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# Phase 3 Trial of Concizumab in Hemophilia with Inhibitors

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## ABSTRACT

### BACKGROUND

Concizumab is an anti–tissue factor pathway inhibitor monoclonal antibody designed to achieve hemostasis in all hemophilia types, with subcutaneous administration. A previous trial of concizumab (explorer4) established proof of concept in patients with hemophilia A or B with inhibitors.

### METHODS

We conducted the explorer7 trial to assess the safety and efficacy of concizumab in patients with hemophilia A or B with inhibitors. Patients were randomly assigned in a 1:2 ratio to receive no prophylaxis for at least 24 weeks (group 1) or concizumab prophylaxis for at least 32 weeks (group 2) or were nonrandomly assigned to receive concizumab prophylaxis for at least 24 weeks (groups 3 and 4). After a treatment pause due to nonfatal thromboembolic events in three patients receiving concizumab, including one from the explorer7 trial, concizumab therapy was restarted with a loading dose of 1.0 mg per kilogram of body weight, followed by 0.2 mg per kilogram daily (potentially adjusted on the basis of concizumab plasma concentration as measured at week 4). The primary end-point analysis compared treated spontaneous and traumatic bleeding episodes in group 1 and group 2. Safety, patient-reported outcomes, and pharmacokinetics and pharmacodynamics were also assessed.

### RESULTS

Of 133 enrolled patients, 19 were randomly assigned to group 1 and 33 to group 2; the remaining 81 were assigned to groups 3 and 4. The estimated mean annualized bleeding rate in group 1 was 11.8 episodes (95% confidence interval [CI], 7.0 to 19.9), as compared with 1.7 episodes (95% CI, 1.0 to 2.9) in group 2 (rate ratio, 0.14 [95% CI, 0.07 to 0.29]; P<0.001). The overall median annualized bleeding rate for patients receiving concizumab (groups 2, 3, and 4) was 0 episodes. No thromboembolic events were reported after concizumab therapy was restarted. The plasma concentrations of concizumab remained stable over time.

### CONCLUSIONS

Among patients with hemophilia A or B with inhibitors, the annualized bleeding rate was lower with concizumab prophylaxis than with no prophylaxis. (Funded by Novo Nordisk; explorer7 ClinicalTrials.gov number, NCT04083781.)

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*A list of the explorer7 investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Current guidelines for treatment of hemophilia recommend prophylaxis for all severe bleeding phenotypes to prevent arthropathy and improve quality of life.[1] Patients with hemophilia A or B can be treated with intravenous factor VIII or IX concentrates, respectively, including extended half-life products.

Repeated venipuncture is not always feasible, especially in children, and a central venous access device is often required. Treatment burden is further increased by potential complications related to the central venous access device (e.g., infections and thrombosis related to the device).[2,3] The development of inhibitors (neutralizing antibodies to factor-replacement products) may limit the effectiveness of factor-replacement therapies, thereby increasing disease burden.[4,5] Despite the growing availability of non–factor-replacement therapies, treatment for breakthrough bleeding with bypassing agents (e.g., recombinant activated factor VII or activated prothrombin complex concentrate) may be needed in patients with inhibitors that could further increase the difficulty and complexity of treatment.[6] Overall, these features may negatively affect treatment adherence and outcomes.[7]

To address these issues, research has focused on non–factor-replacement therapies that can either promote coagulation independently of factor VIII and factor IX, such as the factor VIII–mimetic emicizumab (approved for subcutaneous prophylaxis in hemophilia A with or without inhibitors), or inhibit anticoagulant pathways.[8,9] Subcutaneous prophylaxis, as compared with intravenous bypassing agents, may reduce treatment burden in patients with inhibitors. Guidelines from the World Federation on Hemophilia recommend emicizumab prophylaxis over bypassing agents for patients with hemophilia A and persistent inhibitors in whom induction of immune tolerance had failed or was never attempted.[1] However, bypassing agents may be needed to treat breakthrough bleeding episodes in patients with hemophilia A with inhibitors, even if they are receiving emicizumab prophylaxis.

For patients with hemophilia B with inhibitors, no effective prophylactic treatments or easily administered subcutaneous therapies are available. Success rates with induction of immune tolerance among patients with hemophilia B with inhibitors remain low, and such therapy has potentially severe consequences, including nephrotic syndrome.[1] Overall, these factors result in poor outcomes for patients with hemophilia B with inhibitors.[1]

Concizumab is a monoclonal antibody to tissue factor pathway inhibitor (TFPI) that is under investigation for subcutaneous prophylaxis in all hemophilia subtypes.[10] Concizumab inhibits TFPI activity through high-affinity binding to the TFPI Kunitz-2 domain, blocking TFPI binding to active factor X (and thereby preventing its inhibition) and maintaining factor Xa production by the tissue factor–factor VIIa complex. These activities normalize thrombin generation and result in a reduction in the number of bleeding episodes.[10-12]

Results from the phase 2 explorer4 trial of concizumab established proof of concept in patients with hemophilia A or B with inhibitors.[13,14] Phase 3 trials of concizumab in patients with hemophilia are ongoing, although they were temporarily paused in March 2020 owing to nonfatal thromboembolic events in three patients receiving concizumab. The trials resumed after thorough investigation of all available data and subsequent implementation of risk-mitigation measures.[15,16] We report here the findings of the phase 3 explorer7 trial, which aimed to confirm the efficacy and safety of daily subcutaneous concizumab prophylaxis in patients with hemophilia A or B with inhibitors.

