of 1 MD female (#3505). There was no evidence of necrosis in the tissues affected by thrombosis in cynomolgus monkeys administered concizumab (≤ 9 mg/kg/day) for 52-weeks. (Subendothelial Intimal Thickening) Subendothelial intimal thickening (minimal or marked) in isolated small to medium-sized arteries in the lung was observed in 1 HD male (#4002) and 2 HD females (#4502 and #4503) after 13 weeks. Note: Similar findings were reported to have been observed in the large intestine (colon) of 1 HD female (#4503) in the interim study report but was eventually removed from the histopathology descriptions, summary tables, and the individual animal data in the final study report after the Applicant's reanalysis of the data. Subendothelial intimal thickening (moderate) in isolated small to medium-sized arteries in the lung and liver was observed in 1 HD male (#4006) after 26 weeks. Subendothelial intimal thickening (mild to moderate) in isolated small to medium-sized arteries in the lung was observed in 1 MD female (#3505) and 1 HD male (#4012) after 52 weeks. The reversibility of these vascular changes was not assessed, and these findings are consistent with the pharmacological effects of an antihemorrhagic when administered to cynomolgus monkeys in a normo-coagulative state. (Tissue Necrosis): The combination of multifocal thrombosis and subendothelial intimal thickening in the left caudal lung lobe resulted in complete luminal obstruction of the pulmonary vasculature in 1 HD female (#4502) at Week 13. This condition was associated with partial necrosis of the left caudal lung lobe, which likely resulted from infarction of the affected area and corresponded with the dark focus observed grossly during necropsy. The reversibility of the vascular changes at the HD (Week 13) was not assessed, and these findings are consistent with the pharmacological effects of an antihemorrhagic when administered to cynomolgus monkeys in a normo-coagulative state. (Brain): Lymphocytic plasmacytic infiltration (minimal) was present in the choroid plexus of 1 HD male (#4001) at Week 13 and is

Parameters	Major Findings
	consistent with an immunogenic response to a foreign protein in an immunocompetent cynomolgus monkey (No Recovery Data). Lymphocytic plasmacytic infiltration (minimal to marked) was present in the choroid plexus of 1 LD male (#2004), 1 MD male (#3002) and 2 HD females (#4506 and #4508) at Week 26. Microscopic findings in the choroid plexus were not observed in HD males or in LD/MD females. This extent of this condition was deemed adverse in MD male (#3002) where the infiltration (lymphocytes, plasma cells, pigmented macrophages, multinucleated giant cells, and eosinophils) of the choroid plexus was marked and there was formation of a lymphoid follicle-like structures. The reversibility of this condition was not assessed and findings in the choroid plexus are considered consistent with an immunogenic response in immunocompetent cynomolgus monkeys. Lymphocytic plasmacytic infiltration (minimal) was present in the choroid plexus of cynomolgus monkeys dosed at ≥ 0.5 mg/kg/day and the incidence was increased in HD females at Week 52 (No Recovery Data). (Injection Site): Lymphocytic perivascular infiltrates (minimal to mild) were present at the subcutaneous administration sites in control and concizumab-dosed cynomolgus monkeys at Week 13. Plasma cell infiltrates were observed only in cynomolgus monkeys administered concizumab and is consistent with a local immunogenic effect (No Recovery Data). Lymphocytic perivascular infiltrates (minimal to mild) were present at the subcutaneous administration sites in control and concizumab-dosed cynomolgus monkeys at Week 26. Plasma cell infiltrates were observed only in cynomolgus monkeys administered concizumab and is consistent with a local immunogenic effect (No Recovery Data). Lymphocytic perivascular infiltrates (minimal to mild) were present at the subcutaneous administration sites in control and concizumab-dosed cynomolgus monkeys at Week 52. Plasma cell and eosinophil infiltrates were observed only in cynomolgus monkeys administered concizumab for 52 weeks and is consistent with a localized immunogenic effect (No Recovery data).

Source: Reviewer constructed summary table of the toxicology Study (213542) submitted to the BLA.
Abbreviations: ADA, anti-drug antibody; APTT, activated partial thromboplastin time; AUC₀₋₂₄, area under the time-concentration curve from time zero to time 24 hours; C_{max}, maximum plasma concentration; ECG, electrocardiogram; HD, high dose; LD, low dose; MD, mid dose; QRS, Q wave, R wave and S wave complex; PR, pulse rate; PROS, protein S; PT, prothrombin time; Rac_{Obs}, RR, heart rate; TFPI, tissue factor pathway inhibitor; TGT, thrombin generation test; t_{max}, time to reach maximum concentration

13.1.2.2. Genotoxicity Studies

Concizumab is a monoclonal antibody (mAb) consisting of naturally occurring amino acids, and is not expected to be genotoxic or to interact directly with DNA or other chromosomal material. There were no mechanistic data submitted which suggested that concizumab had mutagenic or proliferative potential, and as a result, genotoxicity studies were not performed with concizumab.

13.1.2.3. Carcinogenicity Studies

As concizumab is not functionally active in rodents, standard regulatory carcinogenicity studies in rats and/or mice would not be expected to provide a valuable assessment of carcinogenicity.

Therefore, the Applicant conducted a carcinogenicity assessment of concizumab using a weight of evidence approach (Study 321420) that considered the mode of action, a review of the relevant literature (that included an evaluation of >670 publications) and an evaluation of the nonclinical and clinical data, consistent with the guidance provided in ICH S6 (R1). A summary of the Applicant's assessment is provided below.

- Tumor growth and metastasis is a complex and multi-factorial process and the TF/Factor VII (FVIIa) signaling pathway is known to contribute to this process. However, physiological levels of Tissue Factor Pathway Inhibitor (TFPI) do not appear to influence these reactions. Instead, at physiological levels, TFPI (and by extension concizumab, a TFPI antagonist) influence signaling via TF/FVIIa/FXa and this signaling pathway has not been associated with tumor development.
- The C-terminal part of TFPI has been suggested to play a role in reducing tumor cell proliferation, angiogenesis, and metastasis. These processes are not expected to be affected by the specific binding of concizumab to the K2 domain of TFPI.
- The inhibition of TFPI by concizumab leads to increased thrombin generation downstream in the coagulation process. Thrombin has been reported to mediate signaling reactions implicated in cancer, and these reactions may proceed if/when hemostasis is restored in hemophilia. Therefore, concizumab (and, in general, any procoagulant agent) has the potential to enhance the effects of thrombin, including the prothrombotic state, observed in many types of cancer.
- Tissue Factor Pathway Inhibitor (TFPI) is present in some cancer cell lines at varying expression levels, and increased expression of TFPI would be expected to dampen the procoagulant effects of TF. Therefore, it is conceivable that concizumab (as well as any other procoagulant agent) could enhance the hypercoagulable state often observed with cancer. Treatment of hemophilia patients with concizumab therefore has the potential to increase the risk of thromboembolic events in subjects with undiagnosed malignancies.
- In individuals with partial TFPI deficiency (e.g., due to specific TFPI polymorphisms, factor V (FV) deficiency or intake of pharmaceutical estrogen products, i.e., oral contraceptives), the effect of reduced TFPI on general cancer risk in humans is considered predominantly neutral.
- Concizumab is a first-in-class mAb directed against TFPI. The available literature reports from three other TFPI antibodies in clinical development did not reveal any information related to human cancer risk.
- Concizumab has been evaluated in nonclinical repeat-dose toxicity studies in cynomolgus monkeys with daily subcutaneous administration for up to 52 weeks. In these studies, no signs of proliferation, neovascularization, immunosuppression, or organ weight changes were observed.

While the reviewer agreed with the Applicant that there were no signs of neovascularization or immunosuppression in cynomolgus monkeys administered concizumab for up to 52 weeks, vascular intimal proliferation/hypertrophy/hyperplasia in the lungs, vascular hypertrophy and/or hyperplasia in the brain (choroid plexus) and/or the presence of a granuloma in the caudate nucleus of the brain were observed in cynomolgus monkeys dosed with concizumab for ≥ 13 weeks. While the Applicant suggests that the proliferative changes in the vasculature are likely the consequence of an immunogenic response to (and not a pharmacological effect of) concizumab, the reviewer contends that these changes are relevant to the overall carcinogenicity risk assessment of concizumab.

- Concizumab is currently being assessed in two clinical Phase 3 studies. The clinical data from the completed Phase 1B study and the two Phase 2 studies as well as serious adverse events reported from the two ongoing Phase 3 studies, have not identified any safety concerns in relation to cancer.

The Applicant considers the carcinogenic potential of concizumab to be adequately evaluated by this weight of evidence evaluation. It is concluded that treatment with concizumab potentially may enhance the prothrombotic conditions observed in some cancer patients, as would be expected for any other procoagulant agent. However, the assessment has not identified evidence that treatment with concizumab may lead to an increased risk of inducing or enhancing tumor development in humans.

- The Division determined that no additional nonclinical studies assessing the carcinogenic potential of concizumab were warranted for the indications of hemophilia A and hemophilia B, and the CDER Executive Carcinogenicity Assessment Committee (ECAC) concurred with the Division's recommendation.

13.1.2.4. Reproductive and Developmental Toxicity

No reproductive and developmental toxicity studies were conducted with concizumab as the intended population is male hemophilia patients, and the clinical development program was conducted exclusively in males. Hemophilia A is inherited in an X-linked recessive manner and the disease which occurs predominantly in males (99%) is extremely rare in females. Concizumab is also being indicated for Hemophilia B (Factor IX deficiency or Christmas disease, caused by mutations in the coagulation factor IX (FIX) gene on the X chromosome) and hence, is predominantly observed in males (some females who carry the gene may display mild or, rarely, severe symptoms of bleeding).

13.1.2.4.1. Fertility and Early Embryonic Development

Consistent with the guidance provided in ICH S6 (R1), specialized evaluations of fertility parameters were included in the 26-week chronic toxicity study conducted in sexually mature cynomolgus monkeys (Study 211087 in [Section 13.1.2.1](#)).

There were no notable effects on the menstrual cycle duration, the length, width and volume of the testis, total sperm count, sperm motility or sperm morphology in cynomolgus monkeys administered concizumab at ≤ 9 mg/kg/day (SC) or 30 mg/kg/week (IV) for 26 weeks.

Histopathological evaluations of the reproductive organs conducted during the repeat-dose toxicity studies (≤ 52 weeks, GLP) in juvenile and sexually mature male and female cynomolgus monkeys did not indicate any adverse effects on the reproductive organs.

13.1.2.4.2. Embryo Fetal Development

In mice, inactivation of the TFPI-gene has been shown to result in embryonic lethality ([Huang et al. 1997](#); [Ellery et al. 2015](#)) and total TFPI deficiency has not been described in humans ([Wood et al. 2014](#)). The Applicant suggests that, as placental transfer of IgG is limited during organogenesis in humans, these findings may not be relevant when administering a monoclonal IgG antibody (i.e., concizumab) to humans ([DeSesso et al. 2012](#)).

It should be noted that an association of recurrent pregnancy loss was observed in women who exhibited TFPI deficiency in combination with an Activated Protein C (APC) resistance phenotype, and in women with anti-TFPI antibodies in combination with antiphospholipid antibodies, suggesting that TFPI may be critical to the maintenance of normal pregnancy in humans ([Martinuzzo et al. 2005](#); [Gardiner et al. 2006](#)).

The reviewer agrees with the Applicant's assessment that the implications of blocking TFPI functionality with a monoclonal antibody in pregnant women are not clear.

13.1.2.4.3. Pre- and Postnatal Development

No pre- and postnatal development studies have been conducted with concizumab as the hemophilia patient population is almost exclusively male.

13.1.2.4.4. Juvenile Animal Studies

Dedicated juvenile animal studies were not conducted with concizumab, consistent with the guidance provided in ICH M3 (R2)².

The Applicant contends that the hemostatic system was the only target organ identified during toxicity assessments. However, the reviewer does not agree with this statement based on the extensive immune-related and vascular toxicity observed in cynomolgus monkeys. The human hemostatic system matures during the early weeks and months of life, and the concentrations of most hemostatic proteins, both in full-term and preterm infants, are comparable to adult values by 6 months of age ([Albisetti 2003](#); [Chalmers 2004](#)).

Consequently, the Applicant argues that the toxicity of concizumab has been adequately characterized through the general toxicology program in juvenile (2 to 3 years of age) and sexually mature (3.5 to 6 years of age) cynomolgus monkeys.

Studies in neonatal and infant monkeys are technically challenging and are unlikely to identify potential reactions that were not identified from studies in fully developed (adult) animals.

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/m3r2-nonclinical-safety-studies-conduct-human-clinical-trials-and-marketing-authorization>

Therefore, the reviewer agrees that dedicated juvenile toxicity studies in animals are not considered warranted for the indications of hemophilia A and hemophilia B.

(b) (4)

13.1.2.5. Other Toxicology Studies

13.1.2.5.1. Coagulation Endpoint Analysis (Repeat-Dose Toxicity Studies)

Evaluation of Plasma Antithrombin and Protein C in the 4- and 13-Week Repeat Dose Toxicity Studies in Cynomolgus Monkeys (Study 212058, non-GLP)

Key Study Findings

- Concizumab elicited minor decreases in plasma antithrombin levels in the 4-week toxicity study particularly in the 30 mg/kg (QW, IV) dose group, and no dose dependent changes were observed in the 13-week study. Protein C levels were not influenced by concizumab in either study.

Reviewer Comments: Minor decreases in plasma antithrombin in cynomolgus monkeys were not considered of clinical relevance in either the 4-week or 13-week (subcutaneous and intravenous administration) toxicity studies of concizumab in cynomolgus monkeys (Study 210130 and Study 209206).

Table 85. Study Information, Study 212058, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The objective of this report was to summarize the analysis of antithrombin and Protein C levels in plasma samples derived from the 4-week and the 13-week subcutaneous and intravenous administration toxicity studies of concizumab in cynomolgus monkeys (Study 210130 and Study 209206).
Methods	Protein C and antithrombin in cynomolgus monkey plasma were determined using hemostasis assays and an automated random-access multiparameter coagulation analyzer equipped with a photo-optical clot-detection unit.

Source: Reviewer constructed summary table of the toxicology Study (212058) submitted to the BLA.
Abbreviation: GLP, good laboratory practices

Evaluation of Plasma Antithrombin and Protein C in the 26-Week Repeat Dose Toxicity Study in Cynomolgus Monkeys (Study 212391, non-GLP)

Key Study Findings

- Concizumab elicited minor decreases (<15%) in plasma antithrombin levels (≥ 3 mg/kg/day, SC and 30 mg/kg/week, IV) and in protein C levels (<19%) at the 30 mg/kg/week (IV) in males only.

Reviewer Comments: Minor decreases in plasma antithrombin/Protein C levels in cynomolgus monkeys were not considered of clinical relevance in the 26-week (subcutaneous and intravenous administration) toxicity study of concizumab conducted in cynomolgus monkeys (Study 211087).

Table 86. Study Information, Study 212391, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The objective of this report was to summarize the analysis of antithrombin and Protein C levels in plasma samples from the 26-week subcutaneous and intravenous administration toxicity study of concizumab in cynomolgus monkeys (Study number 211087).
Methods	Protein C and antithrombin in cynomolgus monkey plasma were determined using hemostasis assays and an automated random-access multiparameter coagulation analyzer equipped with a photo-optical clot-detection unit.

Source: Reviewer constructed summary table of the toxicology Study (212391) submitted to the BLA.
Abbreviation: GLP, good laboratory practices

13.1.2.5.2. Cytokine Release Analysis (Repeat-Dose Toxicity Studies)

Analysis of Cynomolgus Monkey Samples for IL-6, IL-1 β , IFN- γ , TNF α , E-Selectin and ICAM-1 (Study 213528, non-GLP)

Key Study Findings

- Mean serum concentrations for E-Selectin, IL-6, IL-1 β , IFN- λ and TNF- α did not change from pre-study levels at any time-point and no differences between dosing groups were observed.
- ICAM-1 concentrations did not change from pre-study levels (in any group) during the administration period (Week 22 or 26). However, increases were noted in control males (50%) and LD females (50%) during the recovery period (9 or 12 weeks). ICAM-1 changes in recovery monkeys were considered incidental and unrelated to the administration of concizumab.

Reviewer Comments: There were no notable changes in serum E-Selectin, ICAM-1, IL-6, IL-1 β , IFN- λ or TNF- α observed after 22 or 26 weeks of dosing with concizumab or after 9/13-weeks of recovery in cynomolgus monkeys.

Table 87. Study Information, Study 213528, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The objective of this study was to conduct a fit-for-purpose (FFP) assessment of an analytical procedure for the determination of E-Selectin and ICAM-1 in Cynomolgus monkey serum using an ELISA. Cynomolgus monkey serum collected during the 26-week toxicity study by the subcutaneous and intravenous routes of administration with a 13 Week recovery period (211087) were analyzed for E-Selectin, ICAM-1, IL-6, IL-1 β , IFN- γ , and TNF- α .
Methods	The E-Selectin and ICAM-1 (CD54) monkey in vitro ELISA kits were found to be suitable for the analysis of cynomolgus serum samples. The analysis of IL-6, IL-1 β , IFN- γ and TNF- α were conducted with fluorokine MAP multiplex kits and dual laser, flow-based sorting, and detection analyzers.

Source: Reviewer constructed summary table of the toxicology Study (213528) submitted to the BLA.
Abbreviations: ELISA, enzyme-linked immunoassay; FFP, fit-for-purpose; GLP, good laboratory practices; ICAM, intercellular adhesion molecule; IFN, Interferon; IL, Interleukin; MAP, Multianalyte Profiling; TNF, Tumor necrosis factor.

13.1.2.5.3. Mechanistic Analyses

Separation of Concizumab High Molecular Weight Proteins (HMWPs) by Size Exclusion Chromatography (Study 215027, non-GLP)

Key Study Findings

- Concizumab (batch ATfK505001) was separated into monomer, dimer, trimer and multimer fractions to allow for detailed biological characterization of concizumab derived HMWP.

Reviewer Comments: The material assessed in the 26-week cynomolgus monkey toxicity study contained increased levels of high molecular weight proteins (HMWPs) that consisted predominantly of concizumab multimers. In contrast, the material used in the 4-, 13- and 52-week toxicity studies was comparable to the clinical material and contained significantly lower amounts of HMWPs. This study is part of the evaluations that were conducted to assess whether the change in impurity profile could account for the increased toxicity observed in the 26-week cynomolgus monkey study.

Table 88. Study Information, Study 215027, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The preclinical batch of concizumab (ATfK505001) contained 12.8% high molecular weight protein (HMWP) comprising a heterogeneous mixture of species with molecular weights ranging from 300 kDa (corresponding to a dimer) to at least 1 MDa. In order to enable a more detailed biological characterization of concizumab HMWPs, sub-populations of HMWPs were isolated with more narrow size distributions.
Methods	Concizumab (Batch ATfK505001) was subjected to size exclusion chromatography (SEC) and separated into monomer, dimer, trimer, and higher order multimer fractions. The size distribution of the individual fractions was assessed by size exclusion high performance liquid chromatography multi-angle light scattering (SE-HPLC-MALS) analysis. Dimer, trimer and multimer species were found to be relatively stable, i.e., only minor dissociation into monomer was observed upon handling and storage.

Source: Reviewer constructed summary table of the toxicology Study (215027) submitted to the BLA.

Abbreviations: GLP, good laboratory practices; HMWP, high molecular weight protein; SEC, size exclusion chromatography; SE-HPLC-MALS, size exclusion high performance liquid chromatography multi-angle light scattering

Separation Analysis of Anti-Concizumab Antibodies by Size Exclusion Chromatography and Immune Complex (IC) Enzyme-linked Immunoassay (ELISA) in Cynomolgus Monkey Plasma Samples Derived from the 26-Week and 52-Week Toxicity Studies (Study 214449, non-GLP)

Key Study Findings

- Immune complexes (ADA/concizumab) of different sizes developed over time (compared to pre-dose values) in all concizumab dosed (26 and 52 week treatment duration) cynomolgus monkeys. In the control group, no immune complex formation was observed over time.
- There was a trend toward more immune complexes of a high molecular weight in samples derived from cynomolgus monkeys in the 26-week toxicity study (versus the 52-week study) that employed concizumab with an increased level of high molecular weight proteins (HMWPs).
- In the 52-week toxicity study there was a trend towards larger immune complexes at the LD (compared to controls, MD, and HD).

Reviewer Comments: The assay for qualitative detection of ADA/concizumab ICs was considered acceptable and batches of concizumab enriched in multimers tended to form ICs more efficiently in cynomolgus monkeys.

Table 89. Study Information, Study 214449, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The purpose of the study was to evaluate the presence of anti-concizumab antibodies (anti-drug antibodies, ADAs) in complex with concizumab (without interference from free concizumab) in plasma samples derived from the 26-week (211087) and 52-week (213542) toxicity studies in cynomolgus monkeys.
Methods	The present study evaluated samples from cynomolgus monkeys with vascular lesions detected by histopathology as well as samples from controls. Detection of ADA/concizumab immune complexes without interference from free concizumab was achieved by separation of the complexes from the free drug by size exclusion chromatography (SEC) followed by an ELISA that was specific for complexes of ADA/concizumab.

Source: Reviewer constructed summary table of the toxicology Study (214449) submitted to the BLA.

Abbreviations: ADA, anti-drug antibody; ELISA, enzyme-linked immunoassay; GLP, good laboratory practices; SEC, size exclusion chromatography

Immunohistochemistry Study to Investigate Biodistribution of Concizumab-Related Immune Complexes in Tissues Derived from Cynomolgus Monkeys Administered Concizumab for 26 Weeks (Study 214391, non-GLP)

Key Study Findings

- Granular deposits containing concizumab, monkey IgG, IgM, and/or complement component C3 (C3) were observed in a subset of the affected choroid plexus blood vessels or associated macrophages, respectively, in 2/4 (50%) and 3/4 (75%) concizumab-dosed cynomolgus monkeys with choroid plexus endothelial cell hypertrophy, hyperplasia and/or vasculitis.
- Similar granular deposits were observed in affected lung blood vessels of 3/5 (60%) concizumab-dosed cynomolgus monkeys with lung vascular/perivascular alterations.

Reviewer Comments: The presence of granular deposits at vascular and/or inflammatory sites in the lung and choroid plexus of cynomolgus monkeys is consistent with a role of immune complexes in the pathogenesis of these lesions. As only a subset of the affected vessels contained granular deposits, it cannot be ruled out that other factors may have contributed to the histologic alterations in the choroid plexus/lung.

Table 90. Study Information, Study 214391, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	This report presents the immunohistochemistry (IHC) findings in cynomolgus monkeys dosed for 26 weeks either daily at 0, 3 or 9 mg/kg by subcutaneous administration or at 30 mg/kg by once weekly by intravenous administration (Study 211087). The purpose of the IHC phase of the study was to provide information regarding the biodistribution of concizumab and the formation/deposition of immune complexes

Study Features and Methods	Details
	(ICs) containing concizumab, monkey IgG, IgM, and/or C3 in vascular tissues in the brain (including choroid plexus), lung, liver, and/or kidney from selected control and concizumab-dosed cynomolgus monkeys.
Methods	Hematoxylin and eosin (H&E) slides were prepared and evaluated for histopathological alterations including subendothelial intimal thickening, vascular/perivascular inflammation, endothelial cell hypertrophy and/or hyperplasia, and thrombosis. Based on the H&E evaluation, the brain and lung tissues with confirmed vascular/perivascular alterations and corresponding tissues from controls were selected for IHC and were stained for the presence of human IgG (indicative of concizumab), monkey immunoglobulins (IgG and IgM), and/or complement component C3. Granular deposits of human IgG, monkey IgG and IgM, and/or C3 were considered evidence of immune complex deposition.

Study Features and Methods	Details
Results	(Choroid Plexus) Granular deposits were observed (IHC) in intima/media of some affected blood vessels and/or intramural and/or perivascular macrophage infiltrates, respectively, in 2/4 and 3/4 dosed cynomolgus monkeys with endothelial cell hypertrophy and/or hyperplasia or vasculitis in choroid plexus. The granular deposits were either associated with the surface of the macrophages or had been phagocytosed by the macrophages. Granular deposits were not observed in controls or in two concizumab-dosed cynomolgus monkeys without vascular alterations in choroid plexus. In affected blood vessels, the granular deposits were observed in or near the affected portions of the intima/media (typical sites for immune complex deposition), whereas granular deposits were not observed in unaffected blood vessels. Probable granular deposit localization at vascular branch points was identified in a LD (3 mg/kg/day) male (#8) and were characteristic of immune complex deposition. The vascular wall granular deposits were composed of co-localized concizumab (human IgG), monkey IgG and/or IgM (likely ADA) but did not contain C3. In choroid plexus macrophages, the granular deposits contained human IgG and IgM and/or C3. It's unclear whether the differences in granular deposit composition between the vascular wall and the macrophages reflected differential processing or a differential uptake by macrophages. (Lung) Granular deposits containing concizumab, monkey IgG, IgM, and/or C3 were observed in the intima/media of a subset of affected blood vessels in 3/5 concizumab-dosed cynomolgus monkeys with vascular/perivascular inflammation or other alterations in lung blood vessels but were not observed in controls without vascular and/or perivascular inflammation. The granular deposits were observed in intima/internal elastic lamina and/or at vascular branch points of relatively early lesions in lung in a LD male (#6) and in a 30 mg/kg IV dosed male (#17). Concizumab-, monkey IgG-, and IgM-containing granular deposits were also observed in at least one thrombus in the 30 mg/kg IV dosed male (#17). In a 30 mg/kg (IV) dosed male (#18), the granular deposits associated with the intimal thickening were composed of IgM and C3, however the presence of concizumab was not detected.

Source: Reviewer constructed summary table of the toxicology Study (214391) submitted to the BLA.
Abbreviations: ADA, anti-drug antibody; C3, component 3; GLP, good laboratory practices; H&E, hematoxylin and eosin; IgG, immunoglobulin G; IgM, immunoglobulin M; IHC, immunohistochemistry; LD, low dose.

**Analysis of Complement Activation and Circulating Immune Complexes in Samples
Derived from the 52-Week Cynomolgus Monkey Toxicity Study (Study 214471, non-GLP)**

Key Study Findings

- Circulating immune complexes (CIC) were present in all concizumab-dosed cynomolgus monkeys at Week 26 (prior to dose administration) and were significantly elevated at the HD. Following the administration of concizumab (Week 26), significant increases in CIC levels were observed at 4 hours (post-dose) in all concizumab-dosed cynomolgus monkeys.
- Classical complement pathway activity (50% Hemolytic Complement equivalent, CH50) was not notably affected in blood sample derived from cynomolgus monkeys administered concizumab for 26-/52-weeks (≤ 9 mg/kg/day).
- The results of the complement fragment C3a assay were inconclusive at Week 26, and there were no notable effects observed at Week 52.

Reviewer Comments: The assays for CIC, CH50 and C3a were considered acceptable and indicated that concizumab elicited the formation of CICs but did not increase complement activation in cynomolgus monkeys.

Table 91. Study Information, Study 214471, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The purpose of the study was to investigate complement activation in samples from the 52-week cynomolgus monkey toxicity Study (213542) using three different assays.
Methods	Samples were obtained during Week 26 and Week 52 when steady state plasma concentrations of concizumab had been established. Circulating immune complexes (CIC) were assessed using an enzyme immunoassay (EIA) that measures circulating immune complexes containing C3 fragments. Classical complement pathway activity (50% Hemolytic Complement equivalent (CH50)) was assessed using an EIA that measures the total classical complement pathway activity. Complement fragment C3a was assessed in an EIA where C3a binds to microwell plates coated with a monoclonal antibody against C3a. Analyses were performed on samples collected at pre-dose, 4-, 8- and 24-hours after dosing (SC).

Source: Reviewer constructed summary table of the toxicology Study (214471) submitted to the BLA.
Abbreviations: C3(a), component 3(a); CH50, 50% hemolytic complement equivalent; CIC, circulating immune complexes; EIA, enzyme immunoassay; GLP, good laboratory practices; SC, subcutaneous

**Evaluation of Endothelial Activation Markers Induced by Different Batches of
Concizumab (Study CNGU130901, Non-GLP)**

Key Study Findings

- Concizumab (monomeric) or multimers of concizumab did not influence the cell surface expression of ICAM-1, E-selectin, or VCAM-1 in HUVEC cells and neither form of

concizumab acted in synergy with the cytokines (TNF- α /IL-1 β) to induce a further up-regulation.

- Culturing of HUVEC cells with concizumab (monomeric) or multimers of concizumab in the presence or absence of cytokines (TNF- α /IL-1 β) did not result in surface expression of Fc γ RI, Fc γ RII and Fc γ RIII. Note: These Fc γ -receptor were not expressed on resting HUVEC cells, and these cytokines (TNF- α /IL-1 β) alone were unable to trigger their expression (in vitro).

Reviewer Comments: The levels of endothelial cell activation were comparable between monomeric and multimeric batches of concizumab and suggest that aggregates of concizumab do not elicit biological effects that are different from the parent (monomeric) protein (in vitro).

Table 92. Study Information, Study CNGU130901, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The purpose of the study was to assess the cell surface expression of endothelial activation markers and to evaluate if two different batches of concizumab containing varying levels of HMWPs could induce a change in the surface expression of these markers on vascular endothelial cells.
Methods	Markers of endothelial activation (E-selectin, ICAM-1, and VCAM-1) were assessed in the presence of concizumab containing a low level of HMWP (1.4%) or in a batch of concizumab containing mainly HMWP (multimers, 93.6%). Endothelial surface expression of Fc γ -receptors (Fc γ R) was also evaluated. These experiments were conducted using human umbilical vein endothelial cells (HUVECs). The level of surface marker expression was assessed by flow cytometry.

Source: Reviewer constructed summary table of the toxicology Study (CNGU130901) submitted to the BLA.
Abbreviations: Fc γ R, Fc γ -receptors; GLP, good laboratory practices; ICAM, intercellular adhesion molecule; HMWP, high molecular weight protein; HUVEC, human umbilical vein endothelial cell; VCAM, vascular cell adhesion molecule

Immunohistochemistry Study to Investigate Biodistribution of Concizumab-Related Immune Complexes in Tissues from Cynomolgus Monkeys Administrated Concizumab for 13, 26, or 52 weeks (Study 214400, non-GLP)

Key Study Findings

- Granular deposits were observed in a subset of the affected blood vessels that presented with vascular/perivascular alterations in the lungs of concizumab-dosed cynomolgus monkeys: 1/3 (33%) at 13 weeks, 1/1 (100%) at 26 weeks, and 2/2 (100%) at 52 weeks.
- Granular deposits were also present in the affected blood vessels or in stroma of choroid plexus, with inflammatory alterations: 1/2 (50%) at 13 weeks, 2/4 (50%) at 26 weeks, and 4/7 (57%) at 52 weeks.

Reviewer Comments: The presence of granular deposits at vascular and/or inflammatory sites in the lung and choroid plexus of cynomolgus monkeys is consistent with a role of immune complexes in the pathogenesis of these lesions. As only a subset of the affected vessels contained

granular deposits, it cannot be ruled out that other factors may have contributed to the histologic alterations in the lung/choroid plexus.

Table 93. Study Information, Study 214400, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The purpose of the IHC phase of the study was to provide information regarding concizumab biodistribution and the formation/deposition of immune complexes (ICs) containing concizumab, monkey IgG, IgM, and/or complement component C3. This report presents the IHC findings in cynomolgus monkeys from Study 213542 and contains the data from selected cynomolgus monkeys dosed for 13-, 26-, and 52-weeks.
Methods	Hematoxylin and eosin (H&E) slides were prepared and evaluated for histopathological alterations. Based on the H&E evaluation, the lung, liver, and brain-choroid plexus with vascular/inflammatory changes (subendothelial intimal thickening/plasmacytic/histiocytic infiltration) were selected for IHC and were stained for the presence of human IgG (indicative of concizumab), monkey immunoglobulins (IgG and IgM), and/or complement component C3. Granular deposits of human IgG, monkey IgG and IgM, and/or C3 were considered evidence of immune complex deposition.

Results	(13-Week Interim Sacrifice) Granular deposits containing concizumab, IgM, and/or C3 were observed in a subset of affected blood vessels but not in any unaffected blood vessels in the lungs of 1/3 (33%) of the dosed cynomolgus monkeys with lung vascular and/or perivascular alterations. All three (100%) cynomolgus monkeys had resolving or chronic lesions (days to weeks old) characterized by intimal thickening while a single HD female (4502) had active (days old) lung lesions characterized by coagulative necrosis, thrombosis, and neutrophilic/mononuclear cell infiltration. In this female, granular deposits were observed in the intima/media of the vascular wall and/or at branch points of a subset of actively affected blood vessels with ongoing inflammation (consistent with immune complex-mediated vascular alterations). In this same female, granular deposits were also observed in neutrophils, monocytes/macrophages, and/or alveolar macrophages associated with the vascular lesions and likely represent phagocytosis and/or processing of immune complexes. Granular deposits composed of concizumab, IgG, and C3 were also observed in the choroid plexus stroma in 1/2 (50%) of the concizumab-dosed cynomolgus monkeys that presented with inflammatory cell infiltration in the choroid plexus. No granular deposits were observed in the 13-week interim controls. (26-Week Interim Sacrifice) Granular deposits were observed in the choroid plexus of 2/4 (50%) of the cynomolgus monkeys that presented with inflammatory alterations in the choroid plexus. The alterations consisted of inflammatory cell infiltration (including plasma cells) in 1 MD male (3002) where the granular deposits were associated with the intima/media of blood vessels. In a HD female (4506) lymphocytic and/or plasmacytic infiltration and granular deposits were located in the choroid plexus stroma. Various stages of vascular/perivascular alterations including thrombosis (occasionally with partial resolution) and pleural inflammation were observed in the lungs and/or liver in a single HD male (4006). No clear granular deposits were observed in this male; however, macrophage phagocytosis of concizumab, monkey IgG, IgM, and C3-coated erythrocytes and platelets were present in the lungs. This male also presented with increases in intraluminal staining of concizumab, monkey IgG, IgM, and C3 in resolving and/or recanalizing thrombi in the liver and lungs. These observations may indicate macrophage processing of immune complexes in the lung and possible local intravascular apposition and/or formation of immune complexes in liver and lung. No granular deposits were observed in the 26-week interim controls.

