Marstacimab (haemophilia A)

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

EXTRACT

Project: A25-16 Version: 1.0 Status: 29 Apr 2025 DOI: 10.60584/A25-16_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Marstacimab (Hämophilie A) – Nutzenbewertung gemäß § 35a SGB V*. 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

Marstacimab (haemophilia A) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

3 February 2025

Internal Project No.

A25-16

DOI-URL

https://doi.org/10.60584/A25-16_en

Address of publisher

Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Siegburger Str. 237
50679 Köln
Germany

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

Recommended citation

Institute for Quality and Efficiency in Health Care. Marstacimab (haemophilia A); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A25-16_en.

Keywords

Marstacimab, Hemophilia A, Child, Adolescent, Adult, Benefit Assessment

Medical and scientific advice

- Helmut Ostermann, LMU Hospital, 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.

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Dragana Mitrovic.

IQWiG thanks the respondent and the Deutsche Hämophiliegesellschaft e.V. (German Haemophilia Society) for participating in the written exchange and for their support. Neither the respondent nor the German Haemophilia Society were involved in the actual preparation of the dossier assessment.

IQWiG employees involved in the dossier assessment

- Charlotte Zeitler
- Dorothee Ehlert
- Jona Lilienthal
- Sabine Ostlender
- Anne-Kathrin Petri
- Daniela Preukschat
- Min Ripoll
- Claudia Selbach

Part I: Benefit assessment

I Table of contents

I List of tables[2]

Page

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

I List of abbreviations

Abbreviation	Meaning
ABR	annualized bleeding rate
ACT	appropriate comparator therapy
EMA	European Medicines Agency
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
SGB	Sozialgesetzbuch (Social Code Book)

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 marstacimab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 3 February 2025.

Research question

The aim of this report is to assess the added benefit of marstacimab compared with the appropriate comparator therapy (ACT) as routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors.

The research question presented in Table resulted from the ACT specified by the G-BA.

Table 2: Research question for the benefit assessment of marstacimab

Therapeutic indication	**ACT**[a, b]
Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors	Treatment of physician's choice, selecting from either routine prophylaxis with recombinant or human plasma-derived coagulation factor VIII products, or emicizumab
a. Presented is the ACT specified by the G-BA. b. Comments from the G-BA: ▫ It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor VIII substitution. ▫ On-demand treatment alone is not an adequate ACT for the given therapeutic indication. ▫ Additional on-demand treatment must fundamentally be possible in all study arms. ▫ A single-comparator study with a coagulation factor VIII product is sufficient for the benefit assessment. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

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. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Results

Consistent with the findings of the company, a review of the completeness of the study pool did not identify any randomized controlled trials (RCTs) directly comparing marstacimab with the ACT.

Evidence presented by the company – BASIS study

As the company did not identify any studies for a direct comparison, it conducted an information retrieval for further studies on marstacimab. In doing so, it identified the BASIS study (B7841005) and used this study to derive the added benefit.

The BASIS study is an open-label, single-arm phase 3 study that included male patients aged 12 to 74 years with severe haemophilia A (factor VIII activity < 1%) or moderately severe to severe haemophilia B (factor IX activity ≤ 2%) and a body weight of at least 35 kg.

The study comprised a 6-month observational phase, in which patients continued the treatment strategy (either routine prophylaxis with factor VIII or factor IX products respectively or on-demand treatment) they had received before study inclusion. A 12-month active treatment phase with subcutaneous marstacimab followed. The primary outcome of the study was the non-inferiority of the annualized bleeding rate (ABR) for treated bleeds. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

In Module 4 A of the dossier the company presented analyses of the BASIS study in the form of an intra-individual before-after comparison. The subpopulation analysed included patients with severe haemophilia A without inhibitors who received routine prophylaxis in the observational phase.

BASIS study unsuitable for the benefit assessment

The results of the before-after comparison from the BASIS study presented by the company are not suitable for the derivation of an added benefit for the following reasons.

A before-after comparison with the factor VIII prophylactic treatment in the observational phase and marstacimab in the active treatment phase cannot be meaningfully interpreted due to the differing study conditions of the non-interventional observational phase and the interventional treatment phase of the BASIS study. During the 6-month observational phase, patients were to continue their routine prophylaxis, which had been initiated at least 6 months previously, without any change. However, the company did not explain in Module 4 A which doses were used and to what extent this corresponds to a treatment of the physician's choice with a factor VIII product. Additionally, different recording intervals were planned for the 2 study phases. For example, during the observational phase only telephone visits every 60 days were carried out. In contrast, during the active treatment phase with marstacimab

additional visits at the study centre meant the period between visits was only half as long. Furthermore, it should be noted that there is uncertainty as to whether the observed effects after switching treatment are in fact attributable to the intervention or to other patient-individual factors.

