Delgocitinib
(moderate to severe chronic hand eczema)

Addendum to Project A24-107
(dossier assessment)[1]

ADDENDUM (DOSSIER ASSESSMENT)

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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
HEIS	Hand Eczema Impact Scale
HESD	Hand Eczema Symptom Diary
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)
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
NRI	non-responder imputation
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
TCI	topical calcineurin inhibitors
TCS	topical corticosteroids
VAS	visual analogue scale
WOCF	worst observation carried forward

1 Background

On 25 February 2025, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Project A24-107 (Delgocitinib – Benefit assessment according to §35a Social Code Book V) [1].

The commission comprises the assessment of the DELTA FORCE study, taking into account the information in the dossier [2] as well as all data subsequently submitted by the pharmaceutical company (hereinafter referred to as the "company") in the commenting procedure [3,4].

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

The research question of the benefit assessment in A24-107 [1] was the assessment of the added benefit of delgocitinib in comparison with 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, as appropriate comparator therapy (ACT) in adult patients with moderate to severe chronic hand eczema for whom topical corticosteroids (TCS) are inadequate or inappropriate.

No suitable data on the comparison of delgocitinib with the comparator therapy specified by the G-BA

In its dossier [2], the company presented results of the randomized controlled trial (RCT) DELTA FORCE. The DELTA FORCE study included only patients with severe chronic hand eczema. 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 [5-8].

As described in dossier assessment A24-107 [1], the DELTA FORCE study, which compared delgocitinib with the ACT and was presented by the company, was not included in the benefit assessment because it did not implement the G-BA's ACT. This means that no suitable data on the comparison of delgocitinib with the comparator therapy specified by the G-BA were available. The main reason for the lack of implementation of the ACT was that only alitretinoin monotherapy was available in the control arm of the DELTA FORCE study. For patients with atopic chronic hand eczema in particular, no drugs specifically approved for atopic eczema were available. TCS (as well as systemic corticosteroids for short-term flare treatment) were not allowed outside of rescue treatment. The use of phototherapy was also prohibited.

Based on the available information and data (e.g. inclusion/exclusion criteria or prior therapies, see also dossier assessment A24-107), it was 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.

Overall, the listed points of criticism were not resolved in the comments of the company [3] or in the oral hearing [9]. The treatment recommendations in the S2k guideline on diagnosis, prevention and therapy of hand eczema [10] provide for a stepwise/escalating treatment regimen. The higher levels include all treatment options of the previous levels. Thus, more treatment options become available at each level. At each new level of treatment, a decision is made about which treatments from the available options are appropriate for the patient. However, it must be checked whether treatment options of the previous levels are suitable, e.g. an increase in TCS potency or phototherapy. Combinations such as TCS and alitretinoin

are also possible. Other drugs are additionally available for patients with atopic chronic hand eczema. The uncertainties described in A24-107 remain and it is still unclear whether alitretinoin monotherapy was the most suitable individualized treatment for all patients. Therefore, the dossier assessment's conclusion that the ACT specified by the G-BA had been inadequately implemented remains unchanged. Thus, there are still no suitable data on the comparison of delgocitinib with the comparator therapy specified by the G-BA. An evidence transfer to patients with moderate chronic hand eczema is therefore also not possible.

Analyses subsequently submitted as part of the comments

In addition to the inadequate implementation of the ACT, the company's analyses presented in the dossier were unsuitable: In Module 4 A, the company presented results using the prespecified estimand 'composite strategy' for the efficacy outcomes. Missing values, use of rescue treatment and permanent discontinuation of study medication were rated as treatment failure in the composite strategy (non-responder imputation [NRI] for binary values or worst observation carried forward [WOCF] for continuous values). The estimand 'treatment policy strategy', which was also prespecified, is preferable in the present assessment situation. 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). Overall, however, complete analyses using the treatment policy strategy and further suitable sensitivity analyses on patient-relevant outcomes were missing for Week 24 in order to be able to estimate the robustness of the treatment policy strategy. As part of the comments, the company subsequently submitted analyses using the treatment policy strategy for all efficacy outcomes. No further sensitivity analyses are available.

The dossier also lacked information on the subsequent therapies used after discontinuation of the study medication as well as information on the observation period for side effects. Information on subsequent therapies is not available even with the data subsequently submitted as part of the comments. The company subsequently submitted the observation period for side effects.

2.1 Assessment of the DELTA FORCE study

In compliance with the commission, the DELTA FORCE study is described below, and the data and analyses subsequently submitted by the company are presented.

Table 1: Study pool of the company – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Study category			Available sources		
	Study for the approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)	CSR (yes/no [citation])	Registry entries[b] (yes/no [citation])	Publication (yes/no [citation])
LP0133-1528 (DELTA FORCE)[c]	No	Yes	No	Yes [11]	Yes [12,13]	No

a. Study sponsored by the company.
b. Citation of the trial registry entries and, if available, of the reports on study design and/or results listed in the trial registries.
c. In the tables below, the study will be referred to using this acronym.

CSR: clinical study report; G-BA: Federal Joint Committee; RCT: randomized controlled trial

2.2 Study characteristics

Table 2 and Table 3 describe the DELTA FORCE study.

