IQWiG Reports – Commission No. A19-26

Emicizumab (haemophilia A) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment Emicizumab *(Hämophilie A) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 June 2019). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher:
Institute for Quality and Efficiency in Health Care

Topic:
Emicizumab (haemophilia A) – Benefit assessment according to §35a Social Code Book V

Commissioning agency:
Federal Joint Committee

Commission awarded on:
18 March 2019

Internal Commission No.:
A19-26

Address of publisher:
Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

Medical and scientific advice:

- Wolfgang Eberl, Braunschweig Hospital, Clinic for Paediatric and Adolescent Medicine, Braunschweig, Germany

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.

IQWiG employees involved in the dossier assessment:

- Bent Müller
- Ulrich Grouven
- Thomas Kaiser
- Stefan Kobza
- Petra Kohlepp
- Katrin Nink
- Inga Overesch
- Dominik Schierbaum

Keywords: emicizumab, hemophilia A, benefit assessment

Table of contents

List of tables[2]

Page

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
CI	confidence interval
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
IU	international units
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) 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 emicizumab. 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 18 March 2019.

Research question

The aim of the present report was to assess the added benefit of emicizumab in comparison with the appropriate comparator therapy (ACT) for routine prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research questions of the benefit assessment of emicizumab

Therapeutic indication	**ACT[a]**
Routine prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors	Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company followed the G-BA's specification on 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 6 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Results

Concurring with the company, no relevant RCT on the direct comparison of emicizumab versus the ACT was identified from the check of the completeness of the study pool.

The company explored the possibility of an adjusted indirect comparison, but did not use it to derive the added benefit because it considered the studies it identified to be not sufficiently similar.

The additional data identified by the company for a before-after comparison were unsuitable to draw conclusions on the added benefit of emicizumab in comparison with the ACT.

Indirect comparison

In its dossier, the company explored the possibility of an adjusted indirect comparison for the comparison of routine prophylaxis with emicizumab and routine prophylaxis with factor VIII preparations. Since in the HAVEN 3 study conducted by the company routine prophylaxis with emicizumab was compared with episodic treatment with factor VIII preparations, the latter constituted the common comparator for the indirect comparison. For the ACT, the company identified the SPINART study, which compared routine prophylaxis with factor VIII preparations with episodic treatment with factor VIII preparations.

The company saw clear differences in the annual bleeding rates for the common comparator. From the company's point of view, the similarity of the included studies was therefore not given and, consequently, the indirect comparison not usable.

Deviating from the company's assessment, the patient characteristics and the annualized bleeding rates of the common comparator were considered to be sufficiently similar. Regardless of this, the study durations differed between the 2 studies (HAVEN 3: 6 months; SPINART: 1 year [interim analysis] or 3 years [end of study]).

In summary, the indirect comparison can be used to estimate whether there is a difference between emicizumab and the ACT in terms of bleeding rates. Due to the different study durations, however, no analyses of adverse events (AEs) and thus no overall balancing of an added benefit or lesser benefit is possible.

For the outcomes, treated bleeds and joint bleeds, the calculated indirect comparisons produced no statistically significant differences between emicizumab and routine prophylaxis with a recombinant factor VIII preparation.

Before-after comparison

The company presented a before-after comparison for the comparison of routine prophylaxis with emicizumab versus routine prophylaxis with factor VIII preparations.

The comparison was based on data from patients who participated both in the observational study BH29768 and in the approval study HAVEN 3.

Study BH29768 was a prospectively planned, non-interventional, multinational observational study in patients with congenital haemophilia A. The enrolled patients maintained their ongoing treatment with factor VIII preparations (strategy and dose) during the study and were observed in their respective local care environments. The study had 3 arms. Only arm C, in which patients aged ≥12 years without factor VIII inhibitors were observed, was relevant for the present research question. This arm constituted the before phase of the before-after comparison.

On completion of the BH29768 study, all patients were offered to participate in the subsequent interventional HAVEN 3 study. Allocation to the study arms was according to the previous therapeutic strategy. Only patients who had received prophylactic treatment, which was not

further specified, in the before phase were candidates for the before-after comparison. Of 49 eligible patients, 44 patients were included in arm D of the HAVEN 3 study, where they received routine prophylaxis with emicizumab.

