Delgocitinib
(moderate to severe chronic hand eczema)

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

EXTRACT

Project: A24-107 Version: 1.0 Status: 10 Jan 2025 DOI: 10.60584/A24-107_en

[1] Translation of Sections I 1 to I 6 of the dossier assessment *Delgocitinib (mittelschweres bis schweres chronisches Handekzem) – 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

Delgocitinib (moderate to severe chronic hand eczema) – Benefit assessment according to §35a SGB V

Commissioning agency

Federal Joint Committee

Commission awarded on

15 October 2024

Internal Project No.

A24-107

DOI-URL

https://doi.org/10.60584/A24-107_en

Address of publisher

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Recommended citation

Institute for Quality and Efficiency in Health Care. Delgocitinib (moderate to severe chronic hand eczema); Benefit assessment according to §35a SGB V; Extract [online]. 2025 [Accessed: DD.MM.YYYY]. URL: https://doi.org/10.60584/A24-107_en.

Keywords

Delgocitinib, Eczema, Hand Dermatoses, Benefit Assessment, NCT05259722

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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

No feedback was received in the framework of the present 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
CSR	clinical study report
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HECSI	Hand Eczema Severity Index
IGA-CHE	Investigator Global Assessment of Chronic Hand Eczema
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
JAK	Janus kinase
LOCF	last observation carried forward
MI	multiple imputation
NRI	non-responder imputation
RCT	randomized controlled trial
SGB	Sozialgesetzbuch (Social Code Book)
SPC	Summary of Product Characteristics
TCI	topical calcineurin inhibitor
TCS	topical corticosteroids
WOCF	worst observation carried forward

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 delgocitinib. 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 15 October 2024.

Research question

The aim of the present report is to assess the added benefit of delgocitinib in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe chronic hand eczema for whom topical corticosteroids (TCS) are inadequate or inappropriate.

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 delgocitinib

Therapeutic indication	**ACT[a]**
Adult patients with moderate to severe chronic hand eczema[b] for whom topical corticosteroids are inadequate or inappropriate	An individually optimized treatment regimen[c] consisting of topical and systemic therapy[d, e, f] depending on the severity of the disease, subentity[g] and taking into account prior therapy[h]

a. Presented is the ACT specified by the G-BA.
b. Chronic hand eczema can be divided into several aetiological subentities (irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis) and clinical subentities (hyperkeratotic hand eczema, acute recurrent vesicular hand eczema, nummular hand eczema, pulpitis).
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria. A rationale must be provided for the choice and any limitation of treatment options.
d. The respective approval status of the drugs must be taken into account. Only the drug alitretinoin is explicitly approved for the treatment of chronic hand eczema: "indicated for adult patients with severe chronic hand eczema who do not respond to potent topical corticosteroids".
e. Besides alitretinoin, topical corticosteroids of class II to IV, phototherapy and systemic corticosteroids can be considered for the treatment of all subentities of chronic hand eczema as part of individualized therapy.
f. Systemic corticosteroids should only be used for a short period to treat flares.
g. The subentity "atopic hand eczema" is to be assigned to the therapeutic indication of atopic dermatitis, so that in addition to the mentioned treatment options, topical calcineurin inhibitors (tacrolimus, pimecrolimus) and dupilumab are options for the treatment of atopic eczema.
h. According to the G-BA, the drugs to which the patient did not respond and the number of different drug therapies used prior to treatment with delgocitinib should be documented. Furthermore, the basic therapy should be documented. A definition of non-response must be set out and justified in the dossier. The presence of an intolerance must be documented.

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

The company deviated from the G-BA's definition of the ACT and cited treatment of physician's choice with alitretinoin or, for the subtype of atopic chronic hand eczema, alitretinoin, abrocitinib, dupilumab or upadacitinib, each in addition to topical basic therapy, as the ACT.

