IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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Brodalumab (plaque psoriasis) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Brodalumab (Plaque-Psoriasis) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.1; Status: 1 December 2017). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
BSA	body surface area
DLQI	Dermatology Life Quality Index
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
NAPSI	Nail Psoriasis Severity Index
NB-UVB	narrowband ultraviolet B light (311 nm)
NRI	non-responder imputation
PASI	Psoriasis Area and Severity Index
PSI	Psoriasis Symptom Inventory
PUVA	psoralen and ultraviolet-A light
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
SPC	Summary of Product Characteristics
sPGA	static Physician Global Assessment

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug brodalumab. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter referred to as "the company"). The dossier was sent to IQWiG on 1 September 2017.

Research question

The aim of the present report was to assess the added benefit of brodalumab in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

This resulted in 2 research questions, for which the G-BA specified the ACTs presented in Table 2.

Table 2: Research questions of the benefit assessment of brodalumab

Research question	Subindication[a]	ACT[b]
1	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[c]	Fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[d]
2	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or ustekinumab or secukinumab[d]

a: It is a precondition that topical treatment alone is inadequate for the patients treated.
b: Presentation of the respective ACT specified by the G-BA.
c: The population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question 2.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

For easier presentation and better readability, the present benefit assessment uses the following terms for the 2 research questions:

- Research question 1: adult patients who are candidates for systemic treatment
- Research question 2: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

For both research questions, the company deviated from the specification of the ACT insofar as it did not mention secukinumab because the G-BA specified the ACT after the dossier had been submitted. The deviation from the ACT had no consequence for the assessment because no randomized controlled trials (RCTs) with a direct comparison of brodalumab versus secukinumab were identified for either research question.

The present benefit assessment was conducted in comparison with the ACT specified by the G-BA. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

Results for research question 1: adult patients who are candidates for systemic treatment

The company identified no study of direct comparison with the comparator therapy specified by the G-BA for the assessment of the added benefit of brodalumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic treatment (research question 1). The company therefore presented an adjusted indirect comparison using the studies AMAGINE-1, AMAGINE-2 and AMAGINE-3 on brodalumab (over a period of 12 weeks), and of the BRIDGE study on fumaric acid esters (over a period of 16 weeks). However, this comparison was unsuitable for answering the present research question as the treatment duration was too short in each case.

In summary, no suitable data were available for research question 1. Consequently, there was no hint of an added benefit of brodalumab in comparison with the ACT. An added benefit is therefore not proven.

Results for research question 2: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

The company included the RCTs AMAGINE-2 and AMAGINE-3 for the assessment of the added benefit of brodalumab for the treatment of adults with moderate to severe plaque psoriasis with inadequate response to other systemic treatments or who are unsuitable for these treatments.

Study design

AMAGINE-2 and AMAGINE-3 were randomized, double-blind, multicentre parallel-group studies. The studies included adults with stable moderate to severe plaque psoriasis. The following inclusion criteria for disease severity were used: involved body surface area (BSA) $\geq 10\%$, Psoriasis Area and Severity Index (PASI) ≥ 12, and static Physician Global Assessment (sPGA) ≥ 3.

The study design included a 12-week induction phase, a maintenance phase (week 12 to 52), and an extension phase (from week 52). A rescue phase was additionally planned from week 16.

At the start of the induction phase, 1831 patients in the AMAGINE-2 study and 1881 patients in the AMAGINE-3 study were allocated through stratified randomization in a ratio of 2:2:1:1 to the following treatment arms: brodalumab 210 mg every 2 weeks, brodalumab 140 mg every 2 weeks, ustekinumab, or placebo. For the subsequent maintenance phase of the studies (week 12 to 52), the patients in both brodalumab arms who had received a dose of the study medication at week 12 (1174 patients in the AMAGINE-2 study, and 1200 patients in AMAGINE-3), were re-randomized in an allocation ratio of 2:2:2:1 to the following brodalumab arms: 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks, and 140 mg every 8 weeks. Treatment was continued in the ustekinumab study arm, whereas the patients in the placebo group switched to brodalumab 210 mg every 2 weeks.

In the extension phase (from week 52), all patients who had originally received ustekinumab were switched to brodalumab 210 mg every 2 weeks. The other treatment groups continued their therapies. Due to lack of comparison, the results of the extension phase were not relevant for the present benefit assessment.

Patients from the maintenance phase who fulfilled one of the following criteria for administration of rescue treatment were included in the rescue phase: sPGA ≥ 3 or sPGA = 2 for a period of 4 weeks. For the ustekinumab group, switching treatment to brodalumab 210 mg twice weekly at week 16 was designated as rescue treatment. In case of non-response at a later time point, treatment with ustekinumab was continued. Depending on the dosage, patients treated with brodalumab continued treatment with brodalumab 210 mg every 2 weeks as rescue treatment or were switched to this dosage. In case of persistent non-response, the medication was eventually stopped.

Primary outcome for the comparison of brodalumab versus ustekinumab was PASI 100. Secondary relevant outcomes were all-cause mortality, symptoms, health-related quality of life, and adverse events (AEs).

Subpopulation and analysis time point relevant for the benefit assessment

Due to the approved dosage, patients from the brodalumab group who were allocated to brodalumab 210 mg every 2 weeks both at first randomization and at re-randomization were primarily relevant for the present benefit assessment. For the ustekinumab arm, all patients included were initially to be considered because of the missing re-randomization. Treatment in both groups was conducted without relevant deviations from the respective Summaries of Product Characteristics (SPCs).

From these study arms, patients with inadequate response to systemic treatments (including ciclosporin, methotrexate and psoralen and ultraviolet-A light [PUVA]), or with contraindication or intolerance to such treatments were finally relevant.

The subpopulation presented by the company for answering research question 2 corresponded to about 14.6% of the patients randomized to the brodalumab arm and 51.2% of the patients randomized to the ustekinumab arm. However, the company's construction of the subpopulation was not fully comprehensible. On the one hand, it is possible that patients who should belong to this population according to the G-BA's definition were not included in the subpopulation presented by the company. If included, these patients would constitute about 13.9% to 16.7% of the subpopulation. On the other hand, it remains unclear for other patients (21 to 31%) whether their inclusion in the subpopulation was adequate for research question 2. Together with further relevant aspects (see below), this uncertainty was considered in the derivation of the certainty of conclusions of the results.

The results at week 52 were used for the benefit assessment.

Risk of bias and overall assessment of the certainty of conclusions

No usable data were available for the outcomes "symptoms of nail psoriasis", "patient-reported symptoms", and "infections and infestations". Selecting specific AEs was not possible based on the documents presented by the company. The risk of bias was therefore not assessed for these outcomes. With the exception of all-cause mortality, there was a high risk of bias for further outcomes included for which usable data were available.

The decisive reason was a possible systematic disadvantage for the ustekinumab arm resulting from the design of the studies' rescue phase. In addition, there were uncertainties regarding the allocation of patients to the relevant subpopulation (see above).

In summary, due to these reasons, at most indications, e.g. of an added benefit, could be derived from the meta-analysis of the studies for the outcomes presented.

Mortality

All-cause mortality

No deaths occurred in the brodalumab study arms until the end of the maintenance phase. There were 2 deaths in the ustekinumab group of the AMAGINE-2 study, and no deaths in the corresponding arm of the AMAGINE-3 study. Overall, this resulted in no hint of an added benefit of brodalumab in comparison with ustekinumab; an added benefit is therefore not proven.

Morbidity

Remission (PASI 100)

The meta-analysis of the studies (non-responder imputation [NRI] analysis) showed a statistically significant difference in favour of brodalumab for the outcome "remission",

recorded with the PASI 100. The result for this outcome might be biased, however, because the results of the patients who switched treatment from ustekinumab to brodalumab at week 16 were rated as non-response. For this reason, results of a sensitivity analysis conducted by the Institute were additionally considered. Despite reduced effect size, the result of this analysis still showed a statistically significant difference in favour of brodalumab. Overall, this resulted in an indication of an added benefit of brodalumab in comparison with ustekinumab.

Symptoms of nail psoriasis (Nail Psoriasis Severity Index [NAPSI])

In Module 4 A, the company presented the mean change in NAPSI between the start of the study and week 52. Due to the high proportion of patients not considered in the company's analyses, no usable data were available for this outcome. Overall, there was no hint of an added benefit of brodalumab in comparison with ustekinumab for the outcome "symptoms of nail psoriasis". An added benefit for this outcome is therefore not proven.

