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ADISINSIGHT REPORT

Concizumab: First Approval

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Abstract
Concizumab (Alhemo™), a subcutaneously administered humanised monoclonal IgG4 antibody against tissue factor pathway inhibitor (TFPI), binds to the Kunitz-2 domain of TFPI and prevents TFPI from binding to activated Factor X. Concizumab is being developed by Novo Nordisk for the treatment of hemophilia A and B with and without inhibitors. In March 2023, concizumab was approved in Canada for the treatment of adolescent and adult patients (12 years of age or older) with hemophilia B who have FIX inhibitors and require routine prophylaxis to prevent or reduce the frequency of bleeding episodes. This article summarizes the milestones in the development of concizumab leading to this first approval for the treatment of hemophilia B.

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Concizumab (Alhemo™): Key Points

A humanised monoclonal IgG4 antibody against TFPI that is being developed by Novo Nordisk for the treatment of hemophilia A and B with and without inhibitors

Received its first approval on 10 March 2023 in Canada

Approved for the treatment of adolescent and adult patients (12 years of age or older) with hemophilia B who have FIX inhibitors and require routine prophylaxis to prevent or reduce the frequency of bleeding episodes

1 Introduction

Hemophilia is a rare, X-linked, inherited congenital bleeding disorder caused by mutation in the genes encoding coagulation factor VIII (FVIII) [hemophilia A] or coagulation factor IX (FIX) [hemophilia B], resulting in a deficiency of these coagulation factors. Severe hemophilia (FVIII or FIX < 1 IU/dL) is characterised by frequent, recurrent spontaneous or traumatic bleeding (frequently into joints or soft tissue) that can result in severe arthropathy and/or life-threatening haemorrhage if left untreated [1–4]. The standard of care for patients with hemophilia A or B is lifelong prophylactic replacement therapy with FVIII or FIX concentrates to abolish recurrent joint bleeds and prevention of arthropathy. However, many patients receiving replacement therapy develop anti-FVIII or anti-FIX neutralising antibodies (inhibitors), which reduce the efficacy of FVIII or FIX concentrates and prevent haemostasis. In patients with inhibitors, treatment with bypassing agents [recombinant activated FVII (rFVIIa) and activated prothrombin complex concentrate (aPCC)] is required to achieve haemostasis; however, these agents have a number of limitations when administered as prophylaxis [1–3]. New approaches to the treatment of hemophilia include non-replacement agents that restore thrombin generation by decreasing the function of natural inhibitors that contribute to the downregulation of coagulation, such as antithrombin or tissue factor (TF) pathway inhibitor (TFPI) [2, 4, 5].

Concizumab (Alhemo™), a humanised monoclonal IgG4 antibody against TFPI that binds to the Kunitz-2 domain of TFPI and prevents TFPI from binding to activated Factor X [6], is being developed by Novo Nordisk for the treatment of hemophilia A and B with and without inhibitors [7]. The decrease in TFPI inhibitory activity resulting from concizumab activity allows activated Factor X (FXa), which is produced by the FVIIa/TF complex, to increase thrombin generation and clot formation through the extrinsic coagulation pathway, helping to achieve haemostasis in hemophilia