As was the case in the first assessment of emicizumab, the before-after comparison now presented by the company was also unsuitable for the assessment of the added benefit. Analogous to the first assessment of emicizumab, the following reasons were particularly relevant for this:

- The company did not guarantee that there were similar conditions for conducting adequate prophylactic treatment in the different studies. In the HAVEN 3 study, this treatment was conducted under controlled study conditions. Treatment in the BH29768 study corresponded to an uncontrolled observation.
- This problem was also not solved by the fact that the company operationalized a subpopulation of 22 so-called “formally compliant” patients from the population of 44 patients. Irrespective of the fact that this did not lead to similar study conditions, the criteria chosen by the company were based on the lower limit of the dosage of approved recombinant and plasma-derived factor VIII preparations. These were unsuitable to identify patients with adequate routine prophylaxis with sufficient certainty.
- The effects in bleeding outcomes shown by the company were not large enough that they cannot be explained by the different study conditions alone. The results of the adjusted indirect comparisons conducted as examples showed no statistically significant differences between routine prophylaxis with emicizumab or with a recombinant factor VIII preparation.

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 emicizumab.

Table 3: Emicizumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Routine prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors	Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of emicizumab in comparison with the ACT for routine prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research questions of the benefit assessment of emicizumab

Therapeutic indication	ACT[a]
Routine prophylaxis of bleeding episodes in patients with severe haemophilia A without factor VIII inhibitors	Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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

[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].

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 6 months were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study lists on emicizumab and on the ACT (status: 13 February 2019)
- bibliographical literature search on emicizumab (last search on 11 February 2019)
- search in trial registries for studies on emicizumab (last search on 13 February 2019)
- bibliographical literature search on the ACT (last search on 11 February 2019)
- search in trial registries for studies on the ACT (last search on 13 February 2019)

To check the completeness of the study pool:

- search in trial registries for studies on emicizumab (last search on 29 March 2019)

Concurring with the company, no relevant RCT on the direct comparison of emicizumab versus the ACT was identified from the check of the completeness of the study pool.

The company explored the possibility of an adjusted indirect comparison, but did not use it to derive the added benefit because it considered the studies it identified to be not sufficiently similar.

The additional data identified by the company for a before-after comparison were unsuitable to draw conclusions on the added benefit of emicizumab in comparison with the ACT.

The individual approaches of the company are described below, providing the reasons why the respective data are not suitable for deriving an added benefit.

2.3.1 Indirect comparison

In its dossier, the company explored the possibility of an adjusted indirect comparison for the comparison of routine prophylaxis with emicizumab and routine prophylaxis with factor VIII preparations. Since in the HAVEN 3 study [3-7] conducted by the company routine prophylaxis with emicizumab was compared with episodic treatment with factor VIII preparations, the latter constituted the common comparator for the indirect comparison. For the ACT, the company identified the SPINART study [8-11], which compared routine prophylaxis with factor VIII preparations with episodic treatment with factor VIII preparations (see Figure 1).

