Concizumab (haemophilia B)

Benefit assessment according to §35a SGB V[1]

EXTRACT

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Medical and scientific advice

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Günter Auerswald and one other person.

IQWiG thanks the respondents and the patient organization 'Deutsche Hämophiliegesellschaft e. V.' for participating in the written exchange and for their support. The respondents and the 'Deutsche Hämophiliegesellschaft e. V.' were not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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I List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
aPCC	activated prothrombin complex concentrate
BU	Bethesda unit
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
RCT	randomized controlled trial
rFVIIa	recombinant factor VIIa
SGB	Sozialgesetzbuch (Social Code Book)
SmPC	summary of product characteristics
WFH	World Federation of Hemophilia

I 1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug concizumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the 'company'). The dossier was sent to IQWiG on 29 April 2025.

Research question

The aim of this report is to assess the added benefit of concizumab compared with individualized treatment as the appropriate comparator therapy (ACT) in patients 12 years of age or more with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors.

The research question shown in Table 2 was defined in accordance with the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of concizumab

Therapeutic indication	**ACT**[a]
Routine prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors[b] and of 12 years of age or more	Individualized treatment[c] taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability using: ▪ on-demand treatment or routine prophylaxis with a product with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity)[d] or ▪ on-demand treatment or routine prophylaxis with eptacog alfa[e, f] or ▪ on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX products[g]

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor IX replacement therapy.
c. For the implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account the listed criteria (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
d. It is assumed that the drug FEIBA will continue to be approved for both on-demand treatment and routine prophylaxis in patients with haemophilia B with inhibitors.
e. The use of eptacog alfa as routine prophylaxis as part of individualized treatment is only considered for patients who have a high Bethesda titre (≥ 5 BU) and for whom the use of factor IX-containing products is not possible due to allergic reactions.
f. Due to the possibility of allergic or anaphylactic reactions, routine prophylaxis with products containing factor IX is not an option for some patients. There is no approved treatment option available for this patient group. In accordance with the generally accepted state of medical knowledge, it can therefore be determined that, for this patient population, the off-label use of the above-mentioned treatment option eptacog alfa for routine prophylaxis is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.
g. The scientific and medical associations involved in accordance with §35a(7) sentence 4 SGB V recommend the administration of factor IX concentrate for patients with inhibitor activity below 5 BU. Recombinant activated factor VII and activated prothrombin complex may be considered for patients with inhibitor activity above 5 BU or in cases of failure of factor IX products.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; BU: Bethesda unit; G-BA: Federal Joint Committee; SGB: Social Code Book

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 24 weeks were used to derive the added benefit. This concurred with the company’s inclusion criteria.

Results

Concurring with the company, the partially randomized controlled trial explorer7 was identified.

The explorer7 study provided a potentially relevant study for the benefit assessment of concizumab. However, no data suitable for the benefit assessment were available in the company's dossier. One reason for this was that the available information did not indicate whether the treatments used in the control arm concurred with the ACT. The relevance of the study could therefore not be adequately assessed on the basis of the information available in the dossier. A second reason was that the data presented on the outcomes symptoms, health-related quality of life and side effects were not suitable for the benefit assessment.

Evidence presented by the company – explorer7 study

Study design and patient population

Explorer7 is an open-label, multicentre, partially randomized pivotal study on concizumab consisting of a main phase and an extension phase with 2 randomized and 2 non-randomized arms. The main phase lasted 32 weeks for the concizumab arms and at least 24 weeks for the control arm. The subsequent extension phase lasted up to 128 weeks for the concizumab arms and up to 136 weeks for the control arm. During the main phase of the randomized part of the study, routine prophylaxis with concizumab (intervention arm) was compared with on-demand treatment (control arm).

The study included male adults and adolescents (≥ 12 years) with congenital haemophilia A or B of any disease severity and factor VIII or factor IX inhibitors (≥ 0.6 Bethesda units [BU]) in their medical history. For randomization, patients had to have had at least 6 bleeds in the last 24 weeks (or 12 bleeds in the last 52 weeks) and have received on-demand treatment with a bypassing agent as their treatment strategy. In the randomized part, patients (N = 52) were assigned to the individual arms in a 2:1 ratio and stratified according to haemophilia type (A versus B) and bleeding frequency in the last 24 weeks (< 9 versus ≥ 9 bleeding episodes). This involved a total of 25 patients with haemophilia B.

In the randomized part of the study, patients were assigned to either routine prophylaxis with concizumab (n = 15) or continuation of their on-demand treatment with bypassing agents (n = 10). Routine prophylaxis with concizumab in accordance with the currently valid version of the summary of product characteristics (SmPC) was carried out following resumption of concizumab treatment after a treatment pause for safety reasons (see below). According to the company, 12 of the 15 patients in the intervention arm received an on-label dosage of concizumab. In the control arm, patients were to continue their on-demand treatment with bypassing agents that they were receiving before inclusion in the study.

The randomized part of the study was completed when all patients in the intervention arm had been treated for at least 32 weeks and those in the control arm at least 24 weeks. Subsequently, the patients from the control arm had the opportunity to switch to the extension phase of the study and thus to routine prophylaxis with concizumab. The extension phase of the study is still ongoing and has a planned study duration of up to 128 weeks for patients in the concizumab arm and up to 136 weeks for patients in the control arm.

The primary outcome of the study was the number of treated traumatic and spontaneous bleeding episodes. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and adverse events (AEs).

Concizumab treatment pause in explorer7 and concizumab dose modification

The explorer7 study was initiated in October 2019. Due to non-fatal thromboembolic events during treatment with concizumab (including one patient in explorer7), the study programme and thus also the explorer7 study were paused between March and August 2020. By this time, 11 of the 15 patients had been enrolled in the intervention arm and 7 of the 10 patients in the control arm.