The approach of the company is not appropriate. In addition to systemic treatment with alitretinoin, the G-BA's ACT also includes other treatment options such as topical or systemic corticosteroids, phototherapy or, in patients with atopic chronic hand eczema, treatment with topical calcineurin inhibitors (TCIs) and dupilumab. The treatment recommendations in the S2k guideline on diagnosis, prevention and therapy of hand eczema provide for a stepwise/escalating treatment regimen. The higher levels include all treatment options of the previous levels. At the highest level, which is the level of patients in the present therapeutic indication, treatment may include topical, physical and systemic therapies. According to the guideline recommendations, in individual cases, systemic corticosteroids can be part of the treatment of acute flares. Combinations such as TCS and alitretinoin are also possible.

The present assessment is implemented in comparison with the ACT specified by the G-BA (see Table 2).

The assessment is 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 24 weeks are used for the derivation of added benefit.

Results

No relevant study was identified from the check. The company, in contrast, identified the RCT DELTA FORCE and used it in its assessment of the added benefit of delgocitinib.

DELTA FORCE study unsuitable for the benefit assessment

The DELTA FORCE study is a completed, partially blinded, multicentre RCT comparing delgocitinib versus alitretinoin. The efficacy outcomes (Investigator Global Assessment of Chronic Hand Eczema [IGA-CHE] and Hand Eczema Severity Index [HECSI]) were assessed by a blinded investigator, all other outcomes by non-blinded investigators. The patients were not blinded to the allocated treatment. The treatment phase lasted up to 24 weeks.

The study included adult patients with severe chronic hand eczema who had a documented history of inadequate response to treatment with TCS within the last 12 months or for whom TCS was otherwise medically not indicated (e.g. due to side effects).

Patients in the intervention arm were largely treated in compliance with the Summary of Product Characteristics (SPC). According to the SPC, delgocitinib should be continued until the skin is clear or almost clear. Treatment should be discontinued if no improvement is seen after

12 weeks of continuous treatment. However, in the DELTA FORCE study, delgocitinib was used until Week 16 independent of response. At Week 16, treatment could be discontinued in patients with a clinical response (IGA-CHE value of 0 or 1) or without a clinical response (IGA-CHE 4). The IGA-CHE data show that, at Week 12 in the intervention arm, only a very small proportion of patients (2.6%) showed no response, in the sense of an IGA-CHE score of 4, and should therefore have discontinued treatment in accordance with the SPC. However, 29% of patients might have been able to discontinue treatment before Week 16 because at Week 12 their skin was already clear according to an IGA-CHE score of 0 (9.4%) or almost clear according to an IGA-CHE score of 1 (19.6%). It remains unclear whether continued treatment until potentially clear skin was indicated for patients whose skin was almost clear. For this reason, a proportion of patients, which cannot be accurately estimated, continued an unchanged treatment regimen until Week 16 despite clear or almost clear skin. Treatment in the control arm was in compliance with the requirements of the SPC of alitretinoin.

Appropriate comparator therapy not implemented in the DELTA FORCE study

In the control arm of the DELTA FORCE study, only alitretinoin monotherapy was available to the investigator. TCS or systemic corticosteroids for short-term flare treatment were not allowed outside of rescue treatment. The use of phototherapy was also prohibited. For patients with atopic chronic hand eczema, no drugs specifically approved for atopic eczema were available either. Based on the available data, it is not guaranteed that alitretinoin monotherapy was the most appropriate treatment option for the enrolled patients, or that all alternative treatment options to alitretinoin (as monotherapy) had been exhausted or were unsuitable.

Additional aspects: Presented analyses unsuitable for the benefit assessment

The primary and prespecified estimand of the DELTA FORCE study was composite strategy. The company presented results for this estimand in Module 4 A. Missing values, use of rescue treatment and permanent discontinuation of study medication were rated as treatment failure in the composite strategy.