Study Features and Methods	Details
	(52-Week Terminal Sacrifice)
	Granular deposits were observed in the choroid plexus of 4/7 (57%) of the cynomolgus monkeys that presented with inflammatory alterations in the choroid plexus after 52-weeks. All four of these cynomolgus monkeys [1 LD male (2007) 1 LD female (2507), 1 MD female (3505) and 1 HD female (4510)] presented with lymphoplasmacytic infiltrates that were associated with monkey IgG, IgM, and/or C3 containing granular deposits in the choroid plexus stroma. Two of these cynomolgus monkeys [1 LD female (2507) and 1 MD female (3505)] also presented with associated eosinophilic infiltrates.
	Granular deposits containing concizumab (human IgG), IgM, and/or C3 were observed in a subset of affected blood vessels but not in any unaffected blood vessels in 2/2 (100%) of the cynomolgus monkeys that presented with lung vascular and/or perivascular alterations. The alterations in the pulmonary vessels of these two cynomolgus monkeys [1 MD female (3505) and 1 HD female (4012)] were comparable to those observed in HD males and females after 13-weeks and 26-weeks. No granular deposits were observed in the 52-week controls.

Source: Reviewer constructed summary table of the toxicology Study (214400) submitted to the BLA
Abbreviations: C3, component 3; GLP, good laboratory practices; HD, high dose; H&E, hematoxylin and eosin; IC, immune complexes; IgG, immunoglobulin G; IgM, immunoglobulin M; IHC, immunohistochemistry; LD, low dose; MD, mid dose.

In Vitro Functional Characterization of Multimer and Monomer Forms of Concizumab (Study CCOC130901, non-GLP)

Key Study Findings

- A minimal (albeit significant) increase in the half maximal inhibitory concentration (IC₅₀) was observed for the multimeric form of concizumab in a FXa generation assay (in the presence or absence of 25µM phospholipids) and suggests that the TFPI neutralizing capacity of the high molecular weight protein (HMWP) form of concizumab may be reduced relative to the monomeric form.
- In contrast, when FXa generation was assessed using endothelial cells that expressed surface associated TF and TFPI, a lower half maximal inhibitory concentration (IC₅₀)(non-significant) was achieved with the multimeric form of concizumab relative to the monomeric form.
- In a thrombin generation assay (employing platelet-poor plasma with added phospholipids) significantly higher procoagulant activity (thrombin peak height) was achieved with the multimeric form of concizumab (P1) relative to the monomeric form (P4) and this effect was enhanced (dose dependently) as the level of TF was reduced. Thrombin peak heights were

comparable between the multimeric and monomeric forms of concizumab when employing platelet-rich plasma in the thrombin generation assay.

- The procoagulant effects in whole blood were comparable between the multimeric form and the monomeric form of concizumab when assessed by thromboelastography.

Reviewer Comments: The study suggests that the multimeric form of concizumab can elicit altered biological effects (relative to the monomeric form) in blood coagulation assays under certain in vitro conditions (e.g., a thrombin generation assay employing platelet-poor plasma and low TF concentrations as a catalyst).

Table 94. Study Information, Study CCOC130901, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The purpose of the study was to evaluate the effect of concizumab containing different amounts of high molecular weight proteins (HMWPs) in blood coagulation assays.
Methods	The antibodies assessed included concizumab (2% HMWP), concizumab multimer (92.9 % HMWP), size exclusion chromatography isolated concizumab monomer P4 (0.5 % HMWP) and size exclusion chromatography isolated concizumab multimer P1 (90% HMWP). The ability of concizumab to neutralize FXa inhibition through TFPI was assessed in a FXa generation assay, the activity of concizumab in plasma was assessed using a thrombin generation assay and the activity in whole blood was evaluated using thromboelastography.

Source: Reviewer constructed summary table of the toxicology Study (CCOC130901) submitted to the BLA
Abbreviations: FXa, factor Xa; GLP, good laboratory practices; HMWP, high molecular weight protein; TFPI, tissue factor pathway inhibitor

Dose Formulation Analysis of Return Samples from Toxicity Studies (211087 and 213542) Conducted with Concizumab in Cynomolgus Monkeys (Study 215023, non-GLP)

Key Study Findings

- Minimal (negligible) changes in the content of monomeric and multimeric forms of concizumab were observed in the dose formulation samples over the 26- and 52-week observation periods, when stored at or below -70°C. A similar result was observed when dose formulation samples were stored at 5°C for 7 days prior to storage at or below -70°C.

Reviewer Comments: The study indicates that the percentages of monomeric, dimeric, and polymeric concizumab were relatively stable in dose formulation samples when stored at or below -70°C for up to 52 weeks.

Table 95. Study Information, Study 215023, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The report summarizes the results for the dose formulation analysis from the 26 week (211087) and the 52 week (213542) toxicity studies conducted in cynomolgus monkeys. The concizumab employed in these two studies differed in the content of high molecular weight protein (HMWP, i.e., increased dimers and polymers) and the concizumab batch for Study 211087 (26-Weeks) was deliberately enriched with HMWP polymers whereas the batch for Study 213542 (52-weeks) was of the same quality as the clinical study material.
Methods	The percentages of monomers, dimers, and polymers in the concizumab formulations used in the two toxicity studies were measured after storage of concizumab at or below -70°C for the length of the study. A second aliquot (213542) of all concentrations of the dose formulation samples were stored at 5°C for seven days following sampling before being frozen and stored at or below -70°C until analysis. Size exclusion liquid chromatography (SE-HPLC) was employed to determine the content of monomers and HMPWs in the monoclonal antibody samples.

Source: Reviewer constructed summary table of the toxicology Study (215023) submitted to the BLA
Abbreviations: GLP, good laboratory practices; HMWP, high molecular weight protein; SE-HPLC, size exclusion liquid chromatography

Assessment of Binding and Internalization of Different Batches of Concizumab by Endothelial Cells (Study CNGU131001, Non-GLP)

Key Study Findings

- The binding of concizumab and concizumab multimer batches to endothelial cells was TFPI-specific and concentration-dependent, and the specific binding affinity was found to be comparable (0.3 µg/mL) between the two batches.
- Concizumab and concizumab multimer batches competed for each other's binding to TFPI equally, supporting further that the binding affinities were comparable between these batches.
- A comparable degree (minimal) of cellular internalization was observed between the batches of concizumab (monomeric and multimeric) over time and was found to be specific and saturable.
- The amount of concizumab internalized (specific) by endothelial cells was reduced significantly relative to the amount of cell surface binding (specific) with both the monomeric batch (15-fold lower) and the multimeric batch (20-fold lower) of concizumab and suggests that the cellular target (TFPI) is either internalized minimally/slowly or recycled rapidly to the cell surface.

Reviewer Comments: The study indicates that there were no notable differences between the monomeric and multimeric batches of concizumab with regards to binding affinity and cellular internalization by endothelial cells (in vitro), and suggests that aggregates of concizumab are not likely to elicit biological effects different from those of the parent protein (monomeric concizumab).

Table 96. Study Information, Study CNGU131001, Non-GLP

Study Features and Methods	Details
GLP compliance	No
Objective	The aim of this study was to evaluate and compare the cellular binding and internalization of two different batches of concizumab containing varying levels of high molecular weight proteins (HMWPs) using vascular endothelial cells.
Methods	One batch of concizumab contained a low level of HMWP (1.4%) and the second batch of concizumab contained a high level of HMWP (93.6%) which was the isolated multimer fraction purified from the batch used in the 26-Week cynomolgus monkey toxicity Study (211187). The two batches of concizumab were iodine (125I)-labeled and assessed in assays (in vitro) designed to assess the direct cellular binding and internalization by an endothelial cell line (EA.hy926) and primary human umbilical vein endothelial cells (HUVEC). The specificity of the binding was determined by an excess addition of unlabeled concizumab.

Source: Reviewer constructed summary table of the toxicology Study (CNGU131001) submitted to the BLA

Abbreviations: GLP, good laboratory practices; HMWP, high molecular weight protein; HUVEC, human umbilical vein endothelial cell

13.2. Individual Reviews of Studies Submitted With the New Drug Application

All nonclinical studies submitted to the BLA were also submitted and reviewed under the IND.

14. Clinical Pharmacology

14.1. In Vitro Studies

rFVIIa and activated prothrombin complex concentrates (aPCC) are used to treat bleeds in hemophilia patients with inhibitors and may be used for treatment of breakthrough bleeds in patients on concizumab prophylaxis. Likewise, FVIII and FIX are used to treat bleeds in patients with hemophilia A or B without inhibitors. To evaluate the potential for pharmacodynamic interaction between hemostatic agents and concizumab, the following in vitro studies were conducted.

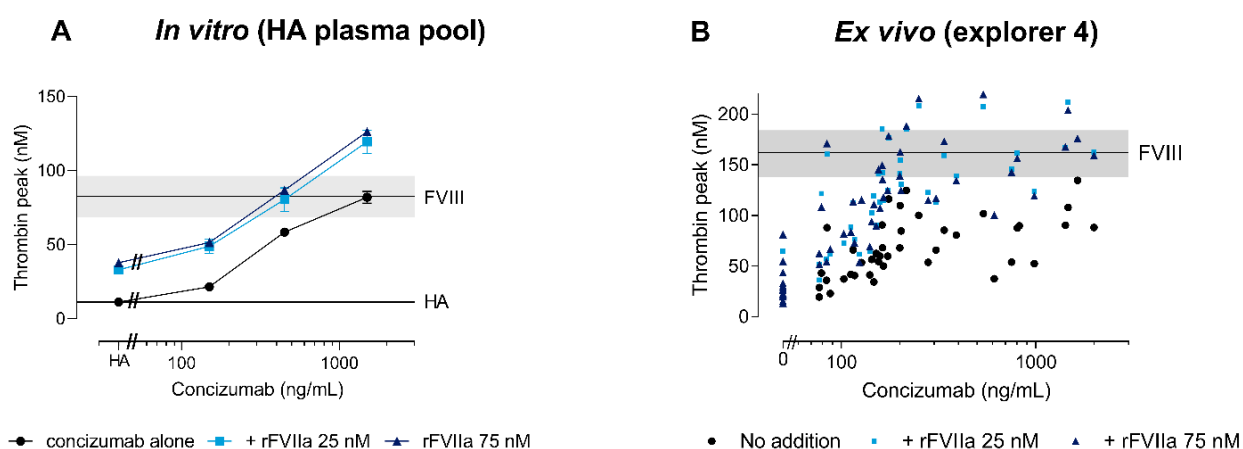
14.1.1. Drug-Drug Interaction Between Concizumab and rFVIIa, Study 319076

The effects of concizumab and rFVIIa were quantified in a thrombin generation assay with HA plasma pool and plasma from patients on concizumab prophylaxis in Studies 4310 and 4255.

- In the HA plasma pool ([Figure 18](#), left), the effects of concizumab and rFVIIa were mainly additive. A statistically significant synergistic effect ($p < 0.05$) was observed for 25nM or 75nM rFVIIa and 1500 ng/mL concizumab. The additive effects accounted for around 85% of the total observed effect for 1500 ng/mL concizumab combined with either 25nM (85.5%) or 75nM (84.7%) rFVIIa (mean values for $n = 3$).
- rFVIIa increased thrombin peak in plasma from HA patients with inhibitors (Study 4310) or without inhibitors (Study 4255) on concizumab prophylaxis ([Figure 18](#), right). The effects of concizumab and rFVIIa were mainly additive accounting for $60 \pm 38\%$ (25nM rFVIIa, Study 4255, mean and standard deviation (SD) of data from 28 subjects), $67 \pm 8\%$ (75nM rFVIIa, Study 4255, mean and SD of data from 24 subjects) and $78 \pm 14\%$ (75nM rFVIIa, Study 4310, mean and SD of data from 15 subjects) of the total observed effects.

Overall, a significant synergistic effect between rFVIIa and concizumab was observed in plasma accounting for up to 40% of the total observed effect.

Figure 18. Thrombin Peak After Adding rFVIIa and Concizumab In Vitro to a Hemophilia A Plasma Pool or Ex Vivo to Plasma Samples From Hemophilia A Patients With Inhibitors on Concizumab Prophylaxis



Source: 2.6.2 Pharmacology Written Summary Figure 18

Note: The grey area depicts (A) the mean $\pm$ 1 SD of thrombin peak observed upon addition of normal level of rFVIII (1 IU/mL) to the hemophilia A (HA) plasma pool ($n=3$) or (B) the mean and 95% CI of rFVIII (1 IU/mL) added to noninhibitor hemophilia A plasma (Trial NN7415-4255, $n=30$ baseline samples). The left datapoint on both graphs depicts the effect of rFVIIa in the absence of concizumab.

Abbreviations: HA, hemophilia A; FVIII, factor VIII; rFVIIa, recombinant factor VIIa

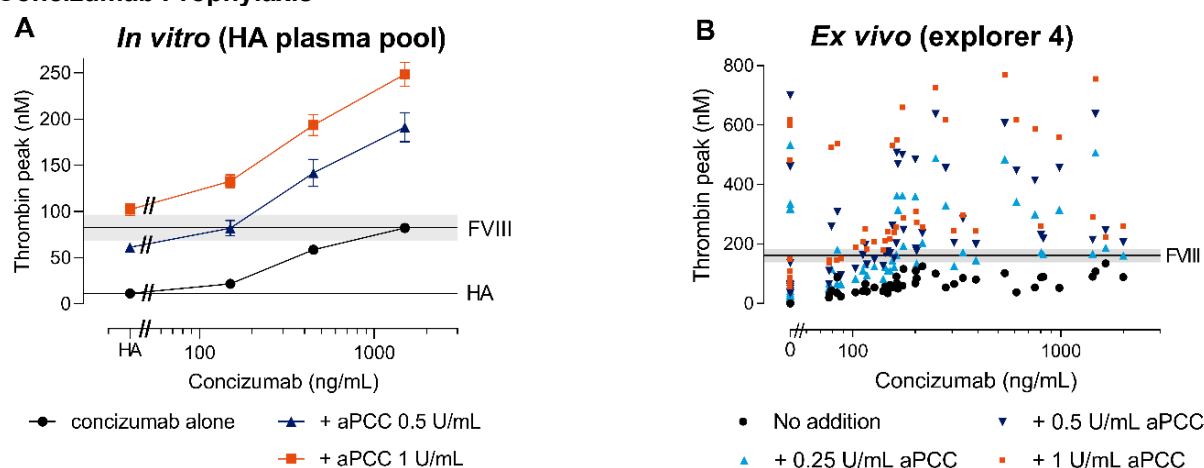
14.1.2. Drug-Drug Interaction Between Concizumab and aPCC, Study 319076

Drug interactions between concizumab and aPCC was evaluated in thrombin generation assay. aPCC enhanced the thrombin peak both in the absence and presence of concizumab in a HA plasma pool (Figure 19, left) and in plasma from HA patients with inhibitors (Study 4310) and without inhibitors (Study 4255) on concizumab prophylaxis (Figure 19, right).

- The effect of concizumab and aPCC were mainly additive accounting for between 83% (150 ng/mL concizumab combined with 1 U/mL aPCC) and 67% (1500 ng/mL concizumab combined with 0.5 U/mL aPCC) of the total observed effects in the plasma pool.
- In the patient samples, the additive effects of concizumab and 1 U/mL aPCC corresponded to $80 \pm 22\%$ of the total observed effects (Study 4310, mean and SD of data from 15 subjects). No significant synergistic effect was observed in Study 4255.

Overall, the data demonstrated that aPCC enhanced the thrombin generation in plasma containing concizumab and that the effect of concizumab and aPCC were mainly additive with a significant synergistic effect of up to 33% of the total effect.

Figure 19. Thrombin Peak After Adding Concizumab and aPCC In Vitro to a Hemophilia A Plasma Pool or aPCC Ex Vivo to Plasma Samples From Hemophilia A Patients With Inhibitors on Concizumab Prophylaxis



Source: 2.6.2 Pharmacology Written Summary Figure 19

Note: The grey area depicts (A) the mean $\pm$ 1 SD of the thrombin peak observed upon addition of normal level of rFVIII (1 IU/mL) to the hemophilia A (HA) plasma pool (n=3) or (B) the mean and 95% CI of rFVIII (1 IU/mL) added to non-inhibitor hemophilia A plasma (Trial NN7415-4255, n=30 baseline samples). The left datapoint on both graphs depicts the effect of aPCC in the absence of concizumab.

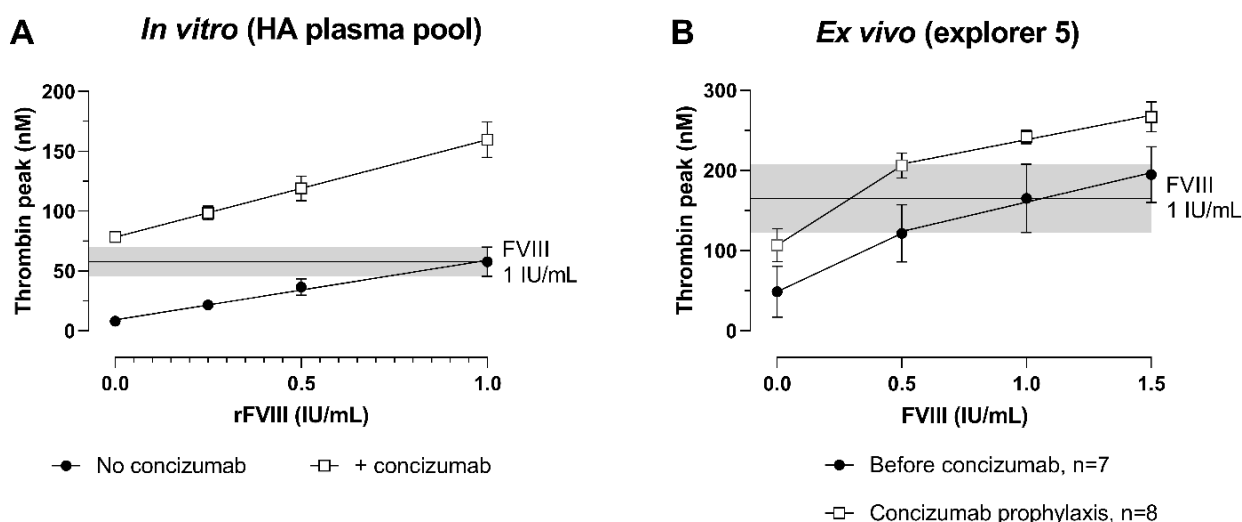
Abbreviations: aPCC, activated prothrombin complex concentrate; HA, hemophilia A; FVIII, factor VIII; rFVIIa, recombinant factor VIIa

14.1.3. Drug-Drug Interaction Between Concizumab and rFVIII, Study 321538

rFVIII was added to an HA plasma pool alone or together with concizumab (Figure 20, left) and to 33 plasma samples from 8 patients on concizumab prophylaxis, where free TFPI levels (TFPI not in complex with concizumab) were below detection limit of the assay (Figure 20, right). For

comparison, rFVIII was added to pre-dose plasma samples available for seven of these patients. rFVIII increased the thrombin peak both in the absence and presence of concizumab. In the plasma pool, a statistically significant synergistic effect was observed for 1 IU/mL rFVIII combined with 1500, 4500 and 15000 ng/mL concizumab, for 0.5 IU/mL rFVIII combined with 1500 and 4500 ng/mL concizumab and for 0.25 IU/mL rFVIII combined with 4500 and 15000 ng/mL concizumab. In these cases, the additive effects of concizumab and rFVIII corresponded to between 78% (1 IU/mL rFVIII combined with 4500 ng/mL concizumab) and 90% (0.25 IU/mL rFVIII combined with 15000 ng/mL concizumab) of the total observed effects. In patient plasma, no significant synergistic effect between rFVIII and concizumab was observed. Thus, when rFVIII was combined with concizumab, between 0 and 22% of the total effect was caused by a synergistic effect.

Figure 20. Thrombin Peak After Adding rFVIII and Concizumab In Vitro to a HA Plasma Pool or FVIII Ex Vivo to Plasma Samples From Hemophilia A Patients Concizumab Prophylaxis



Source: 2.6.2 Pharmacology Written Summary Figure 20

Note: The grey area depicts (A) the mean $\pm$ 1 SD of the thrombin peak observed upon addition of normal level of rFVIII (1 IU/mL) to the hemophilia A (HA) plasma pool in the absence of concizumab (n=4) or (B) the mean $\pm$ 1 SD of rFVIII (1 IU/mL) added to pre-dose plasma (n=7). Data for 1500 ng/mL concizumab is shown in A (open squares), while data for other concentrations are available in Study ID 321538.

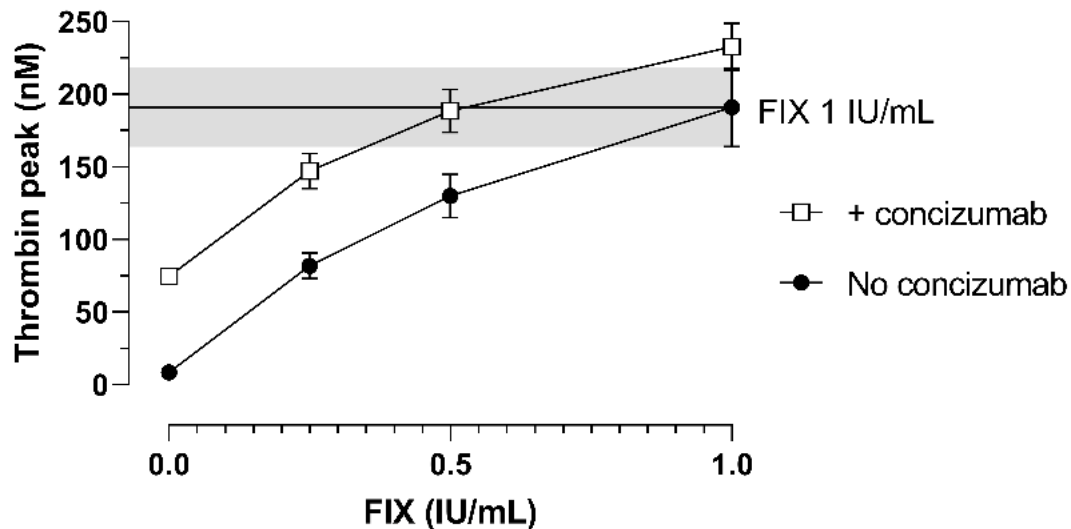
Abbreviations: HA, hemophilia A; FVIII, factor VIII; n, number of subjects; rFVIIa, recombinant factor VIIa

14.1.4. Drug-Drug Interaction Between Concizumab and rFIX, Study 321538

rFIX was added to a HB plasma pool alone or together with concizumab. rFIX enhanced the thrombin peak in HB plasma both in the absence and presence of concizumab (Figure 21). Drug interaction was observed for 1 IU/mL rFIX combined with concizumab at 1500 ng/mL, 4500 ng/mL and 15000 ng/mL and for 0.5 IU/mL rFIX combined with 100nM concizumab. The additive effects of concizumab and 1 IU/mL rFIX corresponded to between 111% (1500 ng/mL concizumab) and 113% (15000 ng/mL concizumab) of the total observed effects, and the additive effects of 0.5 IU/mL rFIX and 15000 ng/mL concizumab corresponded to 112% of the total observed effects.

Overall, the data suggest an additive effect when combining rFIX with concizumab.

Figure 21. Thrombin Peak After Adding Concizumab and rFIX In Vitro to a Hemophilia B Plasma Pool



Source: 2.6.2 Pharmacology Written Summary Figure 21

Note: The grey area represents the mean $\pm$ 1 SD of thrombin peak obtained by adding normal level of rFIX (1 IU/mL) to the hemophilia B plasma (n=3). Data for 1500 ng/mL concizumab is shown (open squares), while data for other concentrations are available in Study ID 321538.

Abbreviations: FIX, factor IX; rFIX, recombinant factor IX

14.2. In Vivo Studies

14.2.1. Single Ascending Dose in Healthy and Hemophilia Subjects, Study 3813

Study Design

This is a randomized, double-blind, placebo-controlled, single-dose, dose-escalation study investigating safety, pharmacokinetics, and pharmacodynamics of concizumab administered intravenously and subcutaneously to healthy male subjects and patients with hemophilia (HA or HB). A total of 52 subjects (28 healthy subjects and 24 hemophilia subjects) were randomized and completed the study. The subjects were randomized in a 3:1 manner to receive concizumab or placebo. The studied doses are listed below:

- Intravenous administration
 - Healthy subjects (12): 0.5, 5, 50, 250 μ g/kg
 - Hemophilia patients (9 HA, 3 HB): 250, 1000, 3000, 9000 mg/kg
 - Placebo (4 healthy subjects and 4 hemophilia patients)
- Subcutaneous administration
 - Healthy subjects (9): 50, 250, 1000 mg/kg
 - Hemophilia patients (6 HA): 1000, 3000 mg/kg
 - Placebo (3 healthy subjects and 2 hemophilia patients)

Serial PK and PD samples were collected at pre-dose, 0, 5, 15 and 30 minutes, 1, 4, 8, 12, 24, 36, and 48 hours post-dosing, at each study visit till the end of study (i.e., up to 43 days after dosing). Validated ELISA and chromogenic assay were used for the PK and PD assessment, respectively.

Results

Concizumab concentration-time profiles following IV and SC administration are presented in [Figure 22](#) with PK parameters summarized in [Table 97](#) and [Table 98](#).

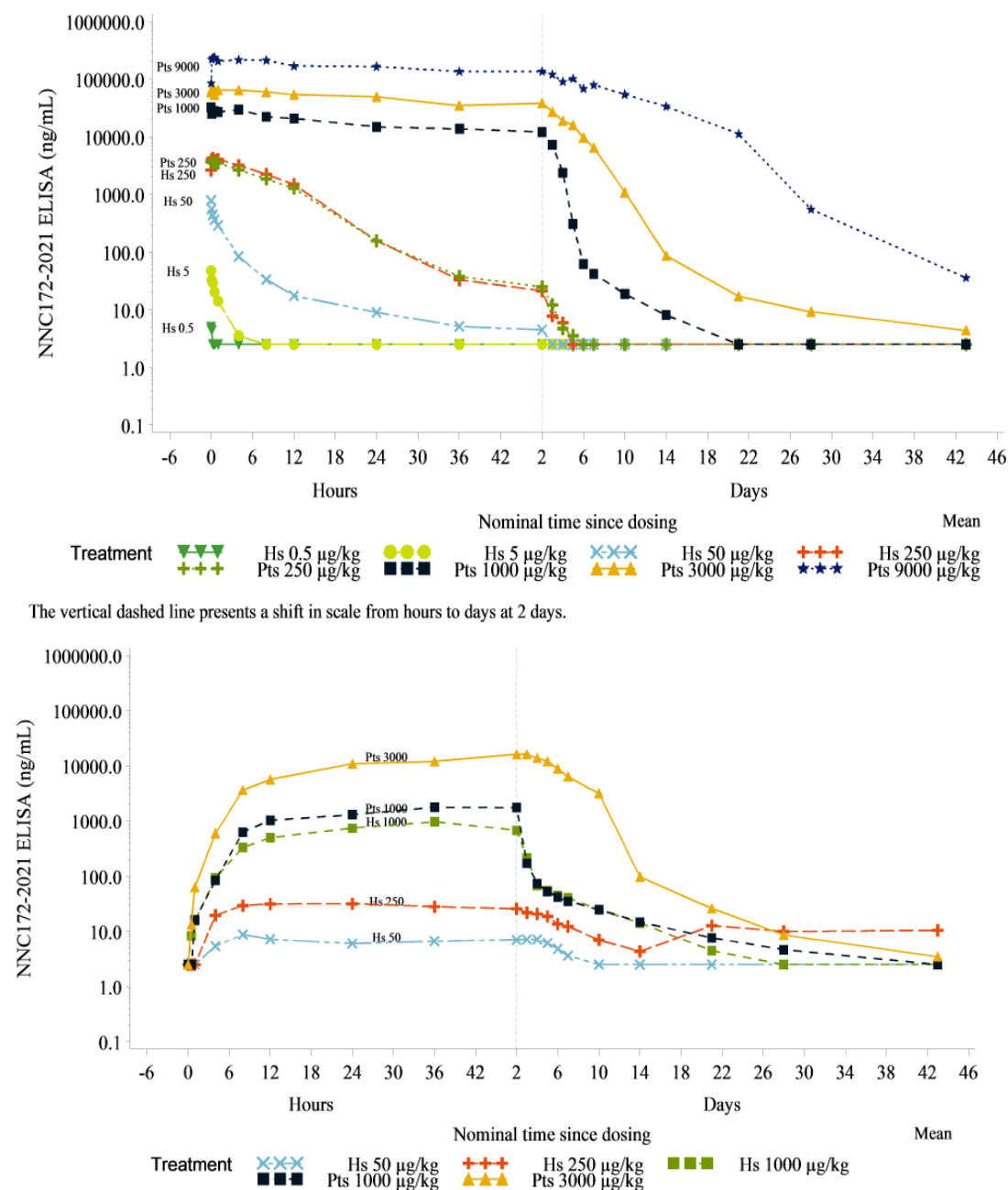
- Across dose levels, concizumab exposure (maximum plasma concentration ($C_{\max}$) and area under the concentration-time curve) increased with increasing dose in a greater than dose proportional manner following IV and SC administration. For example, there was a 23-fold decrease in mean clearance with a 12-fold increase in concizumab doses (i.e., 250 to 3000 $\mu\text{g/kg}$). The non-linear PK was considered to be mainly due to target-mediated drug disposition, which is a common characteristic of monoclonal antibodies.
- PK profiles were similar between healthy subjects and hemophilia patients and between HA and HB patients.
- The median $t_{\max}$ across dose cohorts ranged from 0.5 to 2.9 days following SC administration.
- Following a single dose IV injection of 0.25 mg/kg, the half-life was about 26 to 31 hours.

Mean plasma profiles for free tissue factor pathway inhibitor (free TFPI, the PD marker) concentrations following IV and SC administration of concizumab to healthy subjects and patients with hemophilia are presented in [Figure 23](#) and [Figure 24](#).

- The free TFPI levels decreased with increasing concizumab doses following both IV and SC administration in both healthy subjects and hemophilia patients. Duration of free TFPI suppression increased with increasing concizumab dose. Following a single IV administration, the free TFPI level was completely suppressed for approximately 12 hours and a week for 0.25 mg/kg and 3 mg/kg, respectively.

Concizumab was well-tolerated and there were no deaths or other serious adverse events observed in this study.

Figure 22. Mean Plasma Concentration-time Profiles of Concizumab (NNC172-2021) Following Single-dose Intravenous (Top) and Subcutaneous (Bottom) Administration in Healthy Subjects and Hemophilia Patients, Study 3813



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

Source: Study report 3813 Figures 11-1, 11-3

Abbreviation: ELISA, enzyme-linked immunoassay

Table 97. PK Parameters in Healthy Subjects and Hemophilia Patients Following Intravenous Administration of Concizumab, Study 3813

Parameter	Healthy subjects – i.v. – trial 3813			
	0.0005 mg/kg ^a	0.005 mg/kg	0.05 mg/kg	0.25 mg/kg
N	2	3	3	3
C _{max} (ng/mL) (geometric mean (CV%))	6.19 (15.3)	45.3 (36.7)	785 (16.0)	4457 (5.9)
AUC _{0-∞} (ng*h/mL) (geometric mean (CV%))	0.288 (11.1)	28.5 (81.0)	1513 (33.6)	44575 (15.1)
CL (mL/h/kg) (geometric mean (CV%))	1750 (10.0)	176 (75.9)	33.4 (38.2)	5.78 (16.6)
t _½ (h) (geometric mean (CV%))	-	-	-	25.7 (4.4)

Parameter	Haemophilia patients – i.v. – trial 3813			
	0.25 mg/kg	1 mg/kg	3 mg/kg	9 mg/kg
N	3	3	3	3
C _{max} (ng/mL) (geometric mean (CV%))	3997 (8.7)	35252 (14.7)	74342 (3.1)	239053 (30.8)
AUC _{0-∞} (ng*h/mL) (geometric mean (CV%))	38256 (9.8)	1175441 (24.5)	5176337 (9.3)	32865565 (30.0)
CL (mL/h/kg) (geometric mean (CV%))	6.53 (11.0)	0.913 (24.5)	0.564 (13.0)	0.27 (30.2)
t _½ (h) (geometric mean (CV%))	31 (12.3)	49.3 (9.8)	73.1 (21.6)	65.2 (16.7)

Data Source: Study Report 3813 TFL Tables 14.2.10 and 14.2.11

^a 3 subjects in the cohort were dosed with concizumab, but 1 subject had concizumab plasma measurements below the lower limit of quantification (5 ng/mL).