## METHODS

### TRIAL DESIGN

The explorer7 trial is a prospective, multicenter, open-label, phase 3a trial that compared concizumab prophylaxis with no prophylaxis. The trial included two randomization groups (groups 1 and 2) and two nonrandomization groups (groups 3 and 4) (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Patients with hemophilia A or B with inhibitors (of any severity) were included if they were at least 12 years of age when providing written informed consent (which was obtained for all trial patients), had a body weight of at least 25 kg at screening, and had previously received a prescription of or had been treated with bypassing agents in the 24 weeks before screening (if not being transferred from the explorer4 trial). Exclusion criteria are provided in the Supplementary Methods section in the Supplementary Appendix.

Patients receiving on-demand treatment with



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bypassing agents (including those from the noninterventional explorer6 study [ClinicalTrials.gov number, NCT03741881]) were randomly assigned in a 1:2 ratio to continue to receive on-demand treatment (i.e., no prophylaxis) for 24 weeks or more (group 1) or to receive concizumab prophylaxis for 32 weeks or more (group 2). On completion of the main part of the trial, the patients in group 1 could receive concizumab prophylaxis. Patients who had previously received concizumab in the explorer4 trial were transferred to group 3 and received concizumab prophylaxis. Patients who had received prophylaxis with a bypassing agent and additional patients receiving on-demand treatment were recruited to group 4 and received concizumab prophylaxis.

The sponsor (Novo Nordisk) was responsible for designing the trial, preparing the initial trial protocol and statistical analysis plan, and performing the statistical analyses. Data were collected locally by explorer7 investigators. The authors vouch for the accuracy and completeness of the data and for the adherence of the trial to the protocol, available at NEJM.org. All the authors contributed to the interpretation of the data and to the writing of the manuscript. Medical writing support (funded by Novo Nordisk) was provided by Ashfield MedComms, an Inizio company, under the supervision of the authors. All the authors approved the final version of the manuscript to be submitted for publication. The trial was conducted in accordance with the provisions of the Declaration of Helsinki, applicable Good Clinical Practice guidelines of the International Council for Harmonisation, and applicable laws and regulations. An independent data monitoring committee reviewed and evaluated the data at predefined time points and ad hoc and provided recommendations regarding ongoing trial conduct to protect patient safety.

### END POINTS AND OBJECTIVES

The primary objective was to compare the effect of concizumab prophylaxis with no prophylaxis (i.e., on-demand treatment with bypassing agents) in reducing the number of bleeding episodes in adult and adolescent patients with hemophilia A or B with inhibitors. The primary end point was the number of treated spontaneous and traumatic bleeding episodes, as assessed at the cutoff for the primary analysis, defined as the date when all the patients in group 1 had completed at least 24 weeks of treatment or had withdrawn and all the patients in group 2 had completed at least 32 weeks of treatment or had withdrawn. Additional details of the primary, supplementary, and sensitivity analyses of primary-end-point data are provided in the Supplementary Methods section.

A secondary objective was to compare patient-reported outcomes after concizumab prophylaxis with those after no prophylaxis among adult and adolescent patients with hemophilia A or B with inhibitors. Key secondary end points were the change in bodily pain and physical functioning scores on the 36-Item Short-Form Health Survey, version 2 (SF-36v2), from the start of treatment to week 24. Supportive secondary and exploratory end points, including safety, are listed in the Supplementary Methods.

### TREATMENT PAUSE

Concizumab treatment in the phase 3 explorer7 and explorer8 (NCT04082429) trials was paused by the safety committee of the sponsor, as recommended by the data monitoring committee (see the Supplementary Methods section) in March 2020, owing to nonfatal thromboembolic events in three patients receiving concizumab, including one from the explorer7 trial who had a renal infarct; a subsequent clinical hold was issued by the Food and Drug Administration.[15,16] On-demand treatment in group 1 continued during the pause. Patients in the concizumab prophylaxis groups (groups 2, 3, and 4) switched to alternative therapies at the investigator's discretion.

After a thorough investigation of all available data, risk-mitigation measures were implemented, and trial protocols were updated before the clinical hold was lifted and concizumab treatment resumed. Treatment was restarted with updated guidance for the management of breakthrough bleeding episodes (Table S1) and a new dose regimen. The new concizumab regimen included a loading dose of 1.0 mg per kilogram, followed by an initial daily dose of 0.2 mg per kilogram, with an initial dose-adjustment period of 5 to 8 weeks, during which the dose was increased to 0.25 mg per kilogram (if the concizumab plasma concentration was less than 200 ng per milliliter), decreased to 0.15 mg per kilogram (if the concizumab plasma concentration was greater than 4000 ng per milliliter), or maintained at 0.2 mg per kilogram (see the Supplementary Methods section). Owing to a lack of common risk fac-



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tors among the three patients with thromboembolism, no changes were made to the exclusion criteria.[15,16]

### SAFETY AND OTHER ASSESSMENTS

Information on all adverse events were collected from the time of the first trial-related activity after informed consent had been obtained and throughout the trial. Details of the assays for antibodies to concizumab, as well as the pharmacokinetic and pharmacodynamic assessments, patient-reported outcomes, and physical activity tracker, are provided in the Supplementary Methods section.