In addition, within the BASIS study the mean ABR for treated bleeds for the patients with severe haemophilia A on routine prophylaxis was at 9.16 comparably high, so that it is unclear whether treatment with routine prophylaxis was adequately implemented.

Finally, the statistically significant differences shown by the company are not so large that they could not be explained by the differing study conditions for the respective treatment phases described above alone.

Results on added benefit

Since no relevant studies are available for the benefit assessment, there is no hint of an added benefit of marstacimab 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 shows a summary of the probability and extent of the added benefit of marstacimab.

[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: Marstacimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors	Treatment of physician's choice, selecting from either routine prophylaxis with recombinant or human plasma-derived coagulation factor VIII products, or emicizumab	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor VIII substitution.
- On-demand treatment alone is not an adequate ACT for the given therapeutic indication.
- Additional on-demand treatment must fundamentally be possible in all study arms.
- A single-comparator study with a coagulation factor VIII product is sufficient for the benefit assessment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The G-BA decides on the added benefit.

I 2 Research question

The aim of this report is to assess the added benefit of marstacimab compared with the ACT as routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors.

The research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question for the benefit assessment of marstacimab

Therapeutic indication	**ACT**[a, b]
Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors	Treatment of physician's choice, selecting from either routine prophylaxis with recombinant or human plasma-derived coagulation factor VIII products, or emicizumab

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor VIII substitution.
- On-demand treatment alone is not an adequate ACT for the given therapeutic indication.
- Additional on-demand treatment must fundamentally be possible in all study arms.
- A single-comparator study with a coagulation factor VIII product is sufficient for the benefit assessment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

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. Studies with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs 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 marstacimab (status: 22 November 2024)
- Bibliographical literature search on marstacimab (last search on 22 November 2024)
- Search of trial registries/trial results databases for studies on marstacimab (last search on 22 November 2024)
- Search on the G-BA website for marstacimab (last search on 22 November 2024)

To check the completeness of the study pool:

- Search of trial registries for studies on marstacimab (last search on 17 February 2025); for search strategies, see I Appendix A of the full dossier assessment

Consistent with the findings of the company, the review of the completeness of the study pool did not identify any RCTs directly comparing marstacimab with the ACT.

As the company did not identify any studies for a direct comparison, it conducted an information retrieval for further studies on marstacimab. In doing so, it identified the BASIS study (B7841005) [3] and used this study to derive the added benefit. The company did not conduct an information retrieval for the ACT.

Evidence presented by the company – BASIS study

The BASIS study is an open-label, single-arm phase 3 study that included male patients aged 12 to 74 years with severe haemophilia A (factor VIII activity < 1%) or moderately severe to severe haemophilia B (factor IX activity ≤ 2%) and a body weight of at least 35 kg. The patients were assigned to either the inhibitor cohort (patients with factor VIII/factor IX inhibitors) or the non-inhibitor cohort (patients without factor VIII/factor IX inhibitors).

The study comprised a 6-month observational phase, in which patients continued the treatment strategy (either routine prophylaxis with factor VIII or factor IX products respectively or on-demand treatment) they had received before study inclusion. Patients who received routine prophylaxis with factor concentrates prior to study inclusion were required to demonstrate therapy compliance of ≥ 80% within the 6 months prior to study inclusion. Patients for whom a significant increase in the dose or frequency of routine prophylaxis was necessary during the observational phase were to be excluded from the study at the investigator's discretion. A 12-month active treatment phase with subcutaneous marstacimab followed. Following a starting dose of 300 mg, a weekly dose of 150 mg marstacimab was

administered. An increase to 300 mg after 6 months was allowed for patients who fulfilled the criteria for a dose escalation. The primary outcome of the study was the non-inferiority of the ABR for treated bleeds. Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

In Module 4 A the company presented analyses of the BASIS study in the form of an intra-individual before-after comparison. The subpopulation analysed included patients with severe haemophilia A without inhibitors who received routine prophylaxis in the observational phase.

BASIS study unsuitable for the benefit assessment

The results of the before-after comparison from the BASIS study presented by the company are not suitable for the derivation of an added benefit for the following reasons.

A before-after comparison with the factor VIII prophylactic treatment in the observational phase and marstacimab in the active treatment phase cannot be meaningfully interpreted due to the differing study conditions of the non-interventional observational phase and the interventional treatment phase of the BASIS study. During the 6-month observational phase, patients were to continue their routine prophylaxis, which had been initiated at least 6 months previously, without any change. However, the company did not explain in Module 4 A which doses were used and to what extent this corresponds to a treatment of the physician's choice with a factor VIII product. Additionally, different recording intervals were planned for the 2 study phases. For example, during the observational phase only telephone visits every 60 days were carried out. In contrast, during the active treatment phase with marstacimab additional visits at the study centre meant the period between visits was only half as long. Furthermore, it should be noted that there is uncertainty as to whether the observed effects after switching treatment are in fact attributable to the intervention or to other patient-individual factors.