Abbreviations: AUC_{0-∞}, area under the concizumab plasma concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV%, geometric coefficient of variation; IV, intravenous; t_½, terminal half-life

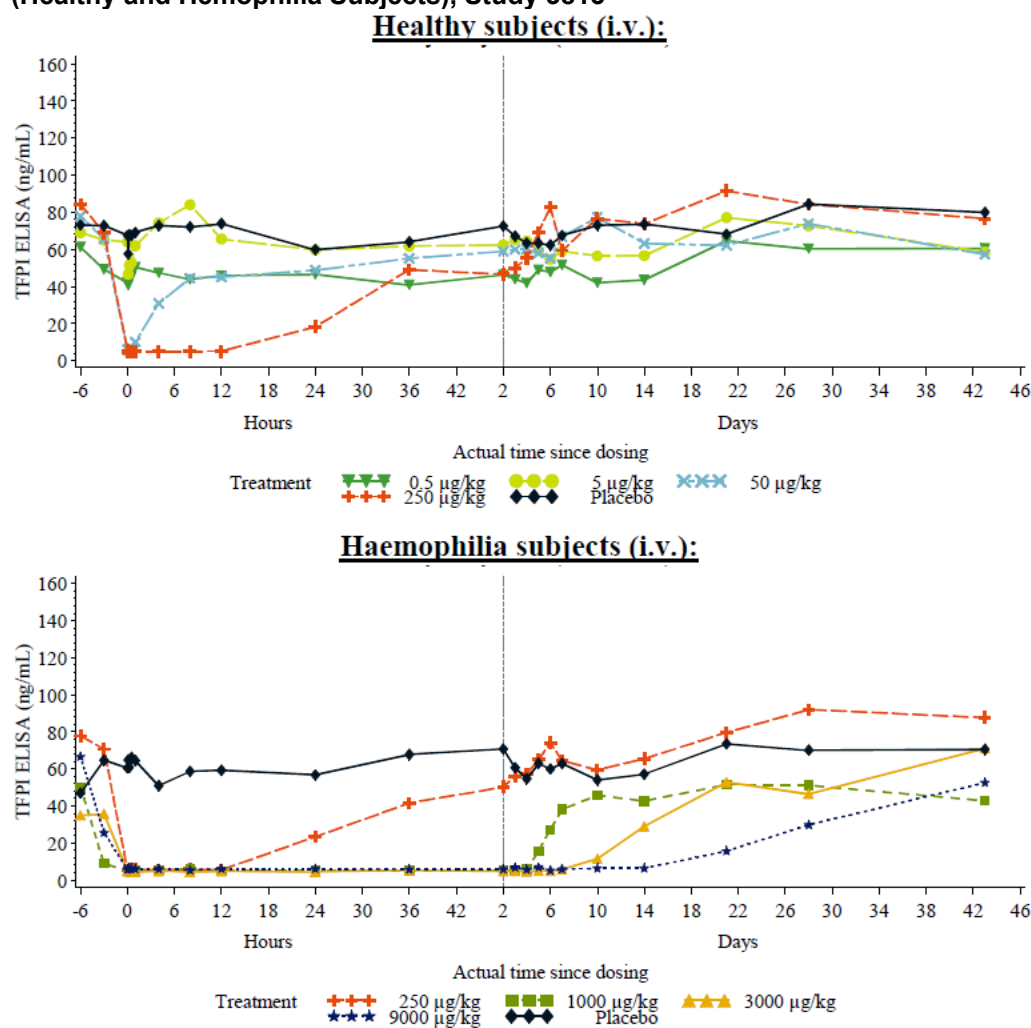
Table 98. PK Parameters in Healthy Subjects and Hemophilia Patients Following Subcutaneous Administration of Concizumab, Study 3813

PK parameter	Healthy subjects – s.c. – trial 3813		
	0.05 mg/kg	0.25 mg/kg	1 mg/kg
N	3	3	3
C _{max} (ng/mL) (geometric mean (CV%))	8.93 (27.3)	35.5 (18.8)	934 (42.7)
AUC _{0-∞} (ng*h/mL) (geometric mean (CV%))	-	8197 (93.4)	52375 (36.8)
CL/F (mL/h/kg) (geometric mean (CV%))	-	30.6 (60.7)	19.1 (33.6)
t _½ (h) (geometric mean (CV%))	-	89.4 (20.1)	114 (4.8)
t _{max} (h) (median)	12	24	36
PK parameter	Haemophilia patients – s.c. – trial 3813		
	1 mg/kg	3 mg/kg	
N	3	3	
C _{max} (ng/mL) (geometric mean (CV%))	838 (88.6)	15437 (42.4)	
AUC _{0-∞} (ng*h/mL) (geometric mean (CV%))	83244 (70.8)	2163346 (52.0)	
CL/F (mL/h/kg) (geometric mean (CV%))	12 (103.0)	1.39 (71.9)	
t _½ (h) (geometric mean (CV%))	104 (59.5)	69.4 (42.0)	
t _{max} (h) (median)	46.4	70.4	

Source: Study Report 3813 TFL Tables 14.2.12 and 14.2.13

Abbreviations: AUC_{0-∞}, area under the concizumab plasma concentration-time curve from time zero to infinity; CL, clearance; C_{max}, maximum plasma concentration; CV%, geometric coefficient of variation; IV, intravenous; SC, subcutaneous; t_½, terminal half-life

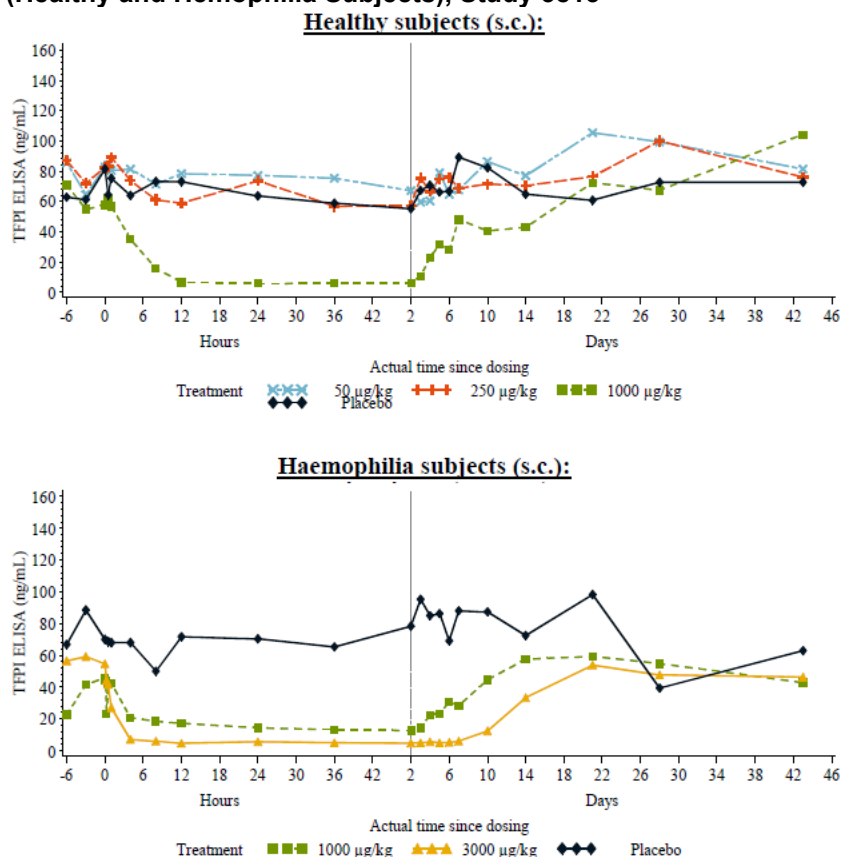
Figure 23. Mean Free TFPI Concentrations in Plasma After IV Administration of Concizumab (Healthy and Hemophilia Subjects), Study 3813



Source: Study Report 3813 Figure 12-7

Abbreviations: ELISA, enzyme-linked immunoassay; IV, intravenous; TFPI, tissue factor pathway inhibitor

Figure 24. Mean Free TFPI Concentrations in Plasma After SC Administration of Concizumab (Healthy and Hemophilia Subjects), Study 3813



The vertical dashed line indicates a shift in scale from hours to days at 2 days.
Samples from visit 1 and pre-dose samples from visit 2 are shown at -6 and -3 hours respectively to increase visibility.

Source: Study Report 3813 Figure 12-8

Abbreviations: ELISA, enzyme-linked immunoassay; IV, intravenous; SC, subcutaneous; TFPI, tissue factor pathway inhibitor

Reviewer's Comments:

- The non-linear elimination of concizumab seems to be due to the target-mediated drug disposition (TMDD) following binding of concizumab to endothelial cell-anchored TFPI (the target) with subsequent endocytosis and degradation (target-mediated clearance). In addition to the drug-target complex elimination pathway, concizumab is also eliminated in a linear fashion, as other monoclonal antibodies, mainly by catabolism with a half-life of approximately 3 weeks.
- TFPI is present on endothelial cells (~92%), platelets (~1%) and in plasma (~7%) (Broze and Girard 2012). Concizumab can readily access the TFPI on the surface of endothelial cells (mTFPI) and the free soluble TFPI circulating in the plasma (sTFPI). While both sTFPI and the TFPI in circulating platelets can migrate to the sites of vessel injury and inhibit coagulation, sTFPI is used as an exploratory pharmacodynamics (PD) marker for assessing hemophilia treatment due to its ease of sampling.
- Nonlinear PK of concizumab was observed after IV and SC dosing in healthy volunteers and patients, reflecting dose-dependent, target-mediated clearance at low doses. The

exact clearance mechanisms at each phase of elimination are not clear. The current hypothesis from the Applicant is that when drug concentrations are high enough to saturate targets, the rate of drug elimination is governed by linear nonspecific routes, together with a fixed rate of target mediated elimination. When drug concentrations go lower, the targets are not all saturated and both nonspecific and target-mediated elimination routes are important, resulting in nonlinear PK. When drug concentrations are even lower such that targets are not saturated, the target mediated elimination becomes the main route of elimination and PK is linear. Evaluation of the concentration-time profile provides an estimate of drug concentrations associated with each of these phases. A change in the slope of the concentration-time curve during the elimination phase, from shallow (target saturated; linear nonspecific routes govern elimination) to steep (targets not all saturated; combination of linear and nonlinear routes govern elimination), and then again from steep to shallow (targets not saturated; linear routes govern elimination) will be apparent for profiles that have high enough concentrations to fully saturate the target receptor and PK sampling sufficient to capture the phase when concentrations fall well below the threshold.

14.2.2. Single Dose Study in Healthy Japanese Subjects, Study 3981

Study Design

This was a randomized, placebo-controlled, double-blind, single-dose study to assess the PK of SC administered concizumab in healthy male Japanese subjects. A total of 8 subjects received a single SC dose of concizumab (250 µg/kg or 1000 µg/kg) or placebo. In each dose cohort, 3 subjects received active treatment and 1 subject received placebo. Blood sampling was done prior to dosing and up to 33 days post-dosing for assessment of PK, PD, and laboratory safety parameters.

Study Results

Mean concizumab concentration-time profiles are presented in [Figure 25](#). Derived PK endpoints are presented in [Table 99](#).

Figure 25. Mean Plasma Concentration-time Profiles of Concizumab, Study 3981

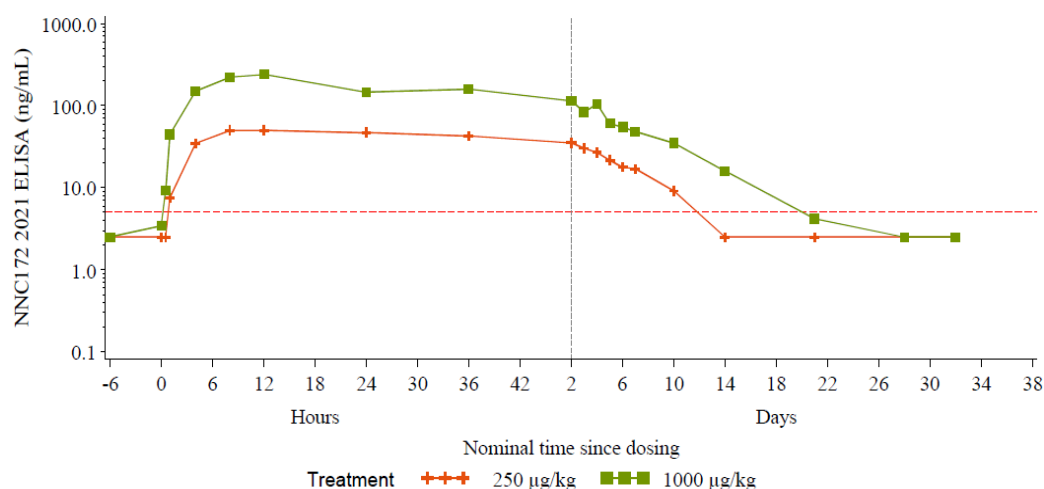


Table 99. PK Endpoints, Study 3981

Dose of NNC172-2021	AUC _{0-∞} (ng·h/mL) Geo. mean (CV)	C _{max} (ng/mL) Geo. mean (CV)	t _{max} (hours) Median (min-max)	MRT (hours) Mean (SD)	t _½ (hours) Mean (SD)	CL/F (mL/h/kg) Mean (SD)	V _z /F (mL/kg) Mean (SD)
250 (µg/kg)	7068 (9.7)	55.2 (3.9)	12.1 (8-24)	139 (13.2)	96.5 (10.1)	35.6 (3.0)	4979 (962)
1000 (µg/kg)	24988 (23.3)	277 (153)	11.8 (8-99)	147 (17.2)	110 (16.6)	40.6 (8.5)	6484 (2019)

Source: Study Report 3981-Table 11-1

Abbreviations: AUC_{0-∞}, area under the time-concentration curve from time zero to infinity; CL/F, clearance after oral administration; C_{max}, maximum plasma concentration; CV, coefficient of variation; MRT, magnetic resonance tomography; PK, pharmacokinetics; SD, standard deviation; t_½, terminal half-life; t_{max}, time to reach maximum concentration; V_z/F, apparent volume of distribution

- Residual TFPI functionality levels in plasma decreased following administration of concizumab at 1000 µg/kg, whereas there were no marked changes at 250 µg/kg when compared to placebo ([Figure 26](#)).
- Free TFPI levels in plasma decreased at 250 and 1000 µg/kg concizumab in a dose-dependent manner. The TFPI profiles had an inverse relation to the PK profiles, i.e., TFPI levels decreased with increasing concizumab concentration in plasma ([Figure 27](#)).
- The mean levels had returned to baseline values at 14 days post-dosing for both dose cohorts.
- No anti-concizumab antibodies were detected during the study.
- There were no deaths or serious adverse events observed in this study.

Figure 26. Mean Residual TFPI Functionality in Plasma, Study 3981

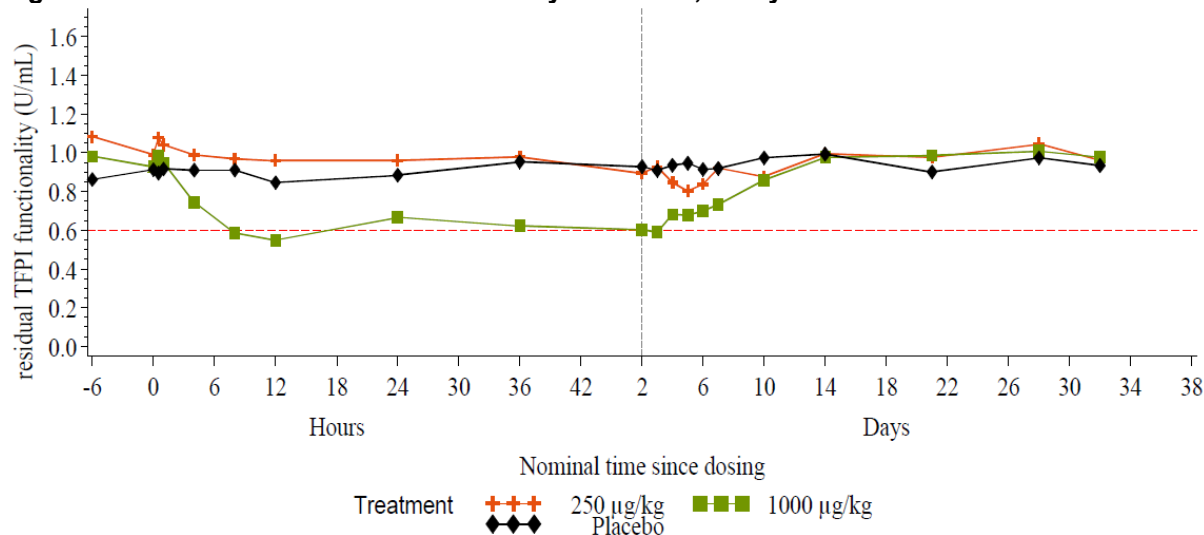
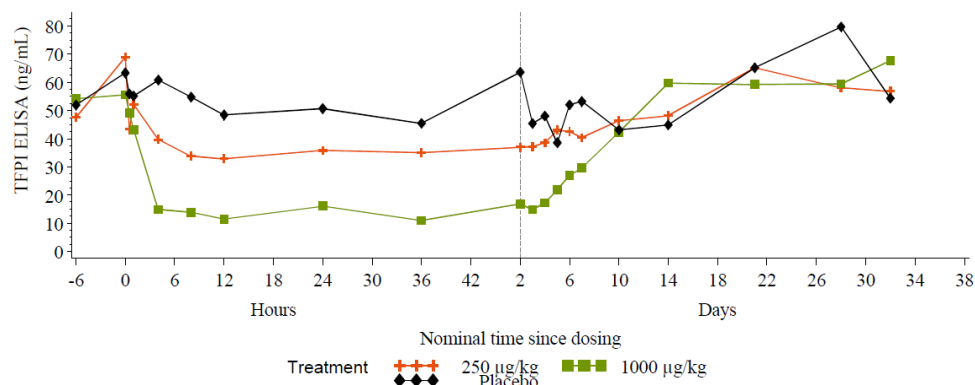


Figure 27. Mean Profiles of Free TFPI Concentrations in Plasma, Study 3981



14.2.3. Multiple Dose Study in Healthy Subjects, Study 3986

Study Design

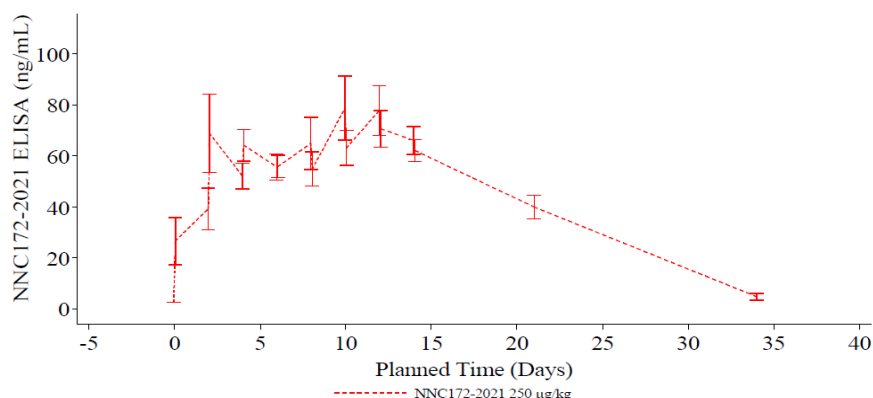
This was an open-label, multiple-dosing study investigating safety, PK, and PD of concizumab administered subcutaneously to healthy male subjects and hemophilia subjects. The study was planned to include 3 ascending dose tiers: 250 µg/kg (healthy subjects), 500 µg/kg (hemophilia subjects) or 1000 µg/kg (hemophilia subjects) every other day (EOD) 8 times. At each dose tier,

four subjects were planned to be included. Because of premature end of the study,³ only the low dose tier (250 µg/kg EOD 8 times) in 4 healthy subjects was included in this study. PK and PD samples were collected at pre-dose and 1 hour post-dose at each study visit and up to 35 days post-dosing.

Study Results

- The mean trough level (C_{trough}) prior to the last SC dose administration (Day 15) was 66.1 ng/mL, ranging from 50 to 75 ng/mL ([Figure 28](#)).
- Free TFPI plasma levels decreased from baseline during the concizumab treatment period ([Figure 29](#)). The mean free TPFI plasma levels were reduced by 68.1% from 79.9 ng/mL at baseline to 25.5 ng/mL on the last day of concizumab treatment (Day 15) and had returned to baseline values at the end-of-study visit.
- No anti-concizumab antibodies were detected during the study.
- There were no deaths or serious adverse events observed in this study.

Figure 28. Mean (SD) Plasma Concentration-time Profiles of Concizumab, Study 3986

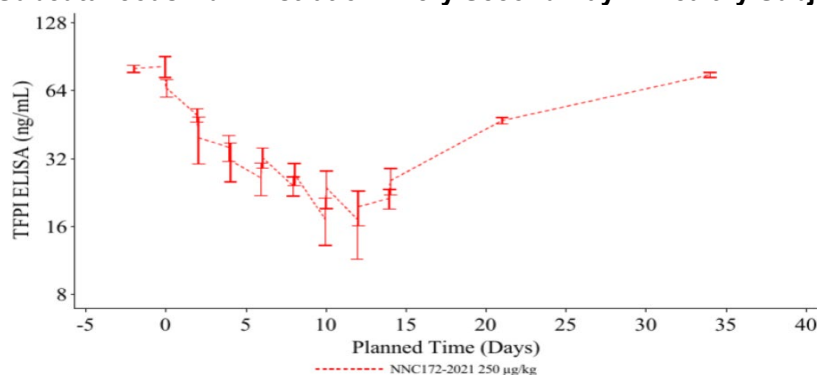


Source: Study Report 3986 Figure 11-1

Abbreviations: ELISA, enzyme-linked immunoassay; SD, standard deviation

³ During the conduct of the study, nonclinical safety findings were seen in the nonclinical program for concizumab, which had to be investigated before exposing further human subjects to the study product. Therefore, the study was set on hold and a decision to prematurely end the study was subsequently made.

Figure 29. Mean (SD) Plasma Concentration-time Profiles of Free TFPI Following Multiple-Dose Subcutaneous Administration Every Second Day in Healthy Subjects, Study 3986



Source: Study Report 3986 Figure 11-3

Abbreviations: ELISA, enzyme-linked immunoassay; SD, standard deviation; TFPI, tissue factor pathway inhibitor

14.2.4. Multiple Dose Study in Hemophilia Patients, Study 4159

Study Design

This was a randomized, double-blind, placebo-controlled, multiple-dose, dose-escalation study in 18 patients with hemophilia A without inhibitors. Three dose levels of concizumab (0.25, 0.5, 0.8 mg/kg) were administered SC every fourth days for 12 times over a 42-day period. However, to rapidly reach steady state at the targeted plasma concentration, the first two doses were given on two consecutive days. All study products were administered to the study subjects at the clinic under the surveillance of medically trained study site staff. At each dose level, eight patients were randomized in a 3: 1 ratio to receive concizumab or placebo treatment. Blood samples for PK and PD assessment were collected pre-dose at each day of dose administration, 4 hours after administration on Days 18 and 42, and 48 hours after the last dose on Day 42.

Study Results

- Non-linear PK of concizumab was observed in HA patients. Relative to the 0.25 mg/kg group, geometric mean AUC_τ (planned Day 38-42) values were 3-fold higher in the 0.50 mg/kg group and nearly 11-fold higher in the 0.80 mg/kg group ([Figure 30](#) and [Table 100](#)).
- There was a high between-subject variability following high doses of concizumab.
- A clear PD response to concizumab dosing was observed as the concentration of free TFPI in plasma was inversely correlated with that of concizumab. Mean trough levels of free plasma TFPI was reduced by ~27%, 55% and 75% from baseline for the 0.25, 0.5 and 0.80 mg/kg groups, respectively ([Figure 31](#)).
- No ADAs (binding or neutralizing) were detected during this study.

Table 100. Concizumab PK Parameters Following Subcutaneous Administration of 0.25, 0.50 and 0.80 mg/kg Every Fourth Day, Study 4159

Concizumab (ng/mL)	0.25 mg/kg	0.50 mg/kg	0.80 mg/kg
AUC _τ ^a (days×ng/mL)			
Geometric mean	135	396	1470
Min ; Max	113 ; 187	353 ; 441	353 ; 8020
C _{max} ^b (ng/mL)			
Geometric mean	52	265	1442
Min ; Max	42 ; 83	108 ; 2450	154 ; 4630
C _{trough} (ng/mL)			
Geometric mean	30	67	350
Min ; Max	20 ; 42	49 ; 93	90 ; 1180

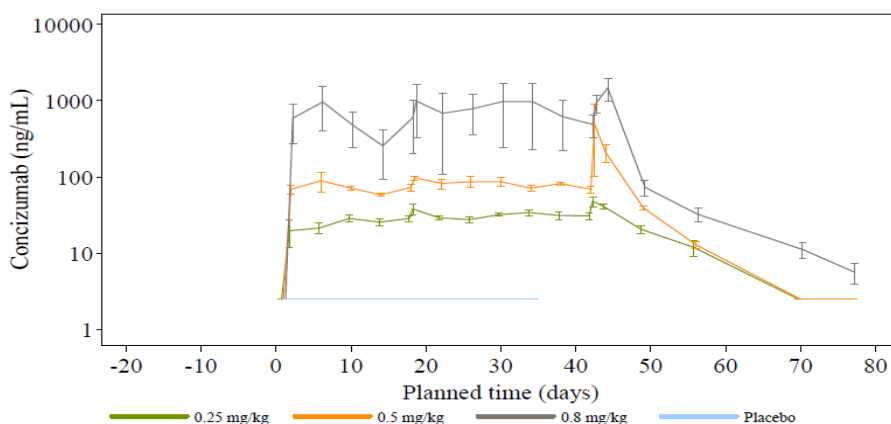
Source: Study Report 4159 Table 11-1

^a Calculated according to the actual dosing interval

^b Maximum plasma concentration: measured 4 hours after first dose of concizumab

Abbreviations: AUC_τ, area under the plasma concentration–time curve calculated from the pre-dose sample taken at the second last dose administration (planned Day 38) to the pre-dose sample taken at the last dose administration (planned Day 42); C_{max}, maximum plasma concentration; C_{trough}, trough concentration; max, maximum; min, minimum; PK, pharmacokinetics

Figure 30. Mean (SE) Concizumab Concentration-Time Profiles Following Subcutaneous Administration of 0.25, 0.50 and 0.80 mg/kg Every Fourth Day, Study 4159

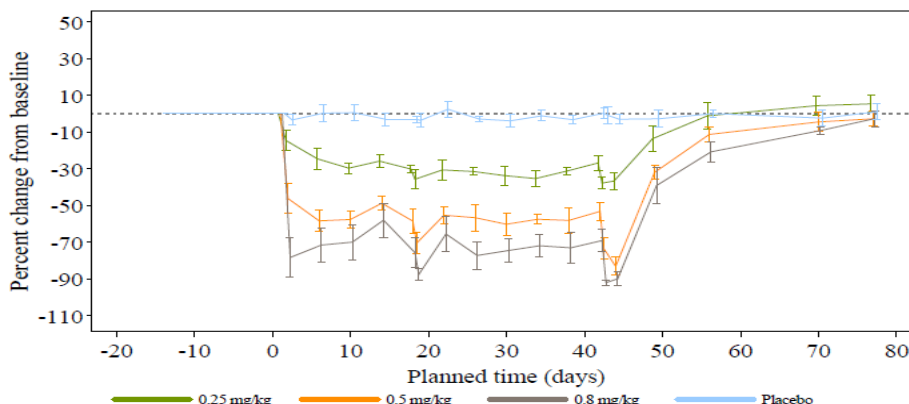


Source: Study Report 4159 Figure 11-1

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

Abbreviation: SE, standard error

Figure 31. Mean (SE) Free TFPI Concentration-Time Profiles Following Subcutaneous Administration of 0.25, 0.50 and 0.80 mg/kg Every Fourth Day, Study 4159



Source: Study Report 4159 Figure 11-2

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

Abbreviation: SE, standard error; TFPI, tissue factor pathway inhibitor

Reviewer's Comments: The study aimed to include five concizumab dose levels, but was stopped after three due to a safety committee decision not to dose-escalate to the fourth concizumab dose level of 1.1 mg/kg, i.e., this study was finalized following the completion of the 0.80 mg/kg group. Blinded preliminary safety and PK/PD data from the 0.80 mg/kg group was reviewed by the safety committee. Marked changes in coagulation parameters were observed, including a decrease from baseline in fibrinogen, and a pronounced increase in D-dimer and F1 + 2 outside of normal range. In addition, a substantial between-subject variation in pro-coagulant response to concizumab was observed. Based on this, the safety committee decided not to proceed to the 1.1 mg/kg concizumab dose level.

- In this study, concizumab was given at doses of 0.25 mg/kg, 0.5 mg/kg and 0.8 mg/kg on Day 1, Day 2 and every 3 days afterward. As shown in [Figure 30](#), slope of the PK curve during the elimination phase was steeper for the 0.8 and 0.5 mg/kg doses than that for the 0.25 mg/kg dose. It is consistent with the observation that non-linear PK due to TMDD plays a dominant role in the target concentration range, leading to a much faster drug clearance at these concentrations. In addition, higher between-subject and within-subject variability were observed at the higher doses of concizumab ([Table 101](#)). Given a significant concentration-dependent clearance due to TMDD, once-daily dosing may minimize within-patient PK variability by minimizing the peak-to-trough differences.*

Table 101. Mean Trough Concentrations and PK Variability of Concizumab Following Subcutaneous Administration 0.25, 0.5 and 1 mg/kg Every Fourth Day

Dose	Subject ID	Geometric Mean	Within Subject CV%	Between-subject CV %
0.25 mg/kg	(b) (6)	30	32	17
		26	31	
		21	28	
		33	22	
		22	20	
		27	16	
0.50 mg/kg	(b) (6)	77	25	10
		75	17	
		78	40	
		80	48	
		66	24	
		62	16	
0.80 mg/kg	(b) (6)	2007	108	170
		410	144	
		231	157	
		82	39	
		186	59	
		98	49	

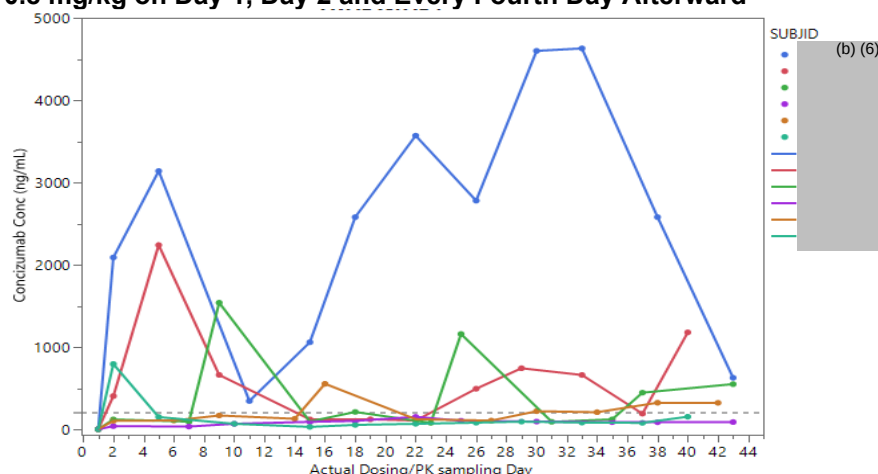
Source: Reviewer's analysis

Intra-subject variability was calculated based on pre-dose PK concentrations at each visit except for Day 1 and Day 2.

Abbreviations: CV, coefficient of variation; PK, pharmacokinetics

- As concizumab was administered at the study site, the dosing records were reliable and complete. This allows for the analysis on the impact of missing doses. [Table 102](#) shows the pre-dose concizumab concentrations at each visit in the 6 subjects who were assigned to the 1 mg/kg group. Although there is large concentration fluctuation due to TMDD, a more than 10-fold change in PK concentration are mostly associated with missing doses. For example, subject ID (b) (6) (represented by the blue line) had a steep drop in concentration from 3140 ng/ml on Day 5 to 346 ng/ml on Day 11, i.e., 3 days later than the expected dosing date. Similarly, in cases where a dose was missed, concizumab concentrations decreased steeply.

Figure 32. Concizumab Trough Concentrations Following Subcutaneous Administration of 0.8 mg/kg on Day 1, Day 2 and Every Fourth Day Afterward



Source: Reviewer's analysis
Abbreviation: PK, pharmacokinetics

Table 102. Concizumab Trough Concentrations Following Subcutaneous Administration of 0.8 mg/kg on Day 1, Day 2 and Every Fourth Day Afterward

Subject		Subject		Subject		Subject		Subject		Subject	
Day		Conc		Day		Conc		Day		Conc	
1	2.5	1	2.5	1	2.5	1	2.5	1	2.5	1	2.5
2	2090	2	406	2	122	2	40	2	106	2	795
5	3140	5	2240	7	95.2	7	35	6	109	5	151
11	346	9	663	9	1540	10	69	9	170	10	69
15	1060	15	123	15	98	15	93	14	130	15	31
18	2580	19	124	18	213	18	104	16	555	18	56
22	3570	22	108	23	81	22	154	22	125	22	69
26	2780	26	495	25	1160	25	106	27	108	26	83
30	4600	29	744	31	93	30	96	30	222	29	96
33	4630	33	662	35	123	35	89	34	210	33	84
38	2580	37	192	37	447	38	88	38	325	37	81
43	628	40	1180	43	551	43	90	42	324	40	155

Source: Reviewer's analysis
Actual dosing and PK sampling day
LLOQ= 2.5 ng/mL
Abbreviations: conc, concentration

14.2.5. Efficacy and Safety Study in Adult and Adolescent Patients With Hemophilia, Study 4311, After Restart

Study Design

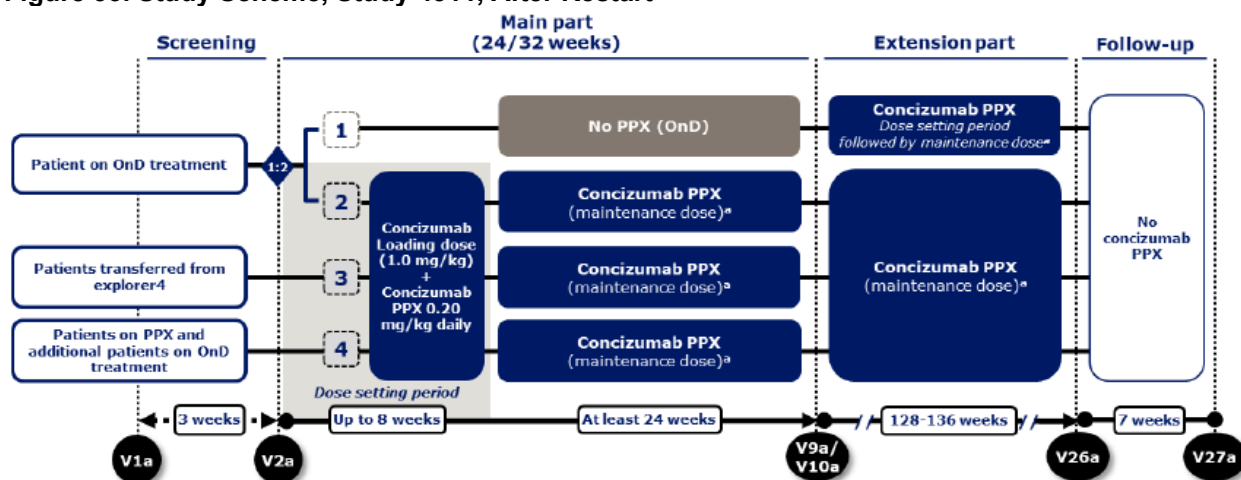
This was a randomized, open-label study to evaluate the efficacy and safety of daily concizumab prophylaxis (PPX) administered SC in patients with HA or HB with inhibitors. Initially, patients

were randomized to concizumab PPX (arm 2) or no PPX (arm 1) or assigned to non-randomized PPX arms (arms 3 or 4) based on their treatment regimen before entering the study. After the restart of the study, patients continued in the treatment arm which they were initially randomized or assigned to. New eligible patients were randomized to concizumab PPX (arm 2) or no PPX (arm 1) or assigned to arm 4. The study consisted of a 3-week screening period, a main part (24-32 week treatment period), an extension part (128-136 week treatment period), and a 7-week follow-up period ([Figure 33](#)).