### ANALYSIS SETS AND CUTOFFS

The full and safety analysis sets included all the patients who had been exposed to concizumab or randomly assigned to receive on-demand treatment before or after the treatment pause. The concizumab prophylaxis groups in the safety analysis set included the patients who had been exposed to concizumab for at least 1 day, as well as the patients from group 1 who had switched to concizumab prophylaxis during the extension part of the trial (128 to 136 weeks of concizumab treatment after the 24-to-32-week treatment period in the main part of the trial). The primary analysis compared data from the two randomization groups (groups 1 and 2) in the full analysis set that were obtained while the patients were receiving the assigned treatment without ancillary therapy (with ancillary therapy defined as the use of factor-containing products not related to treatment of a bleeding episode, with the exception of therapy used for surgery and medical procedures). Data on the initial concizumab regimen for the patients who had been exposed to concizumab both before and after the treatment pause were excluded; however, these data were included for the few patients who had withdrawn before treatment was restarted.

After the treatment pause had been lifted, concizumab was administered to the patients in groups 2, 3, and 4 during a dose-adjustment period of 5 to 8 weeks, followed by a 24-week maintenance period of concizumab prophylaxis and then by an extension period of 128 to 136 weeks. The cutoff for the primary analysis was therefore defined as the date when all the patients in group 1 (no prophylaxis) had completed at least 24 weeks of treatment or had withdrawn and when all the patients in group 2 (concizumab prophylaxis) had completed at least 32 weeks of treatment, which included the 5-to-8-week dose-adjustment period, or had withdrawn.

### STATISTICAL ANALYSIS

We determined the sample size on the basis of simulations from a negative binomial distribution, assuming a yearly overdispersion (i.e., presence of greater variability relative to the mean) of 13 and an annualized bleeding rate of 18 episodes among patients receiving on-demand treatment with bypassing agents and 3 to 5 episodes among those receiving concizumab. Allowing for dropouts, we estimated that a sample size of 51 patients would allow us to detect superiority with more than 88% power at a 5% significance level, with randomized assignment of patients to concizumab prophylaxis or no prophylaxis in a 2:1 ratio.

The primary analysis was a negative binomial regression that included treatment and the stratification factors (type of hemophilia [hemophilia A or B with inhibitors] and bleeding frequency [<9 or ≥9 bleeding episodes during the 24 weeks before screening]), as well as the logarithm of the length of the observation period, as offset. A significant difference between groups 1 and 2 was considered to indicate superiority.

Sensitivity analyses were also performed. In one analysis, multiple imputation was applied to test the robustness of the findings when the data from the patients in group 2 who had been exposed only to the initial concizumab regimen were used in the primary analysis. Another analysis investigated a potential difference in treatment effects between patients who had undergone randomization before the treatment pause and those who had undergone randomization afterward.

A supplementary analysis was performed to provide an estimator for an estimand in which all the intercurrent events were handled according to a treatment policy strategy. In this analysis, the primary analysis was repeated but included all information collected after the discontinuation of treatment and during periods in which ancillary therapy was used.

In the analyses of primary-end-point and other bleeding-related end-point data, missing data were handled by means of the strategy used to address intercurrent events, as described in the estimand. Missing data for continuous end points



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were handled under a missing-at-random assumption. Additional details of the estimand and all statistical analyses are provided in the Supplementary Methods section.

## RESULTS

### PATIENT CHARACTERISTICS

Of 141 patients who had undergone screening, 133 were enrolled, of whom 80 had hemophilia A with inhibitors and 53 had hemophilia B with inhibitors (Fig. 1). With respect to the primary analysis, 19 patients were randomly assigned to group 1 (no prophylaxis) and 33 patients to group 2 (concizumab prophylaxis). In group 1, a total of 13 patients underwent randomization before the treatment pause (5 of whom did not restart treatment), and 6 underwent randomization after the treatment pause. In group 2, a total of 28 patients underwent randomization before the treatment pause (4 of whom did not restart treatment), and 5 underwent randomization after the treatment pause.

A total of 21 patients from the explorer4 trial were recruited to group 3 to continue concizumab prophylaxis (6 did not restart concizumab prophylaxis after the treatment pause); the remaining 60 patients were included in group 4. The demographic characteristics of the patients are summarized in Table S2, and the representativeness of the trial patients is described in Table S3.

### EFFICACY

The estimated mean annualized rate ratio for treated spontaneous and traumatic bleeding episodes between group 1 and group 2 was 0.14 (95% confidence interval [CI], 0.07 to 0.29), a finding that confirms the superiority of concizumab prophylaxis over no prophylaxis (Table 1). The annualized rates of treated spontaneous, joint, and target joint bleeding episodes were also lower in group 2 than in group 1, with annualized rate ratios that were similar to the annualized rate ratio for the primary end point. The annualized rate of all bleeding episodes (treated and untreated) was also lower in group 2 than in group 1. Similar trends were observed when hemophilia subtypes were analyzed separately (Table S4), although the trial was not powered to show superiority according to hemophilia subtype.