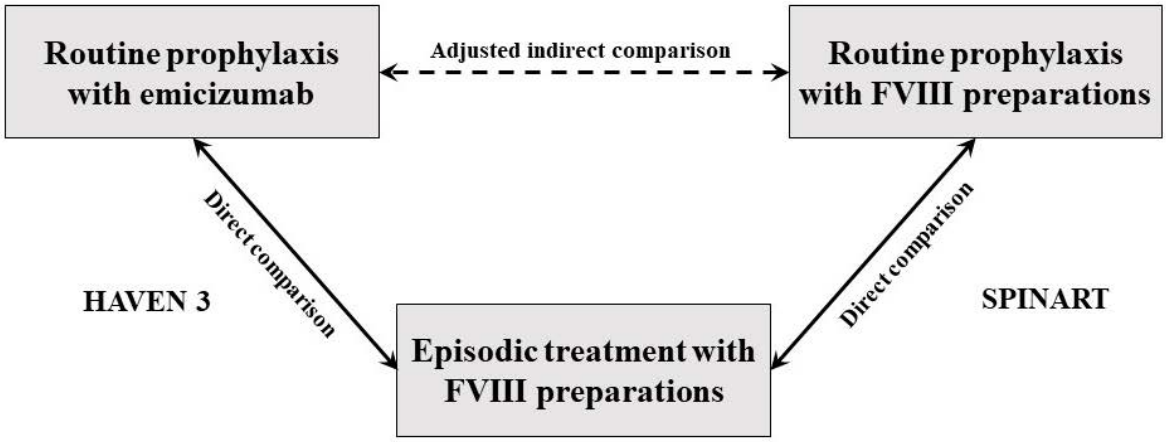

Figure 1: Study pool of the company for the indirect comparison of routine prophylaxis with emicizumab versus routine prophylaxis with factor VIII preparations

The company saw clear differences in the annual bleeding rates for the common comparator. From the company's point of view, the similarity of the included studies was therefore not given and, consequently, the indirect comparison not usable.

Deviating from the company's assessment, the patient characteristics and the annualized bleeding rates of the common comparator were considered to be sufficiently similar. Regardless of this, the study durations differed between the 2 studies (HAVEN 3: 6 months; SPINART: 1 year [interim analysis] or 3 years [end of study]).

Hereinafter, the 2 studies HAVEN 3 and SPINART are described in detail.

Study design

HAVEN 3

The HAVEN 3 study was an open-label, multicentre parallel-group study with 3 randomized and 1 non-randomized arm. The study enrolled adults and adolescents (≥ 12 years) with severe haemophilia A (remaining factor VIII coagulation activity < 1%).

Patients in the randomized part of the study had previously received episodic factor VIII treatment and were randomized in a 2:2:1 ratio to routine prophylaxis with 1.5 mg emicizumab once weekly (arm A), routine prophylaxis with 3 mg emicizumab every 2 weeks (arm B) or episodic factor VIII treatment (arm C). In an additional non-randomized arm, patients received routine prophylaxis with factor VIII preparations, which was not further specified, as pretreatment and were treated in the study with routine prophylaxis with emicizumab (arm D) (for details on this arm, see Section 2.3.2).

The randomized part of the study was completed after 24 weeks. Patients in the control arm (episodic treatment with factor VIII preparations) could then switch treatment and start routine prophylaxis with emicizumab.

Primary outcome of the study was the number of treated bleeds. Relevant secondary outcomes were different operationalizations of bleeding rates, health status, health-related quality of life, and AEs. Further information on the study and intervention characteristics can be found in Table 10 and Table 11 in Appendix A of the full dossier assessment. A schematic presentation of the study design can be found in Figure 2 in Appendix A of the full dossier assessment.

SPINART

The SPINART study was a randomized, open-label, multicentre parallel-group study, which compared routine prophylaxis with recombinant factor VIII preparations (octocog alfa) with episodic treatment with recombinant factor VIII preparations (octocog alfa). It included male patients aged 12 to 50 years with severe haemophilia A (remaining factor VIII coagulation activity < 1%). Deviating from this, patients with remaining factor VIII coagulation activity of 1 to 2% exhibiting clinical severity could also be enrolled. Their proportion was not allowed to exceed 10% of the study population, however.

A total of 84 patients were randomly assigned in a ratio of 1:1. 42 patients each were assigned to the routine prophylaxis arm and to the episodic treatment arm. Randomization was stratified by the factors “presence of a target joint” (yes/no) and “number of bleeding episodes in the last 6 months prior to study entry” (< 15/≥ 15 bleeding episodes).

Treatment in the routine prophylaxis arm included 3 times weekly application of factor VIII preparations with a dosage of 25 international units (IU) per kilogram body weight. Dose adjustments in this arm were possible. With an increased tendency to bleed (≥ 12 bleeding episodes per year), after one year, the dose could be increased to 30 IU per kilogram body weight, and after 2 years, to 35 IU per kilogram body weight. Episodic treatment was at the investigator’s discretion and in compliance with the Summary of Product Characteristics (SPC).