Table 2: Characteristics of the study included by the company – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
DELTA FORCE	RCT, partially blinded[b], parallel	Adult patients with severe chronic hand eczema[c] for whom topical corticosteroids are inadequate or inappropriate[d]	Delgocitinib (N = 254) Alitretinoin (N = 259)	Screening: ≤ 4 weeks Treatment: up to 24 weeks Observation: 2 weeks[e]	103 study centres in Austria, Canada, France, Germany, Italy, Norway, Poland, Slovak Republic, Spain, United Kingdom 6/2022–12/2023	Primary: change in HECSI from baseline to Week 12 Secondary: morbidity, health-related quality of life, AEs

a. Primary outcomes include information without taking into account the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 A.
b. 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.
c. Defined as hand eczema that has persisted for more than 3 months or returned twice or more within the last 12 months; patients had to have an IGA-CHE score of 4 at screening and randomization.
d. 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) 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, within 1 year before enrolment.
e. There were additional pregnancy follow-up visits for women of childbearing potential treated with alitretinoin 5 weeks after the last dose of study medication.

AE: adverse event; IGA-CHE: Investigator Global Assessment of Chronic Hand Eczema; HECSI: Hand Eczema Severity Index; N: number of randomized patients; RCT randomized controlled trial; TCS: topical corticosteroids

Table 3: Characteristics of the intervention – RCT, direct comparison: delgocitinib vs. alitretinoin (multipage table)

Study	Intervention	Comparison
DELTA FORCE	Delgocitinib 20 mg/g cream twice daily, for up to 24 weeks[a, b]	Alitretinoin 30 mg once daily, orally, for up to 24 weeks[a, b]
	Dose adjustment:	
	not possible; the amount of cream applied could be adjusted at the discretion of an unblinded investigator	reduction to 10 mg once daily permitted in case of unacceptable toxicity
	Background therapy ▪ patients were advised to adhere to standard non-medicated skin care, including avoidance of known irritants and allergens, and continue their usual skin care routine, e.g. in the form of emollients	
	Disallowed prior and concomitant treatment ▪ systemic treatment with immunosuppressive drugs (e.g. methotrexate, ciclosporin, azathioprine), immunomodulating drugs, retinoids (e.g. alitretinoin), or corticosteroids ≤ 28 days prior to randomization[c] ▪ use of tanning beds, phototherapy (e.g. UVB, UVA1, PUVA), or bleach baths on the hands ≤ 28 days prior to randomization ▪ previous or current treatment with JAK inhibitors (including delgocitinib), systemic or topical ▪ cutaneously applied treatment with immunomodulators (e.g. PDE4 inhibitors, pimecrolimus, tacrolimus) or TCS on the hands ≤ 14 days prior to randomization ▪ use of systemic antibiotics or cutaneously applied antibiotics on the hands ≤ 14 days prior to randomization ▪ other transdermal or cutaneously applied therapy on the hands (except for the use of emollients) ≤ 7 days prior to randomization ▪ cutaneously applied treatments in regions other than the hands, which could interfere with clinical trial evaluations or pose a safety concern ≤ 7 days prior to randomization ▪ treatment with any biological agent (including immunoglobulin, anti-IgE, and dupilumab)[d] ▪ treatment with CYP3A4 inhibitors (e.g. ketoconazole), strong CYP2C9 inhibitors (e.g. fluconazole, miconazole, oxandrolone) or strong CYP2C8 inhibitors (e.g. gemfibrozil), CYP2C8 substrates (e.g. amiodarone, paclitaxel, rosiglitazone, repaglinide), simvastatin or tetracyclines ≤ 7 days prior to screening[e]	

a. Patients with an IGA-CHE score ≥ 2 at Week 16 in the intervention arm or at Week 12 in the control arm who, in the investigator's opinion, had a benefit from continued treatment, could continue treatment until Week 24. Patients with an IGA-CHE score ≤ 1 at Week 16 in the intervention arm or at Week 12 in the control arm were to discontinue treatment. Patients with an IGA-CHE score = 4 at Week 16 in the intervention arm or at Week 12 in the control arm were to discontinue treatment. If symptoms recurred (IGA-CHE ≥ 2) after a clinical response, treatment was to be re-initiated.
b. Treatment chosen by an unblinded investigator (with the exception of alitretinoin) was available as rescue treatment. The medical necessity of rescue treatment was determined by a blinded investigator.
c. Steroid eyedrops and inhaled or intranasal steroids corresponding to ≤ 1 mg prednisolone for allergic conjunctivitis, asthma, or rhinitis were allowed.
d. Any cell-depleting agents including but not limited to rituximab ≤ 6 months prior to randomization or until lymphocyte count returned to the normal range (whichever was longer); other biologics ≤ 3 months or 5 half-lives (whichever was longer) prior to randomization.
e. Topical treatment with CYP2C9 inhibitors (e.g. fluconazole, miconazole, oxandrolone) on areas of the body other than hands was allowed.

Table 3: Characteristics of the intervention – RCT, direct comparison: delgocitinib vs. alitretinoin (multipage table)

Study	Intervention	Comparison
IGA-CHE: Investigator Global Assessment of Chronic Hand Eczema; IgE: immunoglobulin E; JAK: Janus kinase; PDE4: phosphodiesterase type 4; PUVA: psoralen and ultraviolet-A light; RCT: randomized controlled trial; TCS: topical corticosteroids; UVB: ultraviolet B light; UVA1: ultraviolet A1 light		

A detailed characterization of the partially blinded RCT DELTA FORCE and a detailed description of the lack of implementation of the ACT – 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 – can be found in dossier assessment A24-107.