After evaluation of the cases by the company, the dosage of bypassing agents for the treatment of breakthrough bleeding while on concizumab prophylaxis was modified. The concizumab dosage was also changed from an originally fixed body weight-dependent regimen (0.25 mg/kg body weight) to a variable regimen dependent on the concizumab plasma concentration at Week 4 and to be adjusted by Week 8, which corresponded to the ultimately approved dosage according to the SmPC.

The newly introduced dose-finding period extended the treatment duration in the intervention arm from the original 24 weeks to 32 weeks. The treatment duration in the control arm, on the other hand, remained unchanged (24 weeks).

During the treatment pause, patients who had been included in the intervention arm by that point switched to their on-demand treatment prior to study inclusion. In contrast, patients in the control arm were asked to continue as planned, and to complete the visits according to the study design and to report bleeding episodes to the investigators.

The pause to concizumab treatment in explorer7 and the subsequent adjustments to the study design undertaken by the company meant that for a large proportion of the patients in the study, the observation between the arms did not run in parallel. The lack of temporal parallelism between the 2 study arms impaired the internal validity of the study and was taken into account for the risk of bias across outcomes. The differences resulting from the treatment pause in treatment durations and observation periods in the randomized study phase (32 weeks in the intervention arm versus 24 weeks in the comparator arm) could in principle

be addressed by means of adequate analyses if the first 24 weeks of observation are taken into account in both study arms.

Characteristics of the study population

The patients in the potentially relevant subpopulation of explorer7 were on average 23 years old and the proportion of adolescents (12 to 17 years) was 50% in both arms. The majority of patients were Asian (33% in the intervention arm and 40% in the control arm) or white (33% and 30% respectively). All patients in the intervention arm and 9 patients (90%) in the control arm received on-demand treatment prior to study entry.

The median annualized bleeding rate was higher in the control arm (10.9) than in the intervention arm (7.4) under on-demand treatment. The dossier did not contain any information on patient characteristics such as time since factor IX inhibitor diagnosis, number of bleeds in the 24 weeks prior to study entry, or previous immune tolerance induction.

Suitability of the comparator therapy used in explorer7 could not be adequately assessed

ACT defined by the G-BA

The G-BA defined individualized treatment as the ACT, taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability (see also Table 2). Bypassing agents, including human plasma fraction enriched with factor VIII inhibitor bypassing activity, or eptacog alfa, as well as recombinant or human plasma-derived factor IX products, are possible treatment options in the context of individualized treatment, either as part of on-demand treatment or routine prophylaxis. The selection and, where applicable, restriction of treatment options must be justified, according to the G-BA.

The company's argumentation regarding implementation of the ACT

The company considered the on-demand treatment with bypassing agents (eptacog alfa or FEIBA) in the control arm of explorer7 to be an implementation of the ACT specified by the G-BA. It argued that patients with clinically relevant inhibitors receive treatment using bypassing agents in clinical practice, that treatment with factor IX products is only recommended to a limited extent by expert associations, and that sufficient longer-term routine prophylaxis with bypassing agents is not possible due to their short half-lives. In addition, the company stated that a treatment decision depending on the inhibitor titre is not meaningful, as these are generally historical values.

Evaluation of the implementation of the ACT

The patients included in the randomized part of explorer7 were to continue their previous on-demand treatment with a bypassing agent if they were allocated to the control arm. On-demand treatment with factor IX products and routine prophylaxis with factor IX or bypassing agents were not used in the control arm. Thus, in explorer7, concizumab

prophylaxis was compared exclusively with the continuation of on-demand treatment with bypassing agents. The company neither provided a systematic justification regarding which patient-specific criteria were used to determine on-demand treatment with a bypassing agent as the appropriate individualized treatment, nor was this apparent from the information available in the dossier.

The information provided by the company in the dossier shows that 50% of the patients for whom values from the disease history were available had a high inhibitor titre (≥ 5 BU). At baseline, however, the most recent inhibitor titre was available for 11 patients in the intervention arm and for 8 patients in the control arm. Of these, only 1 patient in the intervention arm (9%) and 4 patients in the control arm (50%) had a high inhibitor titre (≥ 5 BU), which would be an argument against the use of factor IX-containing products. However, the remaining patients had an inhibitor titre below 5 BU, for which on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX products may also be considered, as long as no allergic/anaphylactic reactions occur in connection with these. The dossier did not contain any information on factor IX tolerability or whether immune tolerance induction was previously conducted and was successful.

The dossier also showed that 7 patients (58%) in the intervention arm and 6 patients (60%) in the control arm had ≥ 9 bleeds in the last 24 weeks and thus more than 1 bleed per month. Precise data on bleeding frequencies were not recorded prior to entry into the study and were therefore not available. However, it can be assumed that routine prophylaxis should be attempted whenever possible if there is an increased frequency of bleeding. The fact that prophylaxis is entirely possible in these patients was also evident from one of the non-randomized arms of explorer7, which included 20 patients with haemophilia B with inhibitors, 15 of whom (75%) received prophylactic treatment with a bypassing agent before entering the study.

Summary

Based on the available information, it could not be adequately assessed whether the unchanged continuation of on-demand treatment with bypassing agents in the control arm represented an adequate implementation of individualized treatment for all patients in explorer7, taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability. Therefore, based on the available information, explorer7 was not suitable for drawing conclusions on the added benefit of concizumab.

A supplementary presentation of the results of the explorer7 study can be found in the appendix of the full dossier assessment.