Upon restart of the study, the dosing regimen was a loading dose of 1.0 mg/kg concizumab SC on the first day of treatment, followed by an initial daily dose of 0.20 mg/kg concizumab. Within the initial 5 to 8 week maintenance dose setting period on 0.20 mg/kg concizumab, the dose was either increased to 0.25 mg/kg if the concizumab exposure was below 200 ng/mL, decreased to 0.15 mg/kg if the exposure was above 4000 ng/mL or maintained at 0.20 mg/kg if exposure was between 200-4000 ng/mL. The dose setting was based on the concizumab exposure level after 4 weeks of concizumab exposure at visit 4a. The investigational drug product consisted of the drug constituent (concizumab 40 mg/mL and 100 mg/mL), and a device constituent (a ^{(b) (4)} pen-injector).

For patients on concizumab PPX (patients in arms 2, 3 and 4), two 24-hour PK/PD-sessions were conducted at visits 2a and 9a. The concizumab dose was administered in the abdomen and blood samples were drawn pre-dosing, 3, 6, 9 and 24 hours after dosing. In addition to the two PK/PD sessions, pre-dose trough concizumab plasma concentration (C_{trough}) was measured throughout the concizumab treatment period.

Figure 33. Study Scheme, Study 4311, After Restart



Source: Study NN7415-4311 Clinical Study Report, Figure 9-1 (p.42)
Abbreviations: OnD, on demand; PPX, prophylaxis; V, Visit

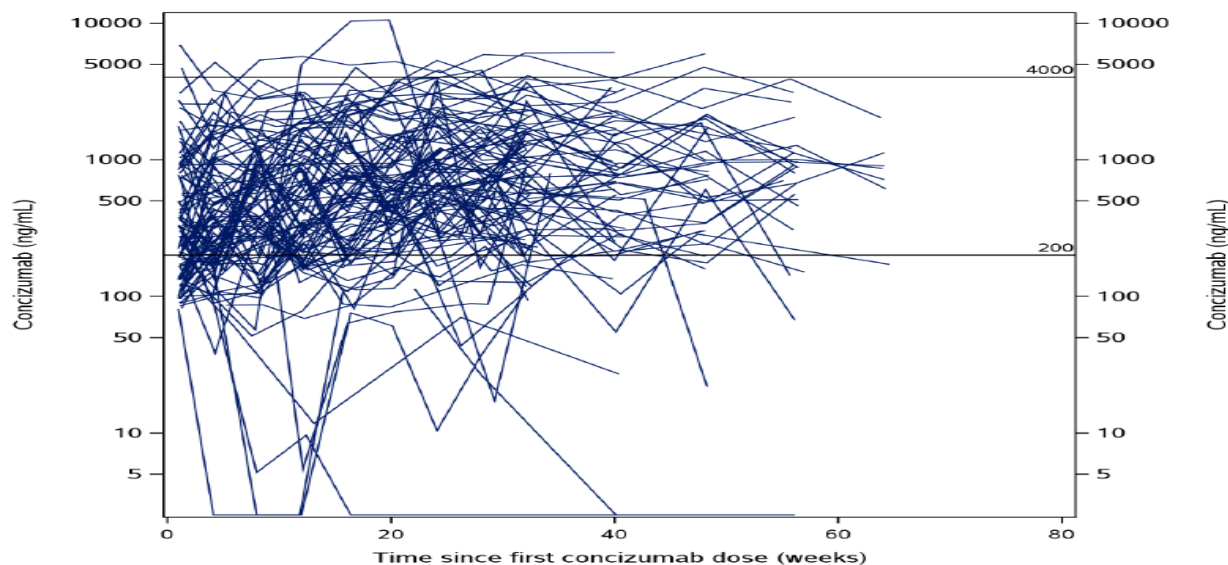
Study Results

- The concizumab plasma concentrations measured at Week 4 were used to determine the maintenance dose for each patient following an initial dose of 0.20 mg/kg. One (1) patient (1.0%) had a concizumab plasma concentration >4000 ng/mL prior to maintenance dose setting and was decreased to a maintenance dose of 0.15 mg/kg. Twenty-four (24) patients (24.7%) had concizumab plasma concentrations <200 ng/mL prior to maintenance dose

setting and were increased to a maintenance dose of 0.25 mg/kg. Seventy-two patients (74.2%) remained on a maintenance dose of 0.20 mg/kg.

- At Week 24, the geometric mean (CV%) C_{trough} concentration of concizumab was 665.4 (220%) ng/mL in 94 patients who received concizumab treatment. The median concentration was 786 ng/mL ([Figure 34](#)).
- Geometric mean plots for the 24-hour profiles on Day 1 and at Week 24 are presented in [Figure 35](#). The geometric mean (CV%) C_{max} values were 383 (410%) on Day 1 and 1167.1 (270%) ng/mL and at Week 24. The mean (SD) AUC_t value were 12870 (16705) ng*h/mL on Day 1 and 33784 (31052) ng*h at Week 24. The mean C_{max}/C_{trough} ratio at Week 24 was 2.2.
- The geometric mean pre-dose free TFPI levels decreased from 88.3 ng/mL at baseline to 10.7 ng/mL at Week 24 for patients on concizumab PPX (arms 2-4). After the initial decrease, the levels remained stable over time. Patients on no PPX (arm 1) maintained baseline levels for free TFPI ([Figure 36](#)).
- The geometric mean pre-dose thrombin peak levels were increased from 13.5 nmol/L at baseline to 105.4 nmol/L (within range of normal plasma) at Week 24 for patients on concizumab PPX (arms 2-4). After the initial increase, the levels remained stable over time. Patients on no PPX (arm 1) maintained baseline thrombin peak levels ([Figure 37](#)).

Figure 34. Pre-Dose Trough Concizumab Plasma Concentration (ng/mL) in Patients With HAwI + HBwI on Concizumab PPX Treatment, Study 4311, After Restart

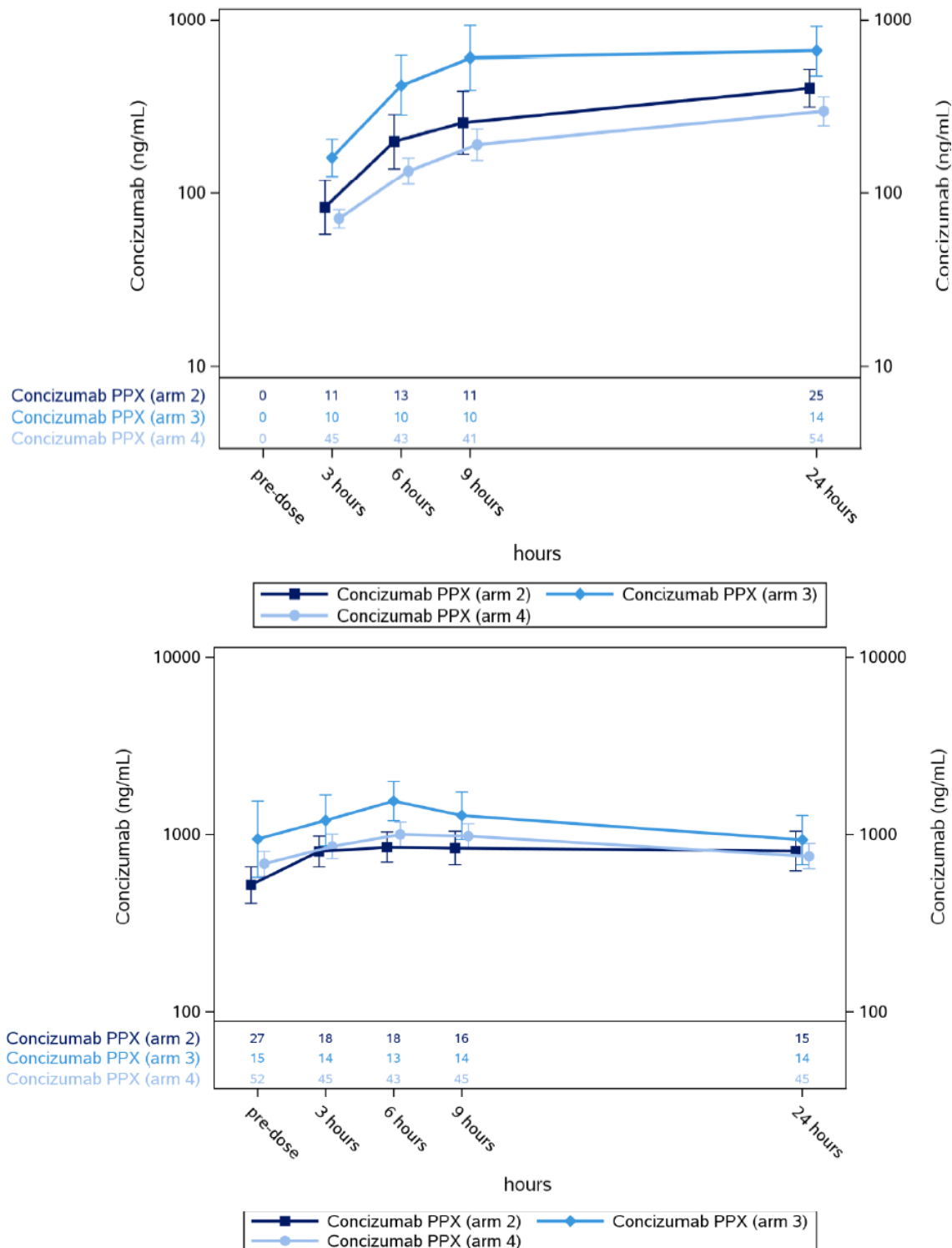


Source: Study Report 4311 Figure 11-7

LLOQ= 5 ng/ml

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; PPX, prophylaxis

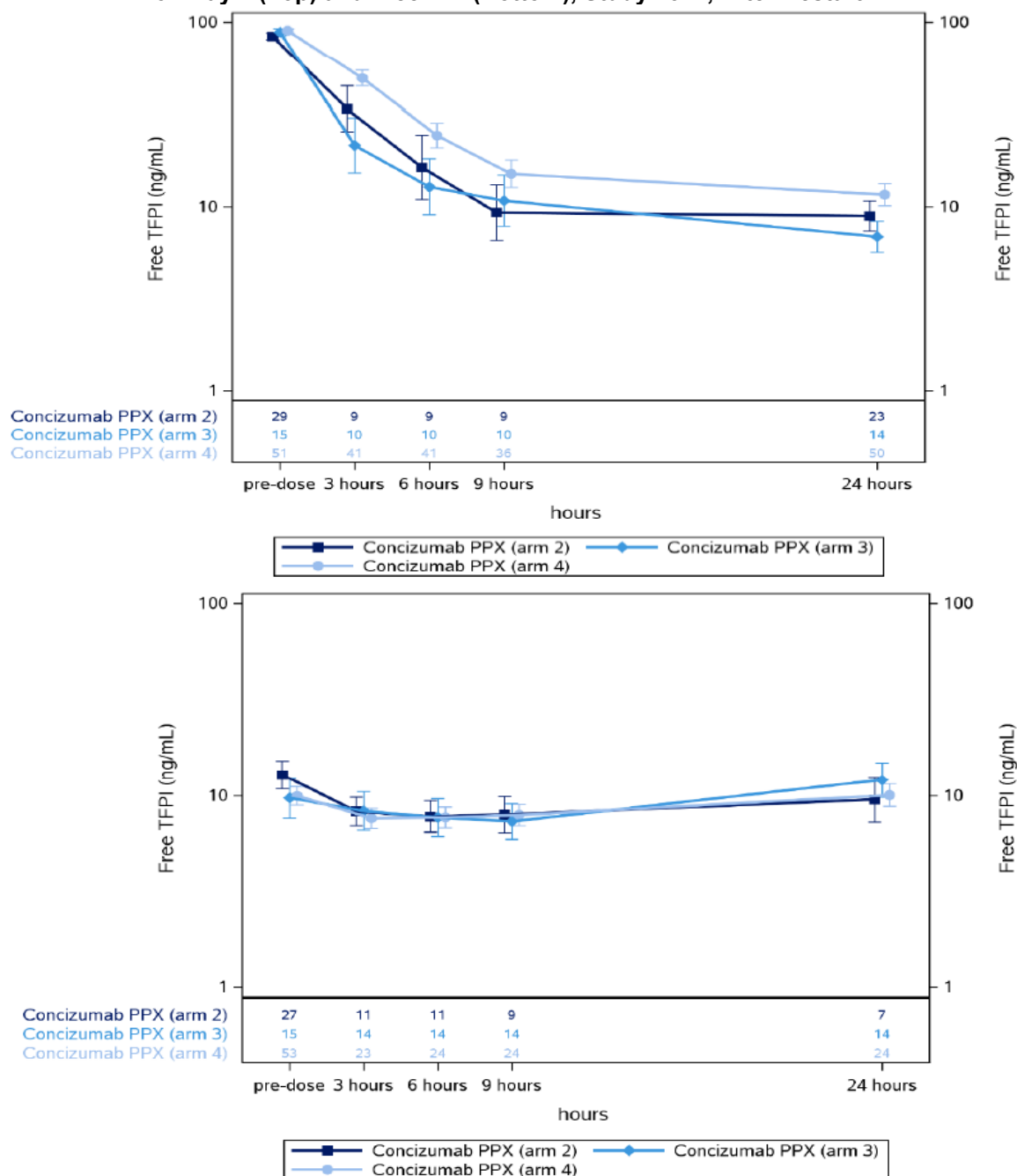
Figure 35. Concizumab Geometric Mean (SE) Plasma Concentration (ng/mL) - Time Profile in Patients With HAwi + HBwi on Day 1 (Top) and Week 24 (Bottom), Study 4311, After Restart



Source: Study Report 4311 Figure 14.2.108 and Figure 14.2.109

Abbreviations: HAwi, hemophilia A with inhibitors; HBwi, hemophilia B with inhibitors; PPX, prophylaxis; SE, standard error

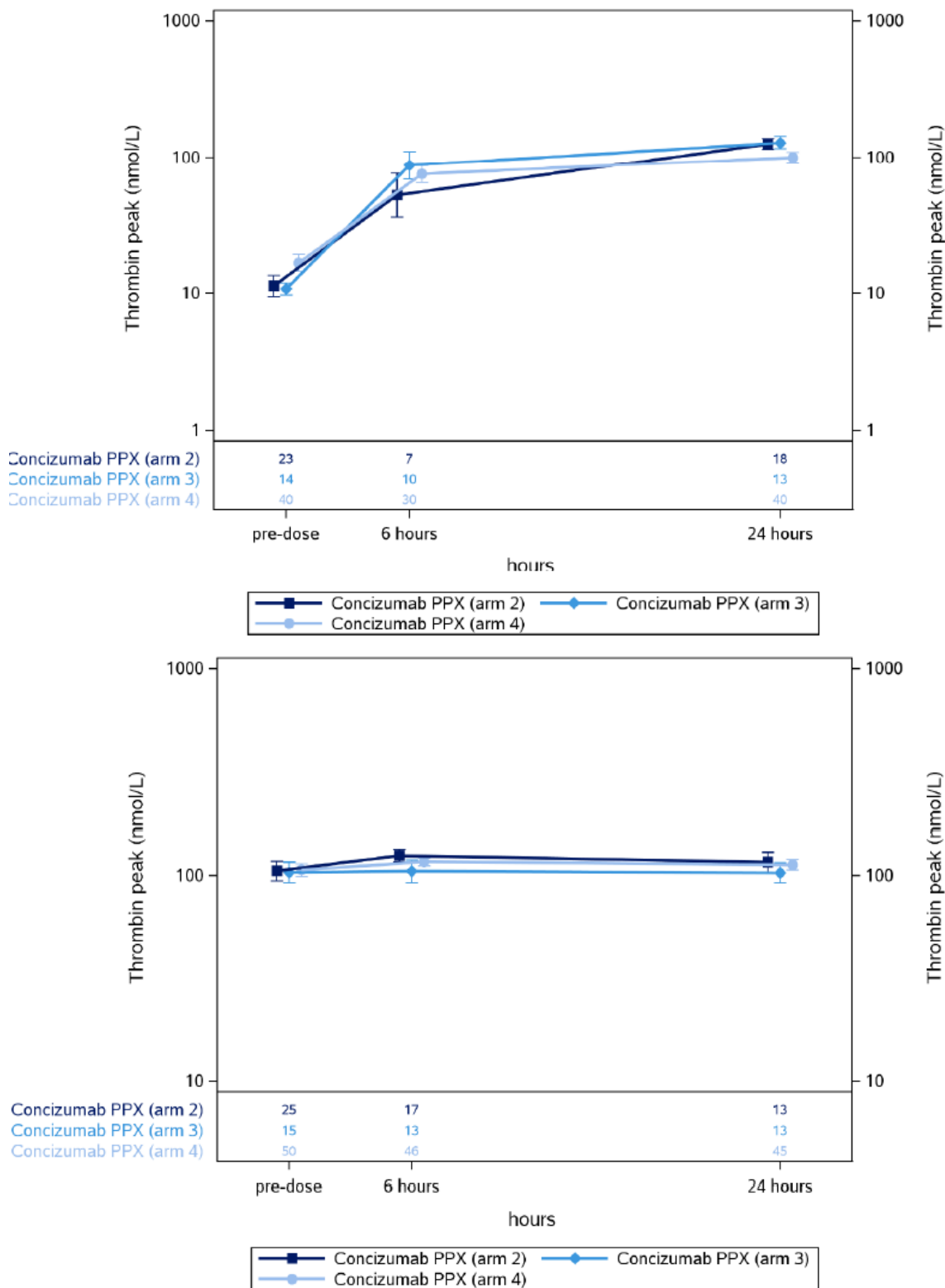
Figure 36. Free TFPI Geometric Mean (SE) Concentration - Time Profile in Patients With HAwI + HBwI on Day 1 (Top) and Week 24 (Bottom), Study 4311, After Restart



Source: Study Report 4311 Figure 11-10 and Figure 11-11

Abbreviations: HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; PPX, prophylaxis; SE, standard error; TFPI, tissue factor pathway inhibitor

Figure 37. Thrombin Peak Geometric Mean (SE) – Time Profile in Patients With HAWI + HBWI on Day 1 (Top) and Week 24 (Bottom)



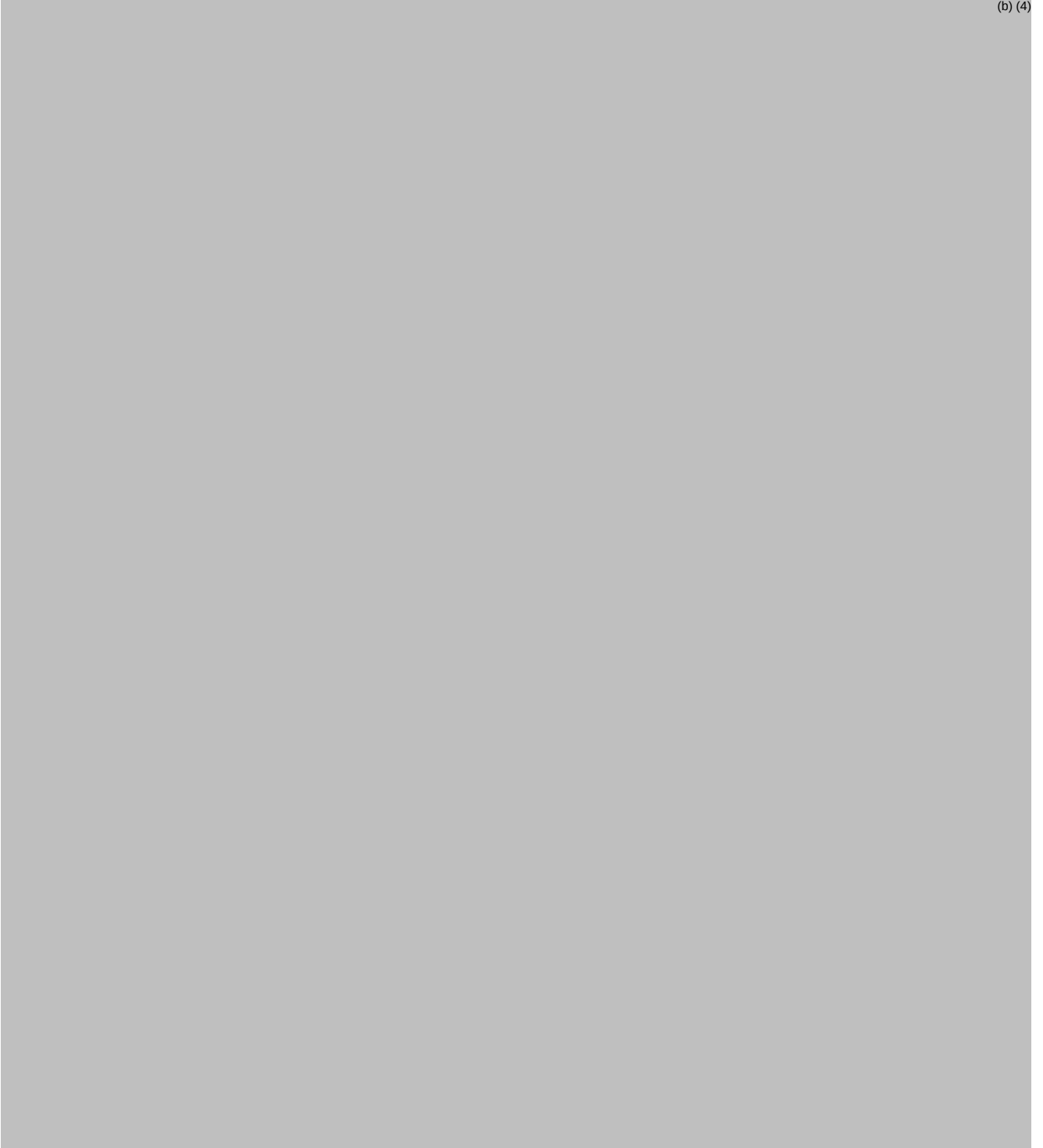
Source: Study Report 4311 Figure 11-13 and Figure 11-14

Abbreviations: HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; PPX, prophylaxis; SE, standard error

14.3. Bioanalytical Method Validation and Performance

14.3.1. Bioanalytical Method for PK Assessment

(b) (4)



14.3.2. Bioanalytical Method for PD Assessment

Validated PD assays were used to measure the levels of free TFPI (not bound to concizumab), and thrombin generation in plasma.

Free TFPI

Free TFPI in plasma, i.e., TFPI not bound to concizumab, was quantified using a commercially available ELISA kit (Asserachrom® Total TFPI, Diagnostica Stago, Asnières-sur-Seine, France). The assay uses 2 monoclonal anti-TFPI antibodies where the catching antibody competes with concizumab resulting in specific detection of TFPI not bound to concizumab. Validation parameters for free TFPI are presented below in [Table 107](#).

Table 107. Validation Parameters for Free TFPI

Validation parameter	(b) (4)		
Calibrator	3.2% citrated human plasma with a known concentration of TFPI		
LLOQ	12.5 ng/mL	17.1 ng/mL	9.6 ng/mL
Precision	≤ 20%		
Stability at RT	6 hours		
Long-time stability	12 months at -80°C		
Validation Study ID	211073	(b) (4) 240159	(b) (4) -2015-009

Source: Summary of biopharmaceutical studies and associated analytical methods Table 1-5

Abbreviations: LLOQ, lower limit of quantification; RT, room temperature; TFPI, tissue factor pathway inhibitor

Thrombin Generation

Thrombin generation is a process that determines the extent of the thrombin burst which is crucial for the formation of a stable fibrin clot. The TG assay (TGA) was an exploratory assay for a global measurement of the potential of platelet-poor plasma to support hemostasis. The assay is validated as an exploratory biomarker with regards to concizumab interference and precision.

Table 108. Validation Parameters for Thrombin Generation

	ETP	ETPR	Lag Time (min)	Peak Height (nM)	Time to Peak (min)	Velocity Index (nM/min)
Validated response ranges	225 – 1456	0.30 – 1.88	4.1 – 8.8	9 – 119	12.4 – 27.6	1 – 14
Normal reference range ^{A)}	408 – 1394	0.57 – 1.56	2.0 – 11.3	26 – 147	6.4 – 16.4	2 – 36
Haemophilia A donor response range ^{B)}	92 – 715	0.10 – 0.54	2.6 – 4.9	3 – 35	10.8 – 28.1	0 – 4
Precision	≤ 20.0%					
Sample long-term stability at -20°C	Up to 3 months					
Sample long-term stability at -70°C	Up to 12 months (Up to 6 months for ETP only)					
Sample freeze-thaw cycle stability	Up to additional 3 freeze/thaw cycles					
Short term sample stability on bench top (20±5°C)	Up to 6 hours					

Source: Summary of biopharmaceutical studies and associated analytical methods Table 1-6.

^{A)} The normal reference range was determined by measuring the TGA parameters and normalized TGA parameters from N=40 ostensibly healthy normal donor plasma samples. Reference ranges were calculated using the mean response ±2SD.

^{B)} The TGA response range for TGA parameters and normalized TGA parameters was determined by testing N=10 congenital Hemophilia A donor plasma samples.

Note: Validation Study MVR-CT-2015-011, the assay was tested at three concentrations of concizumab (2, 10 and 20 µg/mL) as well as unspiked with concizumab (0 µg/mL).

Abbreviations: ETP, endogenous thrombin potential; ETPR, ETP ratio (relative to normal plasma).

14.4. Immunogenicity Assessment—Impact of PK/PD, Efficacy, and Safety

Development of anti-concizumab antibodies was investigated in all clinical studies (Phase 1 single dose studies 3813 and 3981, Phase 1 multiple dose studies 3986 and 4159, Phase 2 multiple dose studies 4310 and 4255, and Phase 3 multiple dose Study 4311). ADA samples were collected with time-matched PK samples. The sampling intervals in each of the clinical studies are shown in [Table 109](#).

Table 109. Anti-concizumab Antibody Sample Collection Time Points – Phase 1, 2 and 3 Studies With ADA Assessment Included in the Summary

Phase	Trial	Pre-treatment sampling	Sampling during treatment ^a : Visits	Follow-up sampling
1	4159	At screening and before dosing	Approx. every 3 weeks: week 3 and 6	5 weeks post treatment stop (week 11)
2	4255	At screening and before dosing	Approx. every 4 weeks for the first year of treatment: week 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 44 and 48 Approx. every 8 weeks after the first year of treatment: week 56, 64, 72 and 76	7 weeks post treatment stop (week 84)
	4310	At screening and before dosing	Approx. every 4 weeks for the first year of treatment: week 1, 4, 8, 12, 16, 20, 24, 25, 28, 32, 36, 40, 44 and 48 Approx. every 8 weeks after the first year of treatment: week 56, 64, 72 and 76	7 weeks post treatment stop (week 84)
3	4311	At screening and before dosing	Approx. every 4 weeks for the first half year of treatment: week 4, 8, 12, 16, 20 and 24 Approx. every 8 weeks after the first half year of treatment: week 32, 40, 56, 80, 104, 128 and 160 During treatment pause: sampling according to flowchart to the extent possible	7 weeks post treatment stop (week 167)

Source: Integrated summary of immunogenicity Table 3-1.

^a For patients restarting concizumab treatment after the treatment pause, these weeks apply to both first round of treatment (before the treatment pause) and second round of treatment (after treatment restart).

Abbreviation: ADA, anti-drug antibody

No anti-concizumab antibodies (ADAs were detected in Phase 1 studies. Of the 185 patients treated with concizumab in the multiple-dose studies throughout the clinical development program (Studies 4159, 4310, 4255 and 4311 up until PACO), 25.4% (47 patients) tested positive for binding anti-concizumab antibodies at one or more visits after first concizumab dose. Twelve patients (6.5%) tested positive for anti-concizumab antibodies with in vitro neutralizing effects ([Table 110](#)).

Table 110. Overview of ADA-Positive Patients by Trial - HA, HAWI and HBWI – Studies 4159, 4310, 4255 and 4311 – Safety Analysis Set

	Trial ID				
	4159	4255	4310	4311	Total
Number of patients exposed to concizumab	18	36	25	127	185
Number of ADA-negative patients ¹ N (%)	18 (100)	27 (75.0)	19 (76.0)	94 (74.0)	138 (74.6)
Number of ADA-positive patients ² N (%)	0	9 (25.0)	6 (24.0)	33 (26.0)	47 (25.4)
Number of <i>in vitro</i> -neutralising ADA-positive patients N (%)	0	1 (2.8)	3 (12.0)	8 (6.3)	12 (6.5)

Source: Integrated summary of immunogenicity Table 4-1

¹ All samples after first exposure to concizumab were negative.

² One or more samples after first exposure to concizumab were positive.

Abbreviations: ADA, anti-drug antibody; HA, hemophilia A; HAWI, hemophilia A with inhibitors; HBWI, hemophilia B with inhibitors; N, number of patients

Of the 47 patients testing positive for ADAs, binding anti-concizumab antibody titers were generally low. Apart from 1 patient with medium level titers and 1 patient with high titers, for 96% of ADA-positive patients, titers ranged from 100 to 6400 (equals 1-64 without the MRD factored).

- Medium-level ADA titers: One ADA-positive patient (1/47; 2%) had a maximum ADA titer at 25600. This patient had anti-concizumab antibody titers declined to 12800 after 24 weeks, where they stayed constant until the data cut-off for this summary.
- High-level ADA titers: One patient (subject ID (b) (6)) first tested positive for ADAs (titer 1600) about 12 weeks, peaked at 12800, and returned to titer 1600 at the Week 32. The patient discontinued concizumab treatment in Week 33 due to surgery after an accident leading to bone fracture in the hand. Following the surgery, the patient experienced hemorrhagic shock after arterial puncture during blood sampling. The patient restarted concizumab treatment at week 40. ADA titers had increased to medium levels (51200) at Week 40 to high levels (204800) at Week 56 and 64, likely caused by a combination of a boosted immune response after the traumatic events experienced by the patient and re-initiation of concizumab treatment.

It should be noted ADA and neutralizing antibody assays were not considered fully validated by OBP reviewers. See Complete Response (CR) letter for comments related to immunogenicity assays.

Impact of Immunogenicity on Concizumab Exposure (PK)

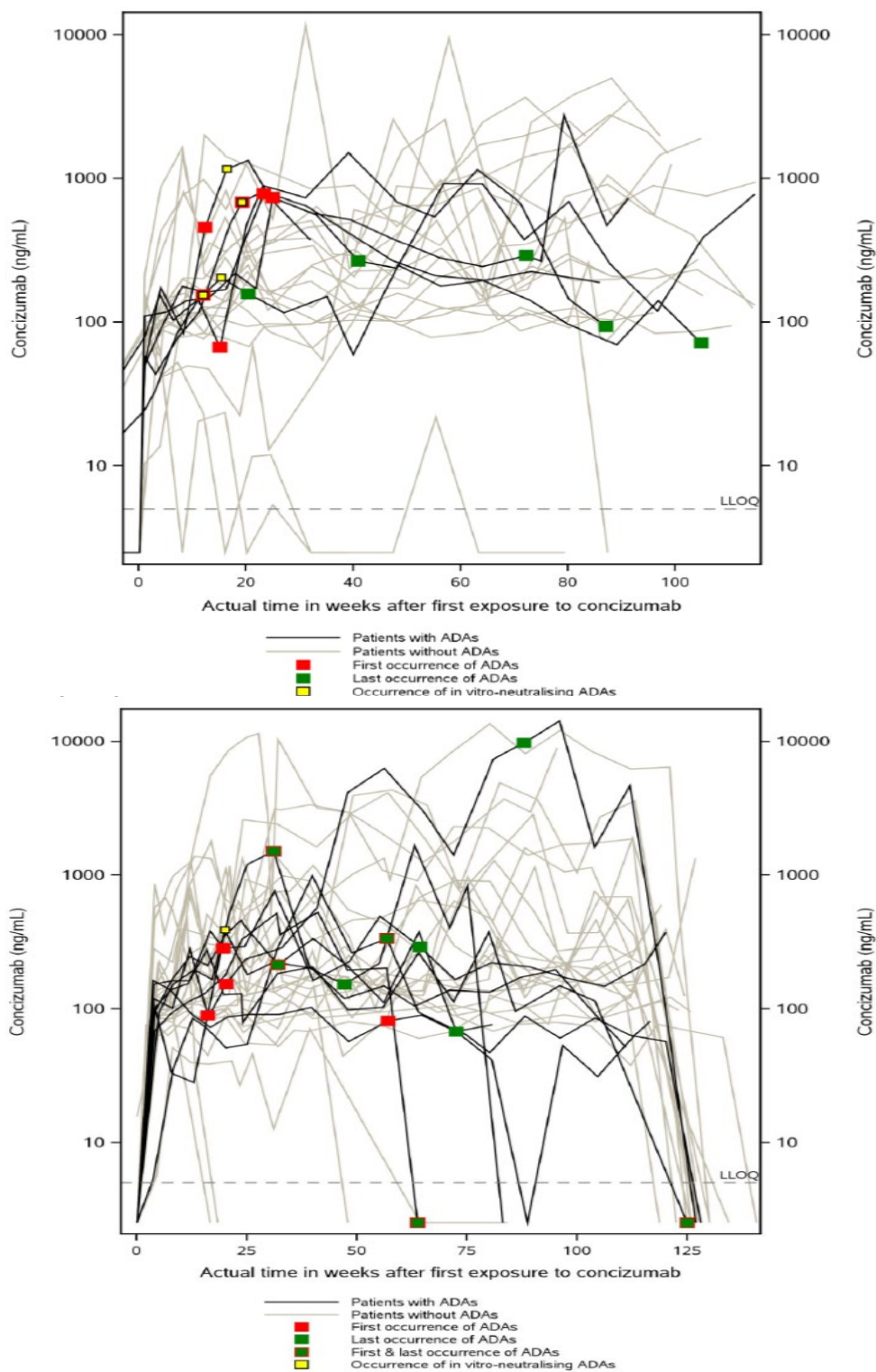
For almost all patients (except for subject ID (b) (6)) positive for anti-concizumab antibodies in Phase 2 and 3 studies, the presence of anti-concizumab antibodies, some with *in vitro*-neutralizing effects, appeared to not affect concizumab exposure:

- In both Phase 2 and Phase 3, concizumab exposure over time after first dose was similar between patients positive and negative for anti-concizumab antibodies ([Figure 38](#) and [Figure](#)

[39](#)). Seroconversion, or occurrence of anti-concizumab antibodies with in vitro-neutralizing effects, did not appear to cause a change in exposure.