Patient characteristics

Table 4 presents the patient characteristics in the DELTA FORCE study.

Table 4: Characteristics of the study population as well as study/treatment discontinuation – RCT, direct comparison: delgocitinib vs. alitretinoin

Study **Characteristic** **Category**	**Delgocitinib** **N = 254**	**Alitretinoin** **N = 259**
DELTA FORCE		
Age [years], mean (SD)	45 (14)	44 (15)
Sex [F/M], %	66/34	64/36
Region, n (%)		
Europe	229 (90)	230 (89)
Canada	25 (10)	29 (11)
Duration of disease [years], mean (SD)	9.1 (10.3)	8.1 (10.0)
HECSI score, mean (SD)	90.9 (54.7)	92.7 (54.9)
Main diagnosis n (%)[a]		
Allergic contact dermatitis	58 (22.8)	54 (20.8)
Irritant contact dermatitis	75 (29.5)	76 (29.3)
Atopic hand eczema	66 (26.0)	57 (22.0)
Acute recurrent vesicular hand eczema	22 (8.7)	36 (13.9)
Hyperkeratotic hand eczema	31 (12.2)	32 (12.4)
Not reported	2 (0.8)	4 (1.5)
Prior therapies up to 12 months before enrolment, n (%)		
TCS	253 (100)	259 (100)
Very potent	122 (48.0)	110 (42.5)
Potent	120 (47.2)	141 (54.5)
Moderate	6 (2.4)	4 (1.5)
Mild	4 (1.6)	1 (0.4)
Unknown	1 (0.4)	3 (1.2)
TCI	77 (30.3)	80 (30.9)
Oral corticosteroids	39 (15.4)	37 (14.3)
Oral retinoids	7 (2.8)	7 (2.7)
Phototherapy and other procedures[b]	30 (11.8)	35 (13.5)
Treatment discontinuation, n (%)[c]	34 (13.4)	93 (35.9)
Study discontinuation, n (%)[d]	29 (11.4)	74 (28.6)

a. Subtype determined by investigator based on the medical history and morphology of the lesions present at baseline.
b. The company did not provide any further information on what is covered by 'other procedures'.
c. Common reasons for treatment discontinuation in the intervention arm vs. the control arm were patient decision (5.9% vs. 12.7%), lack of efficacy (3.1% vs. 10.0%), AEs (0.8% vs. 9.3%).
d. Information on study discontinuations relates to the entire course of study. Common reasons for study discontinuations in the intervention arm vs. the control arm were patient decision (9.1% vs. 27.4%), lost to follow-up (2.4% vs. 0.4%); 88.6% vs. 71.4% of patients completed the Week 24 visit.

AE: adverse event; F: female; HECSI: Hand Eczema Severity Index; n: number of patients in the category; N: number of randomized patients; RCT: randomized controlled trial; SD: standard deviation; TCI: topical calcineurin inhibitor; TCS: topical corticosteroids

The demographic and disease-specific characteristics are largely comparable between the 2 DELTA FORCE study arms. The mean age of the patients was about 45 years, and the proportion of female patients (about 2 thirds) was higher than the proportion of male patients in both arms. The most common subtype of chronic hand eczema was irritant contact dermatitis with around 29% in both treatment arms. The second most common subtype was atopic hand eczema with 26% in the intervention arm and 22% in the control arm.

All patients had received TCS in the 12 months prior to enrolment, approximately half of them a potent TCS and half of them a very potent TCS. Topical calcineurin inhibitors (TCIs) were given to around 30% of patients in each treatment arm.

The proportion of patients with treatment discontinuation or study discontinuation was notably higher in the control arm (35.9% and 28.6%) than in the intervention arm (13.4% and 11.4%). The most common reason for treatment or study discontinuation was patient decision.

Risk of bias across outcomes (study level)

Table 5 shows the risk of bias across outcomes (risk of bias at study level).

Table 5: Risk of bias across outcomes (study level) – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patients	Treating staff			
DELTA FORCE	Yes	Yes	No	No[a]	Yes	Yes	Low

a. The DELTA FORCE study is a partially blinded study; the efficacy outcomes (IGA-CHE and HECSI) were assessed by a blinded investigator, all other outcomes by non-blinded investigators.

IGA-CHE: Investigator Global Assessment of Chronic Hand Eczema; HECSI: Hand Eczema Severity Index; RCT: randomized controlled trial

For the DELTA FORCE study, the risk of bias across outcomes is rated as low.

Transferability of the study results to the German health care context

The company stated that the patient population of the DELTA FORCE study and the applied intervention with delgocitinib (20 mg/g cream) was in compliance with the approval and Summary of Product Characteristics (SPC) valid in Germany. Since the study participants were recruited in Europe and North America, the company assumed a sufficiently similar health

care standard, and it additionally stated that around a quarter of the study participants in DELTA FORCE came from Germany. The majority of study participants were female (65.1% in DELTA FORCE), which corresponded to the sex distribution of the disease, according to the company. It added that, with regard to the treatment of patients for whom TCS are inadequate or inappropriate, alitretinoin in addition to standard non-medicated skin care is the current treatment standard according to German guidelines. It therefore considered the patients in the DELTA FORCE study to have been treated in accordance with the German health care standard. The DELTA FORCE study primarily investigated patients with the chronic hand eczema subtypes of allergic contact dermatitis, irritant contact dermatitis, atopic hand eczema, acute recurrent vesicular hand eczema, and hyperkeratotic hand eczema. According to the company, the effect of delgocitinib is independent of the chronic hand eczema subtype, which has been confirmed by the CHMP in terms of generalizability of efficacy to all chronic hand eczema subtypes. In summary, the company presumed the study results to be transferable to the German health care context.

