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Brodalumab (plaque psoriasis) –

Addendum to Commission A17-42[1]

Addendum

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Table of contents

List of tables

Page

List of figures

Page

List of abbreviations

Abbreviation	Meaning
ACT	appropriate comparator therapy
AE	adverse event
DLQI	Dermatology Life Quality Index
EQ-5D	European Quality of Life-5 Dimensions
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ICTRP	International Clinical Trials Registry Platform
MedDRA	Medical Dictionary for Regulatory Activities
NAPSI	Nail Psoriasis Severity Index
PASI	Psoriasis Area and Severity Index
PSI	Psoriasis Symptom Inventory
PT	Preferred Term
PUVA	psoralen and ultraviolet-A light
RCT	randomized controlled trial
SAE	serious adverse event
SGB	Sozialgesetzbuch (Social Code Book)
SOC	System Organ Class
VAS	visual analogue scale

1 Background

On 8 January 2018, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A17-42 (Brodalumab – Benefit assessment according to §35a Social Code Book V) [1].

In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") presented results of the 2 randomized controlled trials (RCTs) AMAGINE-2 and AMAGINE-3 for the assessment of the added benefit of brodalumab in comparison with the appropriate comparator therapy (ACT) in patients with moderate plaque psoriasis with inadequate response to other systemic treatments including ciclosporin, methotrexate or psoralen and ultraviolet-A light (PUVA), or with contraindication or intolerance to such treatments (research question 2 of the dossier assessment).

With its written comment on the dossier assessment [3] and after the oral hearing [4], the company submitted further analyses on these studies. With its comment, the company submitted an additional adjusted indirect comparison of brodalumab versus secukinumab for research question 2.

The G-BA commissioned IQWiG with the assessment of the analyses on the Psoriasis Symptom Inventory (PSI) of the newly calculated subgroup analyses from the studies AMAGINE-2 and AMAGINE-3 and the data subsequently submitted on adverse events (AEs) and with the assessment of the indirect comparison.

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

2.1 Assessment of the analyses subsequently submitted on the direct comparison of brodalumab versus ustekinumab (research question 2)

In its comment, the company subsequently submitted different data for the direct comparison of brodalumab versus ustekinumab based on the 2 RCTs AMAGINE-2 and AMAGINE-3, which was already presented in the dossier. These are assessed below and it is evaluated to what extent the data subsequently submitted change the result of dossier assessment A17-42.

2.1.1 Results on the Psoriasis Symptom Inventory (PSI)

The PSI is an instrument for measurement of symptoms. It is used to measure the patients' assessment of the severity of their psoriasis symptoms itching, redness, flaking, burning, stinging, cracking, and pain of skin on a scale of 0 (not at all) to 4 (very severe). The results are added up to a total score with possible values ranging from 0 to 32. Higher total scores indicate more severe symptoms. The PSI was developed with the involvement of people affected with different severity grades of psoriasis and is adequately described in the literature [5-8].

The company did not include the PSI in its assessment and hence presented no results for the relevant subpopulation of the studies AMAGINE-2 and AMAGINE-3 in its dossier. With its comment, the company now presented 2 different operationalizations on the PSI, namely the change from baseline to week 52 and responder analyses. The defined response criterion was a total score of ≤ 8, with no score of > 1 in any of the individual items. This means that no symptom was allowed to be more severe than "mild" in any of the items. In addition, the response criterion was prespecified in each of the studies AMAGINE-2 and AMAGINE-3.

Only the responder analyses were used for the present assessment.

Certainty of results

According to the study documents, the patients who advanced to the rescue phase were imputed as non-responders in all binary outcomes. Hence the same uncertainties that were already described in dossier assessment A17-42 apply to the responder analysis on the PSI as for the other binary outcomes, such as the analyses on the Psoriasis Area and Severity Index (PASI). For this reason, the sensitivity analyses used in the dossier assessment for the PASI and the Dermatology Life Quality Index (DLQI) are also indicated for the outcome "PSI". A description of the sensitivity analyses conducted can be found in the dossier assessment (see Section 2.6.2.2 in [1]).