The effect of the treatment pause was assessed in sensitivity analyses. These analyses indicated that the results of the primary analysis were not affected by the treatment pause (Table S5). The effect of permanent discontinuation of concizumab therapy and of the use of ancillary therapy was assessed in a supplementary analysis, which showed that the inclusion of data obtained after these events did not affect the conclusions of the primary analysis. The overall median annualized rate of treated spontaneous and traumatic bleeding episodes among the patients in the concizumab prophylaxis groups (groups 2, 3, and 4) was zero (interquartile range, 0.0 to 3.3) (Table 2). The patients in group 2 were more likely to have no treated bleeding episodes within the first 24 weeks after randomization than the patients in group 1 (Table S6); 21 of 33 patients (64%) in group 2, of whom 17 had completed 24 weeks of the trial and 4 had withdrawn before 24 weeks, had no bleeding episodes, as compared with 2 of 19 patients (11%) in group 1, of whom 1 had completed 24 weeks of the trial and 1 had withdrawn before 24 weeks.

### SAFETY

There were 112 cumulative patient-years of concizumab exposure. The cumulative patient-years of concizumab exposure were calculated on the basis of 127 patients who were exposed to concizumab, including the patients from group 1 who had switched to concizumab prophylaxis after 24 weeks of receiving on-demand treatment only (Table 3). For the concizumab prophylaxis groups 2, 3, and 4, this period included the time from the start of concizumab treatment to 7 weeks into the treatment pause (as specified for the safety follow-up in the protocol), as well as the time from the start of the new concizumab regimen to the cutoff date for the primary analysis of at least 32 weeks of concizumab prophylaxis. There were 90 cumulative patient-years of concizumab exposure that included only the period after treatment had been restarted. Further details of the observation periods in the trial are provided in the Supplementary Methods section.

The most frequently reported adverse events that occurred in patients who received concizumab during the period when patients were considered to be exposed to concizumab treatment included arthralgia (in 10%), injection-site erythema (in 7%), and upper respiratory tract infection (in 6%) (Table 3). A total of 5 serious adverse events occurred in 3 patients (16%) who received



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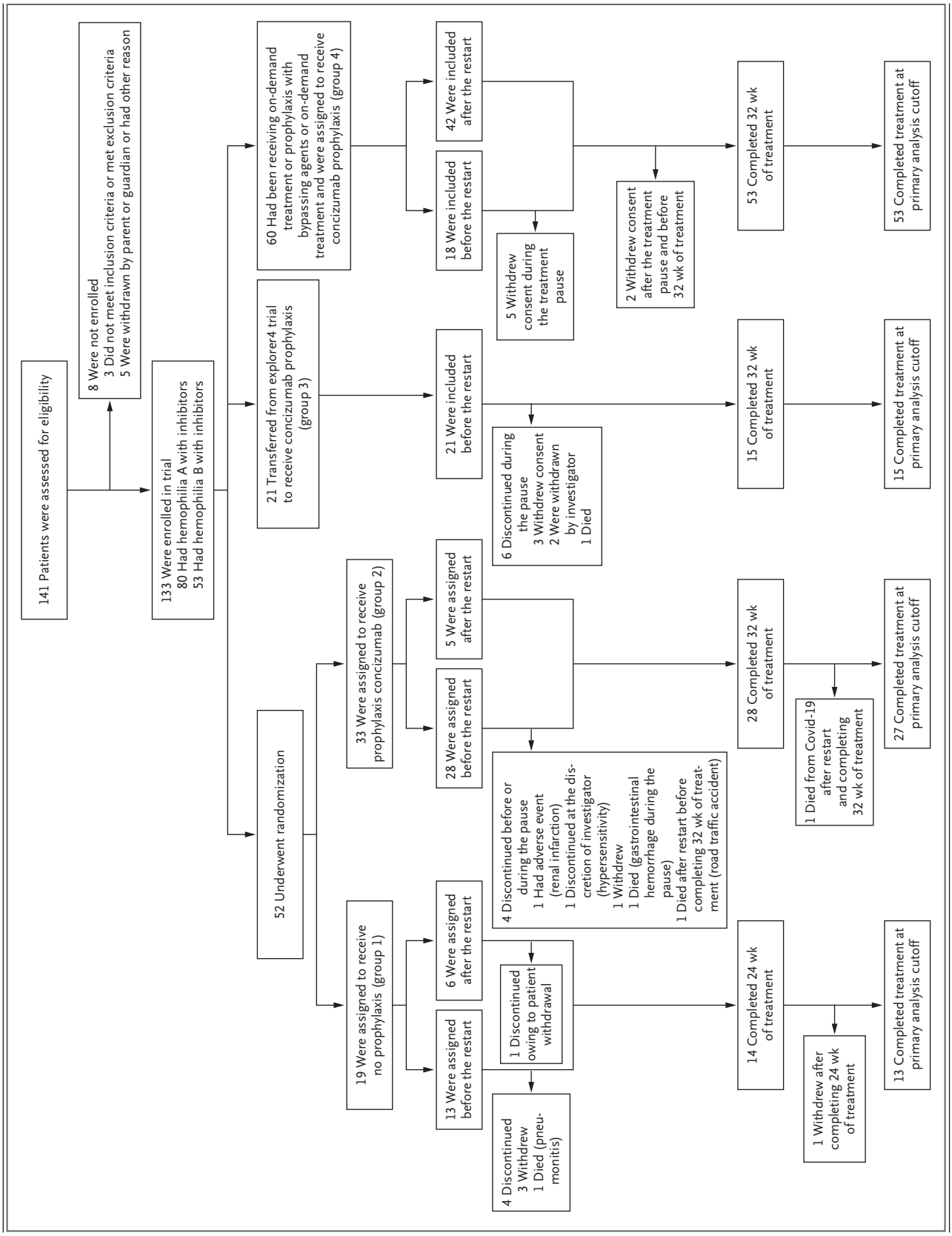