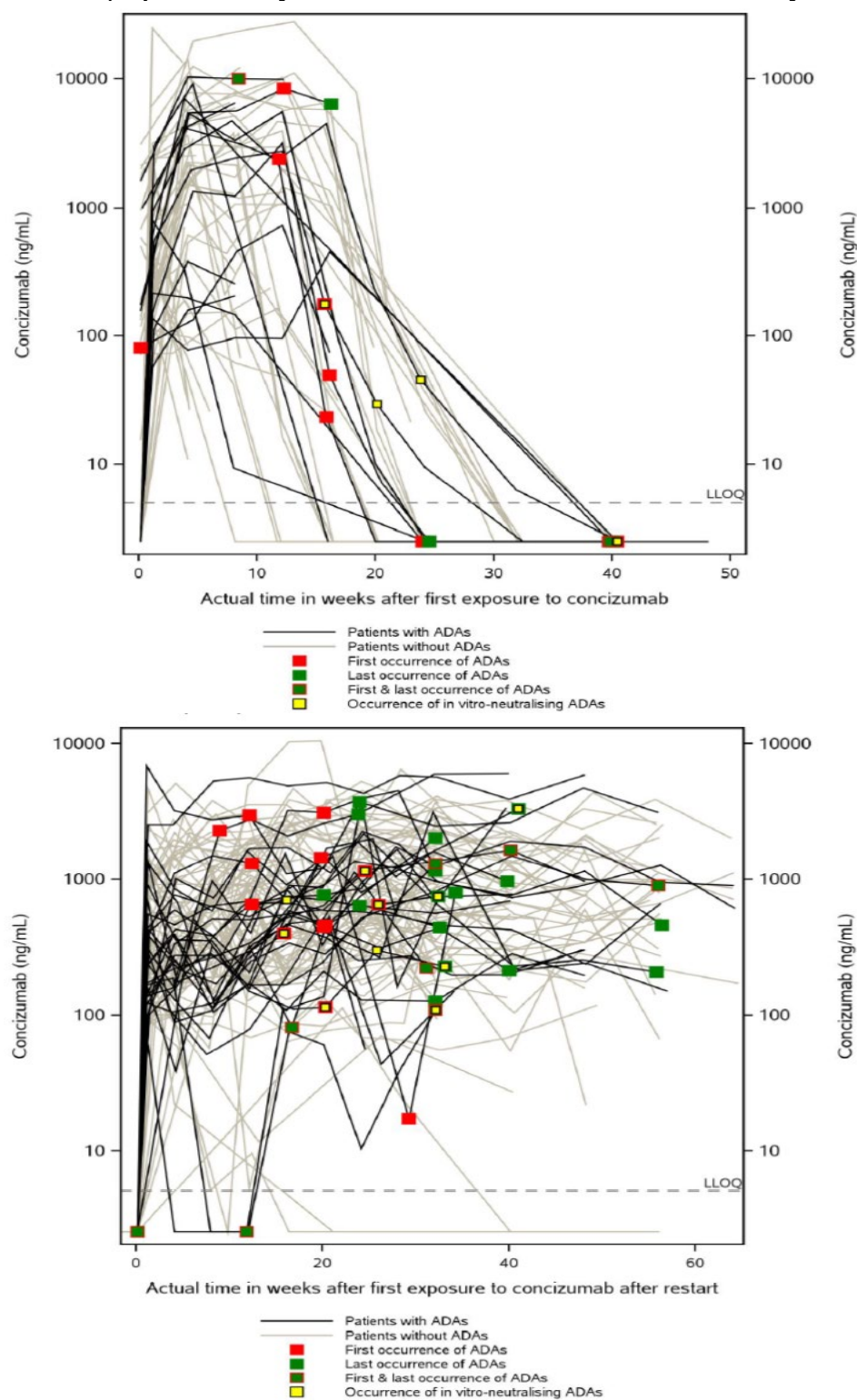
- For the patient with a high titer level (subject ID [REDACTED]^{(b) (6)}), per Applicant, it was not possible to determine whether the high antibody titers reduced concizumab exposure, since plasma concizumab concentration measurements failed, likely due to ADA interference in the PK assay. It is still likely that ADAs increased concizumab clearance leading to decreased drug concentrations, as the PD marker free TFPI returned to the baseline (see next section).

Figure 38. Concizumab Plasma Concentration Over Time – ADA-Positive Versus – Negative Patients (Top Plot: Study 4310 and Bottom Plot: Study 4255)



Source: Integrated summary of immunogenicity Figure 7.1.11 and Figure 7.1.12
 Abbreviation: ADA, anti-drug antibody

Figure 39. Concizumab Plasma Concentration Over Time – ADA-positive Versus – Negative Patients (Top Plot: Study 4311 Before Restart and Bottom Plot: Study 4311 After Restart)



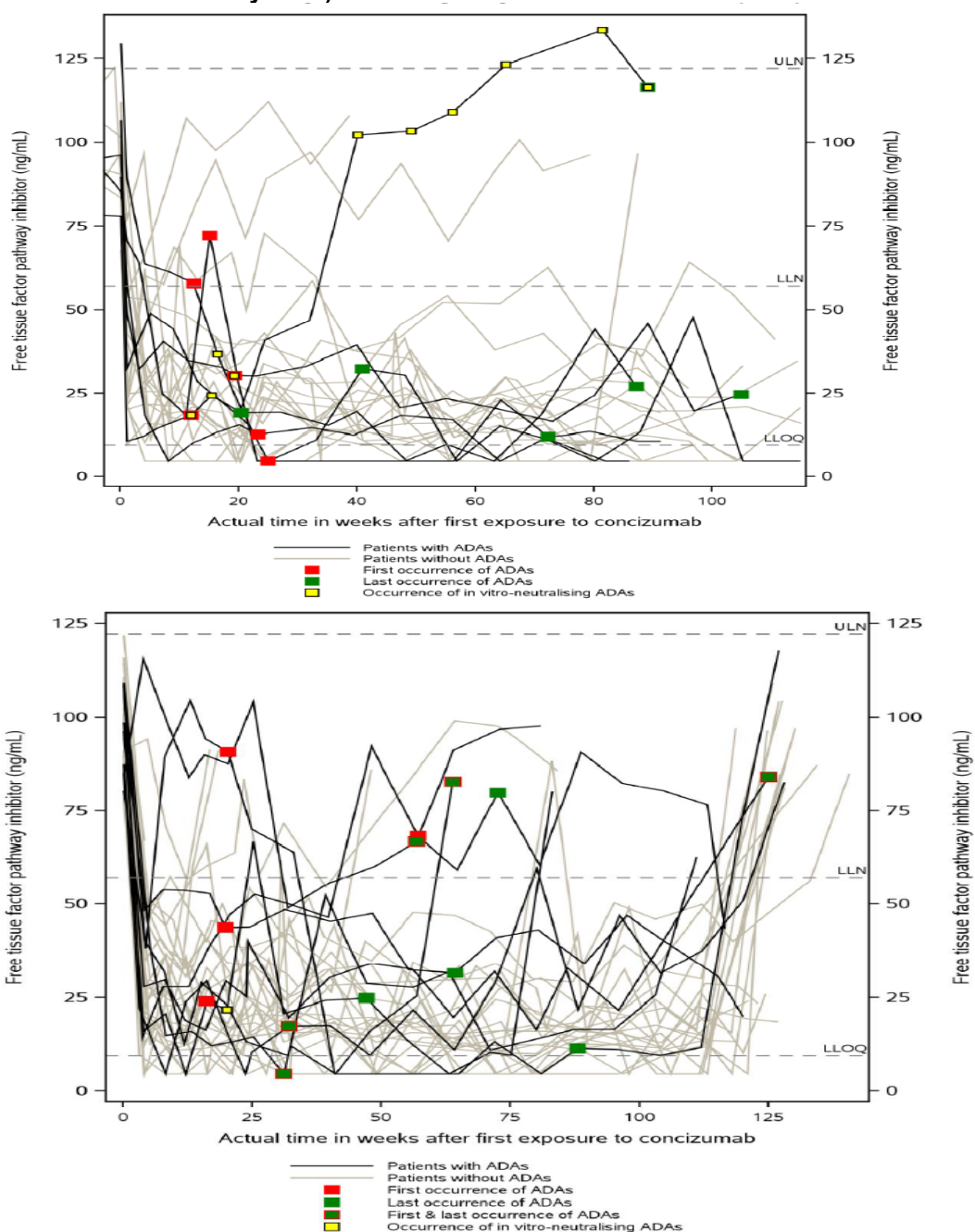
Source: Integrated summary of immunogenicity Figure 7.1.13 and Figure 7.1.14
Abbreviation: ADA, anti-drug antibody

Impact of Immunogenicity on Free TFPI (PD)

The presence of anti-concizumab antibodies, some with in vitro-neutralizing effects, did not appear to generally affect the ability of concizumab to bind TFPI.

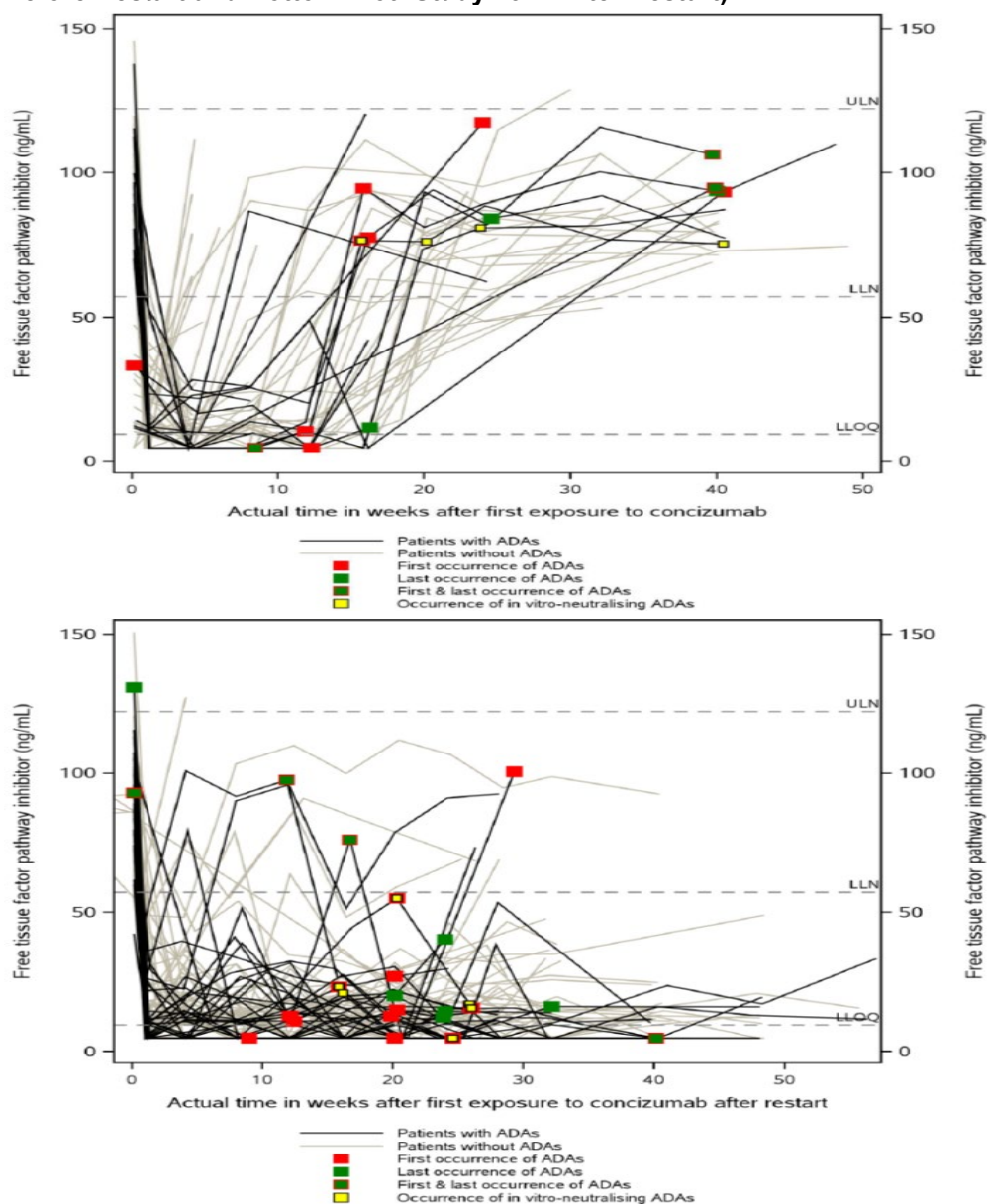
- In both Phase 2 and Phase 3, free TFPI profiles were similar between patients positive and negative for anti-concizumab antibodies ([Figure 40](#) and [Figure 41](#)). Seroconversion did not appear to cause a general change in free TPFI levels in any but one of the anti-concizumab antibody-positive patients.
- A patient in Study 4310 (Subject ID [REDACTED] ^{(b) (6)}) experienced free TFPI return to baseline while he was positive for high titer binding ADAs and for ADAs with in vitro-neutralizing effects.

Figure 40. Free TFPI Over Time – ADA-Positive Versus – Negative Patients (Top Plot: Study 4310 and Bottom Plot: Study 4255)



Source: Integrated summary of immunogenicity Figure 7.1.15 and Figure 7.1.16
Abbreviation: ADA, anti-drug antibody; TFPI, tissue factor pathway inhibitor

Figure 41. Free TFPI Over Time – ADA-Positive Versus – Negative Patients (Top Plot: Study 4311 Before Restart and Bottom Plot: Study 4311 After Restart)



Source: Integrated summary of immunogenicity Figure 7.1.17 and Figure 7.1.18
Abbreviation: ADA, anti-drug antibody; TFPI, tissue factor pathway inhibitor

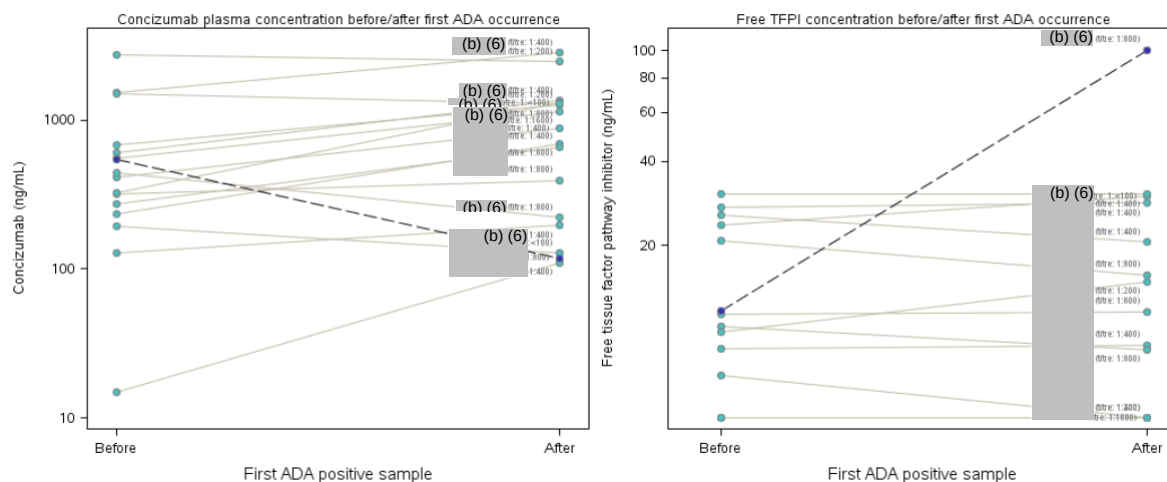
Reviewer's Comments:

- It should be noted that Phase 2 studies 4310, 4255 and Phase 3 Study 4311 before restart had different dosing regimens compared to that in Study 4311 after restart, which was the pivotal Phase 3 study to support the safety and efficacy of concizumab for the proposed indication. Considering that dose, dosing frequency, and duration of treatment are all factors that can affect immunogenicity of a therapeutic protein, the ADA assessment should mainly focus on data from 4311 after restart. Nonetheless, current

data show that the incidence of ADAs, neutralizing antibodies, as well as the impact on PK and PD were comparable across these clinical trials.

- Given the large inter-subject variability observed in the PK and PD profiles, comparisons between ADA positive and negative patients may be not sufficiently sensitive to determine the impact of ADAs on the PK and PD of concizumab. Therefore, the impact of ADA was also evaluated by comparing concizumab PK and PD before and after ADA formation in the individuals who were ADA positive. As shown in [Figure 42](#), the within-subject comparison also supports a lack of impact on concizumab PK and PD due to ADAs.
 - The presence of ADAs, some with in vitro-neutralizing effects, appeared to not affect concizumab exposure or the ability of concizumab to bind TFPI.
 - One patient (Subject ID (b) (6)) in [Figure 42](#) (highlighted with a dotted blue line) showed altered PK/PD (i.e., decreased concizumab concentration and increased free TFPI concentration) after ADA development. This patient had not been treated with concizumab for approximately one month when he tested positive for ADAs on (b) (6). Accordingly, this patient had a single measurement of low concizumab concentration (17.3 ng/mL) and a corresponding high TFPI (100.5 ng/mL) at the same visit. His concizumab concentration went up to 798 ng/mL, and free TFPI went down to 20.7 ng/mL at the next visit. This patient did not have in vitro-neutralizing ADAs.

Figure 42. Geometric Mean Concizumab Trough and Free TFPI Concentrations Before and After First ADA-positive Sample in Individual Patients From Study 4311 Up Until Primary Analysis Cut-off*



Source: Applicant's response to Information Request sent on December 20th, 2022

* Data from patients with at least one PK (concizumab trough concentration) or PD (free TFPI) measurement before the first ADA positive sample and at least one PK/PD measurement afterwards were included. This was to make sure that the individual patients had data both before and after ADA development to facilitate the within-subject comparison. Based on the above criteria, data from 16 patients in Study 4311 (after restart) were included in the PK (concizumab trough concentration) plot and data from 13 patients were included in the PD (free TFPI) plot.

Abbreviations: ADA, anti-drug antibody; PD, pharmacodynamics; PK, pharmacokinetics; TPFI, tissue factor pathway inhibitor

14.5. Pharmacometrics Assessment

14.5.1. Summary of Applicant's Population PK Analysis

The population PK (PPK) model was developed based on all Phase 1 and 2 studies, and the Phase 3 study 4311 in patients with hemophilia A and B with inhibitors. The proposed concizumab regimen (applied in Phase 3) includes a loading dose of 1 mg/kg once on Day 1, and from Day 2 until individual maintenance dose setting, once daily dosing of 0.20 mg/kg. Four weeks after initiation of treatment, concizumab plasma concentration is measured and based on this exposure level, the maintenance dose is set:

- <200 ng/mL: 0.25 mg/kg once daily
- 200 to 4000 ng/mL: 0.20 mg/kg once daily
- >4000 ng/mL: 0.15 mg/kg once daily

The PPK analysis was conducted using 4145 evaluable concizumab concentrations in a total of 232 patients. The concizumab dose level ranges included from 0.0005 to 9 mg/kg administered by IV and 0.05 to 3 mg/kg SC injection. The summary of studies used for PPK analysis are listed in [Table 111](#). Summary statistics of the continuous and categorical covariates that were evaluated in the population PK analysis are shown in [Table 112](#).

Table 111. Summary of Trials Contributing Data to the Population PK and Exposure-response Analyses of Concizumab

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

Source: Population PK Study Report Modeling Report – Phase 3a, Table 4-1.

^a 2 PK samples, one before dose and one after dose.

^b Study 4307 was not completed at the time of this report and does not contribute data to analyses.

Abbreviations: HA, hemophilia A, HB, hemophilia B, HAwI, hemophilia A with inhibitors; HBwI, hemophilia B with inhibitors; LD, loading dose; N, number of subjects receiving concizumab treatment; PK, pharmacokinetics; SD, single dose; w, week

Table 112. Summary Statistics of the Continuous and Categorical Covariates of the PK Population

Category	Group	3813	3981	3986	4159	4255	4310	4311	Total
All	N	38 (15%)	6 (2.4%)	4 (1.6%)	18 (7.1%)	35 (13.8%)	25 (9.9%)	127 (50.2%)	232 (100%)
Phase	Phase 1	38 (100%)	6 (100%)	4 (100%)	18 (100%)	-	-	-	66 (28.4%)
	Phase 2	-	-	-	-	35 (100%)	25 (100%)	-	60 (25.9%)
	Phase 3	-	-	-	-	-	-	127 (100%)	106 (45.7%)
Population	Healthy	20 (52.6%)	6 (100%)	4 (100%)	-	-	-	-	30 (12.9%)
	Haemophilia A	15 (39.5%)	-	-	18 (100%)	35 (100%)	-	-	68 (29.3%)
	Haemophilia B	3 (7.9%)	-	-	-	-	-	-	3 (1.3%)
	Haemophilia A with inhibitors	-	-	-	-	-	15 (60%)	76 (59.8%)	78 (33.6%)
	Haemophilia B with inhibitors	-	-	-	-	-	10 (40%)	51 (40.2%)	53 (22.8%)
Race	White	27 (71.1%)	-	4 (100%)	14 (77.8%)	23 (65.7%)	19 (76%)	76 (59.8%)	146 (62.9%)
	Asian	6 (15.8%)	6 (100%)	-	2 (11.1%)	8 (22.9%)	6 (24%)	34 (26.8%)	58 (25%)
	Black or African American	4 (10.5%)	-	-	1 (5.6%)	-	-	9 (7.1%)	14 (6%)
	Not reported	-	-	-	-	3 (8.6%)	-	5 (3.9%)	8 (3.4%)
	American Indian or Alaska Native	-	-	-	-	-	-	3 (2.4%)	3 (1.3%)
	Other	1 (2.6%)	-	-	1 (5.6%)	1 (2.9%)	-	-	3 (1.3%)
Ethnicity	Not Hispanic or Latino	36 (94.7%)	6 (100%)	4 (100%)	16 (88.9%)	29 (82.9%)	24 (96%)	116 (91.3%)	211 (90.9%)
	Hispanic or Latino	2 (5.3%)	-	-	2 (11.1%)	3 (8.6%)	1 (4%)	7 (5.5%)	14 (6%)
	Not reported	-	-	-	-	3 (8.6%)	-	4 (3.1%)	7 (3%)
Route	SC	15 (39.5%)	6 (100%)	4 (100%)	18 (100%)	35 (100%)	25 (100%)	127 (100%)	209 (90.1%)
	IV	23 (60.5%)	-	-	-	-	-	-	23 (9.9%)
Renal_status	Normal	-	-	-	-	-	21 (84%)	123 (96.9%)	123 (53%)
	Renal impairment	-	-	-	-	-	-	4 (3.1%)	4 (1.7%)
	Not reported	38 (100%)	6 (100%)	4 (100%)	18 (100%)	35 (100%)	4 (16%)	-	105 (45.3%)
Hepatic_status	Normal	37 (97.4%)	6 (100%)	4 (100%)	18 (100%)	35 (100%)	24 (96%)	122 (96.1%)	225 (97%)
	Elevated ALT or AST	-	-	-	-	-	1 (4%)	4 (3.1%)	5 (2.2%)
	Not reported	1 (2.6%)	-	-	-	-	-	1 (0.8%)	2 (0.9%)
Body_weight	Mean (SD)	74.8 (11.8)	62.9 (5)	73.8 (8.8)	74.9 (12.7)	76.8 (20.7)	70.6 (14)	67.4 (20.5)	70.6 (18.7)
	Range	[55.7-99.2]	[57.5-70.2]	[65.2-85.5]	[50-98]	[47.1-130]	[46.9-99.6]	[27-130.7]	[27-130.7]
BMI	Mean (SD)	24.3 (3.2)	21.8 (2.1)	24 (2.5)	24.3 (3.3)	24.8 (5.1)	24 (4.2)	23.4 (5.9)	23.8 (5.1)
	Range	[17.7-30.3]	[19.7-24.7]	[21.9-27]	[18-29.9]	[16.6-37.2]	[16.9-32.5]	[12.2-44.2]	[12.2-44.2]
Age	Mean (SD)	34.1 (11.6)	28.3 (7.1)	44 (22)	34.1 (10.4)	36.7 (13)	35.4 (11.7)	28.1 (13.9)	31.2 (13.5)
	Range	[18-60]	[21-41]	[23-64]	[19-54]	[19-65]	[18-59]	[12-79]	[12-79]

The total column reflects total unique participants; some participants in trial 4310 continued into 4311, and these are therefore counted once. One subject was excluded from Trial 4255 and one from Trial 4310, see [Table 10-1](#).

Renal impairment was defined as eGFR <90 mL/min/1.73 m². Elevated liver enzymes was defined as ALT or AST ≥ 1.5 times the upper limit of normal.

Source: Population PK Study Report Modeling Report – Phase 3a, Table 6-1.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; eGFR, estimated glomerular filtration rate; IV, intravenous; N, number of subjects; PK, pharmacokinetics; SC, subcutaneous; SD, standard deviation

The PK of concizumab was best characterized by a 2-compartment model with combined linear clearance and target mediated drug disposition (TMDD), together with a transit compartment for delayed absorption. Of note, the TMDD was estimated using a quasi-steady-state approximation, which assumes an instant equilibrium between concizumab and TFPI. The final concizumab PK model parameter estimates, and the corresponding 95% confidence intervals (CIs) are presented in [Table 113](#). Due to sparse PK profiles in the Phase 3, data from previous Phase 1 & 2 was used for estimation of PK parameters, then PK parameters were fixed. The only parameter - the total capacity TMDD parameter R_{tot} and covariate effects were then re-estimated using data from Phase 3 Study 4311.

Table 113. Parameter Estimates of the Final Population PK Model

Parameter	Labels	Estimate	95 % CI lower	95 % CI upper	RSE (%)	IIV (% CV)	Shrinkage (%)
CL [L/h]	Clearance	0.00814	Fixed	Fixed	Fixed	NA	NA
V2 [L]	Volume of distribution	2.96	Fixed	Fixed	Fixed	NA	NA
Q [L/h]	Inter compartmental clearance	0.0603	Fixed	Fixed	Fixed	NA	NA
KA1 [1/h]	Absorption rate	0.00963	Fixed	Fixed	Fixed	NA	NA
BA	Bioavailability	0.777	Fixed	Fixed	Fixed	NA	NA
BWCLEXP	Body weight covariate on CL,Q	0.75	Fixed	Fixed	Fixed	NA	NA
BWVEXP	Body weight covariate on V	1	Fixed	Fixed	Fixed	NA	NA
KCOM [1/h]	Elimination rate for complex at endothelium	0.188	Fixed	Fixed	Fixed	NA	NA
KM [ng/mL]	Concentration for 50% saturation of TMDD	96.2	Fixed	Fixed	Fixed	NA	NA
KTR [1/h]	Transit rate constant	1.97	Fixed	Fixed	Fixed	NA	NA
RTOT [mg]	Total capacity of TMDD	3.35	3.21	3.49	2.14	19.3	9.05
BASE [ng/mL]	Complex in plasma	7.88	Fixed	Fixed	Fixed	NA	NA
BWRTOT	Body weight covariate on RTOT	0.63	0.601	0.659	2.36	NA	NA
C4311RTOT	Trial 4311 covariate on RTOT	0.91	0.853	0.967	3.19	NA	NA
Add. Error	Additive error on log data (SD)	0.774	NA	NA	NA	NA	2.29

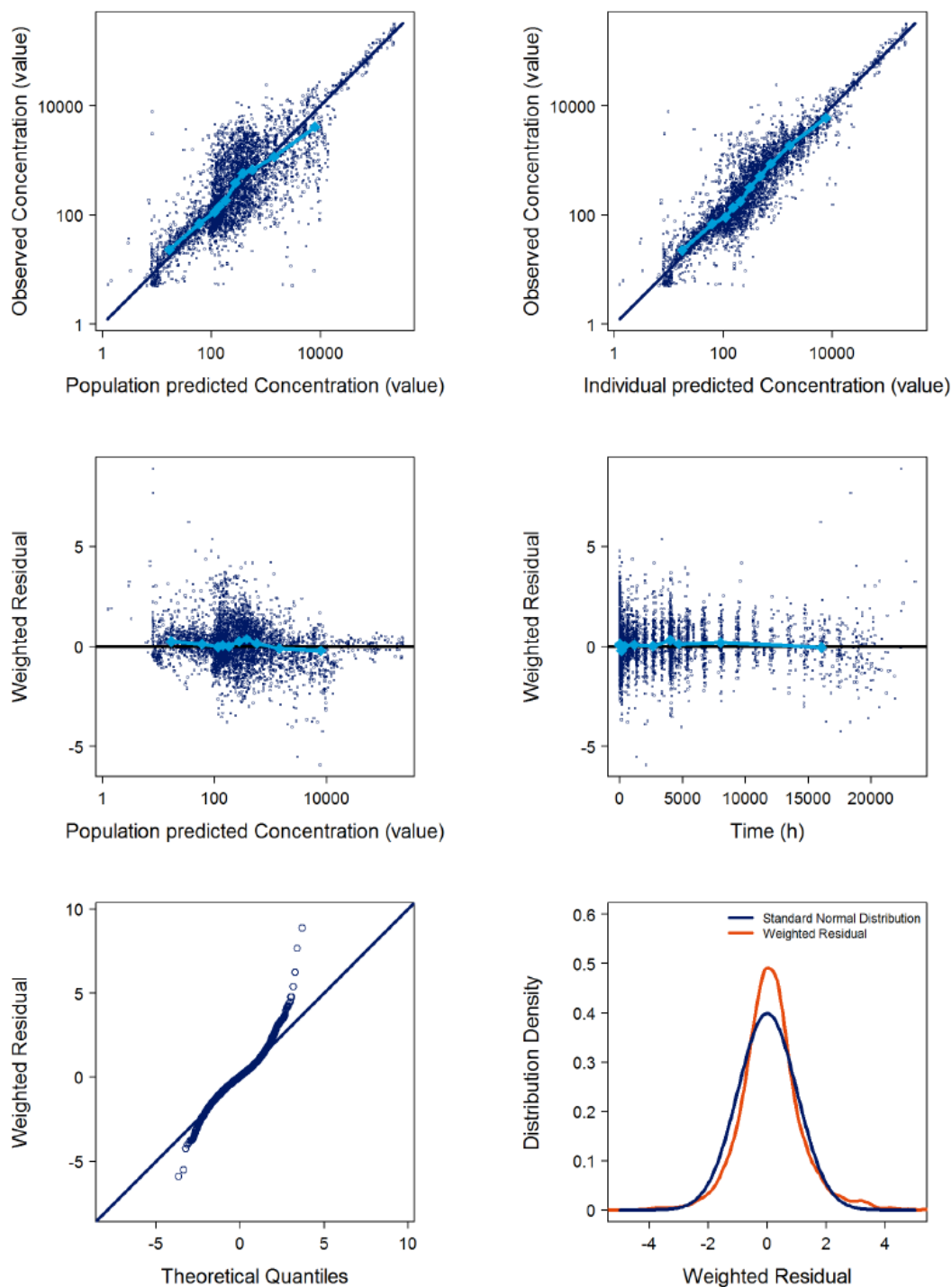
V1 was not estimated, and was instead set to be the same as V2.

Source: Population PK Study Report Modeling Report – Phase 3a, Table 10-5.

Abbreviations: BA, bioavailability; BASE, complex in plasma; BWCLEXP, body weight covariate on CL,Q; BWCEXP, body weight covariate on V; BWRTOT, body weight covariate on RTOT; C4311RTOT, Trial 4311 covariate on RTOT; CI, confidence interval; CL, clearance; CV, coefficient of variation; KA1, absorption rate; KCOM, elimination rate for complex at endothelium; KM, concentration for 50% saturation of TMDD; KTR, transit rate constant; NA, not applicable; PK, pharmacokinetics; Q, inter compartmental clearance; RSE, relative standard errors; RTOT, total capacity of TMDD; SD, standard deviation; TMDD, target mediated drug disposition; V2, volume of distribution

The goodness-of-fit plots for the final concizumab PK model stratified by patient population are presented in the [Figure 43](#). The prediction-corrected visual predictive check (pcVPC) stratified by study ([Figure 44](#)) illustrated the prediction percentiles and corresponding 95% CI of simulated concentrations overlaid on the observed concizumab concentrations and the corresponding 5th and 95th percentiles.