The company did not provide any further information on the transferability of the study results to the German health care context.

2.3 Results

2.3.1 Presented outcomes

The following patient-relevant outcomes are presented in the present addendum:

- Mortality
  - all-cause mortality
- Morbidity
  - symptoms, recorded using the Hand Eczema Severity Index (HECSI)-90
  - symptoms, recorded using the Hand Eczema Symptom Diary (HESD)
  - health status, recorded using the EQ-5D visual analogue scale (VAS)
- Health-related quality of life
  - recorded using the Hand Eczema Impact Scale (HEIS)
- Side effects
  - serious adverse events (SAEs)
  - discontinuation due to adverse events (AEs)
  - other specific AEs, if any

The choice of patient-relevant outcomes deviates from that of the company, which used further outcomes in the dossier and in the data subsequently submitted.

Table 6 shows the outcomes for which data were available in the studies included.

Table 6: Matrix of outcomes – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Outcomes								
	All-cause mortality[a]	Symptoms (HECSI-90)	Symptoms (HESD)	Health status (EQ-5D VAS)	Health-related quality of life (HEIS)	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AE)	Headache (PT, AE)
DELTA FORCE	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes

a. The results on all-cause mortality are based on the information on fatal AEs.

AE: adverse event; HECSI-90: Hand Eczema Severity Index-90; HEIS: Hand Eczema Impact Scale; HESD: Hand Eczema Symptom Diary; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

Notes on the analyses presented

As described in dossier assessment A24-107, the analyses presented by the company showed deficiencies irrespective of the inadequate implementation of the ACT. Due to the difference of > 15 percentage points of missing values at Week 24 between the treatment arms, generally suitable imputation strategies are required to be able to take the data into account.

As described above, the primary and prespecified estimand of the study was the composite strategy. In addition, analyses were also prespecified according to the estimand 'treatment policy strategy'. In the treatment policy strategy, all actually observed values are included in the analysis even after initiation of rescue treatment or permanent discontinuation of the study medication. Missing values are imputed using MI. The company did not present results in Module 4 A, however. As part of the commenting procedure, the company submitted corresponding analyses for all efficacy outcomes using the treatment policy strategy.

For this addendum, the results are presented based on the treatment policy strategy. As already described in dossier assessment A24-107, this procedure is preferable in the present assessment situation. One reason for this is that all patients are included in the analysis with their actually observed values, whereas the composite strategy rated missing values, use of rescue treatment and permanent discontinuation of the study medication as treatment failure, and NRI for binary values or WOCF for continuous values were carried out accordingly.

Secondly, the imputation strategy for missing values (i.e. values of patients who discontinued the study) differs between the 2 estimands (NRI/WOCF [composite strategy] versus MI [treatment policy strategy]).

In the following, the adequate handling of patients who discontinued treatment is first explained again, before discussing the different handling of patients who discontinued the study (here: imputation of missing values is unavoidable) in the composite strategy versus the treatment policy strategy.

NRI/WOCF imputation of patients who discontinued treatment or used rescue treatment is not adequate

Among patients who discontinued treatment, lack of efficacy was frequently given as a reason. In the intervention arm, a total of 34 (13.4%) patients discontinued treatment, 8 of them due to lack of efficacy. In the control arm, a total of 93 (35.9%) patients discontinued treatment, 26 of them due to lack of efficacy. 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 medically indicated. The company did not provide any information on subsequent therapies administered outside rescue treatments. The use of rescue treatments and subsequent therapies can have a relevant influence on the treatment result. For these patients, NRI and WOCF are therefore worst-case assumptions, which assume no improvement in any of these patients by Week 24. Since data were recorded for these patients after treatment discontinuation or use of rescue treatment, they should be included in the analyses with their observed values; an imputation is therefore not appropriate/necessary here.

NRI/WOCF imputation of patients who discontinued the study is not adequate

In the case of NRI imputation, patients with missing values are rated as non-responders or, in the case of WOCF, it is assumed that no further improvement will occur for these patients by Week 24. The main reason for missing values in the DELTA FORCE study is the high proportion of patients who discontinued the study prematurely (11.4% versus 28.6% of patients at Week 24). However, in the DELTA FORCE study it cannot necessarily be assumed that non-response was always the reason for study discontinuation. According to the information in the clinical study report (CSR), the most common reason was the patient's request (see also Table 4). There was no study discontinuation due to lack of efficacy in either treatment arm. There is also a lack of information on the last observed values at the time point of study discontinuation. It is therefore not possible to estimate whether some of the patients discontinued the study for other reasons, despite a response. The majority of patients discontinued the study early in the course of the study (at Week 12 already 6.7% versus 21.6% of patients). For patients who discontinued the study with hand eczema that did not respond adequately to treatment, further treatment outside the study is indicated. For these patients,

it cannot necessarily be assumed that none of them would show an improvement under adequate subsequent therapy by Week 24. An NRI or WOCF for all patients who discontinued the study therefore also is a worst-case scenario.

In contrast to NRI/WOCF (composite strategy), MI (treatment policy strategy) involves multiple imputation of missing values with data generated from a probability distribution based on the observed values. This method is preferable as it is probably based on a more realistic assumption. The company did not present suitable sensitivity analyses on the treatment policy strategy, as requested in dossier assessment A24-107.

