Spesolimab
(generalized pustular psoriasis)

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

EXTRACT

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[1] Translation of Sections I 1 to I 4 of the dossier assessment *Spesolimab (generalisierte pustulöse Psoriasis) – 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.

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

Patient and family involvement

The questionnaire on the disease and its treatment was answered by Marius Grosser.

IQWiG thanks the respondent for participating in the written exchange about how he experienced the disease and its treatment and about the treatment goals. The respondent was not involved in the actual preparation of the dossier assessment.

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Part I: Benefit assessment

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

I List of abbreviations

Abbreviation	**Meaning**
ACT	appropriate comparator therapy
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GPPGA	Generalized Pustular Psoriasis Physician Global Assessment
Intravenously	IV
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 (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 spesolimab. 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 25 January 2023.

Research question

The aim of the present report is to assess the added benefit of spesolimab as monotherapy in comparison with systemic glucocorticoids as appropriate comparator therapy (ACT) for the treatment of flares in adult patients with generalized pustular psoriasis.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of spesolimab (monotherapy)

Therapeutic indication	**ACT**[a]
Treatment of flares in adults with generalized pustular psoriasis[b]	Systemic glucocorticoids[c]
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that the present therapeutic indication refers exclusively to flare therapy for acute treatment. Long-term treatment is not addressed here. c. If patients receive treatment for generalized pustular psoriasis independently of the acute flare, this should be documented. Treatment adjustment during an acute flare should be possible. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company follows the ACT specified by the G-BA and also names systemic glucocorticoids, but at the same time describes that the long-term use of systemic glucocorticoids should be avoided in generalized pustular psoriasis and that the side effects influenced by treatment duration and dose include the triggering of a new flare. Therefore, the use of systemic glucocorticoids is critically discussed by medical experts.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

For the derivation of the added benefit, randomized controlled trials (RCTs) with event-driven study duration are considered useful in the present therapeutic indication, in which, for

example, the time to absence of symptoms or the time to occurrence of the next flare is investigated. At the same time, a minimum duration of 12 weeks should be fulfilled.

Results

No relevant RCT was identified for the direct comparison of spesolimab with the ACT. This departs from the company's approach, which identified the RCT EFFISAYIL 1 comparing spesolimab with placebo as relevant and used it for its assessment. For this study, the company describes that in addition to the administration of placebo, it was possible for patients in the comparator arm to receive treatment of physician's choice as an alternative medication, which was not limited and could therefore also include systemic glucocorticoids. However, within the first week after randomization, only 1 patient out of a total of 18 patients in the comparator arm (5.6%) actually received an alternative medication in addition to placebo, consisting of prednisolone, ciclosporin, methotrexate, betamethasone dipropionate and betamethasone valerate. In contrast, the majority of patients in the comparator arm (94.4%) only received placebo during this period. Thus, the ACT for the treatment of flares specified by the G-BA has not been implemented in the comparator arm of the EFFISAYIL 1 study. Therefore, the analyses on the EFFISAYIL 1 study presented by the company are unsuitable for the present benefit assessment.

Irrespective of the critical discussion about the use of systemic glucocorticoids, which the company addresses in the dossier, the patients in the comparator arm of the EFFISAYIL 1 study also received no other therapy for the treatment of the acute flare and no basic therapy for generalized pustular psoriasis from the onset of the flare until day 8. Instead, the basic therapy, which 18 of the patients in the spesolimab arm (51.4%) and 9 in the placebo arm (50.0%) were still receiving during study inclusion, had to be discontinued before the first dose of spesolimab or placebo, either with a certain lead time or at the latest with the onset of the flare. It is likely that this could lead to additional worsening of the disease, especially in the absence of an alternative treatment. Overall, this approach is not considered appropriate in the present therapeutic indication, irrespective of the discussion on the use of systemic glucocorticoids.