Results on added benefit

Since no suitable data were available for the benefit assessment, there is no hint of an added benefit of concizumab in comparison with the ACT; an added benefit is therefore not proven.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of concizumab.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

Table 3: Concizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Routine prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors[b] and of 12 years of age or more	Individualized treatment[c] taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability using: ▪ on-demand treatment or routine prophylaxis with a product with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity)[d] or ▪ on-demand treatment or routine prophylaxis with eptacog alfa[e, f] or ▪ on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX productsg	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor IX replacement therapy.
c. For the implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account the listed criteria (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
d. It is assumed that the drug FEIBA will continue to be approved for both on-demand treatment and routine prophylaxis in patients with haemophilia B with inhibitors.
e. The use of eptacog alfa as routine prophylaxis as part of individualized treatment is only considered for patients who have a high Bethesda titre (≥ 5 BU) and for whom the use of factor IX-containing products is not possible due to allergic reactions.
f. Due to the possibility of allergic or anaphylactic reactions, routine prophylaxis with products containing factor IX is not an option for some patients. There is no approved treatment option available for this patient group. In accordance with the generally accepted state of medical knowledge, it can therefore be determined that, for this patient population, the off-label use of the above-mentioned treatment option eptacog alfa for routine prophylaxis is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.
g. The scientific and medical associations involved in accordance with §35a(7) sentence 4 SGB V recommend the administration of factor IX concentrate for patients with inhibitor activity below 5 BU. Recombinant activated factor VII and activated prothrombin complex may be considered for patients with inhibitor activity above 5 BU or in cases of failure of factor IX products.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; BU: Bethesda unit; G-BA: Federal Joint Committee; SGB: Social Code Book

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of concizumab compared with individualized treatment as the ACT in patients 12 years of age or more with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors.

The research question shown in Table 4 was defined in accordance with the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of concizumab

Therapeutic indication	ACT[a]
Routine prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors[b] and of 12 years of age or more	Individualized treatment[c] taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability using: ▪ on-demand treatment or routine prophylaxis with a product with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity)[d] or ▪ on-demand treatment or routine prophylaxis with eptacog alfa[e, f] or ▪ on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX products[g]

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor IX replacement therapy.
c. For the implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account the listed criteria (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
d. It is assumed that the drug FEIBA will continue to be approved for both on-demand treatment and routine prophylaxis in patients with haemophilia B with inhibitors.
e. The use of eptacog alfa as routine prophylaxis as part of individualized treatment is only considered for patients who have a high Bethesda titre (≥ 5 BU) and for whom the use of factor IX-containing products is not possible due to allergic reactions.
f. Due to the possibility of allergic or anaphylactic reactions, routine prophylaxis with products containing factor IX is not an option for some patients. There is no approved treatment option available for this patient group. In accordance with the generally accepted state of medical knowledge, it can therefore be determined that, for this patient population, the off-label use of the above-mentioned treatment option eptacog alfa for routine prophylaxis is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.
g. The scientific and medical associations involved in accordance with §35a(7) sentence 4 SGB V recommend the administration of factor IX concentrate for patients with inhibitor activity below 5 BU. Recombinant activated factor VII and activated prothrombin complex may be considered for patients with inhibitor activity above 5 BU or in cases of failure of factor IX products.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; BU: Bethesda unit; G-BA: Federal Joint Committee; SGB: Social Code Book

The company followed the G-BA's specification of the ACT.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of added benefit. This concurred with the company's inclusion criteria.

I 3 Information retrieval and study pool

The study pool for the assessment was compiled on the basis of the following information:

Sources used by the company in the dossier:

- Study list on concizumab (status: 19 February 2025)
- Bibliographical literature search on concizumab (last search on 19 February 2025)
- Search of trial registries/trial results databases for studies on concizumab (last search on 19 February 2025)
- Search on the G-BA website for concizumab (last search on 19 February 2025)

To check the completeness of the study pool:

- Search of trial registries for studies on concizumab (last search on 13 May 2025); for search strategies, see I Appendix A of the full dossier assessment

Concurring with the company, the review identified the partially randomized controlled trial explorer7 [3-7].

Due to its randomized component, explorer7 was a potentially relevant study for the benefit assessment of concizumab. However, no data suitable for the benefit assessment were available in the company's dossier. One reason for this was that the available information did not indicate whether the treatments used in the control arm concurred with the ACT. The relevance of the study could therefore not be adequately assessed on the basis of the information available in the dossier. A second reason was that the data presented on the outcomes symptoms, health-related quality of life and side effects were not suitable for the benefit assessment. The following section begins by describing the uncertainties surrounding the ACT in explorer7. In addition, the results of explorer7 are presented in I Appendix B of the full dossier assessment and the unsuitability of the data presented in the outcome categories symptoms, health-related quality of life and side effects is described.

I 3.1 Evidence presented by the company – explorer7 study

The company presented the study explorer7 for the benefit assessment. The study and patient characteristics are described below.

I 3.1.1 Study and patient characteristics

The characteristics of explorer7 are described in Table 5 and Table 6.

Table 5: Characteristics of the study included by the company – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
explorer7	RCT (partially randomized), open-label, parallel	Patients (≥ 12 years) with congenital haemophilia A or B of any severity with documented inhibitor titre[b] (≥ 0.6 BU) and treatment with bypassing agents prescribed or required 24 weeks prior to screening[c] Randomization criteria: ▪ Patients with on-demand treatment and ≥ 6 documented treated bleeds in the last 24 weeks (or ≥ 12 in the last 52 weeks) before screening or ▪ Patients with on-demand treatment from study NN7415-4322 (explorer6)[d]	RCT part: ▪ Routine prophylaxis with concizumab (N = 33) ▪ On-demand treatment with bypassing agents (N = 19) Non-randomized arms[e]: ▪ Routine prophylaxis with concizumab (N = 21)[f] ▪ Routine prophylaxis with concizumab (N = 60)[g] of which the subpopulation of patients with haemophilia B with inhibitors (randomized arms) evaluated by the company: ▪ Routine prophylaxis with concizumab (n = 12) ▪ On-demand treatment with bypassing agents (n = 10)	Screening: 3 weeks Treatment: **Main phase[h]** ▪ concizumab arms: 32 weeks ▪ On-demand treatment with bypassing agents: 24 weeks **Extension phase[i]** ▪ concizumab arms: 128 weeks ▪ On-demand treatment with bypassing agents: 136 weeks Observation: up to a maximum of 7 weeks after the extension phase[j]	74 study centres: Algeria, Australia, Austria, Bulgaria, Canada, Croatia, Czech Republic, Denmark, France, India, Italy, Japan, Malaysia, Mexico, Norway, Poland, Portugal, Russia, Serbia, South Africa, South Korea, Spain, Sweden, Thailand, Turkey, Ukraine, United Kingdom, United States 10/2019–ongoing[k] Data cut-offs: ▪ 27 December 2021 (primary analysis)[l] ▪ 13 June 2022 (Week 56)[m]	Primary: number of treated spontaneous and traumatic bleeds Secondary: morbidity, health-related quality of life, AEs