The results between the 2 estimands 'composite strategy' and 'treatment policy strategy' differ in that the significant differences in favour of delgocitinib in some outcomes on morbidity and health-related quality of life are lost in the results using the treatment policy strategy. Due to the lack of further sensitivity analyses, it remains unclear to what extent the different handling of missing values causes this difference.

As already mentioned, the following sections present the results based on the estimand 'treatment policy strategy', which is preferable in the present research question due to the handling of the observed values and the imputation of missing values by means of MI.

Notes on the outcomes

Symptoms (HECSI-90)

HECSI is a valid instrument that allows the treating physician to assess the severity of a hand eczema. The HECSI score ranges from 0 to 360, based on the severity of 6 clinical signs (erythema, infiltration/papulation, vesicles, fissures, scaling and oedema) and their extent (area) on each hand area (fingertips, fingers, palm, back of hand and wrists). Higher values indicate more severe symptoms. According to the S2k guideline [10], severity is divided into the following categories based on the HECSI score: clear (HECSI score 0); almost clear (HECSI score 17 – 37); severe (HECSI score 38 – 116); very severe (HECSI score ≥ 117).

The company presented analyses of the predefined HECSI-90 and HECSI-75 (defined as a reduction in HECSI score from baseline by at least 90% and 75%, respectively) both in its dossier and in the subsequently submitted data. Analyses of HECSI-100, i.e. complete resolution, are not available, albeit requested in dossier assessment A24-107. However, complete resolution is an aspired and potentially achievable goal in this therapeutic indication. Based on the available data, it can be seen that at Week 24, 17.0% of patients in the intervention arm and 14.9% of patients in the control arm had an Investigator Global Assessment of Chronic Hand Eczema (IGA-CHE) score of 0 (corresponding to absence of symptoms). In the present therapeutic indication, in which the entire affected skin area is on the hands and thus in the visible area, a 90% reduction in HECSI score (as almost complete absence of symptoms and due to the predefinition) is also considered relevant. The

subsequently submitted responder analyses based on the treatment policy strategy for HECSI-90 are therefore presented in this addendum.

Symptoms (HESD)

The HESD is a well-validated questionnaire developed by the company to record symptoms of chronic hand eczema [14]. A total of 6 questions ask about the worst severity of the symptoms itch, pain, cracked skin, redness, dryness and flaking in the last 24 hours. The patient is asked to indicate the worst severity for each symptom on a rating scale from 0 (no symptom) to 10 (severe symptom). The total score (HESD total score) is calculated from the average of these 6 items and thus ranges from 0 to 10. There is also an HESD Pain score and an HESD Itch score, which only consist of the 2 individual items for these symptoms, however. The company presented responder analyses with an improvement by 4 points for the HESD total score and for the individual items on pain and itch at Week 24. The response threshold of 4 points is based on the validation study [14] and was also prespecified in the study protocol. The response criterion presented by the company thus meets the requirements as explained in the Institute's *General Methods* [15].

Health status (EQ-5D VAS)

Health status recorded using the EQ-5D VAS: The company presented responder analyses on improvement by ≥ 15 points at Week 24 for health status. According to the company, the analysis included patients with a baseline score ≥ 1.5 points. This threshold is not comprehensible. It is assumed that the analysis includes patients who can achieve an improvement, i.e. with a baseline score ≤ 85.

Health-related quality of life (HEIS)

The HEIS is a well-validated questionnaire developed by the company to measure health-related quality of life in patients with chronic hand eczema [16]. The HEIS comprises a total of 9 questions, grouped into 6 domains: daily activities (everyday competence), embarrassment with appearance of the hands, frustration with chronic hand eczema, sleep, work, and physical functioning over the past 7 days. Each question is rated by the patient on a scale from 0 (not at all) to 4 (extremely). The total score is the average of the 9 questions, thus covering a range from 0 to 4. The company presented responder analyses on a reduction in HEIS total score by ≥ 1.5 at Week 24. The response threshold of ≥ 1.5 points was not prespecified and does not correspond to the response threshold from the validation study. The response threshold of ≥ 1.5 points also does not meet the 15% criterion as explained in the Institute's *General Methods* [15]. The corresponding results of the responder analyses are therefore not presented in this addendum. The results of the change in HEIS total score at Week 24 compared with baseline are presented instead.

Health-related quality of life (Dermatology Life Quality Index [DLQI])

As health-related quality of life is adequately measured using the disease-specific HEIS described above, the DLQI is not shown. Moreover, the results do not differ between these 2 instruments.

Side effects

In its comments, the company subsequently submitted the observation periods for the side effects. The mean observation periods were 24.9 weeks in the intervention arm and 22.0 weeks in the control arm. The observation periods are therefore sufficiently comparable. The company did not provide any information on how it handled disease-related AEs. It is therefore assumed that disease-related AEs are included in the corresponding analyses and presentations of the company.

2.3.2 Risk of bias

Table 7 describes the risk of bias for the results of the relevant outcomes.