Patient-reported symptoms (Psoriasis Symptom Inventory [PSI])

The company did not include the outcome "PSI" in its assessment and presented no analyses for the relevant subpopulation. There was no hint of an added benefit of brodalumab in comparison with ustekinumab for the outcome "patient-reported symptoms". An added benefit for this outcome is therefore not proven.

Health-related quality of life

Dermatology Life Quality Index (DLQI)

Regarding the proportion of patients with a DLQI score of 0 or 1 at week 52, the meta-analysis of the studies (NRI analysis) showed a statistically significant difference in favour of brodalumab. The result for this outcome might be biased, however, because the results of the patients who switched treatment from ustekinumab to brodalumab at week 16 were rated as non-response. For this reason, results of a sensitivity analysis conducted by the Institute were additionally considered. This sensitivity analysis showed no statistically significant difference between the treatment groups; the result was therefore not robust. For the reasons stated above, the certainty of conclusions of the results was reduced. Since, in addition, the effect was not robust in the sensitivity analysis, the certainty of conclusions was downgraded from an indication to a hint. Overall, there was a hint of an added benefit of brodalumab in comparison with ustekinumab for DLQI 0 or 1.

Side effects

Serious adverse events and discontinuation due to adverse events

There were heterogeneous results without effects in the same direction for the outcome "serious adverse events [SAEs]". There was no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm of brodalumab in comparison with ustekinumab for these outcomes. Greater or lesser harm is therefore not proven.

Specific adverse events

No analysis of infections and infestations was available for the relevant subpopulation.

Selecting further specific AEs was not possible based on the documents provided by the company in the dossier. Hence there was no hint of greater or lesser harm of brodalumab in comparison with ustekinumab for any of these outcomes. Greater or lesser harm is therefore not proven for this outcome.

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

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

Since there were no relevant data for adults who are candidates for systemic treatment (research question 1), an added benefit of brodalumab is not proven for this research question.

The comprehensive consideration of the data for adults with inadequate response to other systemic treatments or who are not candidates for these treatments (research question 2) showed positive effects of brodalumab in the outcome categories of morbidity and health-related quality of life. Regarding morbidity, there is an indication of an added benefit for the outcome "remission (PASI 100)" and a hint of an added benefit in the area of health-related quality of life for the outcome "DLQI (0 or 1)". In both cases, the extent of added benefit is non-quantifiable, and at most considerable for PASI 100.

No data were available for the assessment of patient-reported symptoms. There were also no data available for the outcome "infections and infestations" and the selection of further specific AEs. Further positive and negative effects could therefore not be assessed based on the data available. However, based on the available information, the positive effects of brodalumab were not completely questioned.

In summary, there is an indication of a non-quantifiable added benefit of brodalumab in comparison with ustekinumab for adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments.

Table 3 presents a summary of the probability and extent of the added benefit of brodalumab.

[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: Brodalumab – probability and extent of added benefit

Research question	**Subindication**[a]	**ACT**[b]	**Probability and extent of added benefit**
1	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[c]	Fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[d]	Lesser benefit/added benefit not proven
2	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or ustekinumab or secukinumab[d]	Indication of an added benefit, extent "non-quantifiable"

a: It is a precondition that topical treatment alone is inadequate for the patients treated.
b: Presentation of the respective ACT specified by the G-BA.
c: The population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question 2.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

2.2 Research question

The aim of the present report was to assess the added benefit of brodalumab in comparison with the ACT in adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy.

This resulted in 2 research questions, for which the G-BA specified the ACTs presented in Table 4.

Table 4: Research questions of the benefit assessment of brodalumab

Research question	Subindication[a]	ACT[b]
1	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[c]	Fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[d]
2	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or ustekinumab or secukinumab[d]

a: It is a precondition that topical treatment alone is inadequate for the patients treated.
b: Presentation of the respective ACT specified by the G-BA.
c: The population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question 2.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

For easier presentation and better readability, the present benefit assessment uses the following terms for the 2 research questions:

- Research question 1: adult patients who are candidates for systemic treatment
- Research question 2: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

For research question 1, the G-BA specified fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB [311 nm]) or secukinumab as ACTs. The ACTs specified by the G-BA for research question 2 comprised adalimumab, infliximab, ustekinumab and secukinumab [3]. For both research questions, the company deviated from the specification of the ACT insofar as it did not mention secukinumab because the G-BA specified the ACT after the dossier had been submitted (see Section 2.6.1 of the full dossier assessment).

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

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

2.3 Research question 1: adult patients who are candidates for systemic treatment

2.3.1 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 brodalumab (status: 8 August 2017)
- bibliographical literature search on brodalumab (last search on 9 June 2017)
- search in trial registries for studies on brodalumab (last search on 7 June 2017)
- bibliographical literature search on the ACTs (last search on 9 June 2017)
- search in trial registries for studies on the ACTs (last search on 6 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on brodalumab (last search on 8 September 2017)

No study of direct comparison was identified from the check.

Since the company identified no relevant study of direct comparison, it conducted an additional search for studies for an adjusted indirect comparison. In this search, the company identified the following studies for an adjusted indirect comparison with placebo as common comparator: AMAGINE-1 [4], AMAGINE-2 [5] and AMAGINE-3 [5] on brodalumab, and the RCT BRIDGE on fumaric acid esters [6]. However, this comparison was not relevant for answering the present research question for the following reason:

The duration of placebo use in the AMAGINE studies was 12 weeks. Treatment duration in the BRIDGE study was 16 weeks. The company presented a meta-analysis of the results of the AMAGINE studies over the duration of 12 weeks and compared it with the results of the BRIDGE study over the duration of 16 weeks using the Bucher method [7]. A minimum duration of 24 weeks is considered necessary for the chronic disease under assessment, however. Consequently, the comparison was unsuitable for the assessment of the added benefit because the treatment duration was too short.

Irrespective of this, the comparison may not be possible anyhow considering the publication of Mrowietz 2017 [6]. The BRIDGE study also included patients who had received prior systemic therapy. The Mrowietz 2017 publication on the BRIDGE study only provided information on the proportion of prior systemic therapies per drug, however. The total number of patients who had received such pretreatment cannot be inferred from the information due to possible double counting. Separate analyses on the subpopulation that was naive regarding systemic treatment were not available.

For research question 1, the company additionally presented results for the subpopulations from the studies AMAGINE-2 and AMAGINE-3 that comprised patients who, according to the company, concurred with the G-BA's criteria for the formation of the subpopulation for research question 1. These studies used ustekinumab as comparator therapy, however. Since ustekinumab was not the ACT specified by the G-BA, these results were not used for the assessment of the added benefit.

2.3.2 Results on added benefit

No usable data were available for the assessment of the added benefit of brodalumab for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic treatment (research question 1). Consequently, there was no hint of an added benefit of brodalumab in comparison with the ACT. An added benefit is therefore not proven.

2.3.3 Extent and probability of added benefit

Since there were no relevant data in comparison with the ACT for adults who are candidates for systemic treatment, an added benefit is not proven. This deviates from the assessment of the company, which derived an indication of considerable added benefit of brodalumab in comparison with fumaric acid esters.

2.3.4 List of included studies

Not applicable as the company presented no relevant data for the present research question.

2.4 Research question 2: adult patients with inadequate response to other systemic treatments or who are unsuitable for these treatments

2.4.1 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 brodalumab (status: 8 August 2017)
- bibliographical literature search on brodalumab (last search on 9 June 2017)
- search in trial registries for studies on brodalumab (last search on 7 June 2017)

To check the completeness of the study pool:

- search in trial registries for studies on brodalumab (last search on 8 September 2017)

The check identified no additional relevant study.

2.4.1.1 Studies included

The studies listed in the following table were included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: brodalumab vs. ustekinumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Study 20120103 (AMAGINE-2[b])	Yes	Yes	No
Study 20120104 (AMAGINE-3[b])	Yes	Yes	No
a: Study sponsored by the company. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

Section 2.4.4 contains a reference list for the studies included.

2.4.1.2 Study characteristics

Table 6 and Table 7 describe the studies used for the benefit assessment.