Table 5: Characteristics of the study included by the company – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 B.
b. An increased inhibitor titre was also determined in the past. This had to be noted in the patient file.
c. Excluding patients who were treated with concizumab in the Phase 2 study NN7415-4310 (explorer4) [8] before the start of the study and who continued to be treated with concizumab in explorer7 without randomization.
d. explorer6 [9] is a prospective, multinational, non-interventional study. Amongst others, patients ≥ 12 years of age with congenital haemophilia A or B of any severity with inhibitors who were receiving on-demand treatment with a bypassing agent and had ≥ 6 treated bleeds in the last 24 weeks or ≥ 12 treated bleeds in the last 52 weeks prior to screening were included.
e. The non-randomized concizumab arms are irrelevant for the assessment and are disregarded in the following tables.
f. Patients ≥ 12 years of age with haemophilia A or B with inhibitors from explorer4 [8].
g. Patients who had received prophylaxis with bypassing agents before the start of the study. In addition, patients who had received on-demand treatment prior to study inclusion and were recruited after the completion of the randomization of arms 1 and 2 could be included in this arm.
h. Treatment with concizumab was interrupted due to 5 non-fatal thromboembolic events in 3 patients in the period from March to August 2020; for details see the following text section.
i. After completion of the main phase of the study, all patients were offered the opportunity to participate in the extension phase and receive prophylaxis with concizumab. Patients in the concizumab arms continued treatment at the maintenance dose from the main phase of the study. Patients from the on-demand treatment arm were switched to the maintenance dose during the first 5 to 8 weeks of the extension phase. The extension phase is not relevant for the assessment and is not shown in the following tables.
j. If the study is discontinued due to withdrawal of consent by the patient before Week 32 in the intervention arm or Week 24 in the control arm, the follow-up examination should be conducted promptly according to the visit planned for Week 32 or 24. In the event of discontinuation of the study after Weeks 32 or 24 respectively, a follow-up examination should be carried out according to the last planned visit for the treatment during the extension phase.
k. Discrepancy between information in Module 4 and Module 5 of the dossier. According to the study design, the end of the study was defined as the date of the last visit of the last patient or 20 June 2024, whichever was earlier. In Module 4 B, however, the company states that the study is expected to end in December 2025.
l. Predefined data cut-off at the end of the main phase at which all patients randomized to the concizumab arm have completed at least 32 weeks of treatment or all patients randomized to the on-demand treatment arm have completed at least 24 weeks of treatment.
m. Predefined data cut-off at which all patients from the randomized concizumab arm and the non-randomized concizumab arms have completed at least 56 weeks of treatment.

AE: adverse event; BU: Bethesda unit; n: subpopulation analysed by the company; N: number of randomized (included) patients; RCT: randomized controlled trial

Table 6: Characteristics of the intervention – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study	Intervention	Comparison
explorer7	Main phase (RCT part): routine prophylaxis with concizumab[a] SC, once daily: ▪ Day 1: 1.0 mg/kg BW ▪ From Day 2: 0.20 mg/kg BW[b] ▪ Week 6 to Week 32 depending on the concizumab plasma concentration: ▫ < 200 ng/mL: 0.25 mg/kg BW ▫ 200–4000 ng/mL: 0.20 mg/kg BW ▫ > 4000 ng/mL: 0.15 mg/kg BW	Main phase (RCT part): on-demand treatment with bypassing agents[c]: ▪ continuation of on-demand treatment with bypassing agents that the patient has already received prior to study inclusion for a period of at least 24 weeks
	Treatment of bleeding episodes – on-demand treatment with bypassing agents ▪ Mild and moderate breakthrough bleeding in the intervention arm was treated with bypassing agents according to protocol (e.g.: rFVIIa and aPCC) using a treatment guideline. ▪ Severe breakthrough bleeding[d] in the intervention arm and severe bleeding[d] in the control arm should be treated on a patient-specific basis as determined by the physician.	
	Allowed prior treatment ▪ On-demand treatment with bypassing agents **Prohibited concomitant treatment** ▪ Heparin, except for sealing of central venous access ports according to local practice ▪ Vitamin K antagonists ▪ Direct oral anticoagulants ▪ Antifibrinolytics[e] ▪ Immune tolerance induction	

a. The dosing regimen for concizumab had to be adjusted during the course of the study following a treatment pause due to safety concerns (see following section). Only the treatment regimen according to the SmPC [10], which patients in the intervention arm underwent after resuming treatment with concizumab, is described below.
b. After 4 weeks, the plasma concentration of concizumab should be determined to establish the maintenance dose from Week 6.
c. The patients included in explorer7 had received on-demand treatment with recombinant factor VIIa (eptacog alfa) or activated aPCC prior to enrolment.
d. The following were categorized as severe bleeds: bleeding in the intracranial or retroperitoneal space as well as internal neck bleeds, muscle bleeds with compartment syndrome or bleeds with a significant decrease in haemoglobin level (< 3 g/dL), for example. In addition, bleeding episodes that required hospitalization or were life-threatening were also considered severe.
e. Except for local/topical application, the administration of single systemic doses was permitted after careful benefit-risk assessment.