In addition to the points of criticism already mentioned, the comparative analyses for the EFFISAYIL 1 study only refer to a period of 8 days, as the majority of patients in the placebo arm received unblinded spesolimab on day 8 (15 of 18 patients [83.3%]). Subsequent recordings in the study therefore mainly refer to the comparison of immediate treatment of the flare with spesolimab versus delayed treatment with spesolimab. However, a comparative analysis over 8 days is considered too short in the present therapeutic indication despite the consideration of the flare therapy. The background to this is that retrospective data on the **patients included in the EFFISAYIL 1 study show that a typical flare lasted 1 to 4 weeks in the majority of patients for whom corresponding data are available. Against this background,

the comparative analyses over a period of 8 days, as available for the EFFISAYIL 1 study, are not sufficient.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of spesolimab 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 probability and extent of the added benefit of spesolimab.

Table 3: Spesolimab (monotherapy) – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of flares in adults with generalized pustular psoriasis[b]	Systemic glucocorticoids[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the present therapeutic indication refers exclusively to flare therapy for acute treatment. Long-term treatment is not addressed here.
c. If patients receive treatment for generalized pustular psoriasis independently of the acute flare, this should be documented. Treatment adjustment during an acute flare should be possible.

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

The G-BA decides on the added benefit.

[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].

I 2 Research question

The aim of the present report is to assess the added benefit of spesolimab as monotherapy in comparison with systemic glucocorticoids as ACT for the treatment of flares in adult patients with generalized pustular psoriasis.

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

Table 4: Research question of the benefit assessment of spesolimab (monotherapy)

Therapeutic indication	**ACT**[a]
Treatment of flares in adults with generalized pustular psoriasis[b]	Systemic glucocorticoids[c]
a. Presented is the ACT specified by the G-BA. b. According to the G-BA, it is assumed that the present therapeutic indication refers exclusively to flare therapy for acute treatment. Long-term treatment is not addressed here. c. If patients receive treatment for generalized pustular psoriasis independently of the acute flare, this should be documented. Treatment adjustment during an acute flare should be possible. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee	

The company follows the ACT specified by the G-BA and also names systemic glucocorticoids, but at the same time describes, with reference to Robinson 2012 [3] and Choon 2014 [4], that the long-term use of systemic glucocorticoids should be avoided in generalized pustular psoriasis and that the side effects influenced by treatment duration and dose include the triggering of a new flare. Therefore, the use of systemic glucocorticoids is critically discussed by medical experts, whereby the company refers to Weisenseel 2016 [5].

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA.

The assessment is conducted by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier.

For the derivation of the added benefit, randomized controlled trials (RCTs) with event-driven study duration are considered useful in the present therapeutic indication, in which, for example, the time to absence of symptoms or the time to occurrence of the next flare is investigated. At the same time, a minimum duration of 12 weeks should be fulfilled. This deviates from the company's inclusion criteria, which formulated no specific requirement for the minimum duration of the studies.

I 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 spesolimab (status: 15 November 2022)
- bibliographical literature search on spesolimab (last search on 16 November 2022)
- search in trial registries/trial results databases for studies on spesolimab (last search on 15 November 2022)
- bibliographical literature search on the ACT (last search on 16 November 2022)
- search in trial registries/trial results databases for studies on the ACT (last search on 15 November 2022)

To check the completeness of the study pool:

- search in trial registries for studies on spesolimab (last search on 7 February 2023); for search strategies, see Appendix I A of the full dossier assessment

The check for completeness of the study pool identified no relevant RCT for the direct comparison of spesolimab with the ACT. This departs from the company's approach, which identified the RCT EFFISAYIL 1 [6] comparing spesolimab with placebo as relevant and used it for its assessment.

The company itself described that administration of systemic glucocorticoids in the placebo arm of the EFFISAYIL 1 study was possible, but not regularly planned. Nevertheless, it used the study for its assessment, arguing that it represents the only available evidence in the present therapeutic indication. Based on its information retrieval, the company neither identified RCTs on the direct comparison of spesolimab with systemic glucocorticoids, nor studies for an adjusted indirect comparison using placebo as common comparator or further studies on the treatment with systemic glucocorticoids in the present therapeutic indication.