Table 6: Characteristics of the studies included – RCT, direct comparison: brodalumab vs. ustekinumab

Study	Study design	Population	Interventions (numbers of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
AMAGINE-2	RCT, double-blind, parallel	Adults (≥ 18 years and ≤ 75 years) with stable plaque psoriasis (BSA ≥ 10, PASI ≥ 12 and sPGA ≥ 3) for at least 6 months before the first dose of the study medication	Brodalumab 210 mg (N = 612) brodalumab 140 mg (N = 610)[b] ustekinumab (N = 300) placebo (N = 309)[b] Relevant subpopulation thereof[c]: brodalumab 210 mg (n = 97) ustekinumab (n = 168)	Screening: ≥ 7 to ≤ 30 days Treatment: induction phase: 12 weeks maintenance phase[d]: week 12 to week 52 extension phase[e]: from week 52 to week 266	142 centres in Australia, Austria, Canada, Czech Republic, France, Hungary, Netherlands, Poland, Portugal, Spain, USA 8/2012–10/2015	Primary: PASI 75[f], PASI 100[g], sPGA success[f] Secondary: all-cause mortality, symptoms, health-related quality of life, AEs
AMAGINE-3	RCT, double-blind, parallel	Adults (≥ 18 years and ≤ 75 years) with stable plaque psoriasis (BSA ≥ 10, PASI ≥ 12 and sPGA ≥ 3) for at least 6 months before the first dose of the study medication	Brodalumab 210 mg (N = 624) brodalumab 140 mg (N = 629)[b] ustekinumab (N = 313) placebo (N = 315)[b] Relevant subpopulation thereof[c]: brodalumab 210 mg (n = 83) ustekinumab (n = 146)	Screening: ≥ 7 to ≤ 30 days Treatment: induction phase: 12 weeks maintenance phase[d]: week 12 to week 52 extension phase[e]: from week 52 to week 266	142 centres in Australia, Belgium, Canada, France, Greece, Hungary, Italy, Latvia, Poland, Russia, USA 9/2012–10/2015	Primary: PASI 75[f], PASI 100[g], sPGA success[f] Secondary: all-cause mortality, symptoms, health-related quality of life, AEs

a: Primary outcomes include information without consideration of its relevance for this benefit assessment. Secondary outcomes exclusively include information on the relevant available outcomes for this benefit assessment.
b: The arm is not relevant for the assessment and is no longer shown in the next tables.
c: According to the information provided by the company in Module 4 A, the subpopulation includes patients with inadequate response, contraindication or intolerance to other systemic treatments including ciclosporin, methotrexate or PUVA (psoralen and ultraviolet-A light) who received continuous treatment with brodalumab or ustekinumab after randomization.
d: At the start of the maintenance phase, patients from the brodalumab arms were re-randomized.
e: In the extension phase, patients in all study arms were treated with brodalumab. Due to lack of comparison, this phase is not relevant for the assessment and is not shown in the next tables.
f: As primary outcome only for the comparison of brodalumab vs. placebo.
g: As primary outcome only for the comparison of brodalumab vs. ustekinumab.
AE: adverse event; BSA: body surface area; n: relevant subpopulation; N: number of randomized patients; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; sPGA: static Physician Global Assessment; vs.: versus

Table 7: Characteristics of the interventions – RCT, direct comparison: brodalumab vs. ustekinumab

Study	Intervention	Comparison
AMAGINE-2	**Induction phase and maintenance phase:** brodalumab 210 mg SC every 2 weeks until week 52, with additional dose in week 1, 13 and 17	**Induction phase and maintenance phase:** ustekinumab depending on body weight: ▪ 45 mg SC ≤ 100 kg ▪ 90 mg SC > 100 kg on day 1 and week 4, 16, 28 and 40
AMAGINE-3	**Induction phase and maintenance phase:** brodalumab 210 mg SC every 2 weeks until week 52, with additional dose in week 1, 13 and 17	**Induction phase and maintenance phase:** ustekinumab depending on body weight: ▪ 45 mg SC ≤ 100 kg ▪ 90 mg SC > 100 kg on day 1 and week 4, 16, 28 and 40
Prior and concomitant treatment (AMAGINE-2, AMAGINE-3): **Pretreatment:** Permitted pretreatment: ▪ highly-potent or potent topical steroids, or topical anthralin (dithranol) until ≥ 28 days before the first dose of the study medication ▪ any other form of topical treatment until ≥ 14 days before the first dose of the study medication ▪ until ≥ 28 days before the first dose of the study medication: UV-A light therapy (with or without psoralen), UV-B light therapy, excimer laser, oral retinoids, methotrexate, ciclosporin, systemic calcineurin inhibitors, azathioprine, tioguanine, hydroxyurea, fumarates, oral or parenteral corticosteroids including intramuscular or intraarticular administration, other non-biologic systemic treatments of psoriasis ▪ live vaccines ≥ 28 days before the first dose of the study medication (or longer, in accordance with local regulations regarding ustekinumab) ▪ ustekinumab and/or anti-IL-17 biological therapy or other experimental or commercially available biological immunomodulators until ≥ 12 weeks before the first study medication ▪ other investigational drugs until ≥ 30 days after the end of the administration **Concomitant treatment:** Concomitant treatment permitted: ▪ upper mid-strength or lower potency topical steroids for face, axillae and groin ▪ emollients without urea or alpha or beta hydroxy acid ▪ shampoo without steroids ▪ otic, nasal, ophthalmic or inhaled corticosteroids within the recommended dosage Concomitant treatment prohibited: ▪ UV-A light therapy (with or without psoralen), UV-B light therapy ▪ methotrexate, mycophenolate mofetil, cyclophosphamide, ciclosporin, systemic calcineurin inhibitors, azathioprine, tioguanine, oral retinoids, hydroxyurea, fumarates, biological immunomodulators (e.g. etanercept, alefacept, anakinra, adalimumab, infliximab and IL-12/IL-23 inhibitors), and any other systemic psoriasis treatment		
IL-17: interleukin 17, RCT: randomized controlled trial; SC: subcutaneous; UV: ultraviolet; vs.: versus		

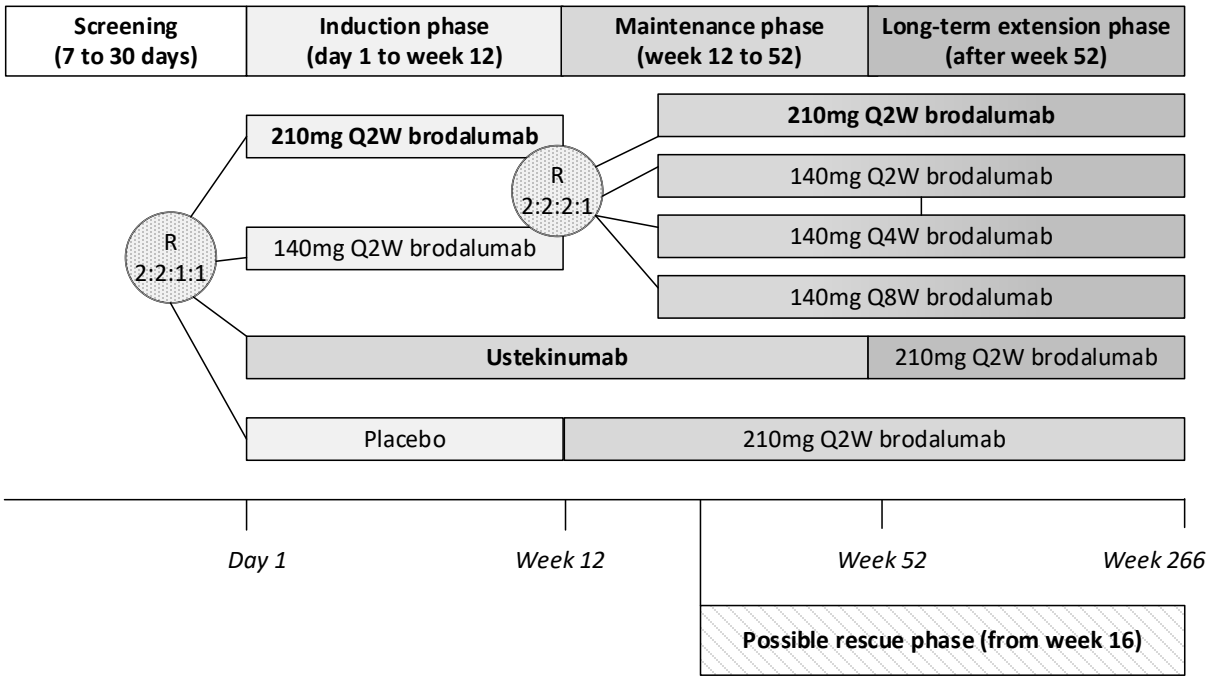
Description of the study design

The studies AMAGINE-2 and AMAGINE-3 were randomized, double-blind multicentre parallel-group studies. The studies investigated brodalumab in different dosages in comparison with placebo and ustekinumab in adults with moderate to severe plaque psoriasis. Patients who were deemed candidates for biological therapy by the investigator (in

accordance with the requirements specified in the respective regional approval) were eligible for study inclusion. Correspondingly, the inclusion criteria were not restricted to the patients of the present research question, i.e. patients with inadequate response to systemic treatment (including ciclosporin, methotrexate and PUVA) or with intolerance or contraindication to such treatment. The company therefore presented the results of a subpopulation (see below).