aPCC: activated prothrombin complex concentrate; BW: body weight; RCT: randomized controlled trial; rFVIIa: recombinant factor VIIa; SmPC: summary of product characteristics

Study design and patient population

Explorer7 is an open-label, multicentre, partially randomized pivotal study on concizumab consisting of a main phase and an extension phase with 2 randomized and 2 non-randomized

arms. The main phase was 32 weeks for the concizumab arms and at least 24 weeks for the control arm (see also 'Concizumab treatment pause in explorer7 and concizumab dose modification'). The subsequent extension phase ran for up to 128 weeks for the concizumab arms and up to 136 weeks for the control arm. During the main phase of the randomized part of the study, routine prophylaxis with concizumab (intervention arm) was compared with on-demand treatment (control arm).

The study included male adults and adolescents (≥ 12 years) with congenital haemophilia A or B of any disease severity and factor VIII or factor IX inhibitors (≥ 0.6 BU) in their medical history. For randomization, patients had to have had at least 6 bleeds in the last 24 weeks (or 12 bleeds in the last 52 weeks) and either have received on-demand treatment with a bypassing agent or have been prescribed a bypassing agent in the 24 weeks prior to screening. In the randomized part, patients (N = 52) were assigned to the individual arms in a 2:1 ratio and stratified according to haemophilia type (A versus B) and bleeding frequency in the last 24 weeks (< 9 versus ≥ 9 bleeding episodes). This involved a total of 25 patients with haemophilia B. In the non-randomized part of the study, one arm included patients receiving concizumab prophylaxis from the explorer4 study [8], and the other arm included patients receiving prophylaxis or on-demand treatment with bypassing agents. Only the analyses of the subpopulation of haemophilia B patients with factor IX inhibitors from the randomized arms of the study for the main phase are considered below.

In the randomized part of the study, patients were assigned to either routine prophylaxis with concizumab (n = 15) or continuation of their on-demand treatment with bypassing agents (n = 10). Routine prophylaxis with concizumab in accordance with the currently valid version of the SmPC [10] was carried out following resumption of concizumab treatment after a treatment pause for safety reasons (see below). According to the company, 12 of the 15 patients in the intervention arm received an on-label dosage of concizumab. In the control arm, patients were to continue their on-demand treatment with bypassing agents that they were receiving before inclusion in the study. The bypassing agents used were almost exclusively factor VIIa products (eptacog alfa) and activated prothrombin complex concentrate (aPCC) (FEIBA). While using concizumab prophylaxis, mild and moderate breakthrough bleeding was also to be treated with the on-demand treatment previously used by the patient. Severe breakthrough bleeding in the intervention arm and severe bleeding in the control arm were to be treated on a patient-specific basis as determined by the physician. The bypassing agents used for the treatment of bleeding episodes in the control arm and breakthrough bleeding in the intervention arm were neither provided by the company nor were their costs covered by the company.

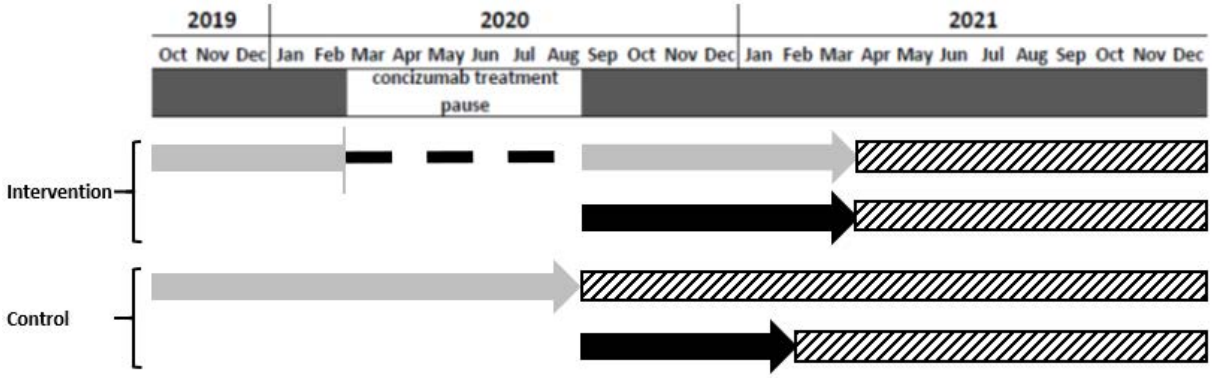
The randomized part of the study was completed when all patients in the intervention arm had been treated for at least 32 weeks and those in the control arm at least 24 weeks. The

initial study design envisaged 24 weeks of treatment in each case. The different treatment durations resulted from a safety-related dose modification in the intervention arm after a pause to the study (see following section). Following the randomized main phase, patients from the control arm had the opportunity to switch to the extension phase of the study and thus to routine prophylaxis with concizumab. The extension phase of the study is still ongoing and has a planned study duration of up to 128 weeks for patients in the concizumab arm and up to 136 weeks for patients in the control arm.

The primary outcome of the study was the number of treated traumatic and spontaneous bleeding episodes. Patient-relevant secondary outcomes were symptoms, health-related quality of life, and AEs.

Concizumab treatment pause in explorer7 and concizumab dose modification

The explorer7 study was initiated in October 2019. Within the concizumab study programme, 5 serious, non-fatal thromboembolic events occurred in 3 patients during treatment with concizumab (including 1 patient in explorer7). As a result, the study programme and thus also explorer7 were paused between March and August 2020 (see Figure 1). By this time, 11 of the 15 patients had been enrolled in the intervention arm and 7 of the 10 patients in the control arm.