In addition to the composite strategy, the estimand ‘treatment policy strategy’ was also prespecified. According to the study protocol, patients also had to complete the Week 24 visit if they discontinued treatment or received rescue treatment. In the treatment policy strategy, all observed values were included in the analysis even after initiation of rescue treatment or permanent discontinuation of the study medication. Missing values were imputed using multiple imputation (MI). This approach is preferable in the present data situation. The company did not present results in Module 4 A, however. In the clinical study report (CSR), only 3 analyses using the treatment policy imputation strategy are available for Week 24 (for 2 operationalizations of the HECSI and one operationalization of the Dermatology Life Quality Index [DLQI]). In some cases, the results of the analyses using the treatment policy strategy

differ notably from the results of the analyses using the composite strategy. These different results between the imputation strategies can also indicate that many patients in the control arm received a more suitable individual treatment option only as part of a subsequent therapy, and that monotherapy with alitretinoin was not the most suitable treatment option for the individual patient. Overall, however, complete analyses using the treatment policy strategy and possibly further sensitivity analyses on patient-relevant recordings are missing for Week 24 in order to be able to estimate the robustness of the treatment policy strategy.

Results on added benefit

Since no relevant study is available for the benefit assessment, there is no hint of an added benefit of delgocitinib 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 delgocitinib.

[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: Delgocitinib – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with moderate to severe chronic hand eczema[b] for whom topical corticosteroids are inadequate or inappropriate	An individually optimized treatment regimen[c] consisting of topical and systemic therapy[d, e, f] depending on the severity of the disease, subentity[g] and taking into account prior therapy[h]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Chronic hand eczema can be divided into several aetiological subentities (irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis) and clinical subentities (hyperkeratotic hand eczema, acute recurrent vesicular hand eczema, nummular hand eczema, pulpitis).
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria. A rationale must be provided for the choice and any limitation of treatment options.
d. The respective approval status of the drugs must be taken into account. Only the drug alitretinoin is explicitly approved for the treatment of chronic hand eczema: “indicated for adult patients with severe chronic hand eczema who do not respond to potent topical corticosteroids”.
e. Besides alitretinoin, topical corticosteroids of class II to IV, phototherapy and systemic corticosteroids can be considered for the treatment of all subentities of chronic hand eczema as part of individualized therapy.
f. Systemic corticosteroids should only be used for a short period to treat flares.
g. The subentity “atopic hand eczema” is to be assigned to the therapeutic indication of atopic dermatitis, so that in addition to the mentioned treatment options, topical calcineurin inhibitors (tacrolimus, pimecrolimus) and dupilumab are options for the treatment of atopic eczema.
h. According to the G-BA, the drugs to which the patient did not respond and the number of different drug therapies used prior to treatment with delgocitinib should be documented. Furthermore, the basic therapy should be documented. A definition of non-response must be set out and justified in the dossier. The presence of an intolerance must be documented.

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

The G-BA decides on the added benefit.

I 2 Research question

The aim of the present report is to assess the added benefit of delgocitinib in comparison with the ACT in adult patients with moderate to severe chronic hand eczema for whom TCS are inadequate or inappropriate.

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 delgocitinib

Therapeutic indication	**ACT[a]**
Adult patients with moderate to severe chronic hand eczema[b] for whom topical corticosteroids are inadequate or inappropriate	An individually optimized treatment regimen[c] consisting of topical and systemic therapy[d, e, f] depending on the severity of the disease, subentity[g] and taking into account prior therapy[h]

a. Presented is the ACT specified by the G-BA.
b. Chronic hand eczema can be divided into several aetiological subentities (irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis) and clinical subentities (hyperkeratotic hand eczema, acute recurrent vesicular hand eczema, nummular hand eczema, pulpitis).
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria. A rationale must be provided for the choice and any limitation of treatment options.
d. The respective approval status of the drugs must be taken into account. Only the drug alitretinoin is explicitly approved for the treatment of chronic hand eczema: "indicated for adult patients with severe chronic hand eczema who do not respond to potent topical corticosteroids".
e. Besides alitretinoin, topical corticosteroids of class II to IV, phototherapy and systemic corticosteroids can be considered for the treatment of all subentities of chronic hand eczema as part of individualized therapy.
f. Systemic corticosteroids should only be used for a short period to treat flares.
g. The subentity "atopic hand eczema" is to be assigned to the therapeutic indication of atopic dermatitis, so that in addition to the mentioned treatment options, topical calcineurin inhibitors (tacrolimus, pimecrolimus) and dupilumab are options for the treatment of atopic eczema.
h. According to the G-BA, the drugs to which the patient did not respond and the number of different drug therapies used prior to treatment with delgocitinib should be documented. Furthermore, the basic therapy should be documented. A definition of non-response must be set out and justified in the dossier. The presence of an intolerance must be documented.

