Concizumab (haemophilia B)

Addendum to Project A25-56 (dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
AESI	adverse events of special interest
aPCC	activated prothrombin complex concentrate
BU	Bethesda units
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
NRI	non-responder imputation
PGIC	Patient Global Impression of Change
PRO	patient-reported outcome
PT	Preferred Term
SAE	Serious AE
SGB	Sozialgesetzbuch (Social Code Book)
SMQ	Standardized MedDRA Query
SOC	System Organ Class

1 Background

On 9 September 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A25-56 (Concizumab – Benefit assessment according to §35a Social Code Book V) [1].

In the commenting procedure, the pharmaceutical company (hereinafter referred to as the 'company') submitted supplementary information from the study explorer7, which went beyond the information provided in the dossier, to prove the added benefit. The commission comprised the assessment of the analyses presented by the company in the commenting procedure [2], taking into account the information in the dossier [3]. In accordance with the commission, this addendum comprises the assessment of the suitability of explorer7, taking into account

- the company's data presented in the written commenting procedure (in particular the analyses on outcomes in the side effects category and on the Patient Global Impression of Change [PGIC]) and
- the documents subsequently submitted by the company after the oral hearing on the number and observation period of patients in explorer7 who did not have an observation period of 24 weeks.

The responsibility for this assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The explorer7 study [4-8] was presented for the benefit assessment of concizumab in comparison with individualized treatment as the appropriate comparator therapy (ACT) in patients of 12 years of age or more with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors. A detailed description of the study can be found in dossier assessment A25-56 [1].

2.1 Suitability of explorer7, taking into account the commenting procedure and the documents submitted after the oral hearing

In the dossier assessment A25-56 it was described that it was not possible to adequately assess whether the unchanged continuation of on-demand treatment with bypassing agents in the control arm of explorer7 represented an adequate implementation of individualized treatment for all patients, taking into account factors such as inhibitor titre, bleeding episodes, bleeding risk and tolerability. Furthermore, it was described in the dossier assessment that it cannot be ruled out that routine prophylaxis with bypassing agents could have been suitable for individual patients in explorer7 and that it cannot be conclusively assessed whether on-demand treatment or routine prophylaxis with recombinant or human plasma-derived factor IX preparations could have been suitable for individual patients.

It became clear from the hearing [9] that providing health care to patients with haemophilia B with factor IX inhibitors is difficult. Clinical experts cited the common occurrence of allergic reactions to factor IX concentrates, including activated prothrombin complex concentrate (aPCC), as well as the limited option of prophylaxis with factor VIIa due to its short half-life and the associated multiple daily administration. Overall, it became clear from the discussion that, as already described in the dossier assessment, the treatment of patients with haemophilia with factor IX inhibitors requires an individual decision depending on the factors mentioned and that, as a result, prophylactic treatment is often not an option.

However, even with the comments, there was still insufficient information available for explorer7 as to whether the continuation of on-demand treatment was an adequate comparator therapy for all patients or for which proportion of explorer7 patients routine prophylaxis might have been suitable. In order to estimate this proportion, information on the number of patients without previous allergic reactions to factor IX in combination with information on their factor IX inhibitor titres would in particular be required. According to the dossier, 4 patients in the control arm had a high inhibitor titre (≥ 5 Bethesda units [BU]), but there was no information on allergic reactions in the patient history.

The relevance of explorer7 was therefore still considered unclear, taking into account the commenting procedure and the documents subsequently submitted after the oral hearing. This assessment concurs with that reached in dossier assessment A25-56. The assessment did

not change on the basis of the commenting procedure and the documents subsequently submitted after the oral hearing, as relevant information, in particular on the presence of allergic reactions to factor IX and the inhibitor titres, was still missing. It was therefore still not possible to estimate the proportion of patients in the control arm for whom on-demand treatment with bypassing agents was the most suitable therapy for each individual patient.