In both studies, disease severity was defined using the following criteria: involved BSA ≥ 10%, PASI ≥ 12, and sPGA ≥ 3. For the present benefit assessment, this definition of the severity grade was rated as adequate representation of moderate to severe psoriasis (see Section 2.6.2.4.1 of the full dossier assessment).

The studies had a comparable study design, outlined in the following figure.



Q2W: every 2 weeks; Q4W: every 4 weeks; Q8W: every 8 weeks; R: randomization

Figure 1: Design of the studies AMAGINE-2 and AMAGINE-3

The studies were divided into 4 phases: screening phase, 12-week induction phase, subsequent maintenance phase until week 52 and extension phase from week 52.

At the start of the induction phase, 1831 patients in the AMAGINE-2 study and 1881 patients in the AMAGINE-3 study were allocated through stratified randomization in a ratio of 2:2:1:1 to the following treatment arms: brodalumab 210 mg every 2 weeks, brodalumab 140 mg every 2 weeks, ustekinumab, or placebo. Stratification criteria were body weight (≤ 100 kg/> 100 kg), prior biological therapy (yes/no) and geographical region. The proportion of patients with prior biological therapy was restricted to 50%.

For the subsequent maintenance phase of the studies (week 12 to 52), the patients in both brodalumab arms who had received a dose of the study medication at week 12 (1174 patients in the AMAGINE-2 study, and 1200 patients in AMAGINE-3), were re-randomized in an allocation ratio of 2:2:2:1 to the following brodalumab arms: 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks, and 140 mg every 8 weeks. Stratification factors were body weight (≤ 100 kg/> 100 kg), sPGA response at week 12, and prior brodalumab dosage (210 mg/140 mg). Treatment was continued in the ustekinumab study arm, whereas the patients in the placebo group switched to brodalumab 210 mg every 2 weeks. Hence only those patients from the brodalumab arms who were randomized to treatment with 210 mg every 2 weeks in the induction phase and in the maintenance phase were relevant for the present benefit assessment (see below).

In the extension phase (from week 52), all patients who had originally received ustekinumab were switched to brodalumab 210 mg every 2 weeks. The other treatment groups continued their therapies. Due to lack of a comparison, the results of the extension phase were not relevant for the present benefit assessment.

In addition to the phases described above, the studies comprised a rescue phase from week 16. Patients from the maintenance phase who fulfilled one of the following criteria for administration of rescue treatment were included in this phase: sPGA ≥ 3 or sPGA = 2 for a period of 4 weeks. The rescue treatment differed between the individual study arms. Patients in the ustekinumab arm who required rescue treatment at week 16 were switched to treatment with brodalumab 210 mg every 2 weeks. If one of the criteria only applied after week 16, ustekinumab treatment was continued, with no treatment switch taking place. Depending on the preceding dosage, rescue therapy for patients treated with brodalumab was either continued treatment with brodalumab 210 mg every 2 weeks or a switch to this dosage. If response after at least 12 weeks of rescue treatment was inadequate (defined as sPGA ≥ 3 for ≥ 4 weeks), rescue treatment was stopped.

Primary outcome for the comparison of brodalumab versus ustekinumab was PASI 100. Secondary relevant outcomes were all-cause mortality, symptoms, health-related quality of life, and AEs.

Subpopulation relevant for the benefit assessment

Due to the approved dosage [8], patients from the brodalumab group who were allocated to brodalumab 210 mg every 2 weeks both at first randomization and at re-randomization were primarily relevant for the present benefit assessment. For the ustekinumab arm, all patients included were initially to be considered because of the missing re-randomization. Treatment in both groups largely concurred with the respective SPCs (see Table 7) [8,9]. The additional medication in week 13 and 17 in the brodalumab study arms resulted in a deviation from the 2-week rhythm mandated in the SPC. Nevertheless, in the present case no substantial influence is expected on the results at the time point relevant for the benefit assessment (week 52, see below).

Only subpopulations of the studies AMAGINE-2 and AMAGINE-3 were relevant for answering research question 2, namely those patients for whom systemic drug treatment is inadequate or contraindicated or who do not tolerate such treatment. The company stated in Module 4 A to have included the patient population described above in its assessment.

However, the company's construction of the subpopulation was not fully comprehensible. On the one hand, it is possible that patients who should belong to this population according to the G-BA's definition were not included in the subpopulation presented by the company. If included, these patients would constitute about 13.9% to 16.7% of the subpopulation. On the other hand, it remains unclear for other patients (21 to 31%) whether their inclusion in the subpopulation was adequate for research question 2. A detailed explanation can be found in Section 2.6.2.4.1 of the full dossier assessment. The subpopulation presented by the company was nevertheless used as sufficient approximation to the subpopulation relevant for research question 2. The existing uncertainties were considered in the derivation of the certainty of conclusions of the results (see Section 2.4.2.2).

In addition, the company's information on the patient characteristics showed that the company did not consider patients in its assessment who had dropped out of observation during the induction phase and before the start of the maintenance phase. In each of the 2 studies, these were about 3.8% in the ustekinumab group, and at most about 10% in the brodalumab group; hence no relevant influence on the results was expected from this approach.

Characteristics of the patient population

Table 8 shows the characteristics of the patients in the studies included.

Table 8: Characteristics of the study populations – RCT, direct comparison: brodalumab vs. ustekinumab

Study **Characteristics** **Category**	**Brodalumab**	**Ustekinumab**
AMAGINE-2	N[a] = 97	N[a] = 168
Age [years], mean (SD)	44 (14)	47 (13)
Sex [F/M], %	32/68	33/67
Ethnicity, n (%)		
White	88 (90.7)	151 (89.9)
Black or African American	2 (2.1)	4 (2.4)
Asian	3 (3.1)	8 (4.8)
Other[b]	4 (4.1)[c]	5 (3.0)[c]
Body weight [kg], n (%)		
≤ 100 kg	75 (77.3)	119 (70.8)
> 100 kg	22 (22.7)	49 (29.2)
Scalp involvement, n (%)	ND	ND
Face and neck involvement, n (%)	ND	ND
Fingernail involvement, n (%)	ND	ND
Genital involvement, n (%)	ND	ND
Duration of disease [years], mean (SD)	19.8 (11.4)	21.6 (13.0)
PASI, mean (SD)	20.6 (8.1)	19.9 (8.2)
DLQI, mean (SD)	16.4 (7.2)	15.1 (7.3)
sPGA, mean (SD)	3.5 (0.6)	3.5 (0.6)
Psoriatic arthritis [yes/no], n (%)	30 (30.9)/67 (69.1)	40 (23.8)/128 (76.2)
Pretreatment with, n (%)		
Systemic drugs [yes/no]	91 (93.8)/6 (6.2)	149 (88.7)/19 (11.3)
Phototherapy [yes/no]	55 (56.7)/42 (43.3)	109 (64.9)/59 (35.1)
Biologics [yes/no]	50 (51.5)/47 (48.5)	82 (48.8)/86 (51.2)
Failure of pretreatment with, n (%)		
Systemic drugs [yes/no]	63 (64.9)/34 (35.1)	112 (66.7)/56 (33.3)
Biologics [yes/no]	26 (26.8)/71 (73.2)	38 (22.6)/130 (77.4)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

(continued)

Table 8: Characteristics of the study populations – RCT, direct comparison: brodalumab vs. ustekinumab (continued)