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

The company deviated from the G-BA's definition of the ACT and cited treatment of physician's choice with alitretinoin or, for the subtype of atopic chronic hand eczema, alitretinoin, abrocitinib, dupilumab or upadacitinib, each in addition to topical basic therapy, as the ACT.

The company justified the deviation from the ACT defined by the G-BA with 3 main arguments:

- In the present therapeutic indication, the German S2k guideline [3] recommends only basic therapeutics (skin care products) and alitretinoin with high strength of

recommendation (“should”) for chronic hand eczema (all subtypes). The other treatment options (TCIs, phototherapy and systemic corticosteroids) are only recommended with lower strength of recommendation and severe restrictions, meaning that they do not reflect the actual treatment situation and therefore cannot be considered as ACT.

- Since delgocitinib is only used in patients for whom TCS are inadequate or inappropriate, treatment with a TCS is not an option, as a non-response has already been established or TCS are generally inappropriate for the patients.
- After the first assessment of dupilumab for the treatment of atopic dermatitis [4], the G-BA specified only dupilumab as the ACT for the therapeutic indication of atopic dermatitis, meaning that the therapies mentioned previously (UV therapy, systemic corticosteroids, etc.) can no longer be considered appropriate. In later procedures, the 2 Janus kinase (JAK) inhibitors abrocitinib and upadacitinib were also found to have considerable added benefit over dupilumab. Of the treatment options for atopic dermatitis, abrocitinib, dupilumab and upadacitinib are therefore used as ACTs for the subentity of atopic chronic hand eczema.

The approach of the company is not appropriate. In addition to systemic treatment with alitretinoin, the G-BA’s ACT also includes other treatment options such as topical or systemic corticosteroids, phototherapy or, in patients with atopic chronic hand eczema, treatment with TCIs and dupilumab. The treatment recommendations in the S2k guideline on diagnosis, prevention and therapy of hand eczema [3] provide for a stepwise/escalating treatment regimen. The higher levels include all treatment options of the previous levels. At the highest level, which is the level of patients in the present therapeutic indication, treatment may include topical, physical and systemic therapies. According to the guideline recommendations, in individual cases, systemic corticosteroids can be part of the treatment of acute flare-ups. Combinations such as TCS and alitretinoin are also possible.

The “should” recommendation for alitretinoin in the S2k guideline described by the company refers to patients for whom topical and/or phototherapy alone is not sufficiently effective. The company also described that the derivation of the ACT with regard to phototherapy as a non-drug treatment option is basically comprehensible. Other drugs are additionally available for patients with atopic chronic hand eczema (e.g. dupilumab or TCIs). The company’s argument that after the first assessment of dupilumab for the treatment of atopic dermatitis only dupilumab was specified as ACT is not correct. In subsequent assessments on atopic dermatitis, the ACT was adapted for patients who are candidates for long-term systemic treatment. However, the combination of dupilumab with TCS or TCI was explicitly permitted [4]. The justification of the resolution also mentions that not all patients with atopic dermatitis require long-term and continuous treatment and can be adequately treated with

individualized therapy consisting of TCS or TCI and short-term flare treatment with systemic corticosteroids [5].

The minutes of the consultation of 6 September 2023 show that the G-BA does not consider JAK inhibitors for the treatment of atopic dermatitis to be part of the ACT [6].

The present assessment is implemented in comparison with the ACT specified by the G-BA (see Table 4).

The assessment is 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 24 weeks are used for the derivation of added benefit. This concurs with the company's inclusion criteria.

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 list on delgocitinib (status: 20 September 2024)
- bibliographical literature search on delgocitinib (last search on 20 September 2024)
- search in trial registries/trial results databases for studies on delgocitinib (last search on 20 September 2024)
- search on the G-BA website for delgocitinib (last search on 27 September 2024)

To check the completeness of the study pool:

- search in trial registries for studies on delgocitinib (last search on 28 October 2024); for search strategies, see I Appendix A of the full dossier assessment

No relevant study was identified from the check.