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**Figure 1 (facing page). Screening, Randomization, and Analysis.**

The full and safety analysis sets included the 19 and 33 patients randomly assigned to groups 1 and 2, respectively, and the 21 and 60 patients nonrandomly assigned to groups 3 and 4, respectively. Covid-19 denotes coronavirus disease 2019.

no prophylaxis in group 1, and 18 serious adverse events occurred in 14 patients (11%) who received concizumab in groups 1 through 4. A total of 3 patients had serious adverse events related to bleeding, and 4 patients had serious adverse events related to infections; the remaining events were single events related to other causes. Details of specific events are provided in Table S7.

One fatal case of pneumonitis occurred in a patient in group 1 who had not transferred to receive concizumab. Two patients who had been receiving concizumab died during the treatment pause after more than 7 weeks since the initial regimen was stopped: one had a hematoma in the laterocervical (neck) region and floor of the mouth that was reported together with urinary tract obstruction, retinal vascular occlusion, and vena cava thrombosis, and the other had gastrointestinal bleeding (the patient had a history of gastrointestinal bleeding). After the pause was lifted and treatment restarted, one patient receiving concizumab died in a road traffic accident (a fracture of the humerus and femur was reported). During the extension part of the trial, the death of a patient was attributed to respiratory complications related to coronavirus disease 2019 (no additional procoagulant or anticoagulant treatments were administered); this patient had stopped concizumab treatment 10 days before death and had additional risk factors (obesity and a history of hypertension).

One patient in group 2 had a serious event of renal infarction that occurred before the treatment pause (Table 3).[15,16] This patient was one of three with thromboembolism (an adverse event of special interest) that led to the treatment pause (Table S8).

Two hypersensitivity-type reactions, one of which was severe, were reported in two patients; both recovered and permanently discontinued concizumab in accordance with the protocol (Table 3). A total of 48 injection-site reactions were reported by 26 of 127 patients (20%). Most of the reactions were mild; however, 1 led to an interruption in the trial regimen. With the development of hypersensitivity in this patient, concizumab treatment was discontinued (Table 3).

Antibodies to concizumab were detected at one or more visits in 33 of 127 patients (26%); all these patients had low antibody titers except for 1, who had a medium titer. Despite serum samples from 8 patients also testing positive for

**Table 1. Efficacy Outcomes at the Cutoff for the Primary Analysis.***

| Outcome | Estimated Mean ABR (95% CI) | | ABR Ratio (95% CI) | P Value |
|---|---|---|---|---|
| | Group 1, No Prophylaxis (N=19) | Group 2, Concizumab Prophylaxis (N=33) | | |
| Primary end point: treated spontaneous and traumatic bleeding episodes | 11.8 (7.0–19.9) | 1.7 (1.0–2.9) | 0.14 (0.07–0.29) | <0.001 |
| Treated bleeding episodes | | | | |
| Spontaneous bleeding episodes | 9.4 (5.2–17.0) | 1.3 (0.7–2.3) | 0.14 (0.06–0.30) | NA |
| Joint bleeding episodes | 9.1 (5.1–16.1) | 1.4 (0.8–2.5) | 0.15 (0.07–0.32) | NA |
| Target joint bleeding episodes | 1.1 (0.3–5.2) | 0.1 (0.0–0.9) | 0.12 (0.02–0.84) | NA |
| All treated and untreated bleeding episodes | 13.3 (7.9–22.5) | 4.4 (2.8–6.9) | 0.33 (0.17–0.64) | NA |

* The analysis included data from groups 1 and 2 in the full analysis set that were obtained while the patients were receiving the assigned treatment without ancillary therapy (with ancillary therapy defined as the use of factor-containing products not related to treatment of a bleeding episode, with the exception of therapy used for surgery and medical procedures). Data on the initial concizumab regimen for the patients who had been exposed to concizumab both before and after the treatment pause were excluded; however, these data were included for those who had withdrawn before treatment was restarted. The cutoff for the primary analysis was defined as the date when all the patients in group 1 had completed at least 24 weeks of treatment or had withdrawn and when all the patients in group 2 had completed at least 32 weeks of treatment or had withdrawn. A P value of less than 0.05 was considered to indicate statistical significance. ABR denotes annualized bleeding rate, and NA not applicable.