2.2 Analyses submitted by the company on outcomes in the categories side effects and morbidity (PGIC) and subsequently submitted information

2.2.1 Subsequently submitted information on observation periods

In the documents submitted by the company after the oral hearing, information was provided on the number and observation period of patients in explorer7 who did not have an observation period of 24 weeks. The company stated that a total of 12 patients were included in the control arm. According to the company, this included 2 patients who had been in the study for less than 24 weeks. It specified that the observation periods for these 2 patients were 4.1 weeks and 16.3 weeks respectively. The company added that for one patient from the intervention arm who died during the study, the observation period was 5.7 weeks. These details deviated from company's description in the dossier in that it was stated there that all patients in the control arm had completed the 24-week observation period. In addition, the comments cited differing patient numbers for the intervention and control arms. For example, the dossier described that a total of 12 patients in the intervention arm received on-label dosage after the treatment pause, and that there was a total of 10 patients in the control arm. It was assumed that this information was confused in the subsequent submission and that the information in the dossier was correct. The proportion of incompletely observed patients was therefore around 8% in the intervention arm and 20% in the control arm.

The incomplete observations of patients with an observation period < 24 weeks were taken into account in the risk of bias (see Section 2.2.4).

2.2.2 Outcomes in the side effects category

For the benefit assessment, the company provided contradictory information in the dossier on the outcomes in the side effects category with regard to the observation periods and the observation periods taken into account. Firstly, this concerned the information that observations from the extension phase were also included in the control arm. Secondly, there were overall discrepancies in the information on which observation periods of the respective study arms were taken into account in the analyses (see the full dossier assessment A25-56, Appendix B.1.1 under side effects). For this reason, the analyses presented were not suitable for the benefit assessment.

In its comments, the company stated that the analyses on the outcomes in the side effects category in Module 4 B were incorrectly presented as results for Week 24. It clarified that the

events and analyses presented covered the maximum observation period, i.e. in the intervention arm the time after the study interruption and thus from the start of the new concizumab dosage to the primary data cut-off, and in the control arm the time from randomization to the end of on-demand treatment (excluding the extension phase). According to the company in the dossier, the median observation periods for the outcomes in the side effects category were 37.6 weeks in the intervention arm and 34.3 weeks in the control arm. Thus, the outcomes of the side effects category were presented. As described in the dossier assessment, no suitable data were available for severe adverse events (AEs).

For the outcome thromboembolic events (serious AEs [SAEs]), the company presented a predefined operationalization of thromboembolic events as an AE of special interest (AESI) and an operationalization with the term 'embolic and thrombotic events' as a Standardized Medical Dictionary for Regulatory Activities (MedDRA) Query (SMQ). For the operationalization of the AESI, the company stated that certain thromboembolic events such as disseminated intravascular coagulation or thrombotic microangiopathy were taken into account. However, it added that the AESIs were not limited to the named events, so the operationalization did not include an exhaustive list of events. As it was not possible to assess which events should ultimately be included in the AESIs, the operationalization using the SMQ 'embolic and thrombotic events' was therefore presented for the outcome 'thromboembolic events' (SAEs). As no events occurred for either the AESI or the SMQ, the choice of operationalization here was of no consequence overall.

2.2.3 Symptoms outcome recorded using the PGIC

In the dossier, the company presented analyses on the outcome 'symptoms', recorded using the PGIC. The patients were asked how they assessed the change in the extent of their physical functionality since starting to take the study medication. The possible answers were very much better, moderately better, a little better, no change, a little worse, moderately worse and very much worse. Patients with an improvement of 'very much better' or 'moderately better' at Week 24 were categorized as responders. In the dossier assessment A25-56, it was described with regard to the patient-reported outcomes (PROs) that these could not be used for the assessment, as the response rates for all PROs were already very low at baseline and in some cases under 50%. In its comments, the company pointed out that no information at baseline is required for the analysis of the PGIC. This is appropriate. The company described that the response rates at Week 24 were 81.8% in the intervention arm and 75.0% in the control arm and were thus sufficiently high. However, the percentages did not relate to the intention-to-treat (ITT) population of 12 patients in the intervention arm and 10 patients in the control arm, but to the number of patients who were still under observation at Week 24. Overall, there was a high and also differential proportion of missing values in both arms (intervention arm: 3/12 [25%]; comparator arm 4/10 [40%]), which were imputed in the analysis. The analysis presented by the company based on the ITT population was based on

non-responder imputations (NRI). In the present case, however, an NRI was not considered appropriate, i.e. it was not sufficiently certain that the patients no longer under observation could not experience any improvement. The results on the PGIC are therefore not presented.