As already discussed in the concept for routine practice data collection for marstacimab [4], in the BASIS study the patients with haemophilia A on routine prophylaxis in the observational phase showed a higher mean ABR for treated bleeds than was the case in other studies. The European Medicines Agency (EMA) assessment also referred to this discrepancy [5]. The reviews by Mannucci 2023 [6] and Graf 2020 [7] show a mean ABR of 3 to 5 for prophylactic treatment. The authors of Mannucci 2023 also found the ABR in observational studies to be higher than in interventional studies. In the resolution on the requirement of routine practice data collection for valoctocogene roxaparvovec for the treatment of severe haemophilia A [8] an ABR of 3 on the comparator therapy was assumed. In the BASIS study the mean ABR for treated bleeds for the patients with severe haemophilia A on routine prophylaxis was at 9.16

comparably high, so that it is unclear whether treatment with routine prophylaxis was adequately implemented.

Finally, the statistically significant differences shown by the company are not so large that they could not be explained by the differing study conditions for the respective treatment phases described above alone.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of marstacimab compared with the ACT as routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors. There is thus no hint of an added benefit of marstacimab 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 marstacimab in comparison with the ACT is summarized in Table 5.

Table 5: Marstacimab – probability and extent of added benefit

Therapeutic indication	**ACT**[a, b]	**Probability and extent of added benefit**
Routine prophylaxis of bleeding episodes in patients 12 years of age and older, weighing at least 35 kg, with severe haemophilia A (congenital factor VIII deficiency, FVIII < 1%) without factor VIII inhibitors	Treatment of physician's choice, selecting from either routine prophylaxis with recombinant or human plasma-derived coagulation factor VIII products, or emicizumab	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Comments from the G-BA:
- It is assumed that the patient population for the therapeutic indication in question is patients with haemophilia requiring factor VIII substitution.
- On-demand treatment alone is not an adequate ACT for the given therapeutic indication.
- Additional on-demand treatment must fundamentally be possible in all study arms.
- A single-comparator study with a coagulation factor VIII product is sufficient for the benefit assessment.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee

The assessment described above concurs with that by the company.

The G-BA decides on the added benefit.

I 6 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. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Allgemeine Methoden; Version 7.0 [online]. 2023 [Accessed: 02.09.2024]. URL: https://www.iqwig.de/methoden/allgemeine-methoden_version-7-0.pdf.

2. Skipka G, Wieseler B, Kaiser T et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2016; 58(1): 43-58. https://doi.org/10.1002/bimj.201300274.

3. Pfizer. Study of the Efficacy and Safety PF-06741086 in Adult and Teenage Participants With Severe Hemophilia A or Moderately Severe to Severe Hemophilia B [online]. 2024 [Accessed: 04.03.2025]. URL: https://clinicaltrials.gov/study/NCT03938792.

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Marstacimab (Hämophilie A und B); Bewertung gemäß § 35a SGB V; AbD-Konzept [online]. 2024 [Accessed: 03.04.2025]. URL: https://doi.org/10.60584/A24-39.

5. European Medicines Agency. Hympavzi; Assessment report [online]. 2024 [Accessed: 07.03.2025]. URL: https://www.ema.europa.eu/en/documents/assessment-report/hympavzi-epar-public-assessment-report_en.pdf.

6. Mannucci PM, Kessler CM, Germini F et al. Bleeding events in people with congenital haemophilia A without factor VIII inhibitors receiving prophylactic factor VIII treatment: A systematic literature review. Haemophilia 2023; 29(4): 954-962. https://doi.org/10.1111/hae.14803.

7. Graf L, Yan S, Shen MC et al. A systematic review evaluating the efficacy and factor consumption of long-acting recombinant factor VIII products for the prophylactic treatment of hemophilia A. J Med Econ 2020; 23(12): 1493-1498. https://doi.org/10.1080/13696998.2020.1828092.

8. Gemeinsamer Bundesausschuss. Beschluss des Gemeinsamen Bundesausschusses über eine Änderung der Arzneimittel-Richtlinie: (AM-RL) Anlage XII – Nutzenbewertung von Arzneimitteln mit neuen Wirkstoffen nach § 35a des Fünften Buches Sozialgesetzbuch (SGB V); Valoctocogen Roxaparvovec (schwere Hämophilie A); Forderung einer anwendungsbegleitenden Datenerhebung und von Auswertungen [online]. 2023 [Accessed: 07.03.2025]. URL: https://www.g-ba.de/downloads/39-261-5866/2023-02-02_AM-RL-XII_Valoctocogen_Roxaparvovec_AbD-002_Forderung_BAnz.pdf.

The full report (German version) is published under https://www.iqwig.de/en/projects/a25-16.html.