As already described above, concurring with the company, no RCTs were identified on the direct comparison of spesolimab with systemic glucocorticoids. The completeness of the company's study pool on the adjusted indirect comparison of spesolimab with systemic glucocorticoids using placebo as common comparator or on further studies on the treatment with systemic glucocorticoids was not checked.

For the placebo-controlled EFFISAYIL 1 study, the company describes that in addition to the administration of placebo, it was possible for patients in the comparator arm to receive treatment of physician's choice as an alternative medication, which was not limited and could

therefore also include systemic glucocorticoids. However, within the first week after randomization, only 1 (5.6%) patient out of a total of 18 patients in the comparator arm actually received an alternative medication in addition to placebo, consisting of prednisolone, ciclosporin, methotrexate, betamethasone dipropionate and betamethasone valerate. In contrast, the majority of patients in the comparator arm (94.4%) only received placebo during this period. Thus, the ACT for the treatment of flares specified by the G-BA has not been implemented in the comparator arm of the EFFISAYIL 1 study. Therefore, the analyses on the EFFISAYIL 1 study presented by the company are unsuitable for the present benefit assessment. b. See Section I 3.2 of the present assessment for more detailed reasoning.

Irrespective of the critical discussion about the use of systemic glucocorticoids, which the company addresses in the dossier (see Chapter I 2), the patients in the comparator arm of the EFFISAYIL 1 study also received no other therapy for the treatment of the acute flare and no basic therapy for generalized pustular psoriasis from the onset of the flare until day 8. This approach is not considered appropriate in the present therapeutic indication, irrespective of the discussion on the use of systemic glucocorticoids (for details see Section I 3.2).

I 3.1 Evidence provided by the company

EFFISAYIL 1 study

The EFFISAYIL 1 study is a double-blind, randomized multicentre study comparing spesolimab with placebo. Included were adult patients with generalized pustular psoriasis with an acute moderate to severe flare. In the study, a flare was defined as a Generalized Pustular Psoriasis Physician Global Assessment (GPPGA) total score ≥ 3 in conjunction with the presence of fresh pustules (new occurrence or worsening of existing pustules), a GPPGA pustule score ≥ 2, and a body surface area of ≥ 5% covered with erythema and pustules.

In the study, allocation to treatment with spesolimab or placebo was performed with the occurrence of the flare. This could either already be present at the time of inclusion in the study or the patients were observed for 6 months after inclusion for the occurrence of a flare. In the latter case, randomization and treatment took place with the occurrence of a flare.

Overall, 53 patients were included and allocated in a 2:1 ratio either to treatment with spesolimab (N = 35) or to placebo (N = 18). Randomization was stratified by region (Japan vs. rest of the world).

The patients received 900 mg spesolimab intravenously (IV) or placebo IV for the treatment of the flare within the framework of the study. In addition, administration of an alternative medication of physician's choice was possible in both study arms in the event of a worsening of the disease (according to the investigator’s assessment), which was not subject to any restrictions. If, at the time of study inclusion, the patients were receiving a basic therapy with

methotrexate, ciclosporin and/or retinoids for the treatment of generalized pustular psoriasis, this could initially be continued until the onset of the flare within the framework of the study. However, the basic therapy had to be discontinued at the latest with the onset of the flare before the first administration of spesolimab or placebo. Other systemic basic therapies for the treatment of generalized pustular psoriasis, such as infliximab, cyclophosphamide or corticosteroids, had to be discontinued with a certain lead time (e.g. 2 months for infliximab, 30 days for cyclophosphamide or systemic corticosteroids) before the treatment of the flare (i.e. before randomization). Topical therapies or phototherapies were also not allowed with the onset of the flare and the start of treatment in the study. Patients who had an immediately life-threatening flare or a flare that required intensive care were excluded from the study.