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**Table 2. Descriptive Statistics for Outcomes in Patients with Hemophilia A or B with Inhibitors at the Cutoff Date for the Primary Analysis.***

| Outcome | No Prophylaxis | Concizumab Prophylaxis | |
|---|---|---|---|
| | Group 1 (N=19) | Group 2 (N=33) | Groups 2, 3, and 4 (N=114) |
| **Treated spontaneous and traumatic bleeding episodes** | | | |
| Median ABR (IQR) | 9.8 (6.5–20.2) | 0.0 (0.0–3.3) | 0.0 (0.0–3.3) |
| Mean ABR | 18.4±24.7 | 3.8±11.7 | 3.2±8.5 |
| **Treated bleeding episodes** | | | |
| Spontaneous bleeding episodes | | | |
| Median ABR (IQR) | 8.4 (3.9–14.3) | 0.0 (0.0–1.3) | 0.0 (0.0–1.6) |
| Mean ABR | 13.3±16.3 | 3.2±11.7 | 2.3±7.8 |
| Joint bleeding episodes | | | |
| Median ABR (IQR) | 6.5 (3.2–13.1) | 0.0 (0.0–2.6) | 0.0 (0.0–2.5) |
| Mean ABR | 14.9±22.5 | 3.4±11.6 | 2.4±7.7 |
| Target joint bleeding episodes | | | |
| Median ABR (IQR) | 0.0 (0.0–2.2) | 0.0 (0.0–0.0) | 0.0 (0.0–0.0) |
| Mean ABR | 3.7±11.8 | 1.8±8.7 | 1.2±5.4 |
| **Treated and untreated bleeding episodes** | | | |
| Median ABR (IQR) | 10.9 (6.5–20.2) | 2.6 (0.0–5.5) | 2.2 (0.0–5.3) |
| Mean ABR | 19.4±24.6 | 7.0±16.2 | 4.8±10.6 |

* Plus–minus values are means ±SD. The analyses included data from groups 1 and 2 in the full analysis set that were collected while the patients were receiving treatment without ancillary therapy. Data on the initial concizumab regimen for the patients who had been exposed to concizumab both before and after the treatment pause were excluded; however, these data were included for those who had withdrawn before treatment was restarted. The cutoff for the primary analysis was defined as the date when all the patients in group 1 had completed at least 24 weeks of treatment or had withdrawn and when all the patients in group 2 had completed at least 32 weeks of treatment or had withdrawn. IQR denotes interquartile range.

in vitro neutralizing antidrug antibodies at one or more visits during the trial, no effect was observed with respect to bleeding patterns, adverse events, and pharmacokinetic or pharmacodynamic measures (data not reported here).

Concizumab plasma concentrations correlated positively with D-dimer levels and levels of prothrombin fragments 1 and 2 (Fig. S2) but had no correlation with levels of fibrinogen or platelets. No changes in antithrombin levels over time were observed (data not reported here).

### PHARMACOKINETICS AND PHARMACODYNAMICS

After the loading dose of 1.0 mg per kilogram on day 1, all the patients receiving concizumab (groups 2, 3, and 4) started with a once-daily dose of 0.2 mg per kilogram from day 2. The concizumab plasma concentration was measured in 97 of 99 concizumab-exposed patients in groups 2, 3, and 4; the remaining 2 patients had withdrawn from the trial before the concentration was measured. Of these 97 patients, 72 (74%) continued with a maintenance dose of 0.2 mg per kilogram. The dose was adjusted in 25 patients (26%) — 24 (25%) received 0.25 mg per kilogram, and 1 (1%) received 0.15 mg per kilogram. The concizumab plasma concentration remained stable over time (Fig. S3A). At week 24, the geometric mean predose (i.e., before the concizumab loading dose of 1.0 mg per kilogram on day 1) trough concizumab plasma concentration among 94 patients was 665.4 ng per milliliter (coefficient of variation, 2.2), and the concizumab plasma concentration ranged from 2.5 to 5300 ng per milliliter.

In groups 2, 3, and 4, the free TFPI plasma concentration decreased from a geometric mean value of 88.3 ng per milliliter at baseline to 10.7 ng



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**Table 3. Overview of Adverse Events.***