Study **Characteristics** **Category**	**Brodalumab**	**Ustekinumab**
AMAGINE-3	N[a] = 83	N[a] = 146
Age [years], mean (SD)	48 (14)	44 (12)
Sex [F/M], %	42/58	34/66
Ethnicity, n (%)		
White	79 (95.2)	133 (91.1)
Black or African American	2 (2.4)	7 (4.8)
Asian	0 (0)	3 (2.1)
Other[b]	3 (3.6)[c]	10 (6.9)[c]
Body weight [kg], n (%)		
≤ 100 kg	58 (69.9)	102 (69.9)
> 100 kg	25 (30.1)	44 (30.1)
Scalp involvement, n (%)	ND	ND
Face and neck involvement, n (%)	ND	ND
Fingernail involvement, n (%)	ND	ND
Genital involvement, n (%)	ND	ND
Duration of disease [years], mean (SD)	20.8 (12.9)	18.6 (10.3)
PASI, mean (SD)	21.1 (8.1)	19.9 (8.0)
DLQI, mean (SD)	15.5 (7.5)	15.3 (7.4)
sPGA, mean (SD)	3.4 (0.6)	3.4 (0.6)
Psoriatic arthritis [yes/no], n (%)	32 (38.6)/51 (61.4)	39 (26.7)/107 (73.3)
Pretreatment with, n (%)		
Systemic drugs [yes/no]	74 (89.2)/9 (10.8)	128 (87.7)/18 (12.3)
Phototherapy [yes/no]	41 (49.4)/42 (50.6)	80 (54.8)/66 (45.2)
Biologics [yes/no]	45 (54.2)/38 (45.8)	73 (50.0)/73 (50.0)
Failure of pretreatment with, n (%)		
Systemic drugs [yes/no]	46 (55.4)/37 (44.6)	100 (68.5)/46 (31.5)
Biologics [yes/no]	20 (24.1)/63 (75.9)	22 (15.1)/124 (84.9)
Treatment discontinuation, n (%)	ND[d]	ND[d]
Study discontinuation, n (%)	ND[d]	ND[d]

a: Number of randomized patients. Data that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b: Includes American Indians or Native Alaskans, Native Hawaiians or Pacific Islanders, and several ethnicities.
c: Institute's calculation.
d: No data for the relevant subpopulation. Information on the total population can be found in Appendix A of the full dossier assessment.

DLQI: Dermatology Life Quality Index; F: female; M: male, n: number of patients in the category; N: number of randomized patients or of patients included in the respective study phase; ND: no data; PASI: Psoriasis Area and Severity Index; RCT: randomized controlled trial; SD: standard deviation; sPGA: static Physician Global Assessment; vs.: versus

The subpopulation used for answering research question 2 corresponded to about 14.6% of the patients randomized to the brodalumab arm and 51.2% of the patients randomized to the ustekinumab arm.

The demographic and clinical characteristics of the patients in these subpopulations were largely balanced both between the individual study arms and between the studies.

The mean age of the participants was about 46 years; most of them were male and white. The mean disease duration was about 20 years. The mean PASI score was about 20, and the mean DLQI score was about 16.

No data were available on the number of treatment and study discontinuations in the relevant subpopulation of AMAGINE-2 and AMAGINE-3. Corresponding proportions in the total population of the study varied depending on the study phase (see Appendix A of the full dossier assessment).

Risk of bias at study level

Table 9 shows the risk of bias at study level.

Table 9: Risk of bias at study level – RCT, direct comparison: brodalumab vs. ustekinumab

Study	Adequate random sequence generation	Allocation concealment	Blinding		Reporting independent of the results	No additional aspects	Risk of bias at study level
			Patient	Treating staff			
AMAGINE-2	Yes	Yes	Yes	Yes	Yes	Yes	Low
AMAGINE-3	Yes	Yes	Yes	Yes	Yes	Yes	Low
RCT: randomized controlled trial; vs.: versus							

The risk of bias at study level was classed as low for both studies. This concurs with the company's assessment.

2.4.2 Results on added benefit

2.4.2.1 Outcomes included

The following patient-relevant outcomes were to be included in the assessment (for reasons, see Section 2.6.2.4.3 of the full dossier assessment):

- Mortality
  - all-cause mortality
- Morbidity
  - remission measured with the PASI 100
  - symptoms of nail psoriasis recorded with the NAPSI
  - patient-reported symptoms recorded with the PSI
- Health-related quality of life
  - recorded with the DLQI
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations (System Organ Class [SOC])
  - if applicable, further specific AEs

The results at week 52 were used for the benefit assessment. The selection of patient-relevant outcomes and partly of the analysis time points deviated from that of the company, which, on the one hand, did not include the outcome “PSI” in the dossier (Module 4 A) and, on the other, considered further outcomes and analysis time points (see Section 2.6.2.4.3 of the full dossier assessment).

Table 10 shows for which outcomes data were available in the studies included.

Table 10: Matrix of outcomes – RCT, direct comparison: brodalumab vs. ustekinumab

Study	Outcomes								
	All-cause mortality	Remission (PASI 100)[a]	Symptoms of nail psoriasis (NAPSI)	Patient-reported symptoms (PSI)	Health-related quality of life (DLQI 0 or 1)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC)	If applicable, further specific AEs
AMAGINE-2	Yes	Yes	No[b]	No[c]	Yes	Yes	Yes	No[d]	No[e]
AMAGINE-3	Yes	Yes	No[b]	No[c]	Yes	Yes	Yes	No[d]	No[e]

a: Improvement in score by 100% compared with the start of the study.
b: No suitable data (see Section 2.6.2.4.3 of the full dossier assessment).
c: The company did not include the outcome in its assessment and presented no analyses for the relevant subpopulation (see Section 2.6.2.4.3 of the full dossier assessment).
d: No analysis available for the relevant subpopulation.
e: No selection of specific AEs is possible based on the documents presented by the company (see Section 2.6.2.4.3 of the full dossier assessment).
AE: adverse event; DLQI: Dermatology Life Quality Index; NAPSI: Nail Psoriasis Severity Index; PASI: Psoriasis Area and Severity Index, PSI: Psoriasis Symptom Inventory; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.4.2.2 Risk of bias

Table 11 describes the risk of bias for the relevant outcomes.

Table 11: Risk of bias at study and outcome level – RCT, direct comparison: brodalumab vs. ustekinumab

Study	Study level	Outcomes								
		All-cause mortality	Remission (PASI 100)[a]	Symptoms of nail psoriasis (NAPSI)	Patient-reported symptoms (PSI)	Health-related quality of life (DLQI 0 or 1)	SAEs	Discontinuation due to AEs	Infections and infestations (SOC)	If applicable, further specific AEs
AMAGINE-2	L	L	H[b]	–[c]	–[d]	H[b]	H[e]	H[e]	–[f]	–[g]
AMAGINE-3	L	L	H[b]	–[c]	–[d]	H[b]	H[e]	H[e]	–[f]	–[g]

a: Improvement in score by 100% compared with the start of the study.
b: Inadequate imputation of missing values after treatment switch in the rescue phase (NRI), unclear approach of the company regarding the consideration of patients in the rescue phase, as well as lack of information on missing values (see Section 2.6.2.2 of the full dossier assessment).
c: In Module 4 A, the company presented only data for the mean change from the baseline score to week 52. This analysis contains a large proportion of patients (> 30%) not considered in the calculations (see Section 2.6.2.4.3 of the full dossier assessment).
d: The company did not include the outcome in its assessment and presented no analyses for the relevant subpopulation (see Section 2.6.2.4.3 of the full dossier assessment).
e: Unclear observation periods and unclear recording or categorization of events.
f: No analysis available for the relevant subpopulation.
g: No selection of specific AEs is possible based on the documents presented by the company (see Section 2.6.2.4 of the full dossier assessment).
AE: adverse event; DLQI: Dermatology Life Quality Index; H: high; L: low; NAPSI: Nail Psoriasis Severity Index; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index, PSI: Psoriasis Symptom Inventory; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

The risk of bias for the outcome “all-cause mortality” (recorded as “fatal AEs” in the present studies) was rated as low. This concurs with the company’s assessment.

The risk of bias for each of the outcomes “remission”, “health-related quality of life”, “SAEs”, and “discontinuation due to AEs” was rated as high.