Primary outcome of the study was the number of bleeding episodes after 1 year of treatment. Relevant secondary outcomes were different operationalizations of bleeding rates, pain, health status, health-related quality of life, and AEs. Further information on the study and intervention characteristics can be found in Table 10 and Table 11 in Appendix A of the full dossier assessment.

Similarity of the studies HAVEN 3 and SPINART

A prerequisite for conducting an adjusted indirect comparison is the sufficient similarity of the included studies. The patient characteristics showed no relevant differences between the study populations (see Table 12 in Appendix A of the full dossier assessment).

The company argued in its dossier that the annual bleeding rates under the common comparator were too different for the 2 studies to be used for an adjusted indirect comparison. This view was not shared. By way of justification, the company compared the medians of the annual bleeding rates in the common comparator arms (SPINART: 27.9 versus HAVEN 3: 40.4), referring for the SPINART study to values from the publication Manco-Johnson 2013 [8].

However, these values were subsequently corrected by the authors [9]. According to the Corrigendum, the correct median of the annual bleeding rates (treated bleeds) was 32.8. With 38.2 bleeds/year (HAVEN 3) and 36.9 bleeds/year (SPINART), the mean annual bleeding rates were almost identical (see Table 5). The joint bleeding rates were also sufficiently similar: medians of 21.3 (HAVEN 3) versus 24.4 (SPINART), and mean of 26.5 (HAVEN 3) versus 29.2 (SPINART) (see Table 5).

The check of the operationalizations of the annual bleeding rates also produced no relevant differences. Both studies only considered treated bleeds both for all bleeds and for joint bleeds. Similarly, in both studies, the patients recorded the bleeding episodes themselves with the help of an electronic diary.

There were differences regarding study durations, however (HAVEN 3: 6 months versus SPINART: 3 years [or analyses after 1 year for several outcomes]). This affected the occurrence of AEs and became visible in the consideration of the AE rates of the potentially relevant studies. In the common comparator arm of the HAVEN 3 study 33% of patients were affected by AEs, whereas in the common comparator arm of the SPINART study 69% of the patients were affected after 1 year and 88% after 3 years. However, this has no expected influence on the evaluation of bleeding rates, as these were annualized (i.e. converted to a yearly rate).

In summary, the indirect comparison can be used to estimate whether there is a difference between emicizumab and the ACT in terms of bleeding rates. Due to the different study durations, however, no analyses of AEs and thus no overall balancing of an added benefit or lesser benefit is possible.

Results of the adjusted indirect comparison

Table 5 shows the results of the adjusted indirect comparison on the outcomes “treated bleeds” and “joint bleeds”, each operationalized as annualized bleeding rate.

Table 5: Results (bleeding episodes) – RCT, indirect comparison using common comparators: routine prophylaxis with emicizumab vs. routine prophylaxis with factor VIII preparations

Outcome category Outcome Comparison Study	Routine prophylaxis with emicizumab or routine prophylaxis with factor VIII preparations N[a]	 Mean [95% CI] or (SD)[b]	Episodic treatment N[a]	 Mean [95% CI] or (SD)[b]	Group difference ABR ratio [95% CI]; p-value
Morbidity					
Treated bleeds – annualized bleeding rate (ABR)					
Treated bleeds (1.5 mg emicizumab[c])					
Routine prophylaxis vs. episodic treatment					
HAVEN 3	36	1.5 [0.89; 2.47]	18	38.2 [22.86; 63.76]	0.04 [0.02; 0.08]; < 0.001
Routine prophylaxis vs. episodic treatment					
SPINART	42	2.2 (5.1)	42	36.9 (23.8)	0.07 [0.04; 0.12]
Indirect comparison using common comparators[d]:					
Routine prophylaxis with emicizumab vs. routine prophylaxis with FVIII					0.61 [0.25 1.47]; 0.268
Treated bleeds (3 mg emicizumab[e])					
Routine prophylaxis vs. episodic treatment					
HAVEN 3	35	1.3 [0.75; 2.25]	18	38.2 [22.86; 63.76]	0.03 [0.02; 0.07]; < 0.001
Routine prophylaxis vs. episodic treatment					
SPINART	42	2.2 (5.1)	42	36.9 (23.8)	0.07 [0.04; 0.12]
Indirect comparison using common comparators[d]:					
Routine prophylaxis with emicizumab vs. routine prophylaxis with FVIII					0.46 [0.19 1.11]; 0.085
Treated bleeds (1.5 mg and 3 mg emicizumab[f])					
Routine prophylaxis vs. episodic treatment					
HAVEN 3	71	1.4 (2.34)	18	38.2 [22.86; 63.76]	0.04 [0.02; 0.07]
Routine prophylaxis vs. episodic treatment					
SPINART	42	2.2 (5.1)	42	36.9 (23.8)	0.07 [0.04; 0.12]
Indirect comparison using common comparators[d]:					
Routine prophylaxis with emicizumab vs. routine prophylaxis with FVIII					0.56 [0.23 1.35]; 0.194