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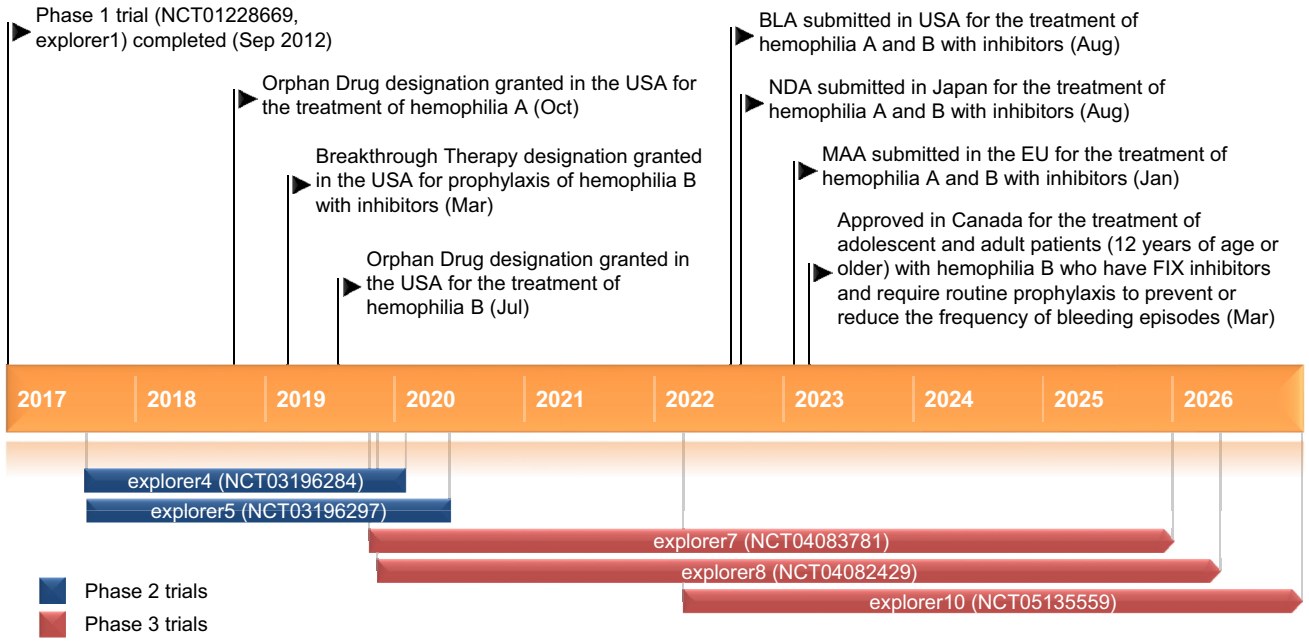

Key milestones in the development of concizumab in hemophilia A and B

[6, 8, 9]. Based on this mechanism of action, concizumab is likely to be effective in hemophilia A and B, regardless of inhibitor status, and does not affect the regulation of coagulation downstream of TFP [8]. In March 2023, concizumab was approved in Canada for the treatment of adolescent and adult patients (12 years of age or older) with hemophilia B who have FIX inhibitors and require routine prophylaxis to prevent or reduce the frequency of bleeding episodes [6, 10]. Concizumab is the first approved anti-TPFI and is the first approved subcutaneous prophylaxis treatment for hemophilia B with inhibitors [10].

Concizumab is administered as a once daily subcutaneous (SC) injection by the patient or caregiver using a single-patient-use prefilled multi-dose pen [6]. Treatment should commence in a non-bleeding state. Prophylactic treatment with bypassing agents should be discontinued before commencing prophylaxis with concizumab (rFVIIa treatment should be discontinued $\geq$ 12 h before and aPCC treatment should be discontinued $\geq$ 48 h before). Serious non-fatal thromboembolic events have been reported in concizumab recipients. These occurred in phase 3 concizumab trials prior to the implementation of the recommended dosage regimen and guidance for breakthrough bleed treatment; three patients with thromboembolic events had underlying risk factors and were exposed to additional haemostatic agents in close to administration of concizumab. If thromboembolic events are suspected during treatment, concizumab should be permanently discontinued. Treatment with concizumab should also be permanently discontinued if allergic-type hypersensitivity reactions occur [6].