The decisive reason for the high risk of bias for the outcomes “remission” and “health-related quality of life” was a possible systematic disadvantage for the ustekinumab arm resulting from the design of the studies’ rescue phase and an inadequate imputation of missing values after treatment switch in the rescue phase (rating as non-response). In addition, the company’s approach regarding the consideration of patients in its analyses and the number of missing values were unclear (see Section 2.6.2.2 of the full dossier assessment).

Unclear observation periods, as well as recording and categorization of events resulted in a high risk of bias for the outcomes “SAEs” and “discontinuation due to AEs” (see Section 2.6.2.4.2 of the full dossier assessment). This deviates from the assessment of the company, which rated the risk of bias as low for these outcomes.

No usable data were available for the outcomes “symptoms of nail psoriasis”, “patient-reported symptoms”, and “infections and infestations”. Selecting specific AEs was not possible based on the documents provided by the company in the dossier. The risk of bias for these outcomes was therefore not assessed.

Overall assessment of the certainty of conclusions

With the exception of the outcome “all-cause mortality”, there was a high risk of bias for all outcomes included for which usable data were available.

The decisive reason was a possible systematic disadvantage for the comparator arm resulting from the design of the studies’ rescue phase. The present benefit assessment addresses this problem with sensitivity analyses conducted by the Institute (see Section 2.6.2.2 of the full dossier assessment). These analyses are subject to assumptions, however, and cannot completely overcome the problem of inadequate consideration of these patients as non-responders.

In addition, there were uncertainties regarding the allocation of patients to the relevant subpopulation (see Section 2.4.1 and Section 2.6.2.4.1 of the full dossier assessment).

In summary, due to these reasons at most indications, e.g. of an added benefit, could be derived from the meta-analysis of the studies for the outcomes presented.

2.4.2.3 Results

Table 12 summarizes the results for the comparison of brodalumab with ustekinumab in adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments or who are not candidates for such treatments. Where necessary, Institute’s own calculations are provided in addition to the data from the company’s dossier. The table presents the outcomes “PASI 90” and “PASI 75” as supplementary information; the PASI 100 was primarily used for the derivation of the added benefit (see also Section 2.6.2.4.3 of the full dossier assessment).

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brodalumab vs. ustekinumab

Outcome category Outcome Study	Brodalumab		Ustekinumab		Brodalumab vs. ustekinumab
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Mortality					
All-cause mortality					
AMAGINE-2	97	0 (0)	168	2 (1.2)	0.34 [0.02; 7.11]; 0.409[a]
AMAGINE-3	83	0 (0)	146	0 (0)	NC
Total					NC
Morbidity					
PASI					
Remission (PASI 100)					
NRI analysis					
AMAGINE-2	97	50 (51.5)	168	37 (22.0)	2.34 [1.66; 3.30]; < 0.001[a]
AMAGINE-3	83	38 (45.8)	146	31 (21.2)	2.16 [1.46; 3.19]; < 0.001[a]
Total					2.26 [1.74; 2.92]; < 0.001[b]
Sensitivity analysis[c]					
AMAGINE-2	97	50 (51.5)	133	44 (33.1)	1.56 [1.14; 2.12]; NC
AMAGINE-3	83	38 (45.8)	110	36 (32.7)	1.40 [0.98; 2.00]; NC
Total					1.49 [1.18; 1.88]; < 0.001[b]
PASI 90					
NRI analysis					
AMAGINE-2	97	61 (62.9)	168	55 (32.7)	1.92 [1.47; 2.50]; < 0.001[a]
AMAGINE-3	83	47 (56.6)	146	49 (33.6)	1.69 [1.26; 2.27]; < 0.001[a]
Total					1.81 [1.49; 2.21]; < 0.001
Sensitivity analysis[c]					
AMAGINE-2	97	61 (62.9)	130	61 (46.9)	1.34 [1.05; 1.70]; NC
AMAGINE-3	83	47 (56.6)	107	52 (48.6)	1.16 [0.89; 1.53]; NC
Total					1.26 [1.05; 1.50]; 0.012[b]
PASI 75					
NRI analysis					
AMAGINE-2	97	63 (64.9)	168	67 (39.9)	1.63 [1.29; 2.06]; < 0.001[a]
AMAGINE-3	83	48 (57.8)	146	61 (41.8)	1.38 [1.06; 1.80]; 0.020[a]
Total					1.51 [1.27; 1.80]; < 0.001[b]
Sensitivity analysis[c]					
AMAGINE-2	97	63 (64.9)	131	71 (54.2)	1.20 [0.97; 1.49]; NC
AMAGINE-3	83	48 (57.8)	109	62 (56.9)	1.02 [0.80; 1.30]; NC
Total					1.11 [0.95; 1.31]; 0.192[b]

(continued)

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brodalumab vs. ustekinumab (continued)

Outcome category Outcome Study	Brodalumab N	Brodalumab Patients with event n (%)	Ustekinumab N	Ustekinumab Patients with event n (%)	Brodalumab vs. ustekinumab RR [95% CI]; p-value[a]
Symptoms of nail psoriasis (NAPSI)	No data[d]				
Patient-reported symptoms (PSI)	No data[e]				
Health-related quality of life					
DLQI (0 or 1)					
NRI analysis					
AMAGINE-2	97	51 (52.6)	168	55 (32.7)	1.61 [1.20; 2.14]; 0.001[a]
AMAGINE-3	83	42 (50.6)	146	52 (35.6)	1.42 [1.05; 1.93]; 0.027[a]
Total					1.52 [1.23; 1.87]; < 0.001[b]
Sensitivity analysis[c]					
AMAGINE-2	97	51 (52.6)	132	58 (43.9)	1.19 [0.91; 1.56]; NC
AMAGINE-3	83	42 (50.6)	111	53 (47.7)	1.06 [0.79; 1.41]; NC
Total					1.13 [0.93; 1.37]; 0.233[b]
Side effects					
AEs (supplementary information)					
AMAGINE-2	*97*	*82 (84.5)*	*168*	*144 (85.7)*	–
AMAGINE-3	*83*	*72 (86.7)*	*146*	*117 (80.1)*	–
SAEs					
AMAGINE-2	97	5 (5.2)	168	14 (8.3)	0.62 [0.23; 1.66]; 0.420[a]
AMAGINE-3	83	7 (8.4)	146	3 (2.1)	4.10 [1.09; 15.45]; 0.024[a]
Total					Heterogeneity: p = 0.02; I^2 = 80%
Discontinuation due to AEs					
AMAGINE-2	97	3 (3.1)	168	6 (3.6)	0.87 [0.22; 3.38]; 0.870[a]
AMAGINE-3	83	2 (2.4)	146	1 (0.7)	3.52 [0.32; 38.21]; 0.328[a]
Total					1.24 [0.40; 3.85]; 0.708[b]
Infections and infestations	No analysis available for the relevant subpopulation				
If applicable, further specific AEs	ND[f]				

(continued)

Table 12: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, direct comparison: brodalumab vs. ustekinumab (continued)

a: Institute's calculation (unconditional exact test, CSZ method according to [10]).
b: Institute's calculation, meta-analysis with fixed effect (Mantel-Haenszel method).
c: Institute's sensitivity analysis: Patients in the ustekinumab arm who were switched to treatment with brodalumab were rated as patients with response in accordance with the response rate in the brodalumab arm. Proportions of patients with treatment switch were approximated based on the information on re-randomized patients of the brodalumab arm and the total ustekinumab group. A correction of variance was conducted based on the data-set re-sizing approach (approach W3 in [11]), leading to a reduction in patient numbers in the control arm (see Section 2.6.2.2 of the full dossier assessment).
d: In Module 4 A, the company presented only data for the mean change in the NAPSI from the baseline score to week 52. This analysis contains a large proportion of patients (> 30%) not considered in the calculations (see Section 2.6.2.4.3 of the full dossier assessment).
e: The company did not include this outcome in its assessment and presented no analyses for the relevant subpopulation.
f: No selection is possible based on the information provided in the dossier (see Section 2.6.2.4 of the full dossier assessment).
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; DLQI: Dermatology Life Quality Index; n: number of patients with (at least one) event; N: number of analysed patients; NAPSI: Nail Psoriasis Severity Index; NC: not calculated; ND: no data; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index; PSI: Psoriasis Symptoms Inventory; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

As shown in Section 2.4.2.2, the certainty of conclusions of the results on the basis of the available data was reduced. At most indications, e.g. of an added benefit, can therefore be derived for individual outcomes. This deviates from the approach of the company, which derived proof for individual outcomes.