Results

The following Table 1 shows the results on the proportion of the responders at week 52. Where necessary, calculations conducted by the Institute are provided in addition to the data from the comment.

Table 1: Results (morbidity) – RCT, direct comparison: brodalumab vs. ustekinumab

Outcome category Outcome	Brodalumab		Ustekinumab		Brodalumab vs. ustekinumab
Study	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
Morbidity					
PSI responder[a]					
AMAGINE-2	97	46 (47.4)	168	54 (32.1)	1.48 [1.09; 2.00]; 0.014[b]
AMAGINE-3	83	34 (41.0)	146	50 (34.2)	1.20 [0.85; 1.68]; 0.408[b]
Total					1.35 [1.07; 1.69]; 0.010[c]

a: Patients with a total PSI score of ≤ 8 at week 52, but no item with a score of > 1, were rated as responders. Patients who were included in the rescue phase were imputed as non-responders.
b: Institute's calculation, unconditional exact test (CSZ method according to [9]).
c: Institute's calculation: p-value from effect estimate and CI under normal distribution assumption.
CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; PSI: Psoriasis Symptom Inventory; RCT: randomized controlled trial; RR: relative risk; vs.: versus

The meta-analysis of the 2 studies AMAGINE-2 and AMAGINE-3 showed a statistically significant difference in favour of brodalumab for the responder analysis on the PSI. This effect was not maintained in the sensitivity analysis (see Figure 3 in Appendix A). An effect modification by age was additionally shown (see Section 2.1.3). A statistically significant difference in favour of brodalumab was shown for patients < 65 years, but not in patients ≥ 65 years.

2.1.2 Results on adverse events

After the oral hearing, the company subsequently submitted results on specific adverse events (AEs). These were not usable for the dossier assessment for various reasons.

First, only the pooled results for both studies AMAGINE-2 and AMAGINE-3 were available, but not also separately for the individual studies. An assessment of possible heterogeneity between both studies was therefore not possible.

In addition, it could not be inferred from the analyses on which patient numbers they were based. Information was only provided on the number of events and on the number of patients for the different System Organ Classes (SOCs) and Preferred Terms (PTs) according to the Medical Dictionary for Regulatory Activities (MedDRA), but not on the number of the patients included in the analysis or on the percentages from which patient numbers could be at least inferred.

Irrespective of this, it is doubtful whether the data subsequently submitted were of sufficient quality. On the one hand, the data were partly incomplete. Regarding the SOC "respiratory, thoracic and mediastinal disorders", for example, 1 serious AE (SAE) occurred in the

brodalumab group and 4 SAEs in the ustekinumab group, but there was no information on the number of patients with event. Partly, the data were not plausible. Regarding the SOC "cardiac disorders", for example, there was 1 discontinuation due to AEs in the brodalumab group; on the other hand, the information provided on the number of patients with discontinuation due to an event in this SOC was n = 0.

In summary, the data on specific AEs subsequently submitted by the company were not usable for the reasons stated above and were not considered further.

2.1.3 Results on subgroup analyses

In its dossier, the company did not present subgroup across the total study pool consisting of AMAGINE-2 and AMAGINE-3. Instead, it conducted interaction tests for the individual subgroup characteristics separately for each study. If there was an effect modification (p-value of the interaction test < 0.05) in one study, it also presented the results of the subgroup analysis only for this study. For this reason, the subgroup analyses presented were not usable for the dossier assessment.

With its comment, the company presented adequate subgroup analyses over the total study pool. These are assessed below.

The subgroup characteristics relevant for the assessments are presented in dossier assessment A17-42 [1]. 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 only presented if there is a statistically significant and relevant effect in at least one subgroup.