(continued)

Table 5: Results (bleeding episodes) – RCT, indirect comparison using common comparators: routine prophylaxis with emicizumab vs. routine prophylaxis with factor VIII preparations (continued)

Outcome category Outcome Comparison Study	Routine prophylaxis with emicizumab or routine prophylaxis with factor VIII preparations N[a]	 Mean [95% CI] or (SD)[b]	Episodic treatment N[a]	 Mean [95% CI] or (SD)[b]	Group difference ABR ratio [95% CI]; p-value
Joint bleeds – annualized bleeding rate (ABR)					
Joint bleeds (1.5 mg emicizumab[c])					
Routine prophylaxis vs. episodic treatment					
HAVEN 3	36	1.1 [0.59; 1.89]	18	26.5 [14.67; 47.79]	0.04 [0.02; 0.09]; < 0.001
Routine prophylaxis vs. episodic treatment					
SPINART	42	1.9 (4.7)	42	29.2 (20.6)	0.07 [0.03; 0.14]
Indirect comparison using common comparators[d]:					
Routine prophylaxis with emicizumab vs. routine prophylaxis with FVIII					0.61 [0.21 1.81]; 0.377
Joint bleeds (3 mg emicizumab[e])					
Routine prophylaxis vs. episodic treatment					
HAVEN 3	35	0.9 [0.44; 1.67]	18	26.5 [14.67; 47.79]	0.03 [0.02; 0.07]; < 0.001
Routine prophylaxis vs. episodic treatment					
SPINART	42	1.9 (4.7)	42	29.2 (20.6)	0.07 [0.03; 0.14]
Indirect comparison using common comparators[d]:					
Routine prophylaxis with emicizumab vs. routine prophylaxis with FVIII					0.46 [0.15 1.38]; 0.166
Joint bleeds (1.5 mg and 3 mg emicizumab[f])					
Routine prophylaxis vs. episodic treatment					
HAVEN 3	71	1.0 (1.9)	18	26.5 [14.67; 47.79]	0.04 [0.02; 0.08]
Routine prophylaxis vs. episodic treatment					
SPINART	42	1.9 (4.7)	42	29.2 (20.6)	0.07 [0.03; 0.14]
Indirect comparison using common comparators[d]:					
Routine prophylaxis with emicizumab vs. routine prophylaxis with FVIII					0.58 [0.19 1.73]; 0.330

a: Number of patients considered in the analysis for the calculation of the effect estimation; the values may be based on other patient numbers.
b: The ABRs are based on bleeding episodes observed over 6 months in the HAVEN 3 study and over 12 months in the SPINART study.
c: ABR for the emicizumab arm is based on patients treated with 1.5 mg emicizumab once weekly.
d: Indirect comparison according to Bucher [12]; Institute's calculation.
e: ABR for the emicizumab arm is based on patients treated with 3 mg emicizumab every 2 weeks.
f: ABR for the emicizumab arm is based on the pooled data from patients treated with 1.5 mg emicizumab once weekly and patients treated with 3 mg every 2 weeks.
ABR: annualized bleeding rate; CI: confidence interval; FVIII: factor VIII; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; vs.: versus

Three adjusted indirect comparisons were calculated for each of the outcomes, treated bleeds and joint bleeds. Data from patients in the HAVEN 3 study with both approval-compliant dosages of 1.5 mg weekly and 3 mg every 2 weeks or the pooled data from both groups were used for emicizumab. Patients from the SPINART study were included in the indirect comparison for routine prophylaxis with factor VIII preparations. Depending on the availability of the data, the calculations were based on the reported effect measures (ratio of the annualized bleeding rates), on the modelled or the observed annualized bleeding rates per treatment arm. None of the calculated indirect comparisons showed statistically significant differences.