Mortality

All-cause mortality

No deaths occurred in the brodalumab study arms until the end of the maintenance phase (week 52). There were 2 deaths in the ustekinumab group of the AMAGINE-2 study, and no deaths in the corresponding arm of the AMAGINE-3 study. Overall, this resulted in no hint of an added benefit of brodalumab in comparison with ustekinumab; an added benefit is therefore not proven.

This concurs with the company's assessment.

Morbidity

Remission (PASI 100)

The meta-analysis of the studies (NRI analysis) showed a statistically significant difference in favour of brodalumab for the outcome "remission", recorded with the PASI 100. The result for this outcome might be biased, however, because the results of the patients who switched treatment from ustekinumab to brodalumab at week 16 were rated as non-response. For this reason, results of a sensitivity analysis conducted by the Institute were additionally considered (see Section 2.6.2.2 of the full dossier assessment). Despite reduced effect size, the result of

this analysis still showed a statistically significant difference in favour of brodalumab. This sensitivity analysis is subject to assumptions, however, and cannot completely overcome the problem of inadequate consideration of these patients as non-responders.

In view of the reduced certainty of conclusions of the results, there was overall an indication of an added benefit of brodalumab compared with ustekinumab for remission (PASI 100).

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome "PASI 100".

Symptoms of nail psoriasis (NAPSI)

In Module 4 A, the company presented the mean change in NAPSI between the start of the study and week 52. Due to the high proportion of patients not considered in the company's analyses (> 30% in relation to the patients with nail psoriasis at the start of the study), no usable data were available for this outcome. Furthermore, there were uncertainties regarding the interpretation of the operationalization presented by the company (see Section 2.6.2.4.2 and 2.6.2.4.3 of the full dossier assessment). Overall, there was no hint of an added benefit of brodalumab in comparison with ustekinumab for the outcome "symptoms of nail psoriasis". An added benefit for this outcome is therefore not proven.

This concurs with the assessment of the company, which determined the added benefit as "not proven" for this outcome based on a statistically not significant and clinically not relevant difference between brodalumab and ustekinumab.

Patient-reported symptoms (PSI)

No analyses were available for the relevant subpopulation for patient-reported symptoms recorded with the PSI. Due to the lack of data, there was no hint of an added benefit of brodalumab in comparison with ustekinumab for the outcome "patient-reported symptoms". An added benefit for this outcome is therefore not proven.

The company did not include this outcome in its assessment and presented no analyses for the relevant subpopulation.

Health-related quality of life

DLQI

Regarding the proportion of patients with a DLQI score of 0 or 1 at week 52, the meta-analysis of the studies (NRI analysis) showed a statistically significant difference in favour of brodalumab. The result for this outcome might be biased, however, because the results of the patients who switched treatment from ustekinumab to brodalumab at week 16 were rated as non-response. For this reason, results of a sensitivity analysis conducted by the Institute were additionally considered (see Section 2.6.2.2 of the full dossier assessment). This sensitivity analysis showed no statistically significant difference between the treatment groups; the result was therefore not robust.

The certainty of conclusions of the results was reduced for this outcome for the reasons described in Section 2.4.2.2. Since, in addition, the effect was not robust in the sensitivity analysis, the certainty of conclusions was downgraded from an indication to a hint. Overall, there was a hint of an added benefit of brodalumab in comparison with ustekinumab for DLQI 0 or 1.

This deviates from the assessment of the company, which derived proof of an added benefit for the outcome "DLQI".

Side effects

Serious adverse events

There were heterogeneous results without effects in the same direction for the outcome "SAEs". These data resulted in no hint of greater or lesser harm of brodalumab in comparison with ustekinumab for the outcome "SAEs". Greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which presented the added benefit as "not proven" due to inconsistent results between the studies.

Discontinuation due to AEs

The meta-analysis of the studies showed no statistically significant difference between the treatment groups for the outcome "discontinuation due to AEs". Hence there was no hint of greater or lesser harm from brodalumab in comparison with ustekinumab; greater or lesser harm is therefore not proven.

This concurs with the assessment of the company, which presented the added benefit for this outcome as "not proven".

Specific adverse events

Infections and infestations

No analysis of the SOC "infections and infestations" was available for the relevant subpopulation. There was no hint of greater or lesser harm of brodalumab in comparison with ustekinumab for this outcome. Greater or lesser harm is therefore not proven for this outcome.

The company did not include this outcome in its assessment (see Section 2.6.2.4.3 of the full dossier assessment).

Further specific adverse events

Selecting specific AEs was not possible based on the documents provided by the company in the dossier (see Section 2.6.2.5.3 of the full dossier assessment). Hence there was no hint of greater or lesser harm of brodalumab in comparison with ustekinumab for further specific AEs. Greater or lesser harm is therefore not proven for this outcome.

The company included a number of specific AEs in its assessment and derived greater harm for some outcomes.

2.4.2.4 Subgroups and other effect modifiers

The following effect modifiers were considered relevant for the present benefit assessment (for information on the selection, see Section 2.6.2.4.3 of the full dossier assessment):

- age (< 65 years/≥ 65 years)
- sex (female/male)
- ethnicity (white, black or African American, Asian, American Indian or Native Alaskan, Native Hawaiian or Pacific Islander, several ethnicities, other)
- region (Canada, Eastern Europe, Western Europe, USA)
- prior biological treatment (yes/no)
- body weight (≤ 100 kg/> 100 kg)

Additionally, severity grade was considered to be a relevant effect modifier. The company's criteria for the differentiation between moderate and severe were unclear, however. The subgroups according to severity grade were therefore not considered.

The company presented no adequate subgroup analyses across the overall study pool (see Section 2.6.2.2 of the full dossier assessment). The available subgroup analyses of the company were therefore not usable and were not used in the benefit assessment.

2.4.3 Probability and extent of added benefit

The derivation of probability and extent of the added benefit is presented below at outcome level, taking into account the different outcome categories and effect sizes. The methods used for this purpose are explained in the *General Methods* of IQWiG [1].

The approach for deriving an overall conclusion on added benefit based on the aggregation of conclusions derived at outcome level is a proposal by IQWiG. The G-BA decides on the added benefit.

2.4.3.1 Assessment of added benefit at outcome level

For adult patients who are not candidates for other systemic treatments including ciclosporin, methotrexate or PUVA due to inadequate response, contraindication or intolerance, the data presented in Section 2.4.2 resulted in an indication of an added benefit for the outcome "remission (PASI 100)" and in a hint of an added benefit for the outcome "health-related quality of life (DLQI [0 or 1])".

No suitable data or no data were available for the outcomes on symptoms (symptoms of nail psoriasis and patient-reported symptoms). There were also no data for specific AEs.

Determination of the outcome category for the outcome "remission (PASI 100)"

Psoriasis is a chronic disease which, due to the location of the lesions and the manifestation of its symptoms can be very burdensome and severely affect the patients. Involvement of certain body regions, such as the facial or the genital area, can cause particular impairment of the patients. Hence the allocation of the outcome "remission (PASI 100)" to a particular outcome category (serious or non-serious) depends on the patients' initial situation, particularly on the severity and the grade of impairment from the symptoms measured with PASI (psoriatic plaque redness, thickness and scaling).

The data recorded in the beginning of the study were used for assessing the severity of the symptoms. Among other information on the relevant subpopulation, the dossier contained the mean scores for the instruments PASI and sPGA. These showed that the PASI score was about 20. No information for the subpopulation was provided on the median score, which is more meaningful for the characterization of the population, however. The median score of the total population was between 17 and 18 points, which rather places it in a non-serious range [12,13].

According to the investigator's assessment (assessed with the sPGA for the symptoms of psoriatic plaque redness, thickness and scaling), the mean symptom severity was 3.4 to 3.5, indicating moderate severity. The total population of the studies included 55.5% patients whose symptom severity was assessed as moderate by the physician (sPGA = 3). The dossier contained no information on the psoriasis involvement of individual body regions that may result in particular impairment of the patient. Based on the available information, the outcome "remission (PASI 100)" was allocated to the category of non-serious/non-severe symptoms for the patients included in the studies.

The extent of the respective added benefit at outcome level was estimated from these results (see Table 13).