The company, in contrast, identified the RCT DELTA FORCE [7,8] and used it in its assessment of the added benefit of delgocitinib. For a transfer of evidence from patients with severe chronic hand eczema from the DELTA FORCE study to patients with moderate chronic hand eczema, the company also used the placebo-controlled RCTs DELTA 1 and DELTA 2 [9-12].

The DELTA FORCE study data presented by the company are unsuitable for drawing conclusions on added benefit of delgocitinib in comparison with the ACT. As no evidence transfer is therefore possible, the placebo-controlled RCTs DELTA 1 and DELTA 2 are not discussed further. The DELTA FORCE study and the reasons why it is not suitable for the present benefit assessment are described in more detail below.

Evidence presented by the company – DELTA FORCE study

Study DELTA FORCE

The DELTA FORCE study is a completed, partially blinded, multicentre RCT comparing delgocitinib versus alitretinoin. The efficacy outcomes (IGA-CHE and HECSI) were assessed by a blinded investigator, all other outcomes by non-blinded investigators. The patients were not blinded to the allocated treatment. The treatment phase lasted up to 24 weeks.

The study included adult patients with severe chronic hand eczema who had a documented history of inadequate response to treatment with TCS within the last 12 months or for whom TCS was otherwise medically not indicated (e.g. due to side effects). According to the study protocol, inadequate response was defined as a failure to achieve and maintain low disease

activity (comparable to an IGA-CHE score of ≤ 2, see following text) despite treatment with a daily regimen of TCS (potent to very potent TCS for the European Union, and medium potency to very/ultra-high potency TCS for Canada), applied for at least 28 days or for the maximum duration by the SPC, whichever is shorter. Severe chronic hand eczema was defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months. An IGA-CHE score of 4 was required at screening. The IGA-CHE is an instrument developed by the company that allows investigators to assess the severity of chronic hand eczema, and ranges from 0 (clear) to 4 (severe). The inclusion criteria are suitable for representing patients with severe chronic hand eczema. Patients with moderate chronic hand eczema, who also fall within the scope of this research question, were not included in the DELTA FORCE study.

The DELTA FORCE study randomly allocated a total of 513 patients at a 1:1 ratio to treatment with delgocitinib (N = 254) or alitretinoin (N = 259). Randomization was stratified by subtype (hyperkeratotic/non-hyperkeratotic) and region (North America/Europe).

Patients in the intervention arm were largely treated in compliance with the SPC [13]. According to the SPC, delgocitinib should be continued until the skin is clear or almost clear. Treatment should be discontinued if no improvement is seen after 12 weeks of continuous treatment. However, in the DELTA FORCE study, delgocitinib was used until Week 16 independent of response. At Week 16, treatment could be discontinued in patients with a clinical response (IGA-CHE value of 0 or 1) or without a clinical response (IGA-CHE 4). The IGA-CHE data show that, at Week 12 in the intervention arm, only a very small proportion of patients (2.6%) showed no response, in the sense of an IGA-CHE score of 4, and should therefore have discontinued treatment in accordance with the SPC. However, 29% of patients might have been able to discontinue treatment before Week 16 because at Week 12 their skin was already clear according to an IGA-CHE score of 0 (9.4%) or almost clear according to an IGA-CHE score of 1 (19.6%). It remains unclear whether continued treatment until potentially clear skin was indicated for patients whose skin was almost clear. For this reason, a proportion of patients, which cannot be accurately estimated, continued an unchanged treatment regimen until Week 16 despite clear or almost clear skin.

Treatment in the control arm, on the other hand, was in compliance with the SPC for alitretinoin [14], and response/non-response and the possibility to discontinue treatment was checked at Week 12, in accordance with the information in the SPC.

After discontinuation of treatment due to a clinical response, treatment could be resumed in both study arms if symptoms recurred (IGA-CHE ≥ 2).