In the study, spesolimab was administered once with 900 mg spesolimab IV at the onset of the flare, according to the recommendations of the SPC [7]. Moreover, unblinded single administration of spesolimab at the same dose was possible in both study arms on day 8, provided that no alternative medication had been given during the course of the study and there was no improvement in symptoms (defined as GPPGA total score ≥ 2 and GPPGA pustule score ≥ 2). The option of such a 2nd administration of spesolimab 1 week after the initial dose also corresponds to the specifications of the SPC for spesolimab in persistent flare symptoms [7].

Up to day 8, the study design offered the option to administer an alternative medication in both study arms if the investigator determined a worsening of the disease, but according to the study protocol it was recommended in the case of stable disease to wait until the primary outcome of the study was recorded on day 8, as on this day an unblinded administration of spesolimab could take place in both study arms - provided that the patients had not previously received an alternative medication. If, during the course of the study (between day 8 and week 12), there was an initial improvement in symptoms (defined as a GPPGA total score of 0 or 1) followed by the occurrence of a new flare (defined as an increase in GPPGA total score by ≥ 2 points and an increase in GPPGA pustule score by ≥ 2), a further unblinded administration of 900 mg spesolimab IV was possible as part of the flare treatment. This could only be given once and was independent of the therapies already received in the previous course of the study. Overall, spesolimab administration was limited to a maximum of 3 times in the intervention arm (twice to treat the flare at baseline and on day 8 of the study as well as once to treat a further flare) and to a maximum of 2 times in the placebo arm (once to treat the flare on day 8 of the study and once to treat a further flare). If further flares occurred, these could only be treated with another alternative medication of physician’s choice.

In fact, only a few patients in the study received an alternative medication up to day 8: 2 patients in the intervention arm (5.7%) and 1 patient in the placebo arm (5.6%). Due to a lack of improvement of the symptoms, however, a large proportion of patients especially in the

placebo arm received unblinded treatment with spesolimab on day 8: 12 patients in the spesolimab arm (34.3%) and 15 patients in the placebo arm (83.3%).

Follow-up of the study participants for up to 16 weeks took place after the last administration of the study medication. Following the study, patients included had the option of participating in an unblinded extension study. In this case, the patients were followed up until the first administration of the study medication in the extension study, but at least until week 12.

Primary outcome of the study was the complete absence of pustules (GPPGA pustule score 0). Further outcomes were recorded in the categories of morbidity, health-related quality of life and side effects.

Analyses presented

Based on the EFFISAYIL 1 study, the company presented analyses for day 8, week 4 and week 12. It used the results at the analysis date "day 8" to derive a conclusion on the added benefit of spesolimab versus systemic glucocorticoids and presented the other analyses dates as supplementary information. It justified this with the argument that the majority of patients in the placebo arm received unblinded spesolimab on day 8 (15 out of 18 patients [83.3%]). Although this justification is basically comprehensible, as, after day 8, the comparison in the study relates primarily to a direct therapy of the flare with spesolimab versus a delayed therapy with spesolimab, no conclusions on the added benefit of spesolimab compared to the ACT specified by the G-BA can be derived on the basis of the analyses on day 8 either (for a detailed explanation, see the following section).

I 3.2 Assessment of the evidence presented by the company

The study EFFISAYIL 1 included by the company is not suitable to derive conclusions on the added benefit of spesolimab in comparison with the ACT for patients with generalized pustular psoriasis. This is explained below.

ACT not implemented in the EFFISAYIL 1 study

As already described in Section I 3.1, in the EFFISAYIL 1 study it was possible for patients to receive an alternative medication of physician's choice. The choice of this alternative medication was not limited, so that in principle there was also the possibility of flare therapy with systemic glucocorticoids or other therapies. However, only 1 of the 18 patients included in the placebo arm of the study actually had received such an alternative medication (including systemic glucocorticoids) by day 8. On day 8, the majority of patients in the placebo arm (83.3%) received unblinded spesolimab, so that subsequent surveys in the study largely refer to the comparison of immediate treatment of the flare with spesolimab versus delayed treatment with spesolimab. Conclusions on the comparison with the ACT specified by the G-BA can therefore neither be derived from the recordings up to day 8 nor from the subsequent

observations in the study. Therefore, the analyses on the EFFISAYIL 1 study presented by the company are unsuitable for the present benefit assessment.