2.3.2 Before-after comparison

The company presented a before-after comparison for the comparison of routine prophylaxis with emicizumab versus routine prophylaxis with factor VIII preparations. The company had already pursued this approach in the first assessment of emicizumab in patients with haemophilia A and inhibitors (dossier assessment A18-20 [13,14]).

The comparison was based on data from patients who participated both in the observational study BH29768 [15-17] and in the approval study HAVEN 3. These patients continued their ongoing prophylactic therapeutic strategy with factor VIII preparations, which was not further specified, in the observational study (before phase) and received routine prophylaxis with emicizumab in the controlled HAVEN 3 study (after phase). As was the case in the first assessment of emicizumab, the before-after comparison now presented by the company was also unsuitable for the assessment of the added benefit. Analogous to the first assessment of emicizumab, the following reasons were particularly relevant for this:

- The company did not guarantee that there were similar conditions for conducting adequate prophylactic treatment in the different studies. In the HAVEN 3 study, this treatment was conducted under controlled study conditions. Treatment in the BH29768 study corresponded to an uncontrolled observation.
- This problem was also not solved by the fact that the company operationalized a subpopulation of 22 so-called “formally compliant” patients from the population of 44 patients. Irrespective of the fact that this did not lead to similar study conditions, the criteria chosen by the company were based on the lower limit of the dosage of approved recombinant and plasma-derived factor VIII preparations. These were unsuitable to identify patients with adequate routine prophylaxis with sufficient certainty.
- The effects in bleeding outcomes shown by the company were not large enough that they cannot be explained by the different study conditions alone. The results of the adjusted indirect comparisons conducted as examples showed no statistically significant differences between routine prophylaxis with emicizumab or with a recombinant factor VIII preparation (see Section 2.3.1).

The before-after comparison conducted by the company is explained in detail below.

Characteristics of the studies BH29768 and HAVEN 3 included by the company in the before-after comparison

Study BH29768 was a prospectively planned, non-interventional, multinational observational study in patients with congenital haemophilia A. The enrolled patients maintained their ongoing treatment with factor VIII preparations (strategy and dose) during the study and were observed in their respective local care environments. The study had 3 arms. Patients with factor VIII inhibitors were enrolled in arms A and B. Only patients aged ≥ 12 years without factor VIII inhibitors were observed in arm C. Hence, arm C of the BH29768 study was the study arm relevant for the present research question and constituted the before phase of the before-after comparison.

On completion of the BH29768 study, all patients from arm C were offered to participate in the subsequent interventional HAVEN 3 study. Allocation to the study arms was according to the previous therapeutic strategy. Only patients who had received prophylactic treatment, which was not further specified, in the before phase were candidates for the before-after comparison. Of 49 eligible patients, 44 patients were included in arm D of the HAVEN 3 study, where they received routine prophylaxis with emicizumab. This arm constituted the after phase of the before-after comparison. The HAVEN 3 study was an open-label, multicentre parallel group study. Besides the non-randomized arm D, 2 different dosages of emicizumab and episodic treatment with factor VIII preparations were compared in the 3 randomized arms of the study (A, B and C). Further details can be found in Section 2.3.1. A presentation of the study and intervention characteristics for the HAVEN 3 study can be found in Table 10 and Table 11 in Appendix A, and for the BH29768 study in Table 13 and Table 14 in Appendix B of the full dossier assessment.