2.2.4 Risk of bias

The dossier assessment A25-56 described that the lack of temporal parallelism between the 2 study arms of explorer7 impaired the internal validity of the study. The risk of bias across all outcomes was therefore assessed to be high. In the comments, the company referred to sensitivity analyses available in the European Public Assessment Report [10], which according to the company showed that the risk of bias was not influenced by the study interruption. Irrespective of the question of whether the analyses presented would be suitable to show that the interruption and lack of temporal parallelism had no influence on the internal validity of the study, these were not available separately for patients with haemophilia A and haemophilia B. The risk of bias across outcomes was therefore still assessed to be high.

Table 1 describes the risk of bias for the results of the relevant outcomes.

Table 1: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study		Outcomes										
	Study level	All-cause mortality[a]	Treated bleeds[b]	Treated joint bleeds[b]	Severe bleeds[c]	Complete freedom from bleeding[d]	Symptoms (PGIC)	Health-related quality of life (SF-36v2)	SAEs	Discontinuation due to AEs	Thromboembolic events (SAEs)[e]	Other specific AEs
explorer7	H[f]	H[g]	H[g, h]	H[g, h]	–[i]	H[g, h]	–[j]	–[i]	H[g]	H[g, k]	H[g]	–[l]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Operationalized as spontaneous and traumatic bleeding episodes or joint bleeding episodes; bleeding episodes that occurred at the same anatomical site (including worsening due to swelling or pain) within 72 hours after the end of treatment with a factor product were pooled into 1 bleeding episode.
c. 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.
d. Number of patients in whom no treated bleeding episodes occurred within the first 24 weeks after starting the new concizumab dosage in the intervention arm and after randomization to on-demand treatment in the control arm.
e. Operationalized with the SMQ 'embolic and thrombotic events'.
f. High risk of bias across outcomes. This leads to a high risk of bias for each outcome.
g. High proportion of patients not included in the analysis or incompletely observed (> 10%) or large difference between the treatment groups (> 5 percentage points).
h. Lack of blinding in a subjective decision to use on-demand treatment for breakthrough haemorrhages in the intervention arm and for bleeds in the control arm.
i. No suitable data available; for justification see benefit assessment A25-56 [1].
j. No suitable data available; for justification see Section 2.2.3.
k. Lack of blinding in subjective recording of outcomes.
l. No further specific AEs were identified based on the AEs occurring in the relevant study.

AE: adverse event; H: high; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36-version 2 Health Survey; SMQ: Standardized MedDRA Query

For a detailed description of the risk of bias of the outcomes already presented in the benefit assessment, please refer to dossier assessment A25-56. In contrast to dossier assessment A25-56, the information subsequently submitted by the company on the duration of follow-up based on incomplete observations results also resulted in a high risk of bias.

The results of the outcomes additionally presented here showed a high risk of bias. This was due to the high risk of bias across the study and incomplete observations for the results for the outcomes of SAEs and thromboembolic events (SAEs), and additionally to the lack of blinding in subjective outcome recording for the results for the outcome discontinuation due to AEs.

2.2.5 Results

Table 2, Table 3 and Table 4 summarize the results comparing concizumab in patients of 12 years of age or more with haemophilia B and factor IX inhibitors. Where necessary, calculations conducted by the Institute are provided in addition to the data from the company's dossier. The results for the overall rates of AEs and SAEs, events for System Organ Classes (SOCs) and Preferred Terms (PTs) according to MedDRA and a complete presentation of all events (SOCs/PTs) that led to discontinuation can be found in Appendix A.

Table 2: Results (mortality, morbidity and side effects, dichotomous) – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study **Outcome category** **Outcome**	**Routine prophylaxis with concizumab**		**On-demand treatment with bypassing agents**		**Routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**RR [95% CI]; p-value**
explorer7					
Mortality					
All-cause mortality[a]	12	2 (16.7)	10	0 (0)	4.23[b] [0.23; 79.10]; 0.207[c]
Morbidity					
Complete freedom from bleeding	12	9 (75.0)	10	1 (10.0)	7.50 [1.14; 49.54]; 0.002[d]
Symptoms (PGIC)[e]	No suitable data[e]				
Side effects					
AEs (supplementary information)	12	6 (50.0)	10	3 (30.0)	–
SAEs	12	2 (16.7)	10	2 (20.0)	0.83[b] [0.14; 4.90]; 0.911[c]
Discontinuation due to AEs	12	1 (8.3)	10	0 (0)	2.54[b] [0.11; 56.25]; 0.512[c]
Thromboembolic events (SAEs)	12	0 (0)	10	0 (0)	–

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Calculation based on the 2x2 table with zero-cell correction (addition of 0.5 in all cells).
c. Calculated using Barnard's test (unconditional exact test).
d. Institute's calculation: effect and CI: asymptotic, p-value: unconditional exact test (CSZ method according to [11]).
e. No suitable data available; see Section 2.2.3 for reasons.

AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z-score; n: number of patients with (at least one) event; N: number of analysed patients; PGIC: Patient Global Impression of Change; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event

Table 3: Results (morbidity: bleeding episodes) – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study **Outcome category** **Outcome**	**Routine prophylaxis with concizumab**		**On-demand treatment with bypassing agents**		**Routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents**
	N	**ABR [95% CI]**	**N**	**ABR [95% CI]**	**ABR ratio[a] [95% CI]; p-value**
explorer7					
Morbidity					
Treated bleeds (ABR)					
Treated bleeds[b]	12	1.37 [0.54; 3.46]	10	7.04 [3.08; 16.08]	0.19 [0.06; 0.65]; 0.008
Treated joint bleeds[b]	12	0.91 [0.37; 2.24]	10	5.25 [2.61; 10.58]	0.17 [0.06; 0.52]; 0.002
Severe bleeds				No suitable data[c]	
Supplementary information:					
Treated target joint bleeds[b]	*12*	*0.21 [0.04; 1.01]*	*10*	*0.92 [0.26; 3.20]*	*0.23 [0.05; 1.13]; 0.070*
All treated and untreated bleeds[b]	*12*	*3.15 [1.60; 6.19]*	*10*	*9.06 [4.56; 18.00]*	*0.35 [0.13; 0.90]; 0.029*

a. Calculated using negative binomial regression adjusted for treatment, bleeding frequency before screening and the logarithm of the length of the observation period as an offset variable.
b. Operationalized as spontaneous and traumatic bleeding episodes or joint bleeding episodes; bleeding episodes that occurred at the same anatomical site (including worsening due to swelling or pain) within 72 hours after the end of treatment with a factor product were pooled into 1 bleeding episode.
c. No suitable data available; for justification see dossier assessment A25-56 [1].

ABR: annualized bleeding rate; AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; RCT: randomized controlled trial; SAE: serious adverse event

Table 4: Results (health-related quality of life, continuous) – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study Outcome category Outcome	Routine prophylaxis with concizumab			On-demand treatment with bypassing agents			Routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents
	N	Values at baseline mean (SD)	Change at Week 24 mean (SE)	N	Values at baseline mean (SD)	Change at Week 24 mean (SE)	Effect [95% CI]; p-value
explorer7							
Health-related quality of life							
SF-36v2	No suitable data[a]						

a. No suitable data available; for justification see dossier assessment A25-56 [1].

CI: confidence interval; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36v2: Short Form 36-version 2 Health Survey

Mortality

All-cause mortality

No significant difference between treatment groups was found for the outcome of all-cause mortality.

Morbidity

Treated bleeds and treated joint bleeds

For the outcomes treated bleeds and treated joint bleeds, each operationalized as annualized bleeding rates, there was a significant difference between the treatment groups in favour of concizumab.

Severe bleeds

No suitable data were available for the outcome severe bleeds (see dossier assessment A25-56).

Complete freedom from bleeding

For the outcome complete freedom from bleeding, there was a significant difference between the treatment groups in favour of concizumab.

Symptoms (recorded using PGIC)

For the outcome symptoms, recorded using the PGIC, no suitable data were available.

Health-related quality of life

No suitable data were available for the outcome of health-related quality of life (recorded using the Short Form 36-version 2 Health Survey [SF-36v2]) (see dossier assessment A25-56).

Side effects

SAEs

There was no statistically significant difference between the treatment arms for the outcome SAEs.

Discontinuation due to AEs

There was no statistically significant difference between the treatment arms for the outcome discontinuation due to AEs.

Thromboembolic events (SAEs)

For the outcome thromboembolic events (SAEs) there were no events in either arm. There was no statistically significant difference between the treatment arms.

2.2.6 Overview of the advantages and disadvantages of concizumab therapy

Overall, there were only advantages of concizumab compared with on-demand treatment with bypassing agents in patients of 12 years of age or more with haemophilia B (congenital factor IX deficiency) and factor IX inhibitors:

Outcomes with advantages for concizumab

All outcomes were assigned to the morbidity outcome category.

- Treated bleeds
- Treated joint bleeds
- Complete freedom from bleeding

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of concizumab from dossier assessment A25-56.