The recommended concizumab dosing regimen is a loading dose of 1 mg/kg on day 1, followed by a once daily dose of 0.20 mg/kg on day 2 and subsequent days until individual maintenance dose setting. At 4 weeks after starting treatment, the concizumab pre-dose plasma concentration should be measured by a validated concizumab enzyme-linked immunoassay (ELISA). Once results are available, the individual once daily maintenance dose is set according to the concizumab pre-dose plasma concentration (0.25 mg/kg in those with a plasma concentration < 200 ng/mL, 0.20 mg/kg in those with a plasma concentration 200–4000 ng/mL and 0.15 mg/kg in those with a plasma concentration > 4000 ng/mL). Maintenance dosing should be started no later than 6–8 weeks after initiating treatment. In patients with a plasma concizumab concentration > 4000 ng/mL and who required a dose reduction to 0.15 mg/kg, a second pre-dose concizumab concentration measurement should be considered, ideally taken 8 weeks after initiation of the 0.15 mg/kg dose to ensure steady state is reached. If the plasma concentration remains > 4000 ng/mL, the benefits of concizumab should be evaluated versus the potential for an increased risk of thromboembolic events. If treatment with concizumab has been temporarily discontinued, treatment can be restarted on the same maintenance dose without a new loading dose [6]. If breakthrough bleeds occur, the concizumab dose should not be adjusted and bypassing agents should be used, if required. If additional treatment with bypassing agents is required for mild or moderate breakthrough bleeds, the lowest possible effective dose of these agents should be administered (including a maximum aPCC dose of 100 U/kg within

24 h). For severe bleeds, the dosing scheme for the specific bypassing agent may need to be followed, taking into account the potential for life-threatening thromboembolic events. Concizumab dosage adjustments are not required for minor surgery; it is recommended that concizumab treatment is paused prior to major surgery with treatment resumed on the same maintenance dose 10–14 days after surgery [6]. Concizumab is under regulatory review in the EU, the USA and Japan for the treatment of hemophilia A and B with inhibitors [7, 11].

2 Scientific Summary

2.1 Pharmacodynamics

Concizumab binds to TPFI with high affinity (K_D 25 pM) [12]. Promotion of clot formation by the addition of concizumab was seen in vitro in hemophilia plasma [EC_{50} 0.58 nM in FVIII-deficient plasma (hemophilia A) and EC_{50} 0.91 nM in FIX-deficient plasma (hemophilia B)] and in FVIII-neutralized human whole blood [EC_{50} (maximum thrombus generator) 2.0 nM)] [12]. In a rabbit hemophilia bleeding model, administration of concizumab before and within 5 min of bleeding initiation dose-dependently reduced cuticle bleeding [12, 13].

After administration of SC concizumab 0.25, 0.5 or 0.8 mg/kg once every 4 days in the phase 1b explorer3 trial (NCT02490787) in patients with severe or moderately severe hemophilia A (FVIII ≤ 2 IU/dL) without inhibitors, free TFPI (i.e. plasma TFPI not bound to concizumab) decreased in a dose-dependent manner, residual TFPI activity decreased and peak thrombin generation increased [14]. In patients with severe or moderately severe hemophilia A or B with inhibitors who were treated with SC concizumab in the phase 3 explorer7 trial (NCT04083781), mean free TFPI decreased from a baseline of 88.3–10.7 ng/mL at week 24 and the mean thrombin peak increased to levels seen in normal plasma [6].

In toxicology studies of weekly IV concizumab for up to 26 weeks and daily SC concizumab 0.5, 1 and 9 mg/kg (corresponding to exposures 85, 310 and 4400-fold human AUC_{24}) for up to 52 weeks in cynomolgus monkeys, pharmacology mediated thrombus formation was observed in lung, heart and other organs in the animals at higher doses (≥ 1 mg/kg/day) [6]. In the 52-week study, the NOAEL (no-observed-adverse-effects-level) was seen at the 0.5 mg/kg/day dosage. At SC doses ≥ 3 mg/kg/day (resulting in exposures ≥ 630-fold human AUC_{24}), slight and occasional prolongations in clotting time parameters [activated partial thromboplastin time (aPTT) and prothrombin time (PT)] and/or a decrease in platelet counts were seen. Consistent with the expected pharmacology of concizumab (i.e., coagulation system activation), increases in coagulation markers (D-dimers and thrombin-anti thrombin) were observed 24 h after the first concizumab dose and decreases in fibrinogen were seen after repeat dosing [6].