Table 13: Extent of added benefit at outcome level: brodalumab vs. ustekinumab

Outcome category **Outcome**	**Brodalumab vs. ustekinumab** **Proportion of events** **Effect estimate [95% CI]; p-value** **Probability[a]**	**Derivation of extent[b]**
Mortality		
All-cause mortality	0% vs. 0–1.2%[c] RR: –[d]	Lesser benefit/added benefit not proven
Morbidity		
Remission (PASI 100) NRI analysis Sensitivity analysis	45.8–51.5% vs. 21.2–22.0%[c] RR: 2.26 [1.74; 2.92] p < 0.001 RR: 1.49 [1.18; 1.88] p < 0.001 probability: "indication"	Outcome category: non-serious/non-severe symptoms/late complications added benefit, extent: "non-quantifiable", at most "considerable"[e]
Symptoms of nail psoriasis (NAPSI)	No data available	Lesser benefit/added benefit not proven
Patient-reported symptoms (PSI)	No data available	Lesser benefit/added benefit not proven
Health-related quality of life		
DLQI (0 or 1) NRI analysis Sensitivity analysis	50.6–52.6% vs. 32.7–35.6%[c] RR: 1.52 [1.23; 1.87] p < 0.001 RR: 1.13 [0.93; 1.37] p = 0.233 probability: "hint"[f]	Outcome category: health-related quality of life added benefit, extent: "non-quantifiable"[e]
Side effects		
Serious adverse events	Heterogeneous results[g] without effects in the same direction	Greater/lesser harm not proven
Discontinuation due to AEs	2.4–3.1% vs. 0.7–3.6%[c] RR: 1.24 [0.40; 3.85] p = 0.708	Greater/lesser harm not proven
Infections and infestations	No analysis available for the relevant subpopulation	Greater/lesser harm not proven
If applicable, further specific AEs	Selection not possible	Greater/lesser harm not proven

a: Probability provided if statistically significant differences are present.
b: Estimations of effect size are made depending on the outcome category with different limits based on CI_u.
c: Minimum and maximum proportions of events in each treatment arm in the studies included.
d: Only 2 events in the control arm of the AMAGINE-2 study, no events in the AMAGINE-3 study.
e: Effect size and extent not quantifiable due to uncertainties in the assumptions of the sensitivity analyses (range: "minor" to "considerable").
f: Due to the not statistically significant result of the sensitivity analysis.
g: No common effect estimate can be provided due to heterogeneous data.

AE: adverse event; CI: confidence interval; CI_u: upper limit of confidence interval; DLQI: Dermatology Life Quality Index; NAPSI: Nail Psoriasis Severity Index; NRI: non-responder imputation; PASI: Psoriasis Area and Severity Index, PSI: Psoriasis Symptom Inventory; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

2.4.3.2 Overall conclusion on added benefit

Table 14 summarizes the results that were considered in the overall conclusion on the extent of added benefit.

Table 14: Positive and negative effects from the assessment of brodalumab in comparison with ustekinumab

Positive effects	Negative effects
Indication of an added benefit, extent "non-quantifiable": remission (PASI 100)	–
Hint of an added benefit – extent: "non-quantifiable": health-related quality of life (DLQI 0 or 1)	–
Patient-reported symptoms: The company presented no data.	
Infections and infestations and further specific AEs if applicable: not assessable on the basis of the data presented by the company	
AE: adverse event; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index	

The overall assessment showed positive effects of brodalumab in the outcome categories "morbidity" and "health-related quality of life". Regarding morbidity, there is an indication of an added benefit for the outcome "remission (PASI 100)", and a hint of an added benefit in the area of health-related quality of life for the outcome "DLQI (0 or 1)". In both cases, the extent of added benefit is non-quantifiable, and at most considerable for PASI 100.

No data were available for the assessment of patient-reported symptoms. There were also no data available for the outcome "infections and infestations" and the selection of further specific AEs. Further positive and negative effects could therefore not be assessed based on the data available. However, based on the available information, the positive effects of brodalumab were not completely questioned.

In summary, there is an indication of a non-quantifiable added benefit of brodalumab in comparison with ustekinumab for adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments. This deviates from the assessment of the company, which claimed proof of a considerable added benefit.

2.4.4 List of included studies

AMAGINE-2

Amgen. Study of efficacy and safety of brodalumab compared with placebo and ustekinumab in moderate to severe plaque psoriasis subjects (AMAGINE-2): full text view [online]. In: ClinicalTrials.gov. 27.07.2015 [Accessed: 12.09.2017]. URL: https://ClinicalTrials.gov/show/NCT01708603.

Amgen. A phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis: AMAGINE-2 [online]. In: EU Clinical Trials Register. [Accessed: 12.09.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000656-34.

Amgen. A phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis: AMAGINE-2: clinical trial results [online]. In: EU Clinical Trials Register. 30.10.2016 [Accessed: 12.09.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-000656-34/results.

Amgen. A phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis: AMAGINE-2; study 20120103; clinical study report [unpublished]. 2015.

Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med 2015; 373(14): 1318-1328.

AMAGINE-3

Amgen. Study of efficacy and safety of brodalumab compared with placebo and ustekinumab in moderate to severe plaque psoriasis subjects (AMAGINE-3): full text view [online]. In: ClinicalTrials.gov. 20.11.2015 [Accessed: 12.09.2017]. URL: https://ClinicalTrials.gov/show/NCT01708629.

Amgen. A phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis: AMAGINE-3: clinical trial results [online]. In: EU Clinical Trials Register. 30.10.2016 [Accessed: 12.09.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/trial/2012-000667-24/results.

Amgen. A phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis: AMAGINE-3; study 20120104; clinical study report [unpublished]. 2015.

Amgen. A phase 3 study to evaluate the efficacy and safety of induction and maintenance regimens of brodalumab compared with placebo and ustekinumab in subjects with moderate to severe plaque psoriasis: AMAGINE-3 [online]. In: EU Clinical Trials Register. [Accessed: 12.09.2017]. URL: https://www.clinicaltrialsregister.eu/ctr-search/search?query=eudract_number:2012-000667-24.

Lebwohl M, Strober B, Menter A, Gordon K, Weglowska J, Puig L et al. Phase 3 studies comparing brodalumab with ustekinumab in psoriasis. N Engl J Med 2015; 373(14): 1318-1328.

MedDerm Associates. Study to evaluate broadlumab vs placebo and ustekinumab (AMAGINE-3): full text view [online]. In: ClinicalTrials.gov. 25.05.2016 [Accessed: 12.09.2017]. URL: https://ClinicalTrials.gov/show/NCT02786732.

2.5 Probability and extent of added benefit – summary

The result of the assessment of the added benefit of brodalumab in comparison with the ACT is summarized in Table 15.

Table 15: Brodalumab – probability and extent of added benefit

Research question	Subindication[a]	ACT[b]	Probability and extent of added benefit
1	Adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment[c]	Fumaric acid esters or ciclosporin or methotrexate or phototherapy (balneo-phototherapy, oral PUVA, NB-UVB) or secukinumab[d]	Lesser benefit/added benefit not proven
2	Adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments	Adalimumab or infliximab or ustekinumab or secukinumab[d]	Indication of an added benefit, extent "non-quantifiable"

a: It is a precondition that topical treatment alone is inadequate for the patients treated.
b: Presentation of the respective ACT specified by the G-BA.
c: The population includes all patients in the approved therapeutic indication, except for the patients mentioned in research question 2.
d: Dosage of the ACT was to concur with the recommendations of the relevant SPCs. A dose-fair comparison under exhaustion of the approval-compliant dosage (if tolerated) was to be conducted.
ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; NB-UVB: narrowband ultraviolet B light (311 nm); PUVA: psoralen and ultraviolet-A light; SPC: Summary of Product Characteristics

In summary, the added benefit of brodalumab in comparison with the ACT is not proven for adult patients with moderate to severe plaque psoriasis who are candidates for systemic treatment (research question 1).

There is an indication of a non-quantifiable added benefit for adult patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or PUVA, or with contraindication or intolerance to such treatments (research question 2).

The assessment described above deviates from the assessment of the company, which derived an indication of considerable added benefit for research question 1 (referred to as "research question A1" in Module 4 A) and proof of considerable added benefit for research question 2 (referred to as "research question A2" in Module 4 A).

The approach for deriving an overall conclusion on the added benefit is a proposal by IQWiG. The G-BA decides on the added benefit.

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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