The following Table 5 shows the result of the benefit assessment of concizumab under consideration of dossier assessment A25-56 and this addendum.

Table 5: 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 G-BA decides on the added benefit.

3 References

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Appendix A Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for MedDRA SOCs and PTs, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, a complete presentation of all events (SOCs/PTs) that resulted in discontinuation is provided.

Table 6: Common AEs[a] – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study	**Patients with event n (%)**	
SOC[b] **PT[b]**	**Routine prophylaxis with concizumab** **N = 12**	**On-demand treatment with bypassing agents** **N = 10**
explorer7		
Overall AE rate	6 (50.0)	3 (30.0)
Eye disorders	0 (0)	1 (10.0)
Redness of the conjunctiva	0 (0)	1 (10.0)
Gastrointestinal disorders	0 (0)	1 (10.0)
Constipation	0 (0)	1 (10.0)
General disorders and administration site conditions	3 (25.0)	1 (10.0)
Pyrexia	1 (8.3)	1 (10.0)
Infections and infestations	3 (25.0)	2 (20.0)
COVID-19	1 (8.3)	1 (10.0)
Respiratory tract infection, viral	0 (0)	1 (10.0)
Subcutaneous abscess	0 (0)	1 (10.0)
Injury, poisoning and procedural complications	2 (16.7)	3 (30.0)
Fracture of the lower limbs	0 (0)	1 (10.0)
Road traffic accident	1 (8.3)	1 (10.0)
Skin abrasion	0 (0)	1 (10.0)
Tibia fracture	0 (0)	1 (10.0)

Table 6: Common AEs[a] – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents (multipage table)

Study	**Patients with event n (%)**	
SOC[b] PT[b]	**Routine prophylaxis with concizumab N = 12**	**On-demand treatment with bypassing agents N = 10**
Investigations	1 (8.3)	1 (10.0)
Blood alkaline phosphatase increased	0 (0)	1 (10.0)
Blood pressure increased	0 (0)	1 (10.0)
Musculoskeletal and connective tissue disorders	0 (0)	1 (10.0)
Back pain	0 (0)	1 (10.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0)	1 (10.0)
Fibroma	0 (0)	1 (10.0)
Nervous system disorders	2 (16.7)	0 (0)
Renal and urinary disorders	0 (0)	1 (10.0)
Haematuria	0 (0)	1 (10.0)
Skin and subcutaneous tissue disorders	1 (8.3)	1 (10.0)
Erythema	0 (0)	1 (10.0)
Pruritus	0 (0)	1 (10.0)
Vascular disorders	1 (8.3)	1 (10.0)
Haematomas	0 (0)	1 (10.0)

a. Events that occurred in ≥ 10% of the patients in at least one study arm.
b. MedDRA version 24.1; SOC and PT notation taken without adaptation from Module 4 B.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 7: Common SAEs[a] – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study	Patients with event n (%)	
SOC[b] PT[b]	**Routine prophylaxis with concizumab N = 12**	**On-demand treatment with bypassing agents N = 10**
explorer7		
Overall SAE rate	2 (16.7)	2 (20.0)
Infections and infestations	1 (8.3)	1 (10.0)
COVID-19	1 (8.3)	1 (10.0)
Injury, poisoning and procedural complications	1 (8.3)	1 (10.0)
Femur fracture	1 (8.3)	0 (0)
Humerus fracture	1 (8.3)	0 (0)
Fracture of the lower limbs	0 (0)	1 (10.0)
Road traffic accident	1 (8.3)	1 (10.0)
Vascular disorders	0 (0)	1 (10.0)
Haematomas	0 (0)	1 (10.0)

a. Events that occurred in ≥ 5% of patients in at least one study arm.
b. MedDRA version 24.1; SOC and PT notation taken without adaptation from Module 4 B.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 8: Discontinuation due to AEs – RCT, direct comparison: routine prophylaxis with concizumab vs. on-demand treatment with bypassing agents

Study	Patients with event n (%)	
SOC PT	**Routine prophylaxis with concizumab N = 12**	**On-demand treatment with bypassing agents N = 10**
explorer7		
Overall rate of discontinuations due to AEs	1 (8.3)	0 (0)
Discontinuation due to AEs according to SOC/PT	ND	

AE: adverse event; n: number of patients with at least one event; N: number of analysed patients; ND: no data; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class