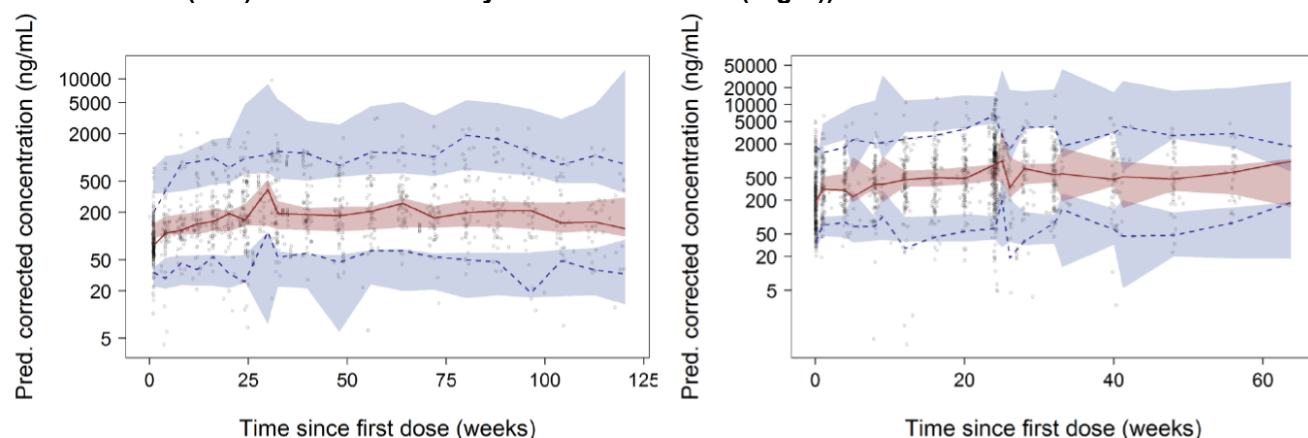
Figure 43. Goodness-of-fit Plots for the Final Population PK Model for Concizumab



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Data are observed concentrations versus population predictions and versus individual predictions, conditional weighted residuals versus population predictions and versus time, QQ-plot of weight residuals and distribution plot of weighted residuals. Light blue lines are median values for quantiles of concentration or time. Data from all included trials, n=232.
Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-4.
Abbreviations: n, number of subjects; PK, pharmacokinetics; QQ-plot, quantile quantile-plot

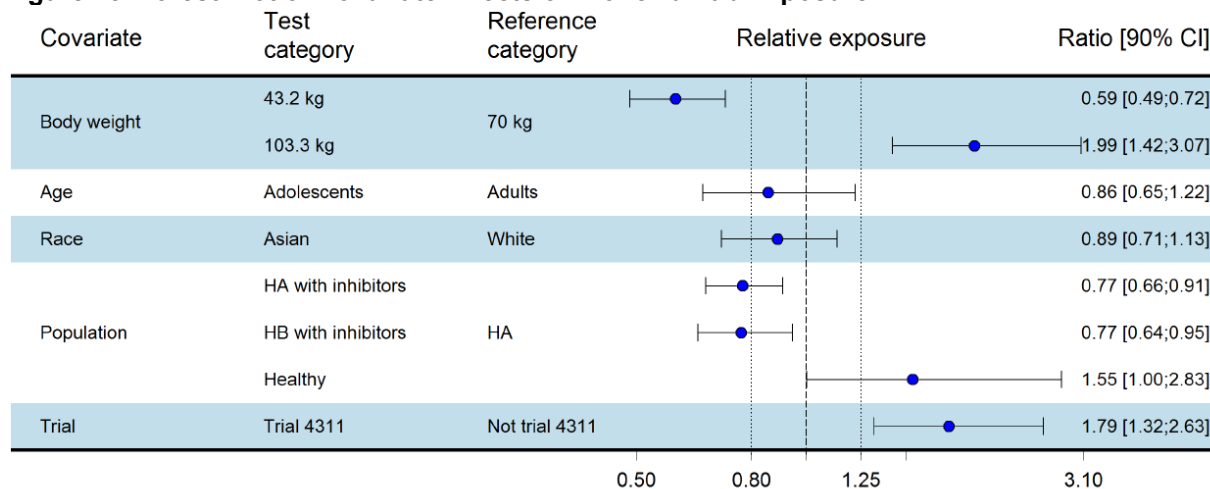
Figure 44. Prediction Corrected Visual Predictive Check for the Final Concizumab Model (Studies 4255 and 4310 (Left) and Phase 3 Study 4311 After Restart (Right))



Symbols are observed data. Lines and shaded areas represent observed and simulated (95% CIs based on 1000 simulations) medians and 5th and 95th percentiles.
Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-7.

Covariate analysis in the final model identified two statistically significant covariates: the effects of body weight, and a factor for the Phase 3 Study 4311 on R_{tot} . Allometric scaling was applied to CL and Volume terms (V_c , V_p) using fixed exponents (0.75 and 1.00 respectively) to account for PK variability related to body weight. The impact of covariates on concizumab exposure was assessed using forest plot with all covariates (Figure 45). The most important covariate for predicting concizumab exposure was body weight, with exposure increasing with increasing body weight (Figure 45).

Figure 45. Forest Plot of Covariate Effects on Concizumab Exposure



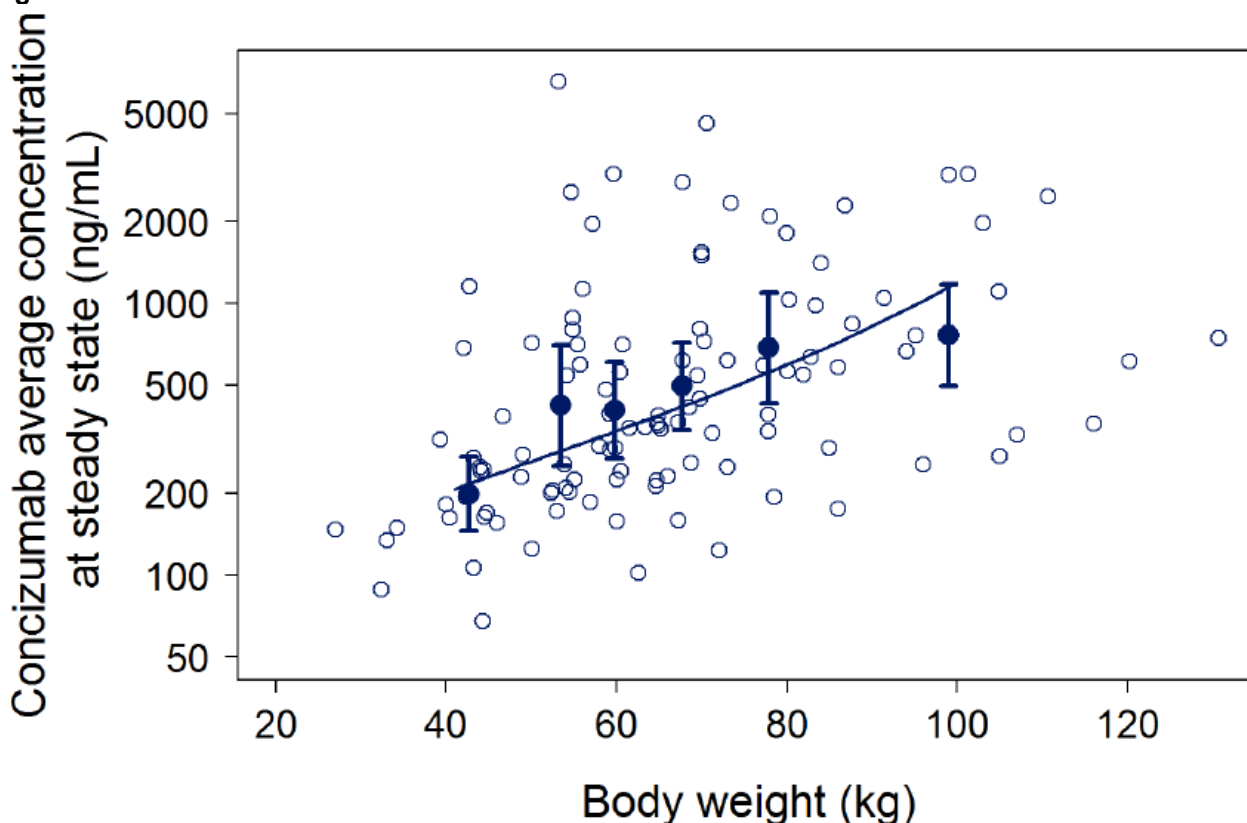
Source: Population PK Study Report Modeling Report – Phase 3a, Figure 6-2.
Abbreviations: CI, confidence interval; HA, hemophilia A

Exposure with Body Weights

PPK simulation results showed the mean concizumab exposure evidently increases with increasing body weight in Study 4311 (Figure 46). In addition, using a flat dose of 15 mg (e.g., a

typical subject with a body weight around 75 kg, 0.20 mg/kg corresponds to 15 mg), the simulation results showed remarkably high exposure for subjects with low body weight and low exposure for subjects with high body weight (Figure 47). This is likely caused by the nonlinear PK due to TMDD. If necessary, a body weight banded dosing approach (either with flat or per kg dosing) could be considered to further reduce exposure variability. Nonetheless, after 4 weeks of treatment, patients with low or high exposure should adjust dose to 0.25 or 0.15 mg/kg, respectively, resulting in more similar exposure across patients.

Figure 46. Individually Predicted Average Exposure at Steady State of 0.20 mg/kg Versus Body Weight

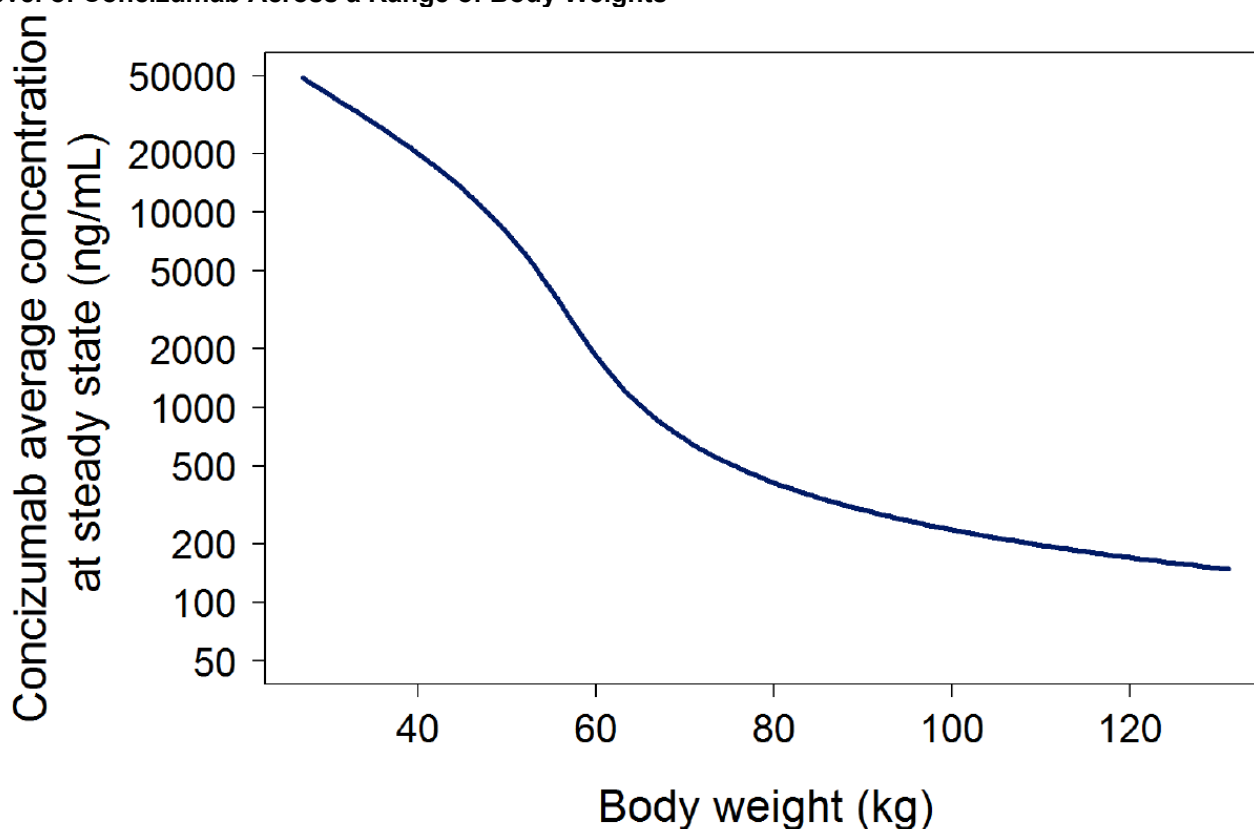


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Relationship between individually predicted average steady-state concentrations at steady state of 0.20 mg/kg (circles) versus body weight for all subjects enrolled in 4311 after the restart based on the final model. Points with bars are geometric mean and 95% CI of the individually predicted average exposure at steady state of 0.20 mg/kg. The solid line represents the model-predicted average exposure at steady state of 0.20 mg/kg versus body weight for the typical subjects.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 6-3.
Abbreviation: CI, confidence interval

Figure 47. Simulated Average Concizumab Concentrations at Steady State for a Flat 15 mg Dose Level of Concizumab Across a Range of Body Weights



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Notes: Simulations are based on the final population PK model for a typical subject in trial 4311 for various body weights.

Source: Adapted from Applicant's IR response dated 11/10/2022, Figure 2-1.

Abbreviation: PK, pharmacokinetics

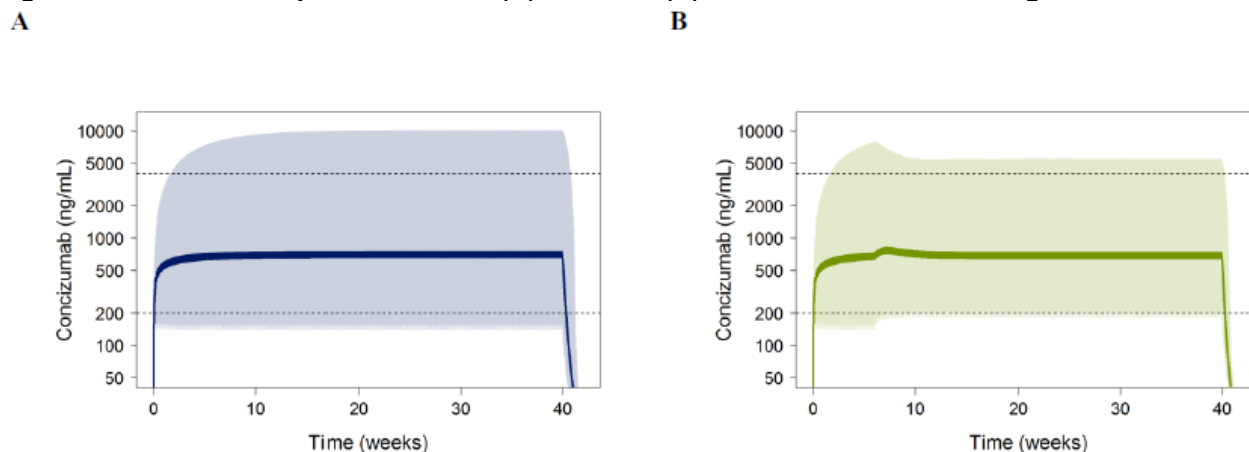
Simulation for Maintenance-Dose Setting

The proposed concizumab regimen (applied in Phase 3) includes a loading dose of 1 mg/kg once on Day 1, and from Day 2 until individual maintenance dose setting, once daily dosing of 0.20 mg/kg. Four weeks after initiation of treatment, concizumab plasma concentration is measured and based on this exposure level, the maintenance dose is set:

- <200 ng/mL: 0.25 mg/kg once daily
- 200 to 4000 ng/mL: 0.20 mg/kg once daily
- >4000 ng/mL: 0.15 mg/kg once daily

Simulations support that maintenance dose setting reduced the total, population-level variability in concizumab exposure ([Figure 48](#)). Specifically, there was a marginal increase in exposure at the low end and a decrease in exposure at the high end ([Table 114](#)).

Figure 48. Simulated Exposure Without (A) and With (B) Maintenance Dose Setting



Individual concentration-time profiles (without RUV) were simulated based on the final model assuming a body weight distribution similar to Trial 4311 (10,000 subjects simulated). Shaded area represents the 90% prediction interval, and dark line represents the geometric mean exposure levels. Maintenance dose setting was implemented as a dose increase or decrease at week 6, based on C_{trough} values (including RUV) occurring at week 4.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 8-1.

Abbreviation: C_{trough} , trough concentration; RUV, residual urine volume

Table 114. Average Steady-State Concizumab Exposure With and Without Maintenance Dose Setting

	Steady-state C_{avg} (ng/mL)		
	5th percentile	Geometric mean	95th percentile
With MTDS	190	710	5500
Without MTDS	150	720	10000

MTDS: maintenance dose setting. Calculated based on individual concentration-time profiles (no RUV) simulated based on the final model assuming a body weight distribution similar to 4311 (10,000 subjects simulated per scenario).

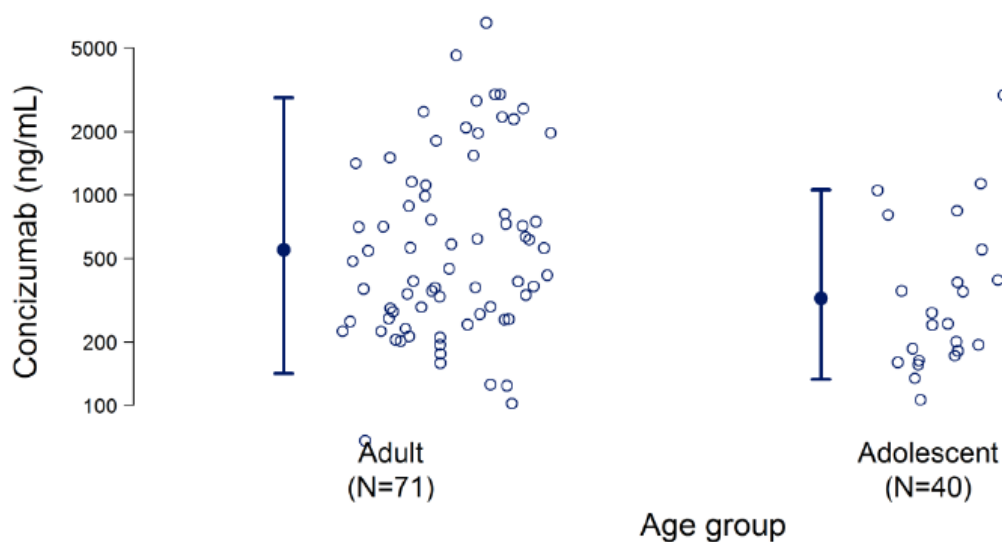
Source: Population PK Study Report Modeling Report – Phase 3a, Table 8-1.

Abbreviations: C_{avg} , average plasma concentration; MTDS, maintenance dose setting; RUV, residual urine volume

Exposure in Pediatric Patients

In Study 4311, individual steady-state exposure estimates for adolescents (12 to 17 years) were overlapping with exposure estimates in adults (>18 years) when treated with 0.20 mg/kg concizumab ([Figure 49](#)).

Figure 49. Individually Predicted Average Exposure at Steady State of 0.20 mg/kg for Adolescents and Adults in Study 4311



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Individually predicted C_{avg} at steady state of 0.20 mg/kg (circles) for adolescent and adult subjects enrolled in 4311 after the restart based on the final model. Points with bars are geometric mean and 95% CI of the individually predicted C_{avg} at steady state of 0.20 mg/kg.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 8-2.

Abbreviations: C_{avg} , average plasma concentration; CI, confidence interval; N, number of subjects

(b) (4)

Reviewer's Comments: The Applicant's PPK model appears adequate to describe the concizumab serum concentration-time profiles in the observed range following the administration of concizumab in patients with hemophilia A and B with inhibitors from Phase 3 Study 4311. The shrinkage value was 9.05% for IIV on R_{tot} , indicating there was no obvious bias in the parameter estimates. Therefore, the PK model is acceptable for simulating post hoc exposure metrics, e.g., C_{avg} and $C_{avg, trial}$ of concizumab for exposure-response (E-R) analyses for efficacy and safety measurements.

Covariate analysis identified two statistically significant covariates: body weight (27-130.7 kg), and Study 4311 on R_{tot} . Allometric scaling was also applied to CL and volume terms (V_c , V_p) using fixed exponents (0.75 and 1.00 respectively) to account for PK variability related to body weight in the PPK model. In addition, the other covariates such as age (12 to 79 years), race

(White (62.9%), Asian (25%), Black or African American (6%), American Indian or Alaska Native (1.3%), other (1.3%)), Ethnicity (Hispanic or Latino (6%), not Hispanic or Latino (91%)) were not identified as significant covariate for the concizumab exposure.

The significant impact of body weight on concizumab PK supported the body-weight-based dosing regimen:

- The concizumab exposure increases with increasing body weight.*
- Using a flat dose (e.g., 15 mg) will result high exposure for subjects with low body weight and low exposure for subjects with high body weight.*

However, the mean concizumab exposure still evidently increases with increasing body weight (with a ~5 fold exposure increase for body weight increasing from 40 kg to 100 kg) despite the per-kilogram dosing. This is likely caused by the nonlinear PK due to TMDD. If necessary, a body weight banded dosing approach (either with flat or per kilogram dosing) could be considered to further reduce exposure variability. Nonetheless, after 4 weeks of treatment, patients with low or high exposure should adjust dose to 0.25 or 0.15 mg/kg, respectively, resulting in more similar exposure across patients.

In addition, PPK simulations further supported maintenance dose setting with an increase in exposure at the low end and a decrease in exposure at the high end, and almost all patients were above the 200 ng/mL concentration level: concentrations at the plateau of effect predicted by exposure-response (E-R) for annualized bleeding rate.

Additional simulation with steady-state exposure estimates for adolescents (12 to 17 years) enrolled in Study 4311 were overlapping with exposure estimates in adults (>18 years) when treated with 0.20 mg/kg concizumab, which indicated no significant effect of age (adolescents [12 to 17 years] versus adults [≥ 18 years]).

(b) (4)

High inter- and intra-subject variability in plasma concizumab concentrations following high doses of concizumab was observed in Phase 3 Study 4311. The high inter-subject variability and wide therapeutic window (200 to 4000 ng/mL) in maintenance setting can have important implications for therapeutic drug monitoring (TDM). Generally, TDM is generally used for narrow therapeutic index drug. In cases where there is high inter-subject variability, it may be difficult to establish a one-size-fits-all dosing regimen for concizumab. The wide therapeutic window can also affect therapeutic drug monitoring, as it may be more challenging to determine the optimal dosage when there is dose delay or dose interruption. The high inter-subject variability and wide therapeutic window may underscore the importance of individualized dosing and the use of therapeutic drug monitoring to optimize treatment outcomes. However, given the large therapeutic window here, the TDM might be ok to reduce potential outliers, and for patients with low or high exposure, the TDM can help to adjust individual dose according to the maintenance dose setting, resulting in more similar exposure across patients.

Although Current PPK model had included nonlinear elimination of concizumab via target mediated drug disposition (TMDD), we noticed several limitations in their PPK model:

- The Current PPK model had some limitations on handling the variabilities: current model tends to put almost all the variability into the residual variabilities with high additive error on log data (SD) = 0.6. This can be problematic because it can make it difficult to determine the true sources of variability. Additionally, this can limit the ability of the model to make accurate predictions.*
- Additionally, current PPK model fixed the most model structure parameters values for TMDD and PK: only R_{tot} with inter-subject variance is allowed to vary, which can limit the flexibility of the model when analyzing complex PK data with large inter- and intra-subject variability that require more flexibility in the model.*

Additional simulation with steady-state exposure estimates for adolescents (12 to 17 years) enrolled in Study 4311 were overlapping with exposure estimates in adults (>18 years) when treated with 0.20 mg/kg concizumab, which indicated no significant effect of age (adolescents [12 to 17 years] versus adults [≥ 18 years]). (b) (4)

In summary, PPK modeling and simulation results support no dose adjustment for proposed dose regimen.

14.5.2. Exposure-Response Analysis

The Applicant's exposure-response (E-R) for efficacy analysis of concizumab was conducted with Phase 3 data. The total number of subjects and samples in each exposure-response model was:

- Free TFPI: 110 subjects with 941 time-matched free TFPI and concizumab plasma concentrations (327 of these samples were below the lower limit of quantification (BLOQ))
- Thrombin peak: 108 subjects with 1048 time-matched thrombin peak and concizumab concentrations
- Bleeding rate model: 117 subjects with 440 bleeding episodes (including data from on-demand treatment)

The demographics for the populations used for the three exposure-response models are presented in [Table 115](#).

Table 115. Demographics for the Exposure-response Models

Category	Group	Free TFPI	Thrombin peak	Bleeding episodes
All	N	110 (100%)	108 (100%)	117 (100%)
Population	Haemophilia A with inhibitors	65 (59.1%)	67 (62%)	71 (60.7%)
	Haemophilia B with inhibitors	45 (40.9%)	41 (38%)	46 (39.3%)
Race	White	63 (57.3%)	64 (59.3%)	67 (57.3%)
	Asian	32 (29.1%)	29 (26.9%)	34 (29.1%)
	Black or African American	8 (7.3%)	8 (7.4%)	8 (6.8%)
	Not reported	4 (3.6%)	4 (3.7%)	5 (4.3%)
	American Indian or Alaska Native	3 (2.7%)	3 (2.8%)	3 (2.6%)
Ethnicity	Not Hispanic or Latino	101 (91.8%)	99 (91.7%)	107 (91.5%)
	Hispanic or Latino	6 (5.5%)	6 (5.6%)	6 (5.1%)
	Not reported	3 (2.7%)	3 (2.8%)	4 (3.4%)
Treatment	Concizumab	97 (88.2%)	96 (88.9%)	98 (83.8%)
	Starting on on-demand treatment ^a	13 (11.8%)	12 (11.1%)	19 (16.2%)
Body weight	Mean (SD)	66.2 (20.4)	67.2 (19.9)	66.6 (20.1)
	Range	[27-130.7]	[27-130.7]	[27-130.7]
BMI	Mean (SD)	23 (6)	23.2 (5.9)	23.1 (5.9)
	Range	[12.2-44.2]	[12.9-44.2]	[12.2-44.2]
Age	Mean (SD)	26.9 (12.8)	27.1 (12.8)	27.8 (13.5)
	Range	[12-61]	[12-61]	[12-67]

a. Starting on on-demand treatment, but later switching to concizumab treatment. Only samples taken during the concizumab treatment were used for the free TFPI and thrombin peak models; data from the on-demand treatment period was used for the bleeding rate model.

Source: Population PK Study Report Modeling Report – Phase 3a, Table 7-1.

Abbreviations: BMI, body mass index; N, number of subjects; SD, standard deviation; TFPI, tissue factor pathway inhibitor

14.5.2.1. Exposure-Response Analysis of Bleeding Episodes (Repeated Time-to-Event Model)

An RTTE analysis using a hazard function was performed to analyze the occurrence of treated bleeds.

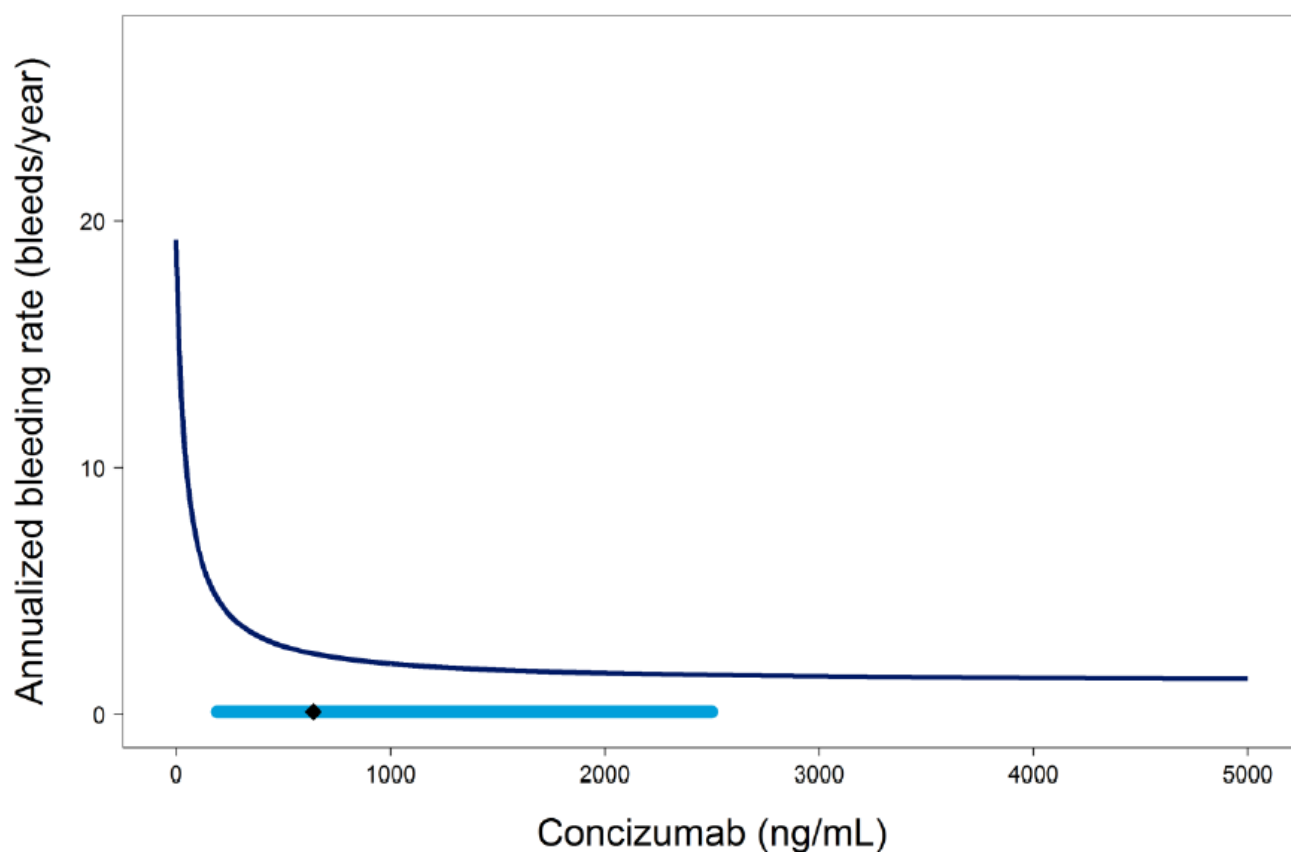
The occurrence of bleeding events in hemophilia patients with inhibitors treated on-demand was described by an exponential Gompertz distribution function. The effect of concizumab exposure on the hazard function was evaluated by inclusion of an inhibitory sigmoidal Emax model, parameterized with a constant baseline hazard (h_0), maximum reduction in instantaneous bleeding rate from baseline (E_{max}), plasma concentration to achieve 50% of maximum response (EC_{50}), and Hill coefficient (n).

Equation 1. Inhibitory Sigmoidal Emax Model for Bleeding

$$h_{(t)} = h_0 \cdot \left(1 - \frac{E_{max} \cdot C^n}{EC_{50}^n + C^n}\right)$$

Exposure-response analysis of bleeding episodes show that the concizumab dosing regimen maintains plasma concentrations at the plateau of effect ([Figure 51](#)). The maximum drug effect (Emax) was predicted to be a 93% reduction in annualized bleeding rate (ABR) ([Table 116](#)). The exposure-response analysis of bleeding episodes provided an adequate description of the occurrence of the first bleeding episode over time for subjects on concizumab and on-demand as evident from [Figure 52](#).

Figure 51. Exposure-response Relationship of Annualized Bleeding Rate



The line is the mean model-based prediction. The horizontal light blue line at the bottom represents the median (diamond) and the 5-95% range of the individual average exposure predicted across the trial duration (only including data after restart of Trial 4311), using $C_{avg,trial}$ estimated from the BOV PK model.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 7-1.

Abbreviations: BOV, between-occasion (within-subject) variability; $C_{avg,trial}$, the average of the individual concentrations predicted across the entire trial duration; PK, pharmacokinetics

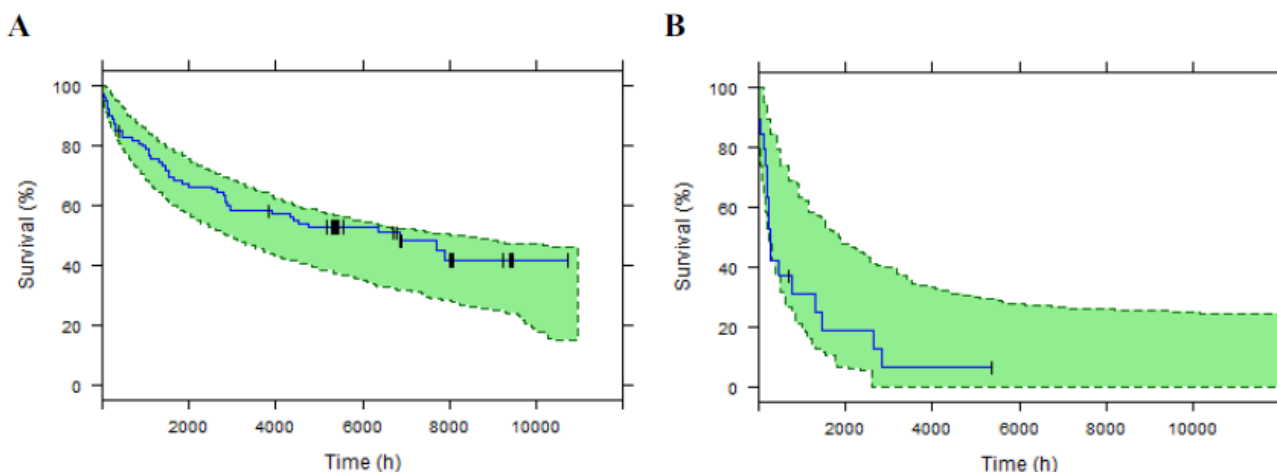
Table 116. Parameter Estimates of the Exposure Response Model of Treated Bleeds

Parameter	Label	Units	Estimates	SIR 95% CI	Shrinkage
BHAZ	Baseline hazard, Gompertz scale factor	1/year	8.21	[5.70; 11.7]	NA
EMAX	Maximum drug effect	fraction	0.934	[0.882; 0.969]	NA
EC50	Concentration which results in half Emax	ng/mL	45.2	[21.3; 79.0]	NA
IIV.BHAZ	IIV on BHAZ (CV%)	%	213	[149; 364]	22.7

Source: Population PK Study Report Modeling Report – Phase 3a, Table 10-12.