In both treatment arms, any therapies directed against chronic hand eczema (such as TCS, systemic corticosteroids, phototherapy, TCIs or dupilumab) were not allowed to be used for

7 days to 3 months prior to enrolment and for the entire duration of the study. In the beginning of and during the study treatment, patients in both study arms thus received monotherapy with delgocitinib or alitretinoin (see also the text section on implementation of the ACT below). Non-drug background therapy such as skin care, e.g. with emollients, and avoidance of known irritants or allergens was permitted or should be maintained both before study entry and throughout the entire study duration.

The primary outcome of the DELTA FORCE study was change in HECSI between baseline and Week 12. Further outcomes were surveyed in the morbidity, health-related quality of life and side effects categories.

Appropriate comparator therapy not implemented in the DELTA FORCE study

For delgocitinib, the G-BA specified an individually optimized treatment regimen consisting of topical and systemic therapy depending on the severity of the disease, subentity and taking into account prior therapy. Besides alitretinoin, TCS of class II to IV, phototherapy and systemic corticosteroids can be considered for the treatment of all subentities of chronic hand eczema as part of individualized therapy. The subentity atopic hand eczema is assigned to the therapeutic indication of atopic dermatitis, so that in addition to the treatment options mentioned, TCIs (tacrolimus, pimecrolimus) and dupilumab are options for the treatment of atopic eczema.

According to the S2k guideline [3], class III (potent) TCS, and also short-term class IV (very potent) TCS should be used as first-line therapy for moderate to severe chronic hand eczema. Patients with moderate to severe chronic hand eczema that is refractory to TCS should undergo phototherapy. If topical and/or phototherapy alone are also not sufficiently effective, alitretinoin should be used. According to the S2k guideline, the efficacy of treatment with alitretinoin can be increased by the additional administration of TCS. For atopic hand eczema, other drugs can be considered in accordance with the notes of the G-BA and the guideline on atopic dermatitis [15] (see above and Table 4).

The DELTA FORCE study did not provide for a patient-specific decision as to which therapy would have been optimal for each individual patient at the time of study entry. In the control arm, only alitretinoin monotherapy was given, regardless of the patient's subentity and prior therapy. Other treatment options such as TCS or phototherapy were explicitly prohibited. Based on the inclusion and exclusion criteria of the DELTA FORCE study and based on the company's presentation in the dossier, it is not guaranteed that monotherapy with alitretinoin was the most suitable treatment option for the patients. This is explained in more detail below.

No other treatment options apart from alitretinoin as monotherapy

In the DELTA FORCE study, TCS were not allowed up to 14 days before study entry and, as already described, for the entire duration of the study. In the 12 months prior to study entry, 54.4% of patients in the control arm received a class III TCS (potent) and 42.5% a class IV TCS (very potent) (see also I Appendix B of the full dossier assessment). It is therefore conceivable that an increase in TCS potency might have initially been a possible treatment option for some of the patients. According to the guideline, a combination of alitretinoin and TCS would also be a potentially suitable treatment option. In addition, a history of an inadequate response to TCS does not mean that further treatment with TCS (possibly in combination with another drug) is generally no longer an option for these patients. TCS should therefore have been available as part of an individually optimized treatment regimen, as described in the G-BA's notes. This is also supported by the fact that TCS were the most frequent rescue treatment (for more information on rescue treatments, see below).

Phototherapy was also prohibited in the DELTA FORCE study within 28 days before enrolment and for the entire duration of the study. In the 12 months before enrolment, 13.5% of patients in the control arm had received phototherapy or another treatment not further specified. The exact proportion of these patients who received phototherapy is not clear from the information in the CSR. The guidelines contain a recommendation for phototherapy, albeit a weaker one than for TCS. As described in the G-BA's notes, it should therefore be possible to use phototherapy as an independent treatment option as part of individually optimized treatment.

Treatment of patients with atopic hand eczema

A total of 22% of the patients included in the control arm of the DELTA FORCE study had atopic hand eczema (see also I Appendix B of the full dossier assessment). According to the ACT specified by the G-BA as well as according to the ACT cited by the company, further drugs are an option for these patients. However, the company did not explain why treatment with alitretinoin was the best individual treatment option for these patients, and not treatment with other drugs specifically approved for atopic eczema (such as TCIs or dupilumab).