| Event | No Prophylaxis | | Concizumab Prophylaxis | | | |
|---|---|---|---|---|---|---|
| | Group 1 (N=19, with 12 PYE) | | Group 2 (N=33, with 32 PYE) | | Groups 1 through 4 (N=127, with 112 PYE) | |
| | *no. of patients (%)* | *no. of events (no. per PYE)* | *no. of patients (%)* | *no. of events (no. per PYE)* | *no. of patients (%)* | *no. of events (no. per PYE)* |
| Any event | 8 (42) | 25 (2.1) | 20 (61) | 60 (1.9) | 80 (63) | 356 (3.2) |
| Serious event | 3 (16) | 5 (0.4) | 6 (18) | 9 (0.3) | 14 (11) | 18 (0.2) |
| Fatal event | 1 (5) | 1 (0.1) | 2 (6) | 4 (0.1) | 2 (2) | 4 (0.0) |
| Drug discontinued | 0 | — | 2 (6) | 2 (0.1) | 4 (3) | 4 (0.0) |
| Thromboembolic event† | | | | | | |
| During the "on-treatment" period | 0 | — | 1 (3) | 1 (0.0) | 1 (1) | 1 (0.0) |
| During the "on-treatment, without data on initial regimen" period‡ | 0 | — | 0 | — | 0 | — |
| Adverse event with additional data collection | | | | | | |
| Hypersensitivity-type reaction | 0 | — | 1 (3) | 1 (0.0) | 2 (2) | 2 (0.0) |
| Injection-site reaction | 0 | — | 6 (18) | 9 (0.3) | 26 (20) | 48 (0.4) |
| Adverse events in >5% of patients receiving concizumab | | | | | | |
| Arthralgia | 0 | — | 2 (6) | 2 (0.1) | 13 (10) | 23 (0.2) |
| Injection-site erythema | 0 | — | 1 (3) | 1 (0.0) | 9 (7) | 13 (0.1) |
| Upper respiratory tract infection | 1 (5) | 1 (0.1) | 2 (6) | 2 (0.1) | 8 (6) | 8 (0.1) |
| Increased levels of prothrombin fragments 1 and 2 | 0 | — | 1 (3) | 1 (0.0) | 7 (6) | 12 (0.1) |
| Covid-19 | 1 (5) | 1 (0.1) | 2 (6) | 2 (0.1) | 6 (5) | 6 (0.1) |
| Pyrexia | 1 (5) | 1 (0.1) | 2 (6) | 2 (0.1) | 6 (5) | 6 (0.1) |

* Data are from the safety analysis set and were collected during the "on treatment" period (i.e., the period during which patients were exposed to on-demand treatment with bypassing agents or concizumab treatment). The data included for "no prophylaxis" were collected from the patients in group 1 from the time of randomization to the start of concizumab treatment in the extension part. The data included for "concizumab prophylaxis" were collected from the patients in groups 2, 3, and 4, as well as from the patients in group 1 who received concizumab prophylaxis in the extension part. The concizumab exposure period was defined as the interval of time from the start of concizumab prophylaxis to 7 weeks into the treatment pause and then from the restart of concizumab treatment to the cutoff date for the primary analysis. Covid-19 denotes coronavirus disease 2019, and PYE patient-years of exposure.
† Thromboembolic events were classified as adverse events of special interest.
‡ "On treatment, without data on initial regimen" was defined as the period during which patients were exposed to on-demand treatment with bypassing agents or concizumab treatment, with the exclusion of the data on the initial concizumab regimen.

per milliliter (predose level) at week 24. After the initial decrease, predose free TFPI levels remained stable over time at all visits after baseline. In group 1, the geometric mean TFPI plasma concentration was 76.0 ng per milliliter at week 24, and the predose levels remained stable over time at levels similar to those at baseline (Fig. S3B).

In groups 2, 3, and 4, predose thrombin peak levels increased from a geometric mean value of 13.5 nmol per liter at baseline to 105.4 nmol per liter at week 24. After the initial increase, predose thrombin peak levels remained stable over time with low variation and within the range of normal plasma at all visits after baseline. In group 1, the geometric mean free thrombin peak concentration was 10.1 nmol per liter at week 24, and predose levels remained stable over time after week 1, at levels similar to those at baseline (Fig. S3C).

### PATIENT-REPORTED OUTCOMES

The results of patient-reported outcomes (Fig. 2) did not differ significantly between group 1 and group 2 with respect to bodily pain and physical functioning scores on the SF-36v2 (key secondary



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end points). Of the 83 patients who had responded to the Hemophilia-Patient Preference Questionnaire, 77 (93%) preferred concizumab to their previous treatment, 5 (6%) had no preference, and 1 (1%) preferred the previous treatment; 16 patients did not respond. The findings from other patient-reported outcome questionnaires (e.g., Hemophilia Quality of Life Questionnaire for Adults and Hemophilia Treatment Experience Measure) are not reported here.

## DISCUSSION

The results of the explorer7 trial confirm the superiority of concizumab over on-demand treatment in significantly reducing the annualized bleeding rate in a large population of patients with hemophilia A or B with inhibitors. Overall, adverse events from concizumab were mainly of low grade, and serious events were rare. Before the treatment pause in the current trial, one serious thromboembolism (renal infarction) occurred, and two patients had thromboembolism in the concurrent explorer8 trial of concizumab in patients with hemophilia without inhibitors.[15,16] After a thorough investigation of all available data, risk-mitigation measures were implemented, including guidance for the management of mild and moderate bleeding (use of the lowest approved dose of the procoagulant agent), and the initial dose regimen of concizumab of 0.25 mg per kilogram was reduced to 0.20 mg per kilogram.