Table 7: Risk of bias across outcomes and outcome-specific risk of bias – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Study level	Outcomes								
		All-cause mortality[a]	Symptoms (HECSI-90)	Symptoms (HESD)	Health status (EQ-5D VAS)	Health-related quality of life (HEIS)	SAEs	Discontinuation due to AEs	Gastrointestinal disorders (SOC, AE)	Headache (PT, AE)
DELTA FORCE	L	L	H[b]	H[b, c]	H[b, c]	H[b, c]	H[d]	H[c, d]	H[c, d]	H[c, d]

a. The results on all-cause mortality are based on the information on fatal AEs.
b. Large difference between treatment groups (> 15 percentage points) with regard to the proportion of imputed values; in addition, a high proportion of patients (> 10%) is not included in the analysis for the outcomes of symptoms (HESD) and health status (EQ-5D VAS).
c. Lack of blinding with subjective recording of outcomes.
d. Incomplete observations for potentially informative reasons due different proportions of study discontinuations (11.4% vs. 28.6%)

AE: adverse event; H: high; HECSI-90: Hand Eczema Severity Index-90; HEIS: Hand Eczema Impact Scale; HESD: Hand Eczema Symptom Diary; L: low; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class

For the results on the outcome of all-cause mortality, the outcome-specific risk of bias is rated as low. For the results on all other outcomes from the morbidity, health-related quality of life,

and side effects categories, the risk of bias is rated as high. For the results on the outcomes of morbidity and health-related quality of life, the reason for this is the high proportion of imputed values, which differed between the treatment arms. In addition, with the exception of the HECSI-90, the lack of blinding with subjective recording of outcomes. The reason for the high risk of bias for the results on the side effects outcomes is the incomplete observation for potentially informative reasons and for the results on SAEs and specific AEs additionally the lack of blinding with subjective recording of outcomes.

2.3.3 Results

Table 8 and Table 9 summarize the results of the comparison of delgocitinib with alitretinoin in adult patients with severe chronic hand eczema for whom TCS are inadequate or inappropriate. Where necessary, calculations conducted by the Institute supplement the data from the dossier and the data subsequently submitted by the company.

The results on common AEs, SAEs and discontinuations due to AEs are presented in Appendix A.

Table 8: Results (mortality, morbidity, side effects) – RCT, direct comparison: delgocitinib vs. alitretinoin (multipage table)

Study Outcome category Outcome Week 24	Delgocitinib N	Delgocitinib Patients with event n (%)	Alitretinoin N	Alitretinoin Patients with event n (%)	Delgocitinib vs. alitretinoin RR [95% CI]; p-value[a]
DELTA FORCE					
Mortality					
All-cause mortality[b]	253	0 (0)	247	0 (0)	–
Morbidity[c]					
Symptoms (HECSI-90[d])	249	109 (43.7)	250	115 (46.2)	0.9 [0.61; 1.34]; 0.613
Symptoms (HESD) – improvement by ≥ 4 points at Week 24[e]	188	93 (49.4)	192	110 (57.6)	0.9 [0.70; 1.06]; 0.146
Itch (supplementary information)	*188*	*93 (49.4)*	*192*	*110 (57.6)*	–
Pain (supplementary information)	*175*	*105 (59.9)*	*180*	*107 (59.5)*	–
Health status (EQ-5D VAS) – improvement by ≥ 15 points at Week 24[f]	201	97 (48.4)	197	99 (50.2)	1.0 [0.78; 1.19]; 0.736
Side effects					
AEs (supplementary information)[g]	253	125 (49.4)	247	188 (76.1)	–
SAEs[g]	253	5 (2.0)	247	12 (4.9)	0.42 [0.15; 1.19]; 0.091
Discontinuation due to AEs[g]	253	3 (1.2)	247	25 (10.1)	0.12 [0.04; 0.38]; < 0.001
Gastrointestinal disorders (SOC, AE)	253	9 (3.6)	247	50 (20.2)	0.18 [0.09; 0.35]; < 0.001
Headache (PT, AE)	253	10 (4.0)	247	80 (32.4)	0.12 [0.07; 0.23]; < 0.001

Table 8: Results (mortality, morbidity, side effects) – RCT, direct comparison: delgocitinib vs. alitretinoin (multipage table)

Study Outcome category Outcome Week 24	Delgocitinib N	Delgocitinib Patients with event n (%)	Alitretinoin N	Alitretinoin Patients with event n (%)	Delgocitinib vs. alitretinoin RR [95% CI]; p-value[a]
a. Cochran-Mantel-Haenszel method, stratified by CHE subtype (hyperkeratotic/non-hyperkeratotic).					
b. The results on all-cause mortality are based on the data on fatal AEs.					
c. Treatment policy strategy: consideration of all observed values even after initiation of rescue treatment or permanent discontinuation of study medication and imputation of missing values by means of multiple imputation under the assumption that these are missing at random (MAR).					
d. Defined as a decrease in score by ≥ 90% from baseline, at a scale range of 0 to 360. Lower (decreasing) values indicate an improvement of symptoms. Patients with a baseline score were included.					
e. Improvement is defined as a decrease by ≥ 4 points from baseline, at a scale range of 0 to 10. Lower (decreasing) values indicate an improvement of symptoms. The analysis included patients with a baseline score ≥ 4 points.					
f. Improvement is defined as an increase by ≥ 15 points from baseline, at a scale range of 0 to 100. Higher (increasing) values indicate an improvement of health status. According to the company, the analysis included patients with a baseline score ≥ 1.5 points. This threshold is not comprehensible. It is assumed that the analysis includes patients who can achieve an improvement, i.e. with a baseline score ≤ 85.					
g. Overall rate of AEs including disease-related events.					
AE: adverse event; CI: confidence interval; HECSI-90: Hand Eczema Severity Index-90; HESD: Hand Eczema Symptom Diary; n: number of patients with (at least one) event; N: number of analysed patients; ND no data; PT: Preferred Term; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; SOC: System Organ Class					