Different study conditions of the before and after phases

The company based its described added benefit of emicizumab versus the ACT on an advantage in the annualized bleeding rates from the presented before-after comparison. Treatment in the BH29768 study consisted in the continuation of the ongoing treatment (strategy and dose) at study entry and observation of the events occurred in this uncontrolled treatment situation. In contrast, treatment with the study medication in the after phase took place under controlled conditions. Patients in arm D of the HAVEN 3 study received routine prophylaxis with 1.5 mg emicizumab per week. This discrepancy in study conditions between both study phases can lead to potentially biased results. In this situation, an advantage for one of the therapies can only be deduced with sufficient certainty from very large differences between the study arms.

Subpopulation of "formally compliant" patients not suitable

These methodological limitations were also not solved by the fact that the company formed a so-called "formally compliant" subpopulation for its analysis of the before-after comparison. For this purpose, the company converted the factor VIII doses documented by the patients during the BH29768 study into weekly doses. Based on this, it was checked whether the dosages corresponded to the lower limit of the approved dosage ranges of the respective preparations.

Short-acting factor VIII preparations had to be administered at a minimum dosage of 47 IU per kilogram body weight per week, and factor VIII preparations with prolonged half-lives at a minimum dosage of 35 IU per kilogram body weight per week. In addition, the frequency of administration had to comply with the SPC. These criteria had to be met for ≥ 80% of the weeks within the BH29768 study. This was the case for 22 patients, which the company included as so-called "formally compliant" patients in its analyses on the before-after comparison.

The operationalization chosen by the company only covered the lower limit of an approval-compliant dosage. The SPC of the recombinant drug octocog alfa [18], for example, recommends doses between 20 and 40 IU of factor VIII per kilogram body weight at intervals of 2 to 3 days, equivalent to a weekly dose range of 47 to 140 IU per kilogram body weight, for bleeding prophylaxis in patients with severe haemophilia A. Patients in the SPINART study, for example, received 75 to 105 IU per kilogram body weight weekly, which is clearly above the dose chosen by the company. Hence, the operationalization conducted by the company cannot be used to identify a subpopulation for which adequate routine prophylaxis can be assumed with sufficient certainty. Rather, it can be assumed that such a population could not be meaningfully operationalized on the basis of the available information, since the lack of controlled conditions in the multinational observational study makes the treatment of patients dependent on regional standards of care and reimbursement conditions.

Effect on bleeding rates not large enough

The company derived an added benefit of emicizumab from the statistically significant difference in favour of emicizumab for the outcome "bleeding events" in the before-after comparison. As described, the before-after comparison is assumed to have a high risk of bias due to the different conditions in the before and after phases. However, the observed effect from this comparison was not large enough not to be explicable by this risk of bias alone (ratio of the annualized bleeding rates [95% confidence interval (CI)]: treated bleeds: 0.47 [0.26; 0.87], joint bleeds: 0.47 [0.20; 1.09], see Table 15 in Appendix B of the full dossier assessment). The results of the indirect comparison showed no statistically significant difference between the treatment arms. Due to the methodological limitations of the before-after comparison, the indirect comparison was principally more suitable to estimate the effect of emicizumab on the annualized bleeding rates.

The company identified no effects in favour of emicizumab for other outcomes, so that, overall, no added benefit of emicizumab in comparison with the ACT resulted from the before-after comparison.

2.4 Results on added benefit

The company presented no suitable data for the assessment of the added benefit of emicizumab in its dossier. Hence, there was no hint of an added benefit of emicizumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of emicizumab in comparison with the ACT is shown in Table 6.

Table 6: Emicizumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Routine prophylaxis in patients with severe haemophilia A without factor VIII inhibitors	Plasma-derived or recombinant coagulation factor VIII preparations used as routine prophylaxis	Added benefit not proven
a: Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The assessment described above deviates from that of the company, which derived a hint of a non-quantifiable added benefit on the basis of the before-after comparison.

The G-BA decides on the added benefit.

2.6 List of included studies

Not applicable as the company presented no relevant data for the benefit assessment.

References for English extract

Please see full dossier assessment for full reference list.

The reference list contains citations provided by the company in which bibliographical information may be missing.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10.07.2017 [Accessed: 04.06.2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58.

3. F. Hoffmann-La Roche, Chugai Pharmaceuticals. A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients without inhibitors: study BH30071; primary clinical study report [unpublished]. 2018.