Rescue treatment is not an adequate implementation of the appropriate comparator therapy

If medically necessary, rescue treatment could be initiated at the investigator's discretion to control intolerable symptoms of chronic hand eczema (with the exception of alitretinoin, all treatment options were available for this purpose). In this case, however, the study medication had to be permanently discontinued. Rescue treatment was given to 4.7% of patients in the intervention arm and 8.1% in the control arm. The most frequent rescue treatment was TCS (4.3% versus 5.8% of patients).

Taking the rescue treatment into account, all drugs mentioned by the G-BA in the ACT were available in the study, but a rescue treatment is not an adequate therapy in the sense of an individually optimized treatment regimen.

Summary of the implementation of the appropriate comparator therapy

In the control arm of the DELTA FORCE study, only alitretinoin monotherapy was available to the investigator. TCS or systemic corticosteroids for short-term flare treatment were not allowed outside the rescue treatment. The use of phototherapy was also prohibited. For patients with atopic chronic hand eczema, no drugs specifically approved for atopic eczema were available either. Based on the available data, it is not guaranteed that alitretinoin monotherapy was the most appropriate treatment option for the enrolled patients, or that all alternative treatment options to alitretinoin (as monotherapy) had been exhausted or were unsuitable.

The ACT was therefore not implemented in the DELTA FORCE study presented, and no data suitable for answering the research question of this benefit assessment are available.

Additional aspects: Presented analyses unsuitable for the benefit assessment

Different proportions of treatment and study discontinuations between the treatment arms; unsuitable imputation strategies of the company

Irrespective of the inadequate implementation of the ACT in the DELTA FORCE study, there are deficiencies in the analyses presented by the company. This is explained below.

There is a notable difference between the treatment arms in the proportion of patients who discontinued study treatment by Week 24. 13.4% of patients in the intervention arm discontinued treatment with delgocitinib, and 35.9% of patients in the control arm discontinued treatment with alitretinoin. A particularly high proportion in the control arm was due to patient decision (12.7%) and lack of efficacy (10.0%) (see also I Appendix B of the full dossier assessment). At Week 12, 4.7% versus 19.3% of patients already discontinued treatment. The proportion of study discontinuations also differs notably between the treatment arms: 88.6% of patients in the intervention arm completed the Week 24 visit, compared with only 71.4% in the control arm. Due to the difference of > 15% missing values at Week 24 between the treatment arms, generally suitable imputation strategies are therefore required to be able to take the data into account.

The primary and prespecified estimand of the DELTA FORCE study was composite strategy. The company presented results for this estimand in Module 4 A. Missing values, use of rescue treatment and permanent discontinuation of study medication are rated as treatment failure in the composite strategy (non-responder imputation [NRI] for binary values or worst observation carried forward [WOCF] for continuous values). In Module 4 A, the company

additionally presented post hoc sensitivity analyses for the composite strategy, in which NRI or WOCF imputation was conducted exclusively for the use of rescue treatment and for treatment discontinuation due to lack of efficacy and due to adverse events. Missing values due to other causes were imputed using last observation carried forward (LOCF).

In addition to the composite strategy, the estimand 'treatment policy strategy' was also prespecified. According to the study protocol, patients also had to complete the Week 24 visit if they discontinued treatment or received rescue treatment. In the treatment policy strategy, all observed values were included in the analysis even after initiation of rescue treatment or permanent discontinuation of the study medication. Missing values were imputed using MI. This approach is preferable in the present data situation. The company did not present results in Module 4 A, however. In the CSR, only 3 analyses using the treatment policy imputation strategy are available for Week 24 (for 2 operationalizations of the HECSI and one operationalization of the DLQI). In some cases, the results of the analyses using the treatment policy strategy differ notably from the results of the analyses using the composite strategy. The analyses using the composite strategy for the change in HECSI show a significant difference between the treatment arms ($p < 0.001$). The respective analysis using treatment policy, however, show no significant difference ($p = 0.217$ and $p = 0.105$). The analyses of the DLQI show a significant difference between the treatment arms for both imputation strategies (composite strategy $p < 0.001$; treatment policy $p = 0.013$). These different results between the imputation strategies can also indicate that many patients in the control arm received a more suitable individual treatment option only as part of a subsequent therapy, and that monotherapy with alitretinoin was not the most suitable treatment option for the individual patient (see also section on the implementation of the ACT). Overall, however, complete analyses using the treatment policy strategy and possibly further sensitivity analyses on patient-relevant recordings are missing for Week 24 in order to be able to estimate the robustness of the treatment policy strategy. The additional operationalization HECSI-100 for complete resolution/remission would also be relevant for the assessment in the present therapeutic indication.