Table 2 shows the subgroup results of brodalumab in comparison with ustekinumab. Where necessary, calculations conducted by the Institute are provided in addition to the data from the comment.

Table 2: Subgroups (morbidity) – RCT, direct comparison: brodalumab vs. ustekinumab

Outcome Characteristic	Brodalumab		Ustekinumab		Brodalumab vs. ustekinumab	
Study Subgroup	N	Patients with event n (%)[a]	N	Patients with event n (%)[a]	RR [95% CI]	p-value
Morbidity						
PSI responder[b]						
Age						
AMAGINE-2						
< 65 years	93	46 (49.5)	153	48 (31.4)	1.58 [1.15; 2.15]	0.005[c]
≥ 65 years	4	0 (0)	15	6	0.26 [0.02; 3.86]	0.153[c]
AMAGINE-3						
< 65 years	72	29 (40.3)	139	45 (32.4)	1.24 [0.86; 1.80]	0.310[c]
≥ 65 years	11	5 (45.5)	7	5 (71.4)	0.64 [0.29; 1.41]	0.398[c]
Total					Interaction:	0.03
< 65 years					1.43 [1.13; 1.81]	0.003[d]
≥ 65 years					0.59 [0.28; 1.27]	0.171[d]

a: Percentages from Institute's calculation.
b: Patients with a total PSI score of ≤ 8 at week 52, but no item with a score of > 1, were rated as responders. Patients who were included in the rescue phase were imputed as non-responders.
c: Institute's calculation, unconditional exact test (CSZ method according to [9]).
d: Institute's calculation: p-value from effect estimate and CI under normal distribution assumption.
CI: confidence interval; CSZ: convexity, symmetry, z score; n: number of patients with (at least one) event; N: number of analysed patients; PSI: Psoriasis Symptom Inventory; RCT: randomized controlled trial; RR: relative risk; vs.: versus

Symptoms (PSI)

There was an effect modification by the characteristic "age" for symptoms measured with the PSI. There was no statistically significant difference between the treatment groups for older patients (≥ 65 years). The meta-analysis showed a statistically significant difference in favour of brodalumab for patients < 65 years. Due to the large proportion of imputed values, the interaction test was already subject to increased uncertainty. In addition, a sensitivity analysis would be indicated for this subgroup. Since no information was provided on the proportion of patients per subgroup who advanced to the rescue phase, such an analysis was not possible.

2.1.4 Effects of the data subsequently submitted on the overall conclusion on the added benefit

In the total population, a statistically significant difference in favour of brodalumab was shown for the PSI. This effect was not maintained in the sensitivity analysis. One subgroup analysis showed an effect in favour of brodalumab for PSI in patients under 65 years of age. The certainty of results was restricted, however. Furthermore, there were no usable results on specific AEs.

These results were not relevant for the overall consideration because the results on other outcomes, particularly on the PASI, were dominant, and the overall conclusion on the added benefit, irrespective of the described uncertainties, was not challenged by the minor effects both in the total population and in the patients < 65 years of age.

In summary, the results on the PSI had no influence on the overall conclusion on the added benefit formulated in the dossier assessment.

2.2 Assessment of the indirect comparison of brodalumab versus secukinumab subsequently submitted (research question 2)

In its dossier, the company presented 2 RCTs of direct comparison (AMAGINE-2 and AMAGINE-3 [2]) for the assessment of the added benefit of brodalumab in comparison with the ACT ustekinumab in adult patients with moderate plaque psoriasis with inadequate response to other systemic treatments or who are not candidates for such treatments (research question 2 of the dossier assessment). Based on the results of these studies, an indication of a non-quantifiable added benefit of brodalumab was derived in dossier assessment A17-42 [1].

With its written comment, the company now subsequently submitted an adjusted indirect comparison of brodalumab versus secukinumab, which was additionally specified as ACT in the course of the procedure, for the assessment of the added benefit for the same research question (research question 2) [10]. In compliance with the commission, this indirect comparison is assessed below to be able to evaluate to what extent it has an influence on the overall assessment on the added benefit of brodalumab in research question 2, under joint consideration with the direct comparison already assessed.