	Proportion of patients with main phase prior to restart	Proportion of patients with main phase after restart
Intervention	0%	100%
Control	70%	30%

Figure 1: Schematic representation of the course of explorer7 from initiation to the primary data cut-off

After evaluation of the cases by the company, it was determined that all patients had received concomitant haemostatic treatment immediately before the event or on the day of the event. In addition, concizumab exposure in 2 of the patients was at the upper limit of the exposure range of the concizumab studies conducted to date. As a consequence, the dosage of bypassing agents for the treatment of breakthrough bleeding while on concizumab prophylaxis was modified. The concizumab dosage was also changed from an originally fixed body weight-dependent regimen (0.25 mg/kg body weight) to a variable regimen dependent on the concizumab plasma concentration at Week 4 and to be adjusted by Week 8, which corresponded to the ultimately approved dosage according to the SmPC [10].

The newly introduced dose-finding period extended the treatment duration in the intervention arm from the original 24 weeks to 32 weeks. The treatment duration in the control arm, on the other hand, remained unchanged (24 weeks). In principle, it would have been possible in the study to extend the treatment and observation period of the randomized phase to 32 weeks in the control arm as well. The company did not provide any information on why it only extended the treatment duration in one arm.

During the treatment pause, patients who had been included in the intervention arm by that point switched to their on-demand treatment prior to study inclusion. In contrast, patients in the control arm were asked to continue as planned, and to complete the visits according to the study design and to report bleeding episodes to the investigators. After the treatment pause, a further 4 patients were randomized to the intervention arm and a further 3 to the control arm.

The pause to concizumab treatment in explorer7 and the subsequent adjustments to the study design undertaken by the company meant that for a large proportion of the patients in the study, the observation between the arms did not run in parallel (see Figure 1). At the time of enrolment in the study, 70% of the randomized patients in the control arm had already completed a treatment duration of at least 24 weeks and thus the main phase. In contrast, for all patients in the intervention arm, the main phase of the study with the new concizumab dosage did not begin until after the treatment pause. The lack of temporal parallelism between the 2 study arms impaired the internal validity of the study and was taken into account for the risk of bias across outcomes. The differences resulting from the treatment pause in treatment durations and observation periods in the randomized study phase (32 weeks in the intervention arm versus 24 weeks in the comparator arm) could in principle be addressed by means of adequate analyses if the first 24 weeks of observation are taken into account in both study arms.

The uncertainties described were taken into account for the risk of bias across outcomes and the outcome-specific risk of bias.

Data cut-offs and analyses presented by the company

According to the study design, 3 data cut-offs were planned:

- The primary data cut-off was to take place when all patients in the intervention arm had completed the visit at Week 32 and in the control arm the visit at Week 24, or had withdrawn their informed consent.
- A further data cut-off was planned for when all patients in the intervention arm and the 2 non-randomized concizumab arms had completed the visit at Week 56 or had withdrawn their informed consent.
- The final analysis is planned for after the end of the extension phase of the study.

In its dossier, the company presented analyses on the primary data cut. In the intervention arm, it considered 12 of the 15 randomized patients who were treated with concizumab according to the SmPC [10]. In the control arm, all 10 randomized patients were included in the analyses. No further information was available in the dossier on the 3 patients in the intervention arm not considered by the company, except that they were not treated according to the SmPC. Based on the information available, it was assumed that these patients discontinued participation in the study during the treatment pause at the latest.

Characteristics of the study population

Table 7 shows the characteristics of the relevant subpopulation enrolled in explorer7.

Table 7: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study Characteristic Category	Routine prophylaxis with concizumab (N[a] = 12)	On-demand treatment with bypassing agents (N[a] = 10)
explorer7		
Age [years], mean (SD)	23.3 (10.4)	23.3 (11.1)
Age group [years], n (%)		
12–17	6 (50.0)	5 (50.0)
18–64	6 (50.0)	5 (50.0)
Family origin, n (%)		
Asian	4 (33)	4 (40)
White	4 (33)	3 (30)
Black/African American	1 (8)	1 (10)
Native American/Alaska Native	1 (8)	1 (10)
Unknown	2 (16)	1 (10)

Table 7: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study **Characteristic** **Category**	**Routine prophylaxis with concizumab (N[a] = 12)**	**On-demand treatment with bypassing agents (N[a] = 10)**
Time since factor IX inhibitor diagnosis [months], mean (SD)	ND	ND
Inhibitor titre [BU] at baseline[b], n (%)	N = 11	N = 8
≥ 0.6 and < 5	4 (36)	1 (13)
≥ 5	1 (9)	4 (50)
Median [min; max]	0.3 [0.3; 23.8]	4.5 [0.3; 15.6]
Inhibitor titre [BU] – historical[c], n (%)	N = 11	N = 7
< 0.6	2 (18)	2 (29)
≥ 0.6 and < 5	4 (36)	2 (29)
≥ 5	5 (46)	4 (57)
Bleeds in the last 24 weeks before study entry, n (%)		
< 9	5 (42)	4 (40)
≥ 9	7 (58)	6 (60)
Bleeds in the last 24 weeks before study entry, mean (SD)	ND	ND
Target joints before study entry, n (%)		
No target joint	6 (50)	3 (30)
Target joint (any type)	6 (50)	7 (70)
1 joint	3 (25)	5 (50)
> 1 joint	3 (25)	2 (20)
Type of prior treatment, n (%)	N = 11	N = 9
On-demand treatment[d]	11 (100)	9 (100)
Prophylaxis	1 (9)	0 (0)
Duration of on-demand treatment [months]	N = 8	N = 5
Mean (SD)	48.4 (47.5)	22.0 (32.1)
Median [Q1; Q3]	31.7 [12.0; 83.6]	12.0 [8.2; 27.6]
ABR while on on-demand treatment	N = 8	N = 5
Mean (SD)	13.6 (11.8)	13.6 (7.1)
Median [Q1; Q3]	7.4 [1.0; 14.8]	10.9 [2.0; 17.6]
Previous ITI treatment, n (%)	ND	ND
Treatment discontinuation, n (%)[e]	5 (33)	–[f]
Reasons for treatment discontinuation, n (%):		
AEs	2 (13)	
Decision of the investigator	1 (7)	
Other reasons	2 (13)	