4. F. Hoffmann-La Roche, Chugai Pharmaceuticals. A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients without inhibitors: study BH30071; statistical analysis plan [unpublished]. 2017.

5. F. Hoffmann-La Roche, Chugai Pharmaceuticals. A randomized, multicenter, open-label, phase III clinical trial to evaluate the efficacy, safety, and pharmacokinetics of prophylactic emicizumab versus no prophylaxis in hemophilia A patients without inhibitors: study BH30071; protocol [unpublished]. 2016.

6. Mahlangu J, Oldenburg J, Paz-Priel I, Negrier C, Niggli M, Mancuso ME et al. Emicizumab prophylaxis in patients who have hemophilia A without inhibitors. N Engl J Med 2018; 379(9): 811-822.

7. Hoffmann-La Roche. A clinical trial to evaluate prophylactic emicizumab versus no prophylaxis in hemophilia A participants without inhibitors (HAVEN 3): study details [online]. In: ClinicalTrials.gov. 19.04.2019. URL: https://ClinicalTrials.gov/show/NCT02847637.

8. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L et al. Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART). Res Pract Thromb Haemost 2013; 11(6): 1119-1127.

9. Manco-Johnson MJ, Kempton CL, Reding MT, Lissitchkov T, Goranov S, Gercheva L et al. Corrigendum to "Randomized, controlled, parallel-group trial of routine prophylaxis vs. on-demand treatment with sucrose-formulated recombinant factor VIII in adults with severe hemophilia A (SPINART)" (J Thromb Haemost 2013; 11(6): 1119-1127). J Thromb Haemost 2014; 12(1): 119-122.

10. Manco-Johnson MJ, Lundin B, Funk S, Peterfy C, Raunig D, Werk M et al. Effect of late prophylaxis in hemophilia on joint status: a randomized trial. J Thromb Haemost 2017; 15(11): 2115-2124.

11. Bayer. Trial to evaluate the effect of secondary prophylaxis with rFVIII therapy in severe hemophilia A adult and/or adolescent subjects compared to that of episodic treatment (SPINART): study details [online]. In: ClinicalTrials.gov. 17.11.2014. URL: https://ClinicalTrials.gov/show/NCT00623480.

12. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol 1997; 50(6): 683-691.

13. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Emicizumab (Hämophilie A): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A18-20 [online]. 27.06.2018 [Accessed: 03.07.2018]. (IQWiG-Berichte; Volume 642). URL: https://www.iqwig.de/download/A18-20_Emicizumab_Nutzenbewertung-35a-SGB-V_V1-0.pdf.

14. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Emicizumab (Hämophilie A): Addendum zum Auftrag A18-20; Auftrag A18-49 [online]. 29.08.2018 [Accessed: 25.09.2018]. (IQWiG-Berichte; Volume 661). URL: https://www.iqwig.de/download/A18-49_Emicizumab_Addendum-zum-Auftrag-A18-20_V1-0.pdf.

15. F. Hoffmann-La Roche. A multicenter, non-interventional study evaluating bleeding incidence, health-related quality of life, and safety in patients with hemophilia A under standard-of-care treatment: study BH29768; NIS protocol [unpublished]. 2015.

16. F. Hoffmann-La Roche. A multicenter, non-interventional study evaluating bleeding incidence, health-related quality of life, and safety in patients with hemophilia A under standard-of-care treatment: study BH29768; final clinical study report [unpublished]. 2017.

17. Hoffmann-La Roche. A prospective study to collect high-quality documentation of bleeds, health-related quality of life (HRQoL), and safety outcomes in patients with hemophilia A treated with standard-of-care treatment: study details [online]. In: ClinicalTrials.gov. 30.05.2017. URL: https://ClinicalTrials.gov/show/NCT02476942.

18. Baxter. ADVATE (Octocog alfa): Fachinformation [online]. 06.2018 [Accessed: 11.02.2019]. URL: https://www.fachinfo.de.

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-26-emicizumab-haemophilia-a-benefit-assessment-according-to-35a-social-code-book-v.11924.html.