2.2.1 Research question

The indirect comparison between brodalumab and secukinumab for adult patients with inadequate response to other systemic treatments or who are not candidates for such treatments is assessed in the following section. The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company. RCTs with a minimum duration of 24 weeks were used for the derivation of the added benefit.

2.2.2 Information retrieval

The study pool of the assessment was compiled on the basis of the following information:

Sources of the company:

- 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 ACT (last search on 28 November 2017)
- search in trial registries for studies on the ACT (last search on 5 December 2017)

To check the completeness of the study pool:

- search in trial registries for studies on brodalumab (last search on 12 January 2018)
- search in trial registries for studies on secukinumab (last search on 12 January 2018)

Assessment of the company's information retrieval

Information retrieval on brodalumab

The company used the data from the dossier for the information retrieval on brodalumab [2]. The last information retrieval by the company there was conducted in the beginning of June and in August 2017, hence exceeding the requirements on up-to-dateness formulated in the dossier templates (at most 3 months). Therefore, the company's information retrieval on brodalumab was unsuitable to ensure the completeness of the search results.

To check the completeness of the study pool presented, a search on brodalumab was conducted in the trial registries ClinicalTrials.gov, International Clinical Trials Registry Platform (ICTRP) Search Portal, EU Clinical Trials Register, and PharmNet.Bund – Klinische Prüfungen.

The check identified no additional relevant study.

Information retrieval on secukinumab

Due to a deficiency in the search in trial registries, the company's information retrieval on secukinumab was unsuitable to ensure the completeness of the search results. This has the following reason: The search syntax for ClinicalTrials.gov contains an error and was therefore not implemented in sufficient sensitivity. In the search syntax in ClinicalTrials.gov, the company wrote the Boolean operator "OR" in lower-case letters, so that the search terms were not executed as the desired "OR" combination, but probably as an "AND" combination. Hence it was not ensured that all studies on secukinumab of potential relevance for the benefit assessment were found.

To check the completeness of the study pool presented, a search on secukinumab was conducted in the trial registries ClinicalTrials.gov, ICTRP Search Portal, EU Clinical Trials Register, and PharmNet.Bund – Klinische Prüfungen.

The check identified no additional relevant study.

2.2.3 Study pool

The company used the studies AMAGINE-2, AMAGINE-3 and CAIN457A2317 for the comparison of brodalumab with secukinumab with the common comparator ustekinumab. The indirect comparison conducted by the company followed the methodological approach of Bucher [11]. This approach was adequate. The company chose ustekinumab as common comparator because studies with brodalumab or secukinumab were only available for ustekinumab. The choice was comprehensible.

Study characteristics/population

The benefit assessments of brodalumab [1] and secukinumab [12] contain descriptions of the studies AMAGINE-2, AMAGINE-3 and CAIN457A2317, as well as tables presenting the study characteristics, the interventions, and the study populations.

Similarity of the studies

The available data on the study and intervention characteristics of the 3 studies showed that the studies were sufficiently similar regarding design, patient characteristics, study duration and common comparator.

The studies listed in the following table were therefore included in the present assessment. The study pool concurred with the one of the company.

Table 3: Study pool – RCT, indirect comparison: brodalumab vs. secukinumab

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
Studies with brodalumab			
Study 20120103 (AMAGINE-2[b])	Yes	Yes	No
Study 20120104 (AMAGINE-3[b])	Yes	Yes	No
Study with secukinumab			
Study CAIN457A2317	No	No	Yes
a: Study for which the company was sponsor. b: In the following tables, the study is referred to with this abbreviated form. RCT: randomized controlled trial; vs.: versus			

Figure 1 presents the study pool and a diagram showing the indirect comparison.