In clinical trials, there was a positive correlation between concizumab plasma concentrations and D-dimer and prothrombin fragment 1.2 plasma levels. In concizumab recipients in explorer7, increased levels of fibrin D-dimer and prothrombin fragment 1.2 occurred in 5.3% (6/114) and 6.1% (7/114) of patients, respectively [6].

In vitro and ex vivo interaction studies indicate that the effects of concizumab co-administered rFVIIa, aPCC, rFVIII or rFIX were mainly additive, with a synergistic effect accounting for up to 40% of the total observed effect [6, 15, 16]. In vitro, concizumab shows no relevant interference on standard PT and aPTT assays and FVIII or FIX activity measurement using clot and chromogenic assays, or relevant effects on assays for inhibitory antibodies to FVIII or FIX (Bethesda assay) [6].

2.2 Pharmacokinetics

The pharmacokinetics (PK) of concizumab are non-linear. Systemic exposure to concizumab (AUC and C_{max}) increases in a greater than dose proportional manner due to target-mediated drug disposition, which occurs when concizumab binds to endothelial cell-anchored TFPI resulting in elimination of the drug-target complex [6, 17]. Exposure to concizumab did not differ between patients with hemophilia A and B [6]. The time to C_{max} after a single SC dose of concizumab 0.05–3 mg/kg in healthy volunteers or hemophilia patients ranged from 8 to 99 h (4 days). According to population PK modelling, concizumab steady state concentrations were achieved at week 4 after SC administration of a loading dose of 1 mg/kg on day 1, followed by 0.20 mg/kg once daily; bioavailability after SC administration was estimated as 77.7% and estimated V_{ss} was 5.92 L [6]. Mean $C_{max,ss}$ was 1167.1 ng/mL, mean $C_{trough,ss}$ was 665.4 ng/mL and the mean C_{max}/C_{trough} ratio was 2.2 during the 24 h dosing interval at week 24 in patients with hemophilia A or B who were receiving maintenance doses (0.15, 0.20 or 0.25 mg/kg) of concizumab ($n = 99$) in explorer7. Linear and non-linear pathways contribute to concizumab elimination; due to non-linear elimination, the half-life is dependent on the concizumab concentration. After a single SC dose of concizumab 0.25–3 mg/kg in healthy volunteers or hemophilia patients, $t_{1/2}$ ranged from 39 h (1.6 days) to 195 h (8.1 days). Based on a population PK analysis, linear CL after multiple SC doses of concizumab was ≈ 0.192 L/day (0.008 L/h), and the estimated $t_{1/2}$ at $C_{trough,ss}$ was ≈ 38 h [6].

Features and properties of concizumab

Alternative names	Alhemo; Anti-TFPI monoclonal antibody; mAb-2021; NN-7415; NNC-0172-0000-2021; NNC-0172-2021
Class	Antihemorrhagics; Monoclonal antibodies
Mechanism of action	Anti-TFPI antibody; prevents TFPI binding to FXa
Route of administration	Subcutaneous
Pharmacodynamics	Binds to TPFI with high affinity (K_D 25 pM); ↓ mean free TFPI from baseline of 88.3 ng/mL to 10.7 ng/mL and ↑ thrombin levels to normal range at week 24 in hemophilia A and B patients Administration before and within 5 min of bleeding initiation dose-dependently reduced cuticle bleeding in a rabbit hemophilia bleeding model No clinically significant interactions in vitro in combination with rFVIIa, aPCC, rFVIII or rFIX
Pharmacokinetics	$C_{max,ss}$ 1167.1 ng/mL, $C_{trough,ss}$ 665.4 ng/mL, C_{max}/C_{trough} ratio 2.2, F 77.7%, V_{ss} 5.92 L, linear CL ≈ 0.192 L/day (0.008 L/h), $t_{1/2}$ at $C_{trough,ss}$ ≈ 38 h
Adverse events	
Most frequent (TEAEs ≥ 5%)	Injection site reactions, arthralgia, URTI, headache, pyrexia
Less common	Thromboembolic events, hypersensitivity
ATC codes	
WHO ATC code	02B-X10 (Concizumab)
EphMRA ATC code	B2D (Blood Coagulation)