In addition, a dose-adjustment step was included.[13,15,16] The cutoff for concizumab plasma concentration at 200 ng per milliliter was based on phase 2 exposure–response analyses that showed a trend toward lower bleeding rates above this concentration.[15,16] The 4000-ng-per-milliliter cutoff was an additional safety precaution to avoid constant, very high concizumab exposure levels (Supplementary Methods).[15,16] It is important to note that the patient in the explorer7 trial who had a thromboembolism had received concomitant treatment for bleeding with a bypassing agent and also had thrombotic risk factors, including obesity, hypercholesterolemia, and multiple removals and replacements of a central venous access device. The two patients in the explorer8 trial who had thromboembolism had received factor-replacement therapy for bleeding episodes and had thromboembolic risk factors — obesity, lower leg edema, and hypertension in one patient and smoking history, hypertension with a history of occasional use of angiotensin-converting–enzyme inhibitors, increased blood pressure at screening, chronic tooth inflammation followed by extraction, and occasional unreported chest pain for the month preceding the thromboembolism in the other patient.[15,16]

Approximately 25% of patients in phase 2 and

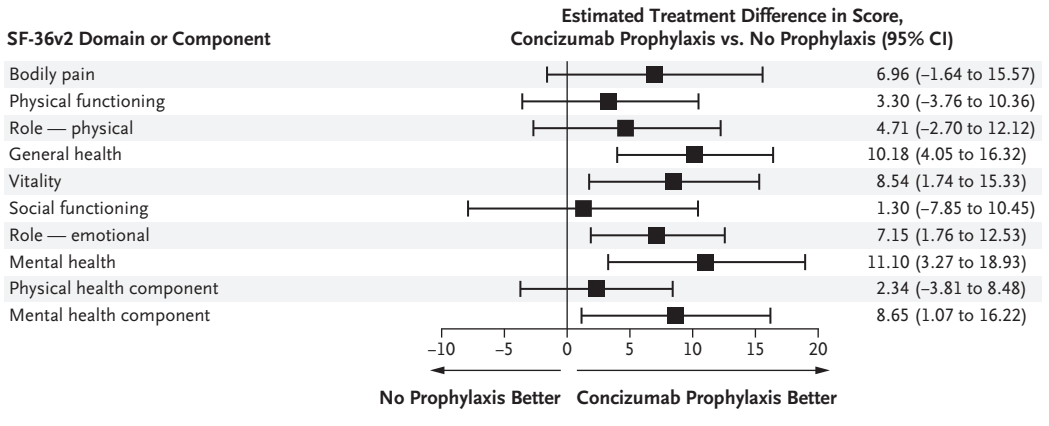


**Figure 2. Change from Baseline in Scores on the 36-Item Short-Form Health Survey, Version 2 (SF-36v2), after 24 Weeks.**

The analysis included data from groups 1 and 2 in the full analysis set that were obtained during the period when the patients were exposed to on-demand treatment with bypassing agents or concizumab treatment, with the exclusion of data on the initial concizumab regimen. A total of 9 patients in group 1 and 23 patients in group 2 contributed data to the analysis.



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3 trials of concizumab had various thrombotic risk factors at baseline, the most common being obesity and hypertension (data on file with Novo Nordisk). Taken together with the lack of common risk factors between the patients with thromboembolism in explorer7 and explorer8, no modifications to exclusion criteria were made. Concizumab works by promoting clotting; as a general issue with procoagulants, the therapeutic index of procoagulants in hemophilia may be narrow, and thromboembolic complications must be considered.

Observed increases in levels of prothrombin fragments 1 and 2 and D-dimers in the patient population may reflect hemostatic potential in patients with hemophilia. Other factors may influence D-dimer levels (e.g., infection or bleeding episodes and patient age), because this is a nonspecific coagulation marker and levels may have been elevated at baseline.[13] D-dimer measurements alone cannot be used to diagnose thromboembolism and should be considered as part of a patient's overall clinical picture when establishing a diagnosis.[17-19]

Formation of antidrug antibodies is a known consequence of monoclonal antibody treatment. Such antibodies do not necessarily prevent therapeutic monoclonal antibody activity,[20] as seen in our results. The antidrug antibodies that were detected in 25% of the patients were generally of low titer with no observed clinical effect. Concizumab has no endogenous counterpart; therefore, even if neutralizing antibodies to concizumab were to develop in a patient, these would be unlikely to influence factor VIII and factor IX activity. The findings for the key secondary end points of change in bodily pain and physical functioning scores on the SF-36v2 from the start of treatment to week 24 were not significant.

Concizumab represents a novel, subcutaneous treatment option in patients with hemophilia A or B with inhibitors that can potentially improve long-term outcomes. The explorer7 trial included 53 patients 12 years of age or older with hemophilia B with inhibitors, who represent 14% of the approximately 370 patients of all ages with clinically confirmed factor IX inhibitors in the annual global survey by the World Federation on Hemophilia in 2020.[21] Trial limitations include the open-label design, any additional unmeasured influence of the treatment pause on the results, and difficulties in collecting sufficient data on patient-reported outcomes, which led to low statistical power and potential bias.

The results of the explorer7 trial show that among patients with hemophilia A or B with inhibitors, the annualized bleeding rate was lower with concizumab prophylaxis than with on-demand treatment.

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## APPENDIX

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