Abbreviations: BHAZ, baseline hazard; CI, confidence interval; CV, coefficient of variation; EMAX, maximum drug effect; EC₅₀, concentration which results in half E_{max}; NA, not applicable

Figure 52. Kaplan-Meier VPC of the Occurrence of First Bleeding Episodes Over Time for Subjects on Concizumab Treatment (A) and on On-Demand Treatment (B)



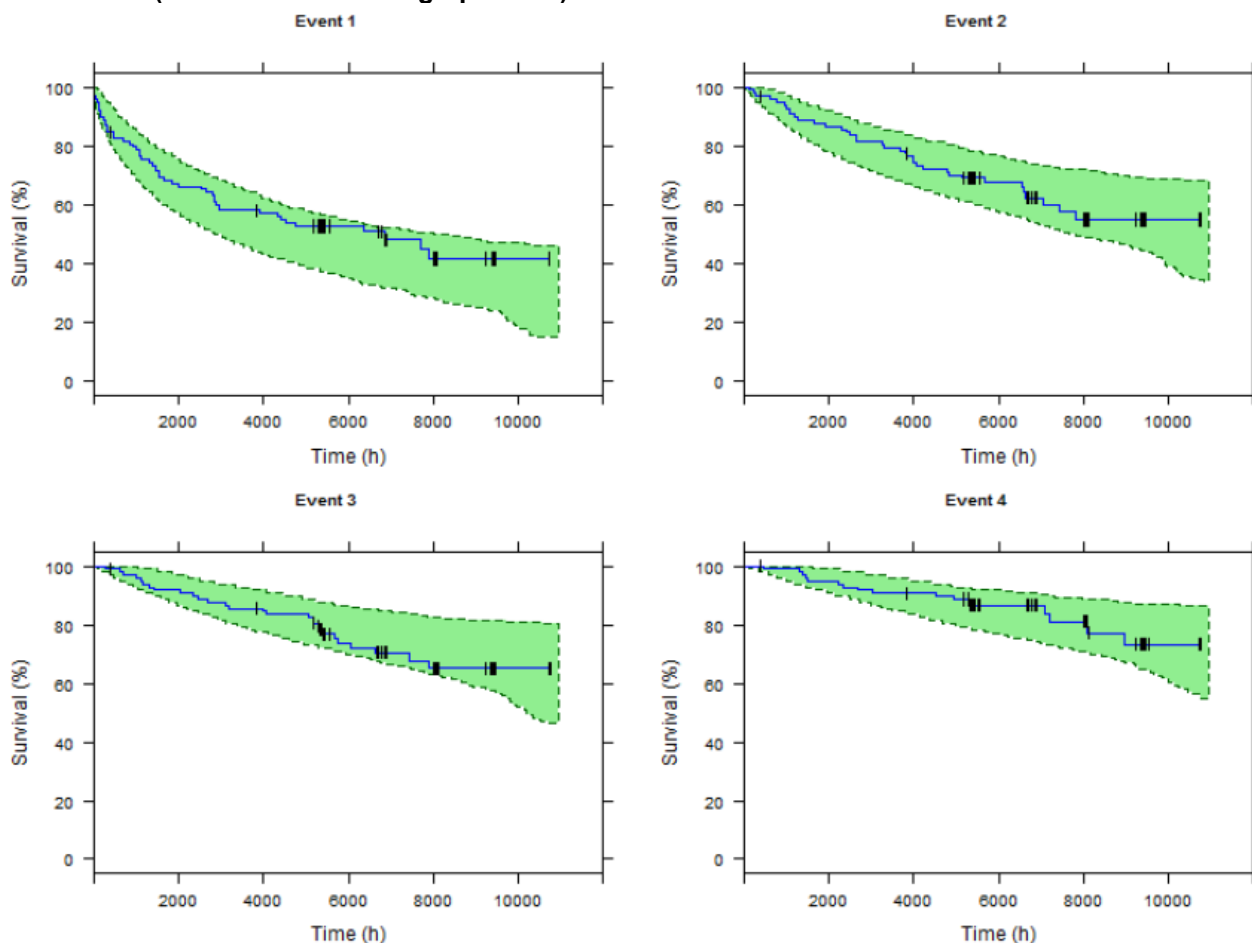
Kaplan-Meier VPC for subjects on concizumab (1000 samples) or on on-demand (1000 samples). The blue line indicates observed percentage of subjects without bleeding events over time for the 1st bleeding event. Vertical black lines across blue line indicates right censoring of subject observations. Green area indicates 95% interval for model predictions of bleeding events over time.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 7-2.

Abbreviations: h, hours; VPC, visual predictive check

Kaplan-Meier VPCs for additional bleeding episodes are presented for concizumab in [Figure 53](#) and for on-demand treatment in [Figure 54](#). All parameter estimates were estimated with acceptable precision, and all BSV parameter estimates had low shrinkage ([Table 116](#)). No significant covariates were identified during the manual covariate search procedure.

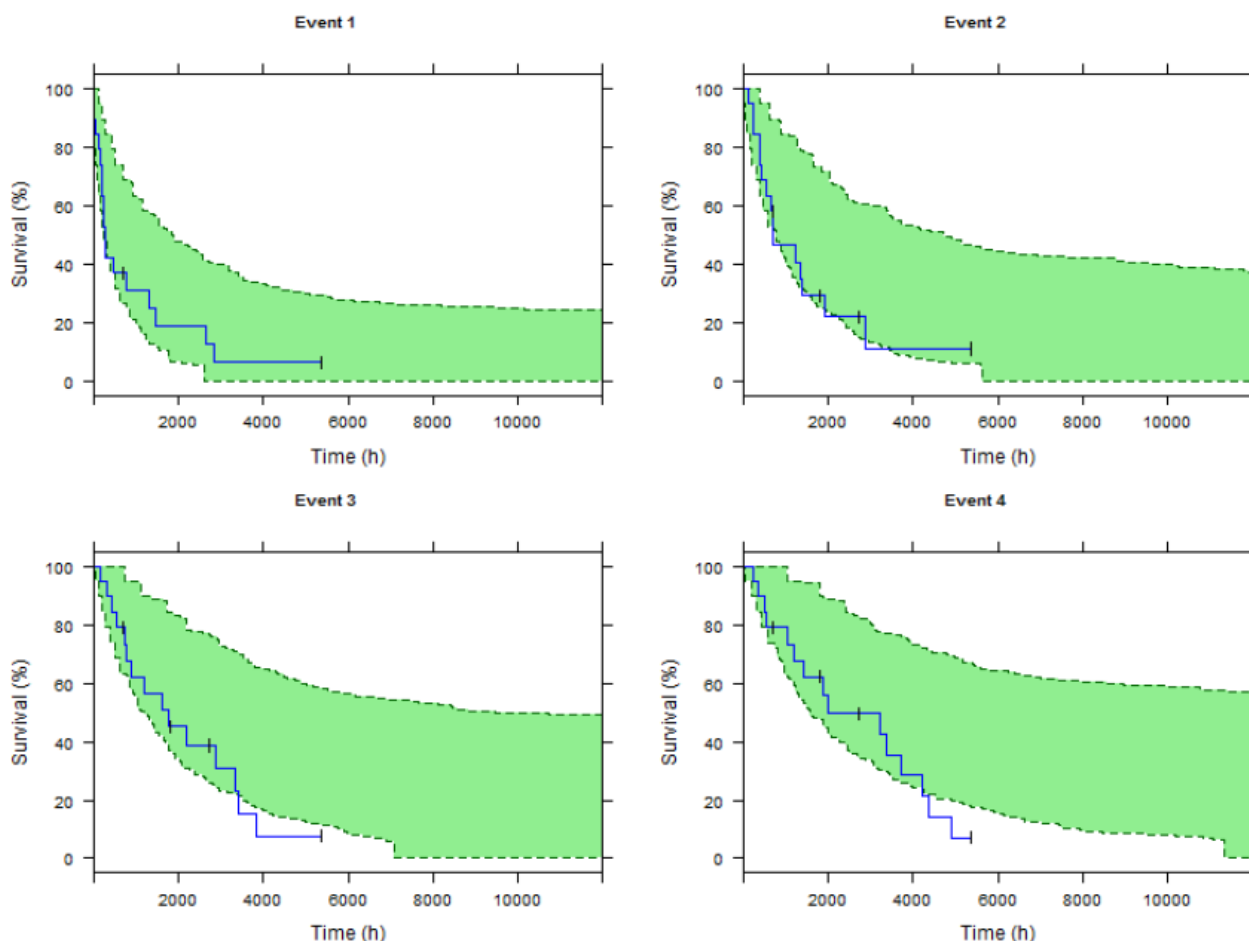
Figure 53. Kaplan-Meier VPC of the Occurrence of Bleeding Episodes Over Time for Subjects on Concizumab (One to Four Bleeding Episodes)



Kaplan-Meier VPC for subjects on concizumab (1000 samples). The blue line indicates observed percentage of subjects without bleeding events over time for the 1st to 4th bleeding event. Vertical black lines across blue line indicates right censoring of subject observations. Green area indicates 95% interval for model predictions of bleeding events over time. Events are defined as bleeding episodes, where event number refers to the number of bleeding episodes in each patient.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-20.
Abbreviations: h, hours; VPC, visual predictive check

Figure 54. Kaplan-Meier VPC of the Occurrence of Bleeding Episodes Over Time for Subjects on On-demand (One to Four Bleeding Episodes)



Kaplan-Meier VPC for subjects on on-demand (1000 samples). The blue line indicates observed percentage of subjects without bleeding events over time for the 1st to 4th bleeding event. Vertical black lines across blue line indicates right censoring of subject observations. Green area indicates 95% interval for model predictions of bleeding events over time. Events are defined as bleeding episodes, where event number refers to the number of patients with at least that many bleeding episodes.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-21.
Abbreviations: h, hours; VPC, visual predictive check

14.5.2.2. Exposure-Response Analysis of Free TFPI

A sigmoidal Emax model was used to describe concizumab concentration (C) versus free TFPI. The model was parameterized with a baseline (E0) and a sigmoidal Emax model parameterized with maximum free TFPI response (Emax), plasma concentration to achieve 50% of maximum response (EC50), and Hill coefficient (n) according to:

Equation 2. Sigmoidal Emax model for Free TFPI

$$E = E_0 - E_{max} \times \frac{C^n}{EC_{50}^n + C^n}$$

The exposure metric for the free TFPI exposure-response models was the observed concentrations with time-matched biomarker concentrations.

All parameter estimates were estimated with acceptable precision, and all BSV parameter estimates had low shrinkage ([Table 117](#)). No significant covariates were identified during the SCM procedure (forward inclusion: p<0.01, backward exclusion: p<0.001).

Table 117. Parameter Estimates of the Exposure Response Model of Free TFPI

Parameter	Label	Units	Estimates	Bootstrap 95% CI	Shrinkage
E0	Baseline free TFPI	ng/mL	87.0	[82.9; 90.7]	NA
EMAX	Maximum drug effect	ng/mL	-79.3	[-83.6; -74.7]	NA
EC50	EC50	ng/mL	57.4	[45.2; 70.0]	NA
HILL	Hill coefficient	NA	1.59	[1.22; 2.06]	NA
IIV.E0	IIV on E0 (CV%)	%	8.92	[5.80; 11.9]	7.69
ADD_ERR	Additive error	ng/mL	5.21	[3.01; 6.79]	NA
PROP_ERR	Proportional error	%	21.3	[14.8; 29.5]	NA

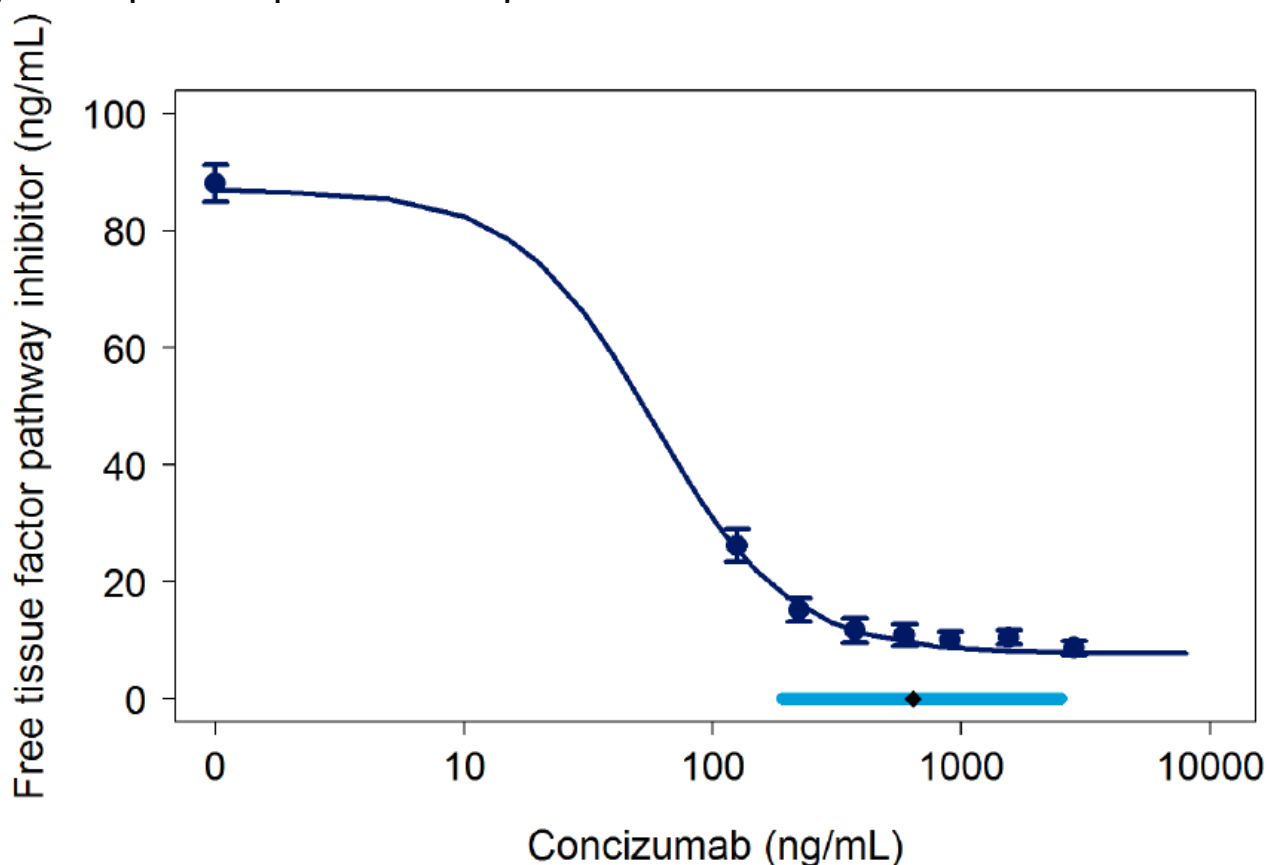
Rate of successful minimization for bootstrap = 1000/1000 samples

Source: Population PK Study Report Modeling Report – Phase 3a, Table 10-13.

Abbreviations: CI, confidence interval; NA, not applicable; TFPI, tissue factor pathway inhibitor

Exposure-response analysis of free TFPI show that the concizumab dosing regimen maintains plasma concentrations at the plateau of effect ([Figure 55](#)). The exposure metric for the free TFPI exposure-response models was the observed concentrations with time-matched biomarker concentrations.

Figure 55. Exposure Response Relationship of Free TFPI Versus Concizumab Concentration



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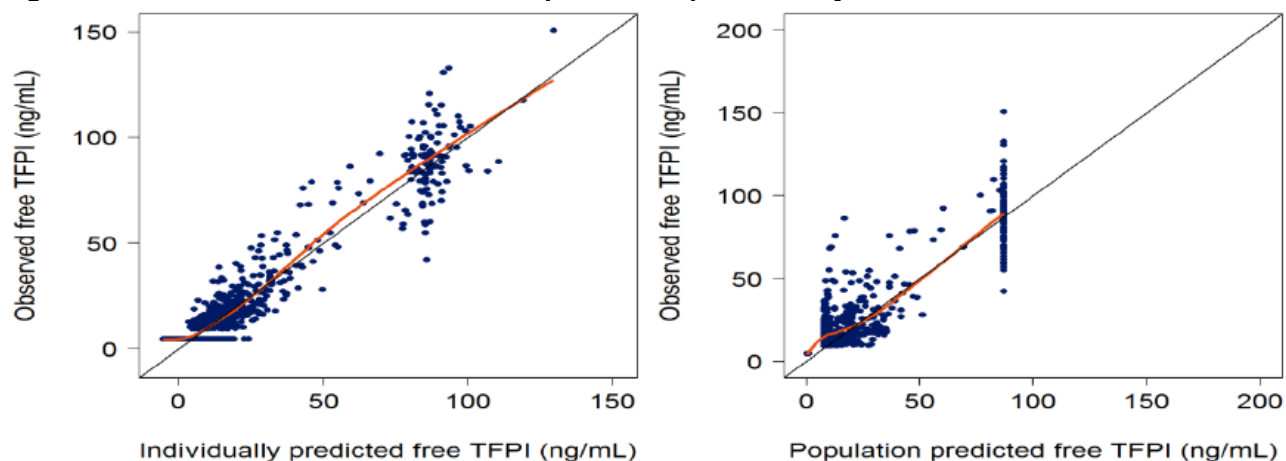
Points with bars are mean and 95% CI of observed free TFPI. The dark blue line is the mean model prediction based on population predictions. The horizontal light blue line at the bottom represents the median (diamond) and the 5-95% range of the individual average exposure predicted across the trial duration (only including data after restart of Trial 4311), using $C_{avg,trial}$ estimated from the BOV PK model.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 7-3.

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

The exposure-response model of free TFPI provided an adequate fit of the data ([Figure 55](#) and VPC in [Figure 57](#)). As concizumab concentrations increased, the proportion of free TFPI samples below lower limit of quantification (LLOQ) increased; however, the model could adequately capture the proportion of samples below LLOQ ([Figure 58](#)). Diagnostic plots ([Figure 56](#)) support that the model adequately captured observed data.

Figure 56. Goodness-of-Fit Plots for the Exposure Response Analysis of Free TFPI



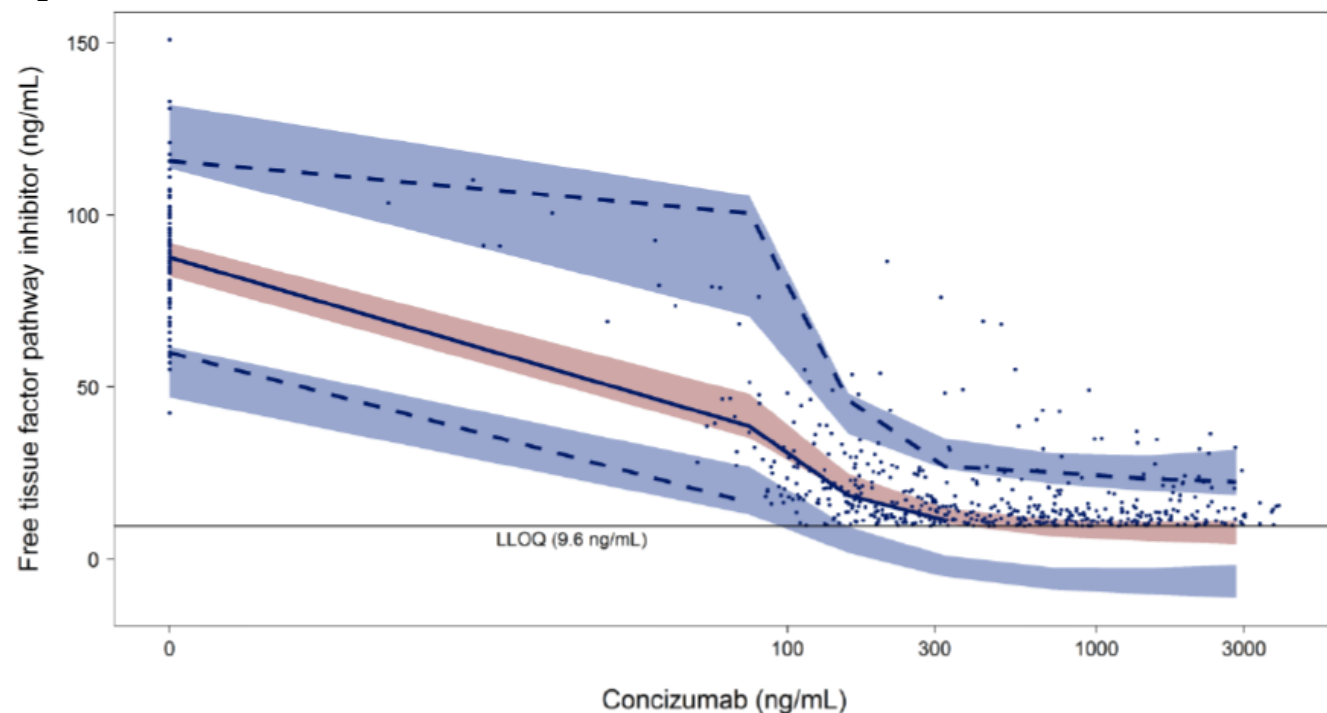
18-may-2022 12:36 E:\Project\761315 - anti-TFPI\761315-ph3model\current\Scripts\4311mean\report\107_GOF_TFPI_TGA.R

Data are observed concentrations of free TFPI versus individual predictions and versus population predictions. Red line indicates loess trend lines for concentration.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-22.

Abbreviation: TFPI, tissue factor pathway inhibitor

Figure 57. VPC of Free TFPI Versus Concizumab Concentration

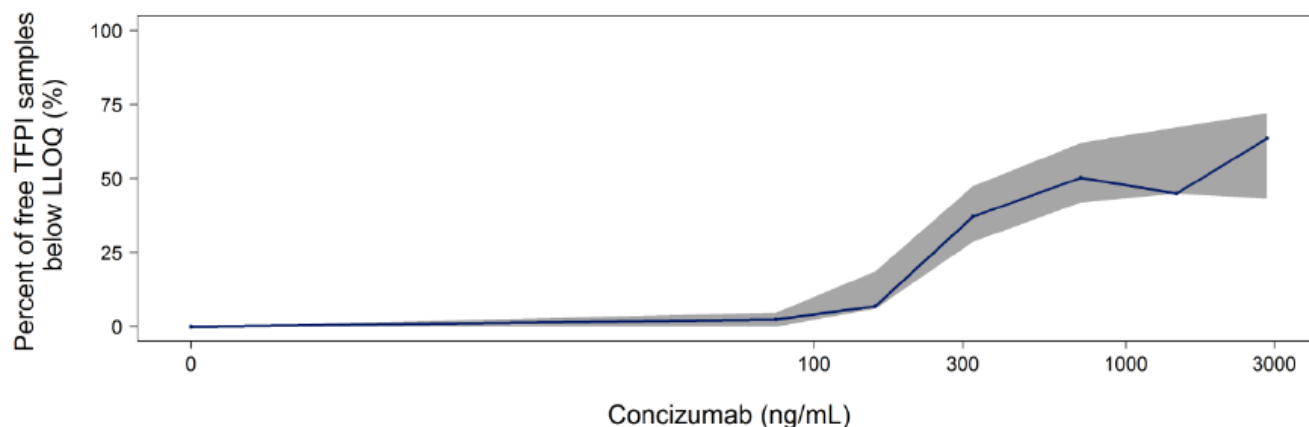


Visual predictive check of the concizumab concentration-free TFPI relationship. Data points are time-matched free TFPI and concizumab concentrations. Solid dark blue line is the median and dashed lines are the 5th (lower) and 95th (upper) percentiles of the observed data. The corresponding 95% CI for the simulated median (gray) and 5th/95th (blue) percentiles are shown by the coloured ribbons (n=1000) using the final model. The horizontal black line represents the LLOQ.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-24.

Abbreviations: CI, confidence interval; LLOQ, lower limit of quantification; n, number of subjects; TFPI, tissue factor pathway inhibitor; VPC, visual predictive check

Figure 58. VPC of Percent of Free TFPI Samples Below the Lower Limit of Quantification (BLOQ)



VPC of the percentage of free TFPI samples BLOQ versus concizumab concentration. Dark line is the observed percentage of free TFPI samples BLOQ, and the grey shaded area is the 95% CI of the model predicted percentage of free TFPI samples BLOQ.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-25.

Abbreviations: BLOQ, below the lower limit of quantification; CI, confidence interval; TFPI, tissue factor pathway inhibitor; VPC, visual predictive check

14.5.2.3. Exposure-Response for Thrombin Peak Model

A sigmoidal Emax model was used to describe the relationship between concizumab concentration (C) and thrombin peak. The model was parameterized with a baseline (E_0), and a sigmoidal Emax model parameterized with maximum thrombin peak response (E_{max}), plasma concentration to achieve 50% of maximum response (EC_{50}), hill coefficient (n) and a hemophilia B with inhibitors factor on E_0 according to:

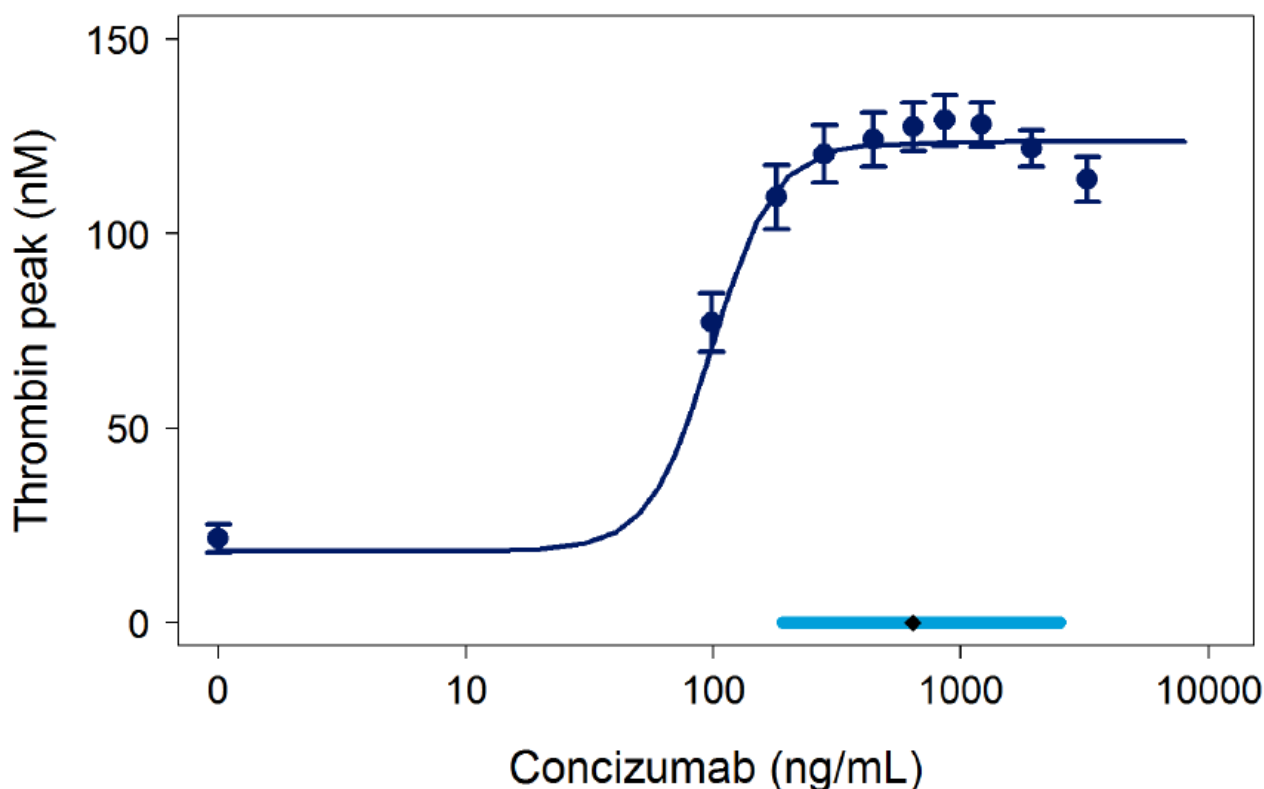
Equation 3. Sigmoidal Emax Model for Thrombin Peak

$$E = E_0 \cdot COV_{HBwI} + E_{max} \times \frac{C^n}{EC_{50}^n + C^n}$$

The exposure metric for the Thrombin peak exposure-response models was the observed concentrations with time-matched biomarker concentrations. All parameter estimates were estimated with acceptable precision, and all BSV parameter estimates had low shrinkage ([Table 118](#)). One significant covariate was identified during the SCM procedure (HBwI was a significant covariate on baseline thrombin peak).

Exposure-response analysis of thrombin peak shows that the concizumab dosing regimen maintains plasma concentrations at the plateau of effect ([Figure 59](#)).

Figure 59. Exposure Response Relationship of Thrombin Peak Versus Concizumab Concentration



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Points with bars are mean and 95% CI of observed thrombin peak concentrations versus measured concizumab concentration at the time of sampling. The dark blue line is the mean model prediction based on population predictions. The horizontal light blue line at the bottom represents the median (diamond) and the 5-95% range of the individual average exposure predicted across the trial duration (only including data after restart of Trial 4311), using $C_{avg,trial}$ estimated from the BOV PK model.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 7-4.

Abbreviations: BOV, between-occasion (within-subject) variability; $C_{avg,trial}$, the average of the individual concentrations predicted across the entire trial duration; CI, confidence interval; PK, pharmacokinetics

Table 118. Parameter Estimates of the Thrombin Peak Exposure-Response Model

Parameter	Label	Units	Estimates	Bootstrap 95% CI	Shrinkage
E0	Baseline peak thrombin	nM	23.1	[18.8; 27.6]	NA
EMAX	Maximum drug effect	nM	105	[101; 110]	NA
EC50	EC50	ng/mL	98.8	[87.1; 111]	NA
HILL	Hill coefficient	NA	3.40	[2.62; 4.24]	NA
E0HB	Population (HBwI) factor on E0	NA	-0.521	[-0.729; -0.330]	NA
IIV.E0	IIV on E0 (CV%)	%	48.9	[0.463; 68.6]	46.4
IIV.EC50	IIV on EC50 (CV%)	%	48.0	[26.3; 66.9]	31.1
IIV.EMAX	IIV on EMAX (SD)	nM	22.6	[18.5; 26.5]	13.9
ADD_ERR	Additive error (SD)	nM	19.6	[17.6; 21.6]	8.03

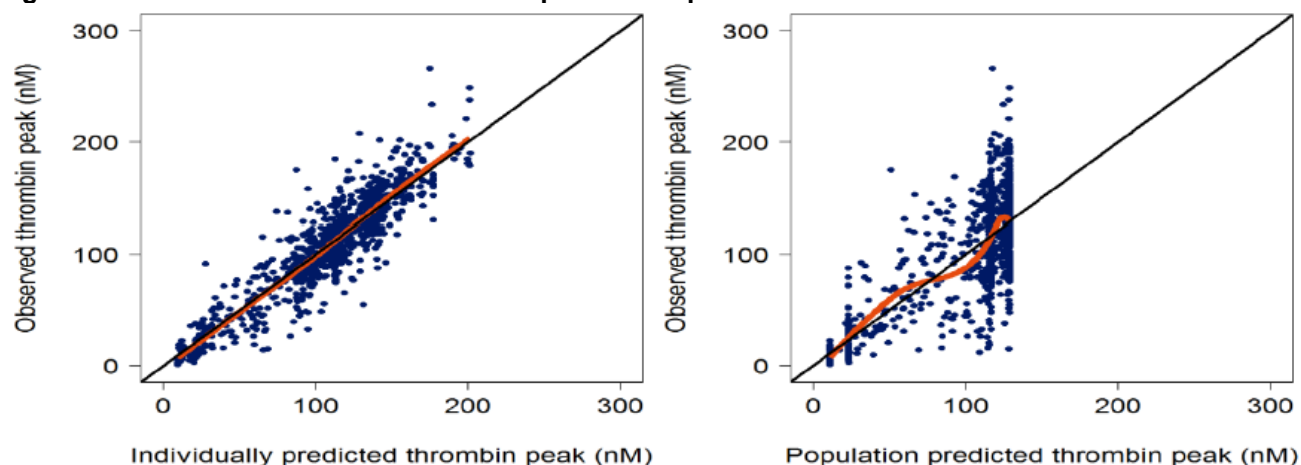
Rate of successful minimization for bootstrap = 991/1000 samples

Source: Population PK Study Report Modeling Report – Phase 3a, Table 10-14.

Abbreviations: E₀, baseline peak thrombin; E_{max}, maximum drug effect; NA, not applicable; SD, standard deviation

The exposure-response model of thrombin peak showed that at the highest exposure quantile, observed thrombin peak appeared lower than predicted by the model ([Figure 59](#)). The model diagnostic plots ([Figure 60](#)) support that the model adequately fit the observed data. However, the observed data were well captured by the model when accounting for variability between subjects (see [Figure 61](#)).