Table 7: Characteristics of the study population and study/treatment discontinuation – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study Characteristic Category	Routine prophylaxis with concizumab (N[a] = 12)	On-demand treatment with bypassing agents (N[a] = 10)
Study discontinuation, n (%)[g]	5 (33)	2 (20)
Reasons for study discontinuation, n (%)		
Withdrawal of the declaration of consent	1 (7)	2 (20)
Decision of the investigator	1 (7)	0 (0)

a. Number of randomized patients who received at least one dose of the respective treatment in accordance with the SmPC. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. In explorer7, the last measurement before the first dose of concizumab in accordance with the SmPC or before randomization was used as the baseline.
c. For inclusion in explorer7, patients had to have at least one documented inhibitor test with a titre ≥ 0.6 BU, which was evaluated by the investigator. Patients may have more than one test result.
d. Eptacog alfa or aPCC were used in the previous treatment.
e. In addition, 11 vs. 8 of the patients completed therapy as planned.
f. Treatment discontinuation in the classic sense is not possible with on-demand treatment. However, it is not known whether the patients changed the drug used as on-demand treatment, e.g. due to AEs.
g. The data also include patients who died during the course of the study (intervention arm: 3 vs. control arm: 0).

ABR: annualized bleeding rate; AE: adverse event; aPCC: activated prothrombin complex concentrate; BU: Bethesda unit; ITI: immune tolerance induction; max: maximum; min: minimum; n: number of patients in category; N: number of randomized patients; ND: no data; Q1: 1st quartile; Q3: 3rd quartile; RCT: randomized controlled trial; SD: standard deviation; SmPC: summary of product characteristics

The patients in the potentially relevant subpopulation of explorer7 were on average 23 years old and the proportion of adolescents (12 to 17 years) was 50% in both arms. The majority of patients were Asian (33% in the intervention arm and 40% in the control arm) or white (33% and 30% respectively). Information on treatment prior to the study was available for 11 of 12 patients in the intervention arm and for 9 of 10 patients in the control arm. All of these patients had received on-demand treatment.

The duration of on-demand treatment with bypassing agents in the intervention arm was a median of 31.7 months, which was notably longer than the median treatment duration of 12 months in the control arm. In contrast, the median annualized bleeding rate for on-demand treatment in the control arm was higher (10.9) than in the intervention arm (7.4), although information on these patient characteristics was only available for 8 patients in the intervention arm and 5 patients in the control arm. No information was available in the dossier on patient characteristics such as time since factor IX inhibitor diagnosis, number of bleedings in the 24 weeks prior to study entry or previous immune tolerance induction.

Suitability of the comparator therapy used in explorer7 could not be adequately assessed

ACT defined by the G-BA

The G-BA defined individualized treatment as the ACT, taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability (see also Table 4). Bypassing agents, including human plasma fraction enriched with factor VIII inhibitor bypassing activity, or eptacog alfa, as well as recombinant or human plasma-derived factor IX products, are possible treatment options in the context of individualized treatment, either as part of on-demand treatment or routine prophylaxis. In its notes on the ACT, the G-BA additionally points out that for implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account the listed criteria (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified, according to the G-BA.

The company's argumentation regarding implementation of the ACT

The company considered the on-demand treatment with bypassing agents (eptacog alfa or FEIBA) in the control arm of explorer7 to be an implementation of the ACT specified by the G-BA. It justified this by stating that patients with clinically relevant inhibitors receive treatment using bypassing agents in clinical practice and that the treatment of patients with haemophilia B and inhibitors with factor IX products is only recommended to a limited extent by expert associations. The company further argued that sufficient long-term routine prophylaxis with bypassing agents such as aPCC or the recombinant activated factor VII eptacog alfa is not possible due to their short half-lives. In addition, the company stated that a treatment decision depending on the inhibitor titre is not meaningful, as these are generally historical values.

Evaluation of the implementation of the ACT

The patients included in the randomized part of explorer7 were to continue their previous on-demand treatment with a bypassing agent if they were allocated to the control arm (see 'Study design and patient population'). On-demand treatment with factor IX products and routine prophylaxis with factor IX or bypassing agents were not used in the control arm. Patients were not assessed for suitability for routine prophylaxis with a bypassing agent or factor IX product, or on-demand treatment with factor IX products, prior to randomization. Thus, in explorer7, concizumab prophylaxis was compared exclusively with the continuation of on-demand treatment with bypassing agents. According to the inclusion criteria, patients receiving on-demand treatment and who had been prescribed a bypassing agent or required such an agent in the 24 weeks prior to screening were to be enrolled in the randomized arms of explorer7. However, the company did not provide a systematic justification regarding which patient-specific criteria were used to determine on-demand treatment with a bypassing agent

as the appropriate individualized treatment at the time of randomization, nor was this apparent from the information available in the dossier.