Information on subsequent therapies is missing

As mentioned above, many patients discontinued study treatment early in the course of the study, particularly in the control arm. For patients who did not discontinue treatment due to resolution of the chronic hand eczema, subsequent therapy is therefore medically indicated. For a meaningful interpretation of an observed effect in an efficacy outcome (e.g. remission), it is necessary to be able to assess whether and which treatment the patients have received and whether this treatment corresponds to adequate guideline-compliant subsequent treatment. No data are available on subsequent therapies. Only for a small proportion of patients is it possible to infer subsequent therapy from the information on rescue therapies administered. For example, 8.1% of patients in the control arm received rescue treatment by

Week 24. However, 35.9% had discontinued therapy by Week 24 in the control arm. It can therefore be assumed that more patients received subsequent therapy after discontinuation of the study medication.

Lack of information on the observation period of side effects

In Module 4 A, the company only provided information on the observation periods of efficacy outcomes. On average, these were 23.2 weeks in the intervention arm and 19.8 weeks in the control arm. For the outcomes on side effects, there is no outcome-specific information on the observation period.

I 4 Results on added benefit

No suitable data are available to assess the added benefit of delgocitinib in adult patients with moderate to severe chronic hand eczema for whom TCS are inadequate or inappropriate. There is no hint of an added benefit of delgocitinib 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 delgocitinib in comparison with the ACT is summarized in Table 5.

Table 5: Delgocitinib – probability and extent of added benefit

Therapeutic indication	**ACT**[a]	**Probability and extent of added benefit**
Adult patients with moderate to severe chronic hand eczema[b] for whom topical corticosteroids are inadequate or inappropriate	An individually optimized treatment regimen[c] consisting of topical and systemic therapy[d, e, f] depending on the severity of the disease, subentity[g] and taking into account prior therapy[h]	Added benefit not proven

a. Presented is the ACT specified by the G-BA.
b. Chronic hand eczema can be divided into several aetiological subentities (irritant contact dermatitis, allergic contact dermatitis, atopic hand eczema, protein contact dermatitis) and clinical subentities (hyperkeratotic hand eczema, acute recurrent vesicular hand eczema, nummular hand eczema, pulpitis).
c. For the implementation of individualized therapy in a study of direct comparison, the investigator is expected to have a selection of several treatment options at disposal to permit an individualized treatment decision taking into account the listed criteria. A rationale must be provided for the choice and any limitation of treatment options.
d. The respective approval status of the drugs must be taken into account. Only the drug alitretinoin is explicitly approved for the treatment of chronic hand eczema: “indicated for adult patients with severe chronic hand eczema who do not respond to potent topical corticosteroids”.
e. Besides alitretinoin, topical corticosteroids of class II to IV, phototherapy and systemic corticosteroids can be considered for the treatment of all subentities of chronic hand eczema as part of individualized therapy.
f. Systemic corticosteroids should only be used for a short period to treat flares.
g. The subentity “atopic hand eczema” is to be assigned to the therapeutic indication of atopic dermatitis, so that in addition to the mentioned treatment options, topical calcineurin inhibitors (tacrolimus, pimecrolimus) and dupilumab are options for the treatment of atopic eczema.
h. According to the G-BA, the drugs to which the patient did not respond and the number of different drug therapies used prior to treatment with delgocitinib should be documented. Furthermore, the basic therapy should be documented. A definition of non-response must be set out and justified in the dossier. The presence of an intolerance must be documented.

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

The assessment described above deviates from that by the company, which derived a hint of considerable added benefit.

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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