Table 9: Results (health-related quality of life) – RCT, direct comparison: delgocitinib vs. alitretinoin

Study Outcome category Outcome	Delgocitinib N[a]	Delgocitinib Values at baseline mean (SD)	Delgocitinib Change at Week 24 mean[b] (SE)	Alitretinoin N[a]	Alitretinoin Values at baseline mean (SD)	Alitretinoin Change at Week 24 mean[b] (SE)	Delgocitinib vs. alitretinoin Effect[c] [95% CI]; p-value
DELTA FORCE							
Health-related quality of life							
HEIS[d]	231	ND	–1.51 (0.06)	237	ND	–1.49 (0.06)	–0.02 [–0.19; 0.14]; 0.789
a. Number of patients taken into account in the effect estimation; values at Week 24 may rest on different patient numbers.							
b. ANCOVA of changes from baseline to Week 24, adjusted for treatment arm, CHE subtype (hyperkeratotic/non-hyperkeratotic) and baseline value.							
c. Hedges' g of ANCOVA changes normalized with estimations of variance of the respective differences.							
d. Lower (decreasing) values indicate improved health-related quality of life; negative effects (intervention minus control) indicate an advantage for the intervention (scale range of 0 to 4).							
ANCOVA: analysis of covariance; CHE: chronic hand eczema; CI: confidence interval; HEIS: Hand Eczema Impact Scale; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error							

Mortality

No deaths occurred in the course of the DELTA FORCE study.

Morbidity

Symptoms (HECSI-90)

At Week 24, no statistically significant difference between treatment groups was shown for the outcome of symptoms, recorded with the HECSI-90.

Symptoms (HESD)

At Week 24, no statistically significant difference between treatment groups was shown for the outcome of symptoms, recorded with the HESD.

Health status (EQ-5D VAS)

At Week 24, no statistically significant difference between treatment groups was shown for the outcome of EQ-5D VAS.

Health-related quality of life

At Week 24, no statistically significant difference between treatment groups was shown for the outcome of health-related quality of life, recorded with the HEIS.

Side effects

SAEs

No statistically significant difference between treatment groups was shown for the outcome of SAEs.

Discontinuation due to AEs

A statistically significant difference between treatment groups in favour of delgocitinib was shown for the outcome of discontinuation due to AEs.

Gastrointestinal disorders (SOC, AE) and headache (PT, AE)

A statistically significant difference between treatment groups in favour of delgocitinib was shown for each of the outcomes of gastrointestinal disorders (System Organ Class [SOC], AE) and headache (Preferred Term [PT], AE).

2.3.4 Subgroups and other effect modifiers

The following subgroup characteristics are relevant for the present analysis:

- age (< 65 years versus ≥ 65 years)
- sex (male versus female)

- disease severity (HECSI score ≤ 116 versus HECSI score > 116)
- chronic hand eczema subtype (allergic contact dermatitis/atopic hand eczema/irritant contact dermatitis/acute recurrent vesicular hand eczema/hyperkeratotic hand eczema)

The company chose the IGA-CHE score (3 versus 4) to represent disease severity. However, as only patients with an IGA-CHE score of 4 were included in the DELTA FORCE study in accordance with the inclusion criteria, this characteristic is not a suitable subgroup characteristic for representing disease severity. Subgroup analyses based on HECSI score are not available. For the subgroup characteristics of age and sex, the company presented subgroup analyses for all outcomes listed in the dossier, except for the HEIS total score in the operationalization of change from Week 24 to baseline.

Interaction tests are performed when at least 10 patients per subgroup are included in the analysis. For binary data, there must also be at least 10 events in at least one subgroup.

Only the results with an effect modification with a statistically significant interaction between treatment and subgroup characteristic (p-value < 0.05) are presented. In addition, subgroup results are presented only if there is a statistically significant and relevant effect in at least one subgroup. Subgroup results where the extent does not differ between subgroups are not presented.

When applying the above-described methods, the available subgroup results show no effect modifications.

2.4 Summary of the results

Based on the DELTA FORCE study, the following advantages at outcome level have been shown for adult patients with severe chronic hand eczema for whom TCS are inadequate or inappropriate:

- advantage of delgocitinib versus alitretinoin for the outcome of discontinuation due to AEs
- advantage of delgocitinib versus alitretinoin for the outcomes of gastrointestinal disorders (AE) and headache (AE)

The G-BA decides on the added benefit.

3 References

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

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Appendix A Results on side effects

For the overall rates of AEs and SAEs, the tables below present events for Medical Dictionary for Regulatory Activities (MedDRA) SOCs and PTs, each on the basis of the following criteria:

- Overall rate of AEs (irrespective of severity grade): events that occurred in at least 10% of patients in one study arm
- Overall rate of SAEs: events that occurred in at least 5% of patients in one study arm
- In addition, for all events irrespective of severity grade: events that occurred in at least 10 patients and in at least 1% of patients in one study arm

For the outcome of discontinuation due to AEs, all events (SOCs/PTs) which resulted in discontinuation are completely presented.