Further points of criticism

Irrespective of the fact that the G-BA's ACT was not implemented in the EFFISAYIL 1 study, almost all of the patients included in the placebo arm of the study received no treatment for their generalized pustular psoriasis until day 8 (neither for the treatment of the acute flare nor as a basic therapy). Patients receiving a basic therapy for generalized pustular psoriasis, e.g. in the form of methotrexate, ciclosporin or infliximab, also had to discontinue this treatment with the onset of the flare at the latest. It could be inferred from the study documents that at study inclusion, 9 patients in the placebo arm (50.0%) and 18 patients in the spesolimab arm (51.4%) were receiving basic therapy (I Appendix B Table 6 of the full dossier assessment) [8]. It is conceivable that without the initiation of an alternative treatment by day 8 of the study an additional worsening of flare symptoms may occur in patients in the placebo arm affected by the discontinuation of a basic therapy.

A retrospective consideration of the patients included in the study also shows that more than 80% of the patients for whom corresponding retrospective surveys are available had received flare therapy for typical flares that had occurred in the past (the available data on typical flares of the included patients can be found in I Appendix B Table 7 of the full dossier assessment; data on specific drugs used to treat the last flare before the start of the study can be found in I Appendix B Table 8 of the full dossier assessment). Although a large proportion of the patients had apparently received flare therapy in the past, almost all of the patients included in the placebo arm received no active flare therapy at all by day 8 of the study despite the theoretical option of receiving an alternative treatment. It is likely that this will lead to an additional worsening of the disease. Against this background, the discussion on the use of systemic glucocorticoids in the present therapeutic indication described by the company is not relevant for the analysis of the EFFISAYIL 1 study. The decision on the relevance of the EFFISAYIL 1 study is thus made independently of the fact that treatment with systemic glucocorticoids might not be suitable or might be rejected by the patients due to the risk of a rebound effect.

In addition to the points of criticism already mentioned, a comparative analysis over 8 days is considered too short in the present therapeutic indication despite the consideration of the flare therapy. The background to this is that retrospective data on the patients included in the EFFISAYIL 1 study show that a typical flare lasted 1 to 4 weeks in about 66% of the patients for whom corresponding data are available. In contrast, a typical flare lasted less than 1 week in only about 11% of the patients. In another approx. 11% of patients, flares typically lasted longer than 12 weeks. Against this background, the comparative analyses over a period of 8 days are not sufficient.

Conclusion

In summary, due to the lack of implementation of the ACT and due to the other points of criticism described above, the EFFISAYIL 1 study is not suitable for drawing any conclusion on the added benefit of spesolimab as monotherapy compared to systemic glucocorticoids for the treatment of flares in adult patients with generalized pustular psoriasis.

I 4 Results on added benefit

No suitable data are available for the assessment of the added benefit of spesolimab as monotherapy versus systemic glucocorticoids for the treatment of flares in adult patients with generalized pustular psoriasis. There is no hint of an added benefit of spesolimab in comparison with the ACT; an added benefit is therefore not proven.

I 5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit for spesolimab in comparison with the ACT.

Table 5: Spesolimab (monotherapy) – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Treatment of flares in adults with generalized pustular psoriasis[b]	Systemic glucocorticoids[c]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. According to the G-BA, it is assumed that the present therapeutic indication refers exclusively to flare therapy for acute treatment. Long-term treatment is not addressed here.
c. If patients receive treatment for generalized pustular psoriasis independently of the acute flare, this should be documented. Treatment adjustment during an acute flare should be possible.

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 of at least considerable extent on the basis of the EFFISAYIL 1 study used by it.

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.

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The full report (German version) is published under https://www.iqwig.de/en/projects/a23-05.html.