IQWiG Reports – Commission No. A18-20

Emicizumab (haemophilia A) –

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

Extract

[1] Translation of the executive summary of the dossier assessment *Emicizumab (Hämophilie A) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 27 June 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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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 27 March 2018.

Research question

The aim of this report is to assess the added benefit of emicizumab in comparison with the appropriate comparator therapy (ACT) in the routine prophylactic treatment of bleeding events in patients with haemophilia A and factor VIII inhibitors.

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

Table 2[2]: Research question of the benefit assessment of emicizumab

Research question	Indication[a]	ACT[b, c]
1	Routine prophylactic treatment of bleeding events in patients of all ages with haemophilia A and factor VIII inhibitors	▪ Routine prophylactic treatment with plasmatic or recombinant clotting factor VIII preparations in higher doses and/or ▪ Routine prophylactic treatment with a preparation with bypassing activity (human plasma fraction spiked with factor VIII inhibitor bypassing activity)
a: It is assumed that the patients in this indication are haemophilia patients requiring factor-VIII substitution. b: Presentation of the respective ACT specified by the G-BA. c: Episodic treatment alone using an agent with bypassing activity is not considered an ACT for the intended treatment objective of routine prophylaxis. Episodic treatment must be possible in all study arms. ACT: appropriate comparator therapy; G-BA: Joint Federal Committee		

The company expanded the ACT specified by the G-BA to include episodic treatment. However, episodic treatment is not an ACT for routine prophylactic treatment. This benefit assessment is therefore based on the ACT specified by the G-BA.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. A minimum study duration of 6 months was specified for deriving a conclusion on the added benefit.

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

Results

The company did not present any relevant data for the assessment of the added benefit of emicizumab in comparison with the ACT.

Direct comparison

For the benefit assessment of emicizumab, the company presented the direct comparative study HAVEN 1. In its randomized part, this open-label, actively controlled phase III study compares routine prophylactic emicizumab treatment to episodic treatment with bypassing agents in adults and adolescents (≥ 12 years of age) with haemophilia A and factor VIII inhibitors.

The direct comparison with episodic treatment with bypassing agents conducted in the HAVEN 1 study fails to address the question of this benefit assessment. The latter exclusively concerns the comparison of routine prophylactic emicizumab treatment versus routine prophylactic treatment with bypassing agents. The HAVEN 1 study presented by the company is therefore not suitable for deriving conclusions on the added benefit of emicizumab in direct comparison with the ACT.

Indirect comparison

For the comparison of routine prophylactic treatment with emicizumab and routine prophylactic treatment with bypassing agents, the company presented an adjusted indirect comparison using a common comparator. The common comparator is episodic treatment with bypassing agents. The company's study pool includes 3 studies: For emicizumab, the company included the pivotal study HAVEN 1. For routine prophylactic treatment with bypassing agents, it included the studies PROOF and ProFEIBA. The company calculated the effects once from the indirect comparison of the HAVEN 1 and PROOF studies and once from the indirect comparison of the HAVEN 1 and ProFEIBA studies. However, the 3 studies included by the company are not sufficiently similar and therefore not suitable for an indirect comparison.

The HAVEN 1 study is an open-label, multicentre pivotal study of emicizumab with 2 randomized and 2 non-randomized arms. The study included previously treated adults and adolescents (≥ 12 years of age) with congenital haemophilia A and factor VIII inhibitors, as well as high-titre factor VIII inhibitors (≥ 5 Bethesda units [BU]) in their history. The patients in the randomized part of the study (N = 53) previously received episodic treatment with bypassing agents and were randomized in a 2:1 ratio to routine prophylactic treatment with emicizumab (Arm A, n = 35) or episodic treatment with bypassing agents (Arm B, n = 18). In addition to these randomized arms, the study also includes 2 other, non-randomized arms (C and D), in which the patients were prophylactically treated with emicizumab.

The ProFEIBA study is a randomized, open-label, multicentre cross-over study. The study included patients (> 2 years of age) previously treated episodically with bypassing agents who had a history of congenital haemophilia A and factor VIII inhibitors, as well as high-titre factor VIII inhibitors (≥ 5 BU). The patients (N = 34) were randomized at a 1:1 ratio and received either routine prophylactic (n = 17) or episodic (n = 17) treatment for 6 months with factor VIII

inhibitor bypassing activity (FEIBA). Following this initial treatment phase and a subsequent 3-month washout period, patients switched to the other treatment (cross-over) for another 6 months.

The PROOF study is a randomized, open-label, multicentre study. The study included patients (≥ 4 to ≤ 65 years of age) who previously received episodic bypassing agent treatment and had a history of congenital haemophilia A or B and factor VIII inhibitors, as well as high-titre factor VIII inhibitors (≥ 5 BU). The patients (N = 36) were randomized to the study arms routine prophylactic FEIBA treatment (n = 17) or episodic FEIBA treatment (n = 19) and treated for 12 months ± 14 days.