According to the World Federation of Hemophilia (WFH) 'Guidelines for the Management of Hemophilia' (as of 2020) [11], factor IX products are recommended as on-demand treatment for patients with a low inhibitor titre (< 5 BU). However, on-demand treatment with bypassing agents is indicated for high inhibitor titres (≥ 5 BU). The WFH guideline also recommends that patients with haemophilia and inhibitors should be considered for routine prophylaxis. For prophylaxis with bypassing agents, recombinant activated factor VII products (e.g. eptacog alfa) are recommended, or, if no allergic reactions are present against factor IX products, aPCC such as FEIBA is recommended. Furthermore, prophylaxis with factor IX products is also possible in principle, albeit only to a limited extent, following successful immune tolerance therapy. According to information from the G-BA, routine prophylaxis with eptacog alfa as off-label use may also be considered for patients for whom routine prophylaxis with factor IX products is not an option due to possible allergic/anaphylactic reactions. The inhibitor titre and tolerability of factor IX products are therefore important patient-specific factors that play a role in the treatment decision.

The information provided by the company in the dossier shows that 50% of the patients for whom values from the disease history were available had a high inhibitor titre (≥ 5 BU). At baseline, however, the most recent inhibitor titre was available for 11 patients in the intervention arm and for 8 patients in the control arm. Of these, only 1 patient in the intervention arm (9%) and 4 patients in the control arm (50%) had a high inhibitor titre (≥ 5 BU), which would be an argument against the use of factor IX-containing products. However, the remaining patients had an inhibitor titre below 5 BU, for which on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX products may also be considered, as long as no allergic/anaphylactic reactions occur in connection with these. The dossier did not contain any information on factor IX tolerability or whether immune tolerance induction was previously conducted and was successful.

The dossier also showed that 7 patients (58%) in the intervention arm and 6 patients (60%) in the control arm had ≥ 9 bleeds in the last 24 weeks and thus more than 1 bleed per month. Precise data on bleeding frequencies were not recorded prior to entry into the study and were therefore not available. However, it can be assumed that routine prophylaxis should be attempted whenever possible if there is an increased frequency of bleeding. The company did not consider routine prophylaxis with bypassing agents to be appropriate due to their short half-lives and the resulting need for frequent administration of the agents. However, this does not fundamentally rule out routine prophylaxis with bypassing agents or, in the case of low inhibitor titres and good tolerability, routine prophylaxis with factor IX products. The fact that prophylaxis is entirely possible in these patients was also evident from one of the non-

randomized arms of explorer7, which included 20 patients with haemophilia B with inhibitors, 15 of whom (75%) received prophylactic treatment with a bypassing agent before entering the study.

Summary

Based on the available information, it could not be adequately assessed whether the unchanged continuation of on-demand treatment with bypassing agents in the control arm represented an adequate implementation of individualized treatment for all patients in explorer7, taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability. On the one hand, it could not be ruled out that routine prophylaxis with bypassing agents might have been suitable for the patients in explorer7 on a patient-specific basis. On the other hand, it was not possible to conclusively assess whether on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX products would have been an option for individual patients. Therefore, based on the available information, explorer7 was not suitable for drawing conclusions on the added benefit of concizumab. Furthermore, if further information would suggest that the comparator therapy used was adequate for the patients included, this study could at best be used to draw conclusions for the proportion of patients for whom on-demand treatment with bypassing agents represents an adequate, individualized treatment. A supplementary presentation of the results of explorer7 can be found in I Appendix B of the full dossier assessment.

I 4 Results on added benefit

No suitable data were available for the assessment of the added benefit of concizumab compared with individualized treatment as the ACT in patients 12 years of age or more with haemophilia B and factor IX inhibitors. There is no hint of an added benefit of concizumab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

The result of the assessment of the added benefit of concizumab in comparison with the ACT is summarized in Table 8.

Table 8: Concizumab – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Routine prophylaxis of bleeding in patients with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors[b] and of 12 years of age or more	Individualized treatment[c] taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability using: ▪ on-demand treatment or routine prophylaxis with a product with bypassing activity (human plasma fraction enriched with factor VIII inhibitor bypassing activity)[d] or ▪ on-demand treatment or routine prophylaxis with eptacog alfa[e, f] or ▪ on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX products[g]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor IX replacement therapy.
c. For the implementation of individualized treatment in a study of direct comparison, the investigator is expected to have a selection of several treatment options at their disposal, enabling them to make individualized treatment decisions taking into account the listed criteria (multicomparator study). The selection and, where applicable, restriction of treatment options must be justified. The decision on individualized treatment with regard to the comparator therapy should be made before group allocation (e.g. randomization). This does not apply to necessary therapy adjustments during the course of the study (e.g. due to the onset of symptoms or similar reasons).
d. It is assumed that the drug FEIBA will continue to be approved for both on-demand treatment and routine prophylaxis in patients with haemophilia B with inhibitors.
e. The use of eptacog alfa as routine prophylaxis as part of individualized treatment is only considered for patients who have a high Bethesda titre (≥ 5 BU) and for whom the use of factor IX-containing products is not possible due to allergic reactions.
f. Due to the possibility of allergic or anaphylactic reactions, routine prophylaxis with products containing factor IX is not an option for some patients. There is no approved treatment option available for this patient group. In accordance with the generally accepted state of medical knowledge, it can therefore be determined that, for this patient population, the off-label use of the above-mentioned treatment option eptacog alfa for routine prophylaxis is generally preferable to the drugs currently approved for the therapeutic indication; §6(2), sentence 3, number 3, AM-NutzenV.
g. The scientific and medical associations involved in accordance with §35a(7) sentence 4 SGB V recommend the administration of factor IX concentrate for patients with inhibitor activity below 5 BU. Recombinant activated factor VII and activated prothrombin complex may be considered for patients with inhibitor activity above 5 BU or in cases of failure of factor IX products.

ACT: appropriate comparator therapy; AM-NutzenV: Regulation for Early Benefit Assessment of New Pharmaceuticals; BU: Bethesda unit; G-BA: Federal Joint Committee; SGB: Social Code Book

The assessment described above deviates from that of the company, which derived a hint of a considerable added benefit.

The G-BA decides on the added benefit.

I 6 References for English extract

Please see full dossier assessment for full reference list.

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