Table 10: Common AEs[a] – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Patients with event n (%)	
SOC[b] **PT[b]**	**Delgocitinib** **N = 253**	**Alitretinoin** **N = 247**
DELTA FORCE		
Overall rate of AEs[c]	125 (49.4)	188 (76.1)
Eye disorders	2 (0.8)	14 (5.7)
Gastrointestinal disorders	9 (3.6)	50 (20.2)
Nausea	1 (0.4)	14 (5.7)
General disorders and administration site conditions	12 (4.7)	16 (6.5)
Infections and infestations	74 (29.2)	85 (34.4)
Urinary tract infection	1 (0.4)	10 (4.0)
Nasopharyngitis	30 (11.9)	34 (13.8)
Injury, poisoning and procedural complications	15 (5.9)	13 (5.3)
Investigations	16 (6.3)	26 (10.5)
Metabolism and nutrition disorders	4 (1.6)	22 (8.9)
Musculoskeletal and connective tissue disorders	17 (6.7)	12 (4.9)
Nervous system disorders	16 (6.3)	89 (36.0)
Headache	10 (4.0)	80 (32.4)
Psychiatric disorders	0 (0)	13 (5.3)
Respiratory, thoracic and mediastinal disorders	9 (3.6)	20 (8.1)
Skin and subcutaneous tissue disorders	21 (8.3)	52 (21.1)
Vascular disorders	3 (1.2)	10 (4.0)

a. Events that occurred in ≥ 10 of patients in at least one study arm.
b. MedDRA version 24.0; SOC and PT notation taken from Module 4 without adaptation.
c. Overall rate of AEs including disease-related events.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class

Table 11: Common SAEs[a] – RCT, direct comparison: delgocitinib vs. alitretinoin

Study	Patients with event n (%)	
	Delgocitinib N = 253	Alitretinoin N = 247
DELTA FORCE		
Overall rate of SAEs[b, c]	5 (2.0)	12 (4.9)

a. Events that occurred in ≥ 10 of patients in at least one study arm.
b. For SAEs, no MedDRA SOCs and PTs met the criterion for presentation.
c. Overall rate of SAEs including disease-related events.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SAE: serious adverse events; SOC: System Organ Class

Table 12: Discontinuation due to AEs[a] – RCT, direct comparison: delgocitinib vs. alitretinoin (multipage table)

Study	Patients with event n (%)	
SOC PT	Delgocitinib N = 253	Alitretinoin N = 247
DELTA FORCE		
Overall rate of discontinuations due to AEs	3 (1.2)	25 (10.1)
General disorders and administration site conditions	2 (0.8)	1 (0.4)
Application site pain	1 (0.4)	0 (0)
Pain	1 (0.4)	0 (0)
Oedema peripheral	0 (0)	1 (0.4)
Immune system disorders	1 (0.4)	0 (0)
Drug hypersensitivity	1 (0.4)	0 (0)
Skin and subcutaneous tissue disorders	1 (0.4)	7 (2.8)
Pain of skin	1 (0.4)	0 (0)
Dermatitis atopic	0 (0)	2 (0.8)
Hand dermatitis	0 (0)	2 (0.8)
Hyperhidrosis	0 (0)	1 (0.4)
Photosensitivity reaction	0 (0)	1 (0.4)
Rash maculo-papular	0 (0)	1 (0.4)
Urticaria	0 (0)	1 (0.4)
Cardiac disorders	0 (0)	1 (0.4)
Palpitations	0 (0)	1 (0.4)
Ear and labyrinth disorders	0 (0)	1 (0.4)
Tinnitus	0 (0)	1 (0.4)

Table 12: Discontinuation due to AEs[a] – RCT, direct comparison: delgocitinib vs. alitretinoin (multipage table)

Study	Patients with event n (%)	
SOC PT	Delgocitinib N = 253	Alitretinoin N = 247
Eye disorders	0 (0)	1 (0.4)
Vision blurred	0 (0)	1 (0.4)
Gastrointestinal disorders	0 (0)	4 (1.6)
Diarrhoea	0 (0)	2 (0.8)
Nausea	0 (0)	3 (1.2)
Infections and infestations	0 (0)	1 (0.4)
Urinary tract infection	0 (0)	1 (0.4)
Investigations	0 (0)	1 (0.4)
Weight decreased	0 (0)	1 (0.4)
Nervous system disorders	0 (0)	14 (5.7)
Dizziness	0 (0)	1 (0.4)
Headache	0 (0)	11 (4.5)
Idiopathic intracranial hypertension	0 (0)	1 (0.4)
Migraine	0 (0)	1 (0.4)
Psychiatric disorders	0 (0)	4 (1.6)
Affective disorder	0 (0)	1 (0.4)
Aggression	0 (0)	1 (0.4)
Anger	0 (0)	1 (0.4)
Anxiety	0 (0)	2 (0.8)
Depressed mood	0 (0)	1 (0.4)
Mood swings	0 (0)	1 (0.4)
Respiratory, thoracic and mediastinal disorders	0 (0)	3 (1.2)
Cough	0 (0)	1 (0.4)
Epistaxis	0 (0)	2 (0.8)
Vascular disorders	0 (0)	1 (0.4)
Hypertension	0 (0)	1 (0.4)

a. MedDRA version 24.0; SOC and PT notation taken unmodified from Module 4 C.

AE: adverse event; MedDRA: Medical Dictionary for Regulatory Activities; n: number of patients with at least one event; N: number of analysed patients; PT: Preferred Term; RCT: randomized controlled trial; SOC: System Organ Class