Figure 60. Goodness-of-Fit Plots for the Exposure-Response Thrombin Peak

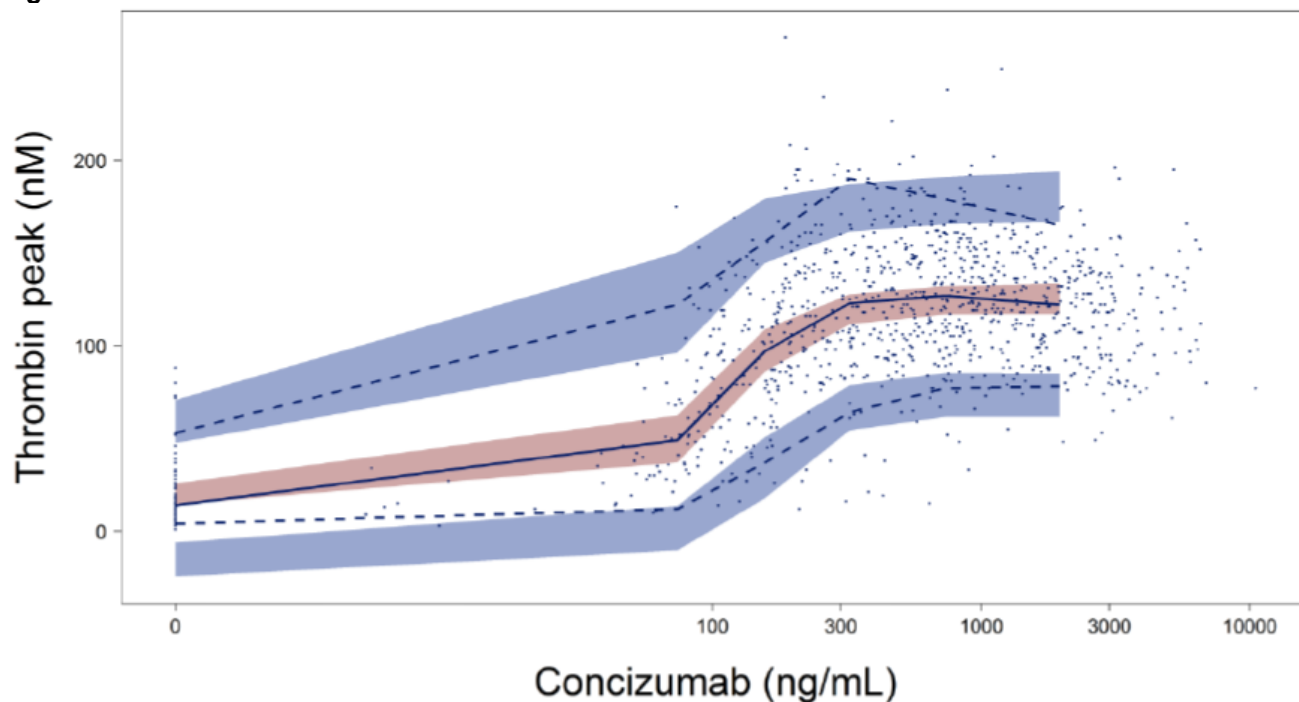


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Data are observed concentrations of thrombin peak versus individual predictions and versus population predictions. Red line indicates loess trend lines of concentration.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-27.

Figure 61. VPC of Thrombin Peak Versus Concizumab Concentration



Visual predictive check of the concizumab concentration-thrombin peak relationship. Data points are time-matched thrombin peak and concizumab concentrations. Solid dark blue line is the median and dashed lines 5th (lower) and 95th (upper) percentiles of the observed data. The corresponding 95% CI for the simulated median (gray) and 5th/95th (blue) percentiles are shown by the coloured ribbons (n=1000) using the final model.

Source: Population PK Study Report Modeling Report – Phase 3a, Figure 10-26.

Abbreviations: CI, confidence interval; n, number of subjects; VPC, visual predictive check

Reviewer's Comments: The Applicant's exposure response model for bleeding rate, free TFPI, and thrombin peak appears acceptable with an adequate fit of the data as evident. The exposure-response analyses showed that the concizumab dosing regimen maintains plasma concentrations at the plateau of effect, in terms of reducing bleeding rate and free TFPI, and increasing peak thrombin in the thrombin generation assay.

Overall, exposure-response analyses support the proposed dosing regimen of concizumab.

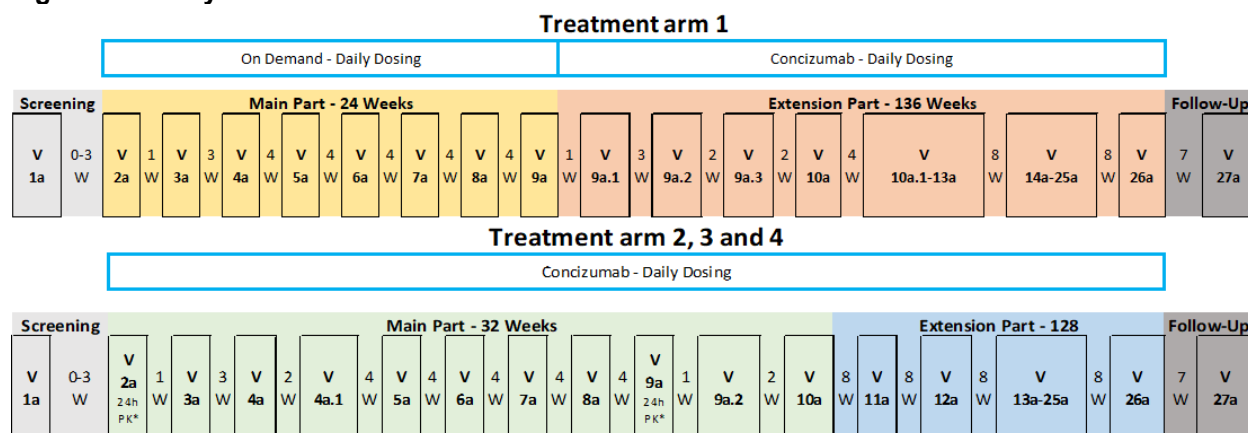
14.6. Pharmacogenetics

Not applicable.

15. Study/Trial Design

Study 4311

Figure 62. Study 4311 Visit Schedule



Source: Applicant's figure Protocol 4311.

^aFor patients who had a 24-hour PK/PD profile measured at visit 2 prior to the treatment pause, only pre-dose (i.e., prior to loading dose) and 24-hour post-dose samples should be taken at visit 2a

Abbreviations: PD, pharmacodynamics; PK, pharmacokinetics; V, visit; W, week

Table 119. Study Schedule of Events

Treatment arm 1	Main Part										Extension Part																				Follow-up						
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a			
Treatment arm 2, 3 and 4	Main Part														Extension Part																				Follow-up		
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a			
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167			
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			
SUBJECT RELATED INFORMATION AND ASSESSMENTS																																					
Informed Consent	X ^d	X ^e								X ^f																											
In/exclusion Criteria	X	X																																			
Demography	X																																				
Concomitant medication	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			

Treatment arm 1	Main Part										Extension Part																				Follow-up							
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a				
Treatment arm 2, 3 and 4	Main Part													Extension Part																				Follow-up				
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a				
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167				
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3				
Concomitant illness	X																																					
Medical history	X																																					
Details of Haemophilia	X																																					
Haemophilia treatment and bleed history	X																																					
Target Joints	X	X ^h								X ^g																												
Treatment discontinuation criteria		X ⁱ	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Withdrawal criteria		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X					
Randomisation		X ^j																																				
EFFICACY																																						
Bleeding Episode		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Treatment arm 1	Main Part										Extension Part																				Follow-up							
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a				
Treatment arm 2, 3 and 4	Main Part													Extension Part																				Follow-up				
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a				
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167				
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3				
Body Measurements ^k	X	X		X		X	X	X	X	X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X						
Thrombin generation		X ^l	X	X		X	X	X	X	X ^l	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Sport activity		X							X ^g			X ^h																					X					
Concizumab ELISA ^m		X ^l	X	X ⁿ		X	X	X	X	X ^l	X	X ^a		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Free TFPI		X ^l	X	X		X	X	X	X	X ^l	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
SAFETY																																						
Adverse Event	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Injection Site Reaction		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				
ECG	X																																					
Coagulation Parameters	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Coagulation Factors ^o	X																																					

Treatment arm 1	Main Part										Extension Part																		Follow-up								
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a			
Treatment arm 2, 3 and 4	Main Part													Extension Part																		Follow-up					
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a			
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167			
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			
Haematology	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Biochemistry	X	X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Urinalysis	X																																				
Physical examination	X	X								X ^g				X ^h						X						X							X	X			
Vital signs	X	X	X	X	X ^p	X	X	X	X	X	X	X	X ^p	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Anti-concizumab antibodies ^m	X	X ^h		X ^h		X ^h	X ^h	X ^h	X ^h	X				X ^h		X				X			X			X							X	X			
FVIII/FIX inhibitor analysis	X																																	X			
Total TFPI		X	X	X		X	X	X	X	X	X	X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
OTHER ASSESSMENTS																																					
PRO questionnaires																																					

Treatment arm 1	Main Part										Extension Part																		Follow-up						
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a	
Treatment arm 2, 3 and 4	Main Part														Extension Part																		Follow-up		
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a	
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167	
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	
SF36 V2.0 Health Survey		X		X		X		X		X				X ^h																					
Patient preference questionnaire										X																									
PROMIS Short Form Upper Extremity		X		X		X		X		X				X ^h																					
PROMIS Numeric Rating Scale - Pain Intensity		X		X		X		X		X				X ^h																					
Haemophilia Treatment Experience Measure		X								X				X ^h																					
Haem-A-QoL ^q	X	X ^r		X		X		X		X				X ^h																					

Treatment arm 1	Main Part										Extension Part																		Follow-up									
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a				
Treatment arm 2, 3 and 4	Main Part														Extension Part																		Follow up					
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a				
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167				
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3				
PGI-S on physical functioning		X		X		X		X		X				X ^h																								
PGI-C on physical functioning				X		X		X		X				X ^h																								
TRIAL MATERIAL																																						
Administration of Trial Product (on site)	X									X ^g																												
Dose Adjustment ⁵					X								X																									
Drug Dispensing	X					X		X		X				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X						
Drug Accountability	X					X		X		X				X		X		X		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X				

Treatment arm 1	Main Part										Extension Part																				Follow-up						
Visits (V)	V 1a	V 2a	V 3a ^a	V 4a	NA	V 5a	V 6a	V 7a	V 8a	V 9a	V 9a.1	V 9a.2	V 9a.3	V 10a	V 10a.1	V 11a	V 11a.1	V 12a	V 12a.1	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a			
Treatment arm 2, 3 and 4	Main Part														Extension Part																				Follow-up		
Visits (V)	V 1a	V 2a	V 3a	V 4a	V 4a.1	V 5a	V 6a	V 7a	V 8a	V 9a	NA	V 9a.2	NA	V 10a	NA	V 11a	NA	V 12a	NA	V 13a	V 14a	V 15a	V 16a	V 17a	V 18a	V 19a	V 20a	V 21a	V 22a	V 23a	V 24a	V 25a	V 26a	V 27a			
Timing of Visit (Weeks)	-3	0 ^b	1	4	6 ^c	8	12	16	20	24	25	28	30 ^c	32	36	40	44	48	52	56	64	72	80	88	96	104	112	120	128	136	144	152	160	167			
Visit Window (Days)	±0	±0	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±1	±3	±7 ^c	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3	±3			
REMINDERS																																					
Human biological specimen for storage ^f	X ^u						X			X ^g				X ^h						X							X						X				
actGraph dispensing ^v	X							X ^g		X ^h																											
actiGraph collection ^v		X								X ^g				X ^h																							
Hand out Direction for Use		X ^h								X ^g																											
Hand out patient ID card and patient material	X	X ^f																																			
Hand out eDiary		X																																			
End of Treatment																																		X			
End of Trial																																			X		

Footnote
a) Phone visit is allowed for patients randomised to arm 1 (on-demand patient)
b) Week 0 is the time of trial restart
c) Visit will take place after the concizumab exposure levels are available according to in Section 9.2.2
d) Only patients enrolled after the treatment pause will sign the Informed Consent at visit 1a
e) Only patients enrolled in the trial before the treatment pause and allocated to arm 2, 3 and 4, will re-consent at Visit 2a
f) Only patients enrolled in the trial before the treatment pause and randomised to arm 1, will re-consent at visit 9a
g) Only applicable for arm 1 patients, who are receiving concizumab at Visit 9a
h) Only applicable for patients in arm 2, 3 and 4, who are receiving concizumab at visit 2a
i) Only applicable for patients enrolled in the trial before treatment pause. Site must ensure patients do not violate discontinuation criteria according to Section 8.1 before reinitiating dosing with concizumab
j) Patients randomised to arm 2 before the treatment pause will not be re-randomised at visit 2a
k) Weight only, except at visit 1 where height is measured
l) For patients having concizumab dosing at visit 2a there will be a 24-hour PK session at visit 2a and 9a. Please see details for PK sampling in Section 2.1 . For on-demand patients (arm 1) only the pre-dose sample will be taken
m) Sample is taken pre-dose. Patients must not inject trial medication on this visit day before the sample is taken
n) Concizumab plasma concentration for dose adjustment (visit 4a for arm 2-4 and visit 9a.2 for arm 1) will be analysed using the concizumab ELISA in vitro diagnostic (IVD) device
o) Only one sample to be taken, either factor VIII for HA patients or factor IX for HB patients
p) Only applicable for patients having site visit due to dose-escalation
q) Only for patients above ≥ 17 years old (at visit 1a)
r) Only applicable for patients enrolled in the trial before the treatment pause
s) Site visit must be performed in case of dose escalation. Phone visit is allowed for patients having dose de-escalation or dose unchanged. See section 9.2.2 for further details
t) A separate Informed Consent Form must be signed before any samples are taken. See section 9.7 for further details
u) Whole blood for DNA is only taken at screening
v) See Section 9.2.5 for further details

Source: Applicant's Table Protocol 4311

Abbreviations: DNA, deoxyribonucleic acid; ELISA, enzyme-linked immunoassay; HA, hemophilia A; HB, hemophilia B; IVD, in vitro diagnostic; PK, pharmacokinetics; TFPI, tissue factor pathway inhibitor; V, visit; W, week

16. Efficacy

16.1. Descriptive Results for Bleeding Episodes Related Endpoints

ABRs for the following bleeding episodes related endpoints were also presented as descriptive statistics for each arm in [Table 120](#):

- Treated spontaneous and traumatic bleeding episodes (the primary efficacy endpoint)
- Treated spontaneous bleeding episodes (pre-specified supportive secondary efficacy endpoint not in statistical testing hierarchy)
- Treated spontaneous and traumatic joint bleeding episodes (pre-specified supportive secondary efficacy endpoint not in statistical testing hierarchy)
- Treated spontaneous and traumatic target joint bleeding episodes (pre-specified supportive secondary efficacy endpoint not in statistical testing hierarchy)
- All treated and untreated spontaneous and traumatic bleeding episodes (not a pre-specified efficacy endpoint)

Note that concizumab PPX arm 1 corresponds to the patients randomized to no PPX (arm 1) that started concizumab PPX before the primary analysis cut-off but after having completed the on-demand treatment in the main part.

Table 120. Descriptive Results for Bleeding Episodes Related Endpoints (FAS and OTwoATexIR), Study 4311

Statistic	No PPX	Concizumab PPX					
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4	Total
N in FAS	19	13	33	21	60	114	127
N in FAS and ADS	19	13	33	21	60	114	127
Person years of exposure in ADS	11.6	9.3	24.2	17.9	41.3	83.4	92.8
Weeks of exposure in ADS							
Median	31.1	49.4	40.1	56.0	32.8	40.0	40.0
P25; P75	16.3 ; 43.9	13.3 ; 56.0	32.1 ; 48.3	16.4 ; 56.9	32.1 ; 40.9	32.1 ; 48.4	32.1 ; 55.7
Mean (SD)	31.9 (18.3)	37.5 (21.5)	38.3 (15.6)	44.4 (22.0)	35.9 (13.7)	38.2 (16.2)	38.1 (16.7)
Min; Max	3.9 ; 72.9	3.0 ; 56.6	3.1 ; 56.3	3.6 ; 64.1	2.0 ; 64.4	2.0 ; 64.4	2.0 ; 64.4
Treated spontaneous and traumatic bleeding episodes							
Number of episodes	166	22	59	47	152	258	280
ABR							
Median	9.8	1.9	0.0	0.8	0.0	0.0	0.0
P25; P75	6.5 ; 20.2	0.0 ; 3.9	0.0 ; 3.3	0.0 ; 3.3	0.0 ; 3.6	0.0 ; 3.3	0.0 ; 3.6
Mean (SD)	18.4 (24.7)	2.1 (1.9)	3.8 (11.7)	2.1 (3.3)	3.2 (7.8)	3.2 (8.5)	3.1 (8.1)
Min; Max	0.0 ; 94.7	0.0 ; 4.7	0.0 ; 66.4	0.0 ; 13.2	0.0 ; 47.5	0.0 ; 66.4	0.0 ; 66.4
Treated spontaneous bleeding episodes							
Number of episodes	123	10	40	19	112	171	181
ABR							
Median	8.4	0.0	0.0	0.0	0.0	0.0	0.0
P25; P75	3.9 ; 14.3	0.0 ; 1.9	0.0 ; 1.3	0.0 ; 1.6	0.0 ; 1.9	0.0 ; 1.6	0.0 ; 1.6
Mean (SD)	13.3 (16.3)	1.0 (1.2)	3.2 (11.7)	0.9 (1.5)	2.4 (6.4)	2.3 (7.8)	2.2 (7.4)
Min; Max	0.0 ; 58.2	0.0 ; 3.9	0.0 ; 66.4	0.0 ; 4.7	0.0 ; 34.5	0.0 ; 66.4	0.0 ; 66.4
Treated spontaneous and traumatic joint bleeding episodes							
Number of episodes	124	18	47	23	116	186	204
ABR							
Median	6.5	1.1	0.0	0.0	0.0	0.0	0.0
P25; P75	3.2 ; 13.1	0.0 ; 2.8	0.0 ; 2.6	0.0 ; 1.8	0.0 ; 2.6	0.0 ; 2.5	0.0 ; 2.5
Mean (SD)	14.9 (22.5)	1.5 (1.7)	3.4 (11.6)	1.1 (1.7)	2.4 (6.2)	2.4 (7.7)	2.3 (7.3)
Min; Max	0.0 ; 81.2	0.0 ; 4.7	0.0 ; 66.4	0.0 ; 5.7	0.0 ; 33.9	0.0 ; 66.4	0.0 ; 66.4
Treated spontaneous and traumatic target joint bleeding episodes							
Number of episodes	28	1	12	3	60	75	76
ABR							

Statistic	No PPX	Concizumab PPX					
	Arm 1	Arm 1	Arm 2	Arm 3	Arm 4	Arms 2-4	Total
Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
P25; P75	0.0 ; 2.2	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0	0.0 ; 0.0
Mean (SD)	3.7 (11.8)	0.1 (0.3)	1.8 (8.7)	0.1 (0.4)	1.2 (3.7)	1.2 (5.4)	1.1 (5.1)
Min; Max	0.0 ; 51.7	0.0 ; 0.9	0.0 ; 49.8	0.0 ; 1.6	0.0 ; 21.4	0.0 ; 49.8	0.0 ; 49.8
All treated and untreated spontaneous and traumatic bleeding episodes							
Number of episodes	181	23	136	58	209	403	426
ABR							
Median	10.9	1.9	2.6	0.9	2.4	2.2	2.2
P25; P75	6.5 ; 20.2	0.0 ; 3.9	0.0 ; 5.5	0.0 ; 3.7	0.0 ; 5.1	0.0 ; 5.3	0.0 ; 5.0
Mean (SD)	19.4 (24.6)	2.2 (2.0)	7.0 (16.2)	2.6 (3.4)	4.5 (8.0)	4.8 (10.6)	4.6 (10.1)
Min; Max	0.0 ; 94.7	0.0 ; 5.6	0.0 ; 83.0	0.0 ; 13.2	0.0 ; 47.5	0.0 ; 83.0	0.0 ; 83.0

Source: Study NN7415-4311 Clinical Study Report, Table 14.2.19 (p.296)

Abbreviations: ABR, annualized bleeding rate; ADS, analysis data set; FAS, full analysis set; HAwI: hemophilia A with inhibitors, HBwI: hemophilia B with inhibitors, Max, maximum; Min, minimum; N, number of subjects; OTwoATexIR: On-treatment without ancillary therapy excl. data on initial regimen for subjects exposed to both regimens; P25/P75, the 25th/75th percentile; PPX, Prophylaxis; SD, standard deviation

17. Clinical Safety

None.

18. Clinical Virology

Not applicable.

19. Clinical Microbiology

Not applicable.

20. Mechanism of Action/Drug Resistance

See Section [5.1](#) and Section [1](#) for discussion on mechanism of action.

21. Other Drug Development Considerations

None.

22. Data Integrity–Related Consults (Office of Scientific Investigations, Other Inspections)

A clinical inspection summary was completed by Dr. Anthony Orencia in the Office of Scientific Investigations, final signature date March 2, 2023. Two foreign clinical study sites and the Applicant's site were selected for evaluation as these sites had the highest patient enrollment (Krakow n = 5 patients and Zagreb n = 4 patients) and overall, a low proportion of patients were enrolled in the US (6/118 patients (5.1%)). Enrollment in other countries in the European Union was higher (e.g., Ukraine 10/118 patients (8.5%)), however due to the ongoing war in Ukraine inspections in these countries were not conducted.

Dr. Orencia states in the review regarding the study site of Dr. Joanna Zdziarska/ Site 480 (ul. Mikolaja Kopernika 17, Krakow, Malopolskie, 31-501, Poland) that a total of six study subjects were screened (one subject was a rescreen); five study subjects were enrolled. Three of the five enrolled subjects completed the study. Two subjects who discontinued were transferred to alternative therapies during the study pause. The study was ongoing at the time of the inspection. Regulatory and source documents were reviewed. The audit involved a review of records and procedures related to the clinical study protocol and its amendments; subject selection criteria and consenting; test article controls, including accountability; source data evaluation, including primary efficacy endpoint of bleeding events; adverse event reporting, including assessment of

under-reporting of serious adverse events, and laboratory testing. Source records for all enrolled study subjects were examined and verifiable. Records were noted to be complete, legible, and organized. Study activities were conducted in compliance with the protocol. The primary efficacy endpoint was verifiable. There was no evidence of under-reporting of adverse events (e.g., no lapses in approvals or failure to file required reports) were noted) and no discrepancies were noted. No significant objectionable findings were found during the inspection. A list of inspectional observations (Form FDA 483) was not issued by FDA at the close-out of the inspection.

Dr. Orenca states in his review regarding the study site of Dr. Ana Boban/Site 385 (Kispaticeva 12, University Hospital Centre, Zagreb 10000 HRV, Croatia) that five study subjects were screened; four study subjects were enrolled and randomized. Three subjects discontinued (withdrew from the study). A single subject was still on treatment during the inspection. Ethics committee approvals, study correspondence, drug accountability, facility adequacy, staff qualifications, and monitoring procedures were reviewed. This inspection covered the safety of study subjects along with serious adverse event reporting, protocol deviations, subject eligibility, overall protocol compliance, and the verification of source documentation related to study endpoint criteria. Adverse event and serious adverse reporting appeared adequate and consistent with the study protocol requirements and the case report form reports. The primary efficacy endpoint (bleeding events) was verifiable. There was no evidence of under-reporting of adverse events (e.g., no lapses in approvals or failure to file required reports were noted). No list of inspectional observations (FDA Form 483) was issued by FDA at the close-out of the site inspection.

Dr. Orenca states in his review regarding the study site of Novo Nordisk Inc./Applicant (800 Scudders Mill Rd., Plainsboro, NJ 08536) that the Applicant inspection involved comprehensive onsite review of study monitor selection, site and clinical investigator selection, clinical site monitoring, form FDA 1572s, financial disclosures, safety reporting and handling, data monitoring committee activities, study documents, standard operating procedures, data collection and handling, protocol deviations, and investigational product disposition. Monitoring actions taken for those clinical investigators who did not comply with the investigational plan appeared to be adequate. Procedure documents for Novo Nordisk's review and processing of serious adverse events (SAEs), such as (a) Q040018 Handling Individual Safety Cases in Argus, (b) Q140826 NNI Product Safety GxP Instructions, and (c) Q148963 NNI Electronic Submission of Expedited Safety Reports were assessed during the inspections. FDA's inspection also assessed safety oversight performed by medical monitors and safety advisors in addition to the data monitoring committee (DMC). No discrepancies were observed for adverse event reporting. At the end of the Applicant inspection, no FDA Form 483 was issued. However, some of the following relevant discussion items at the close out meeting with Applicant deserve mention: (a) Ensure adequate oversight of drug product disposition at clinical sites to track and to evaluate investigative drug products, for example, with temperature deviations, prior to subject dispensing. Sites had no additional checkpoints preventing dispensing of the investigative drug product after initial assignment by interactive web response systems. For example, the audit found that the investigational drug product was administered to Subject (b) (6) (treatment arm not specified) after undergoing a temperature deviation at the clinical site. However, no consequential adverse events were reported following temperature excursions, and (b) Complete query resolution and clarifications between affiliates (that is, affiliate study managers and

monitors) and clinical investigators should be documented allowing for appropriate handling and follow-up. For example, clarification received from a clinical investigator, for the timely reporting of the onset dates of a serious adverse event via e-mail, was not captured in the queries or updated in the electronic data capture data. In general, the Applicant's oversight and monitoring of this clinical study appear to be acceptable.

Dr. Orenca concludes in his review that based on the inspections, the study appears to have been conducted adequately and the study data derived from these clinical investigator sites are considered reliable. The data from Study NN7415-4311 submitted to the Agency for assessment appear acceptable in support of the proposed indication.

Clinical Reviewer Comment: The clinical reviewer agrees with the conclusions in Dr. Orenca's review final signature date March 2, 2023. No additional clinical study site inspections are recommended at this time for Study 4311.

23. Labeling: Key Changes and Considerations

Labeling negotiations were deferred as the application will receive a complete response action.

23.1. Approved Labeling Types

Not applicable.

24. Postmarketing Requirements and Commitments

Postmarketing requirements and commitments are deferred due to complete response action.

25. Financial Disclosure

Table 121. Covered Clinical Studies, Study 4311

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 231		
Number of investigators who are Applicant employees (including both full-time and part-time employees): 1 (Reviewer comment: The investigator was reported to be a Non-US principal investigator based on the spouse or dependent child is an employee of the Applicant and was therefore identified as an employee. The impact of 1/231 investigators participating of which 76 were reported to be principal investigators in the study is expected to be minimal because no single study site enrolled > 5% patients.)		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c), and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 0 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator: 0 Applicant of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3): 0		
Is an attachment provided with the reason:	Yes ☒	No ☐ (Request explanation from Applicant)

Abbreviation: FDA, Food and Drug Administration

26. References

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- Wood, JP, PE Ellery, SA Maroney, and AE Mast, 2014, Biology of tissue factor pathway inhibitor, *Blood*, 123(19):2934-2943.

27. Review Team

Table 122. Reviewers of Integrated Assessment

Role	Name(s)
Regulatory project manager	Courtney Hamilton, PharmD
Nonclinical reviewer	Jeffrey Quinn, PhD
Nonclinical team leader	Pedro DelValle, PhD
OCP reviewer(s)	Li, PhD
OCP team leader(s)	Sudharshan Hariharan, PhD
Clinical reviewer	Andrew Dmytrijuk, MD
Clinical team leader	Carrie Diamond, MD
Biometrics reviewer	Xiaoyu Cai, PhD
Biometrics team leader	Yeh-fong Chen, PhD
Cross-disciplinary team leader	Carrie Diamond, MD
Division director (pharm/tox)	
Division director (OCP)	Doanh Tran, PhD
Division director (OB)	Mark Levenson, PhD
Division director (clinical)	Ann Farrell, MD
Office director (or designated signatory authority)	Lisa Yanoff, MD

Abbreviations: OCP, Office of Clinical Pharmacology; OB, Office of Biostatistics

Table 123. Additional Reviewers of Application

Office or Discipline	Name(s)
OPQ	Massod Rahimi
Microbiology	Michael Shanks, Virginia Carroll
OPDP	Melissa Khashei
OSI	Anthony Orenca
OSE/DEPI	Fang Tian, Orestis Panagiotou
OSE/DMEPA	Hina Mehta, Sue Black
OSE/DRISK	Carolyn Tieu, Timothy Bernheimer
Other	Mallika Mundkur, Florencia Wilson, Yan Cai

Abbreviations: OPQ, Office of Pharmaceutical Quality; OPDP, Office of Prescription Drug Promotion; OSI, Office of Scientific Investigations; OSE, Office of Surveillance and Epidemiology; DEPI, Division of Epidemiology; DMEPA, Division of Medication Error Prevention and Analysis; DRISK, Division of Risk Management

27.1. Reviewer Signatures

See next page.

Table 63. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Andrew Dmytrijuk, MD	OCHEN/DNH	1, 2, 3, 6, 7, 21, 22, 24, 25 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	Signature: Andrew Dmytrijuk -S Digitally signed by Andrew Dmytrijuk -S Date: 2023.04.06 06:41:23 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Carrie Diamond, MD	OCHEN/DNH	All Sections. ☒ Authored ☒ Contributed ☒ Approved
Cross-Disciplinary Team Lead	Signature: Carrie E. Diamond -S Digitally signed by Carrie E. Diamond -S Date: 2023.04.06 08:49:54 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Regulatory Project Management	Julie Van der Waag	ORO/DROCHEN	Section 12 ☐ Authored ☐ Contributed ☒ Approved
Chief, Project Management	Signature: Julie C. Van Der Waag -S Digitally signed by Julie C. Van Der Waag -S Date: 2023.04.05 14:30:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Regulatory Project Management	Courtney Hamilton, PharmD	ORO/DROCHEN	Section 12 ☒ Authored ☒ Contributed ☐ Approved
Regulatory Project Manager	Signature: Courtney V. Hamilton -S Digitally signed by Courtney V. Hamilton -S Date: 2023.04.06 08:54:59 -04'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 63. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical	Ann Farrell, MD	OCHEN/DNH	All sections ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Ann T. Farrell -S Digitally signed by Ann T. Farrell -S Date: 2023.04.07 14:41:04 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Jeffrey Quinn, PhD	OND/DPTCHEN	5, 7, 8, 13 ☒ Authored ☒ Contributed ☐ Approved
Primary Reviewer	Signature: Jeffrey A. Quinn -S Digitally signed by Jeffrey A. Quinn -S Date: 2023.04.05 08:34:03 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Pedro DelValle, PhD, FATS	OND/DPTCHEN	5, 7, 8, 13 ☐ Authored ☒ Contributed ☒ Approved
Supervisor	Signature: Pedro L. Del Valle -S Digitally signed by Pedro L. Del Valle -S Date: 2023.04.05 08:40:39 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Pharmacology/Toxicology	Todd Bourcier, PhD	OND/DPTCHEN	5, 7, 8, 13 ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Todd M. Bourcier -S Digitally signed by Todd M. Bourcier -S Date: 2023.04.05 09:09:04 -04'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Continued: Table 63. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Li Li, PhD	OTS/OCP/DCEP	5, 6, 7, 8, 14 ☒ Authored ☐ Contributed ☐ Approved
Reviewer	Signature: Li Li -S Digitally signed by Li Li -S Date: 2023.04.02 11:03:57 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology/Pharmacometrics	Yuzhuo Pan, PhD	OTS/OCP/DPM	5, 6, 7, 8, 14 ☒ Authored ☒ Contributed ☐ Approved
Primary Reviewer	Signature: Yuzhuo Pan -S Digitally signed by Yuzhuo Pan -S Date: 2023.03.31 11:07:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology/Pharmacometrics	Jiang Liu, PhD	OTS/OCP/DPM	5, 6, 7, 8, 14 ☐ Authored ☒ Contributed ☒ Approved
Associate Director	Signature: Jiang Liu -S Digitally signed by Jiang Liu -S Date: 2023.04.02 23:04:49 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Sudharshan Hariharan, PhD	OTS/OCP/DCEP	5, 6, 7, 8, 14 ☐ Authored ☒ Contributed ☒ Approved
Team Leader	Signature: Sudharshan Hariharan -S Digitally signed by Sudharshan Hariharan -S Date: 2023.04.04 11:46:05 -04'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

Table 63. Signatures of Reviewers

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Clinical Pharmacology	Doanh Tran, PhD	OTS/OCP/DCEP	5, 6, 7, 8, 14 ☐ Authored ☐ Contributed ☒ Approved
Deputy Director	Signature: Doanh C. Tran -S Digitally signed by Doanh C. Tran -S Date: 2023.04.02 21:54:11 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Xiaoyu Cai, PhD	OTS/OB/DBIX	6 and 16 ☒ Authored ☒ Contributed ☐ Approved
Reviewer	Signature: Xiaoyu Cai -S Digitally signed by Xiaoyu Cai -S Date: 2023.03.28 13:46:53 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Yeh-Fong Chen, PhD	OTS/OB/DBIX	6 and 16 ☒ Authored ☐ Contributed ☒ Approved
Team Leader	Signature: Yeh Fong Chen -S Digitally signed by Yeh Fong Chen -S Date: 2023.03.28 13:56:09 -04'00'		

Discipline and Title or Role	Reviewer Name	Office/Division	Sections Authored/ Acknowledged/ Approved ¹
Statistical	Yuan Li Shen, PhD	OTS/OB/DBIX	6 and 16 ☐ Authored ☐ Contributed ☒ Approved
Division Director	Signature: Yuan-li Shen -S Digitally signed by Yuan-li Shen -S Date: 2023.04.13 10:24:11 -04'00'		

¹ Include "IA" for authors who contributed to the Interdisciplinary Assessment.
Abbreviations: IA, Interdisciplinary Assessment; ES, Executive Summary

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/s/

CARRIE E DIAMOND
04/24/2023 11:30:19 AM

LISA B YANOFF
04/24/2023 12:09:05 PM