Lack of similarity of the included studies

Although all 3 studies examined emicizumab or the ACT, making an indirect comparison through a common comparator requires similarity of the included studies. This similarity does not exist in this case:

- When considering the bleeding rates in the common comparator for the outcome intra-articular bleeding, the HAVEN 1 study on the one hand and the studies PROOF and ProFEIBA on the other hand exhibited considerable differences in annual bleeding rates over the course of the study in both the median (PROOF vs. HAVEN 1: 22.9 vs. 1.0) and the mean (PROOF or ProFEIBA vs. HAVEN 1: 30.1 or 21.6 vs. 8.1). This shows that there is a considerable difference in the risk of intra-articular bleeding between the patients of the emicizumab study and those of the studies with the ACT.
- The outcome annualized bleeding rate (ABR) further corroborates this lack of similarity. Assuming that the bleeding events recorded in the studies with the ACT represent treated bleeding events (as done by the company), considerable differences result in the baseline risk of patients in the common comparator arm: the median annual bleeding rates of the PROOF vs. HAVEN 1 studies (28.7 vs. 18.8) are not of a comparable magnitude.
- Regarding patient characteristics, the PROOF and ProFEIBA studies are missing information that would allow for further conclusions to be drawn on the severity of disease, such as the time since factor VIII inhibitor diagnosis, prior immune tolerance induction (ITI) therapy, inhibitor titre at baseline, and number of bleeding events in the last 24 weeks before study inclusion. For the ProFEIBA study, information on ethnicity and number of target joints before study inclusion is also missing. The similarity of the included populations can therefore not be demonstrated by means of the basic characteristics.

Whether the lack of similarity as measured by the joint bleeding rate and overall bleeding rate (ABR) is seen consistently depends on whether only treated bleeding events are considered in the overall bleeding rate, as done by the company. It is unclear whether this was the case in the studies since publications on the PROOF and ProFEIBA studies fail to clearly define the operationalization of the outcome ABR (all bleeding events vs. treated bleeding events).

Conversely, when assuming that all bleeding events are referred to, the assessments from intra-articular bleeding events will not be supported, but the indirect comparison will no longer show a benefit of emicizumab. Contrary to the company's approach, the calculation of the indirect comparison was performed by first combining the two studies PROOF and ProFEIBA through a meta-analysis model with fixed effect and then using the pooled effect estimate of the ABR relationships for the adjusted indirect comparison according to Bucher [3].

Overall, it was found that the studies are not sufficiently similar for an indirect comparison and that, depending on the operationalization of the bleeding rate, no advantage is found for emicizumab.

Other studies

Before-and-after comparisons

For this research question, the company presents 2 before-and-after comparisons. These comparisons are based on the data of patients who participated in the observation study BH29768 as well as one of the approval studies HAVEN 1 (arm C, patients ≥ 12 years of age) or HAVEN 2 (patients < 12 years of age).

Study BH29768 is a prospectively planned, non-interventional, multinational observational study in patients with congenital haemophilia A. Patients were observed in their local care environment and assigned to different cohorts based on their age and inhibitor status:

- Cohort A: Patients ≥ 12 years of age with factor VIII inhibitors (≥ 5 BU), N = 103
- Cohort B: Patients < 12 years of age with factor VIII inhibitors (≥ 5 BE), N = 24

Depending on their respective treatment plan before the start of the study, patients were placed in either the group with prophylactic treatment with bypassing agents (cohort A: n = 28; cohort B: n = 14) or the group with episodic treatment with bypassing agents (cohort A: n = 75; cohort B: n = 10) and continued their treatment from before the start of the study.

HAVEN 2 is a single-arm, multicentre approval study of emicizumab for paediatric patients. The study included children (< 12 years of age) and adolescents (12 to 17 years of age, < 40 kg body weight) previously treated with bypassing agents who had congenital haemophilia A and high-titre factor VIII inhibitors (≥ 5 BU) in their medical history (N = 63).

The company states that the before-and-after comparisons exclusively considered patients who received prophylactic treatment with FEIBA in study BH29768 and were later treated in the studies HAVEN 1 (non-randomized Arm C of the study) or HAVEN 2 with emicizumab prophylaxis. This applied to 18 patients ≥ 12 years of age (comparison BH29768 / HAVEN 1) and 13 patients < 12 years of age (comparison BH29768 / HAVEN 2).

However, the analyses presented by the company are not suitable for deriving an added benefit of emicizumab. This is mainly due to the fact that a large percentage of the subpopulations from

study BH29768 which were considered by the company in the two presented comparisons did not receive adequate prophylactic treatment.

Comparison of individual arms of different studies

The company additionally presented a comparison of individual arms from different studies. This comparison is based on the results of the intervention arm (arm A, emicizumab prophylaxis) of the HAVEN 1 study (n = 35) and the results from all patients who should have received prophylactic treatment with bypassing agents in the BH29768 study (n = 28).

In addition to the fact that a non-adjusted comparison of individual study arms is generally unsuitable, the analyses presented by the company are unsuitable for deriving an added benefit of emicizumab since

- a large percentage of patients included in study BH29768 did not receive adequate prophylactic treatment,
- the included patients from studies BH29768 and HAVEN 1 differ in their prior treatment.

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

On the basis of the results presented, the probability and extent of the added benefit of the drug emicizumab compared with the ACT are assessed as follows:

Table 3 shows a summary of the probability and extent of added benefit of emicizumab.

[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: Emicizumab – probability and extent of added benefit

Indication[a]	**ACT**[b, c]	**Probability and extent of added benefit**
Routine prophylactic treatment of bleeding events in patients of all ages with haemophilia A and inhibitors to factor VIII	▪ Routine prophylactic treatment with plasmatic or recombinant clotting factor VIII at a higher dose and/or ▪ Routine prophylactic treatment with a drug product with bypassing activity (human plasma fraction spiked with factor VIII inhibitor bypassing activity)	Added benefit not proven
a: It is assumed that the patients in this indication are haemophilia patients requiring factor VIII substitution b: Presentation of the respective ACT specified by the G-BA. c: Episodic treatment alone using an agent with bypassing activity is not considered an ACT for the intended treatment objective of routine prophylaxis. Episodic treatment must always be possible in all study arms. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee		

The G-BA decides on the added benefit.

Note:

An addendum (A18-49) to dossier assessment A18-20 has been published.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-20-emicizumab-haemophilia-a-benefit-assessment-according-to-35a-social-code-book-v.9393.html.