2.3 Therapeutic Trials

2.3.1 Phase 3 Trial

Subcutaneous concizumab was effective as prophylaxis in patients aged ≥ 12 years with hemophilia A or B with inhibitors in the phase 3 explorer7 trial (NCT04083781) [6]. Concizumab prophylaxis resulted in an 86% reduction in treated spontaneous and traumatic bleeds compared with no prophylaxis (patients received on-demand treatment with bypassing agents) [18, 19]. The estimated mean annualized bleeding rate (ABR; primary endpoint) in patients randomized to the concizumab prophylaxis arm ($n = 33$) was 1.7 (95% CI 1.01–2.87) compared with 11.8 (95% CI 7.03–19.86) in those randomized to on-demand treatment ($n = 19$) [ABR ratio 0.14 (95% CI 0.07–0.29); $p < 0.001$] [6, 18]. The overall median ABR was 0 in the concizumab arm compared with 9.8 in the on-demand treatment arm and 63.6% of concizumab recipients experienced no treated bleeds compared with 10.5% of those receiving on-demand treatment [18, 19]. Concizumab prophylaxis was effective in reducing ABR compared with on-demand treatment in both hemophilia A and B patients with inhibitors [20].

In explorer7, most patients had severe or moderately severe disease (FVIII or FIX ≤ 2 IU/dL). Of the 133 patients enrolled in the trial, 52 patients (27 with hemophilia A and 25 with hemophilia B) were randomized to receive on-demand therapy with bypassing agents (arm 1) or concizumab prophylaxis (arm 2). A further 81 nonrandomized patients (53 with hemophilia A and 28 with hemophilia B) were enrolled to receive concizumab prophylaxis as part of the overall safety assessment (arms 3 and 4) [6, 18, 20]. Patients randomized to the concizumab arm were initially treated with a 1.0 mg/kg loading dose on day 1 followed by a daily 0.25 mg/kg maintenance dose starting day 2. Due to the occurrence of thromboembolic events associated with concizumab treatment, the study was paused (24 concizumab recipients were temporarily switched to on-demand treatment during the pause) then later resumed with a dosing regimen consisting of a 1 mg/kg loading dose on day 1 followed by a lower daily 0.2 mg/kg maintenance dose starting day 2. At/around week 4 of treatment, the concizumab pre-dose plasma concentration was measured using a validated ELISA. Patients who had a concizumab concentration of 200–4000 ng/mL remained on a daily 0.20 mg/kg maintenance dose; in those with a concizumab concentration < 200 ng/mL the dose was increased to 0.25 mg/kg daily and in those with a concizumab concentration > 4000 ng/mL, the dose was decreased to 0.15 mg/kg daily [6, 18, 21]. Of the 97 patients who had a week 4 concizumab plasma concentration in explorer7, 72 patients (74.2%) remained on the 0.2 mg/kg daily dose as maintenance, 24 patients (24.7%) had their dose increased to 0.25 mg/kg once daily, and 1 patient (1.0%) had their dose decreased to 0.15 mg/kg. The concizumab efficacy results are based on data obtained after the study pause. Efficacy was evaluated by comparing the number of

treated spontaneous and traumatic bleeding episodes between treatment arms when all patients in the on-demand arm had completed ≥ 24 weeks' treatment and all in the concizumab prophylaxis arm had completed ≥ 32 weeks' treatment [6].

2.3.2 Phase 2 Trials

SC concizumab prophylaxis resulted in an 78% reduction in treated spontaneous and traumatic bleeds compared with on-demand eptacog alfa treatment in patients aged ≥ 18 years with hemophilia A or B with inhibitors during at least 24 weeks from treatment initiation in the randomized phase 2 explorer4 trial (NCT03196284). The estimated mean ABR in the concizumab prophylaxis arm ($n = 17$) was 4.5 (95% CI 3.2–6.4) compared with 20.4 (95% CI 14.4–29.1) in the on-demand eptacog alfa arm ($n = 9$). The median ABR was 4.5 for concizumab and 19.7 for eptacog alfa. The ABR ratio was 0.22 (95% CI 0.13; 0.36); clinical proof of concept was demonstrated, as the ABR ratio was < 1 [22]. The estimated mean ABR during the main and extension parts of explorer4 at the last concizumab dose level ($n = 25$) was 4.8 (95% CI 3.2–7.2) and the median ABR was 3.6. In on-demand eptacog alfa recipients who switched to concizumab prophylaxis during the extension part of explorer4 ($n = 8$), the estimated mean ABR at the last dose level decreased from 18.6 (95% CI 12.9–26.9) at the time of switch to 4.9 (95% CI 2.2–10.6) [23].

Treatment with concizumab prophylaxis in the phase 2 explorer5 trial (NCT03196297) in patients aged ≥ 18 years with severe hemophilia A without inhibitors ($n = 36$) resulted in an estimated mean ABR of 7.0 (95% CI 4.6–10.7) and a median ABR of 4.5 during at least 24 weeks from treatment initiation. Clinical proof of concept was demonstrated, because the 95% CI for the ABR was < 12 [22]. The estimated mean ABR during the main and extension parts of explorer5 at the last concizumab dose level was 6.4 (95% CI 4.1–9.9) and the median ABR was 3.8 [23].

In explorer4, patients received a loading dose of concizumab 0.5 mg/kg on day 1, followed by daily concizumab 0.15 mg/kg or eptacog alfa. In explorer5, patients did not receive a loading dose, but were treated with daily concizumab 0.15 mg/kg ($n = 36$) [22, 23]. Both trials comprised a main part (at least 24 weeks) in which clinical proof-of-concept was established, and an extension part (52–102 weeks) to evaluate longer term efficacy and safety of prophylactic treatment with concizumab (total of ≥ 76 weeks of treatment); all eptacog alfa recipients in explorer4 were switched to once daily concizumab prophylaxis during the extension part [23]. In both parts of both trials there was potential for concizumab dose escalation to 0.20 mg/kg or 0.25 mg/kg if patients experienced ≥ 3 spontaneous bleeding episodes within the preceding 12 weeks of concizumab treatment [22, 23]. In the main part of explorer4, 15 of 17 patients remained on the concizumab 0.15 mg/kg daily dose and 2 patients had their dose increased to 0.20 mg/kg. 25 patients entered the extension part; of these, 12 patients remained on the concizumab 0.15 mg/kg daily dose, 9 patients had their dose increased to 0.20 mg/kg and 4 patients had their dose increased to 0.25 mg/kg [22, 23]. In the main part of explorer5, 21 of 36 patients remained on the concizumab 0.15 mg/kg daily dose, 7 patients had their dose increased to 0.20 mg/kg and 8 patients had their dose increased to 0.25 mg/kg. In the extension part, 15 patients remained on the concizumab 0.15 mg/kg daily dose, 10 patients had their dose increased to 0.20 mg/kg and 11 patients had their dose increased to 0.25 mg/kg [22, 23].

Key clinical trials of concizumab (Novo Nordisk)

Drug(s)	Indication	Phase	Status	Location(s)	Identifier
Concizumab	Hemophilia A or B with/without inhibitors	3	Recruiting	Global	NCT05135559, explorer10, EudraCT2020-000504-11, jRCT2031220097
Concizumab	Hemophilia A or B without inhibitors	3	Ongoing	Global	NCT04082429, explorer8, EudraCT2018-004891-36, JapicCTI195046
Concizumab	Hemophilia A or B with inhibitors	3	Ongoing	Global	NCT04083781, explorer7, EudraCT2018-004889-34, JapicCTI195045
Concizumab	Hemophilia A without inhibitors	2	Completed	Global	NCT03196297, explorer5, EudraCT2016-000614-29, JapicCTI173682
Concizumab, eptacog alfa	Hemophilia A or B with inhibitors	2	Completed	Global	NCT03196284, explorer4, EudraCT2016-000510-30, JapicCTI173681

2.4 Adverse Events

In the randomized part of the phase 3 explorer7 trial (NCT04083781), adverse events were reported in 60.6% of concizumab prophylaxis recipients and 42.1% of on-demand treatment recipients; serious adverse events were reported in 18.2% and 15.2% of patients, respectively [18]. In the overall safety population ($n = 114$), adverse events and serious adverse events were reported in 63.0% and 11.0% of concizumab prophylaxis recipients [6, 18]. The most frequent treatment-emergent adverse events were injection site reactions [22.8%; the most common were injection site erythema (7.9%) and injection site bruising (3.5%)], arthralgia (11.4%), upper respiratory tract infection (7.0%), pyrexia (5.3%) and headache (5.3%) [6]. The adverse events profile of concizumab in adolescent ($n = 36$) and adult ($n = 78$) patients in explorer7 was similar [6].

In the phase 3 explorer7 and explorer8 (NCT04082429) trials, three patients with thrombotic risk factors who had used concomitant factor-containing treatment on the day of/days preceding the event developed non-fatal thromboembolic events. Treatment was permanently discontinued in these patients and concizumab clinical trials were paused. A risk mitigation plan, including updated breakthrough bleeding management guidance and a modified concizumab dosage regimen, was implemented and clinical trials were restarted [21]. Hypersensitivity reactions were reported in 2.6% of concizumab recipients in clinical trials [6].

In clinical trials, anti-concizumab antibodies developed in 25% of concizumab recipients (47/185 patients) and in 6.5% of concizumab recipients (12/185) neutralizing anti-concizumab antibodies were detected using an in vitro assay, with no apparent clinical effect; in all but one patient with anti-concizumab antibodies, concizumab plasma concentrations were unchanged and there was no increase in bleeding events or other safety concerns [6].

The safety analysis of explorer7 includes adverse events reported in patients receiving concizumab 1.0 mg/kg loading dose on day 1 followed by a daily 0.25 mg/kg maintenance dose starting day 2 (dosage regimen before the clinical trial pause) plus adverse events reported in patients treated with the modified dosing regimen after treatment resumption (concizumab 1 mg/kg loading dose on day 1 followed by a daily 0.2 mg/kg maintenance dose starting day 2) [6].

2.5 Ongoing Clinical Trials

The phase 3 explorer7 (NCT04083781) and explorer8 (NCT04082429) trials of concizumab in male adolescents and adults aged ≥ 12 years with hemophilia A and B with and without inhibitors are ongoing, and the phase 3 explorer10 (NCT05135559) trial in male children aged < 12 years with hemophilia A and B and male patients of any age with hemophilia A and B with and without inhibitors is recruiting.

3 Current Status

Concizumab received its first approval on 10 March 2023 in Canada for the treatment of adolescent and adult patients (12 years of age or older) with hemophilia B who have FIX inhibitors and require routine prophylaxis to prevent or reduce the frequency of bleeding episodes [6, 10].

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Declarations

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Ethics approval, Consent to participate, Consent to publish, Availability of data and material, Code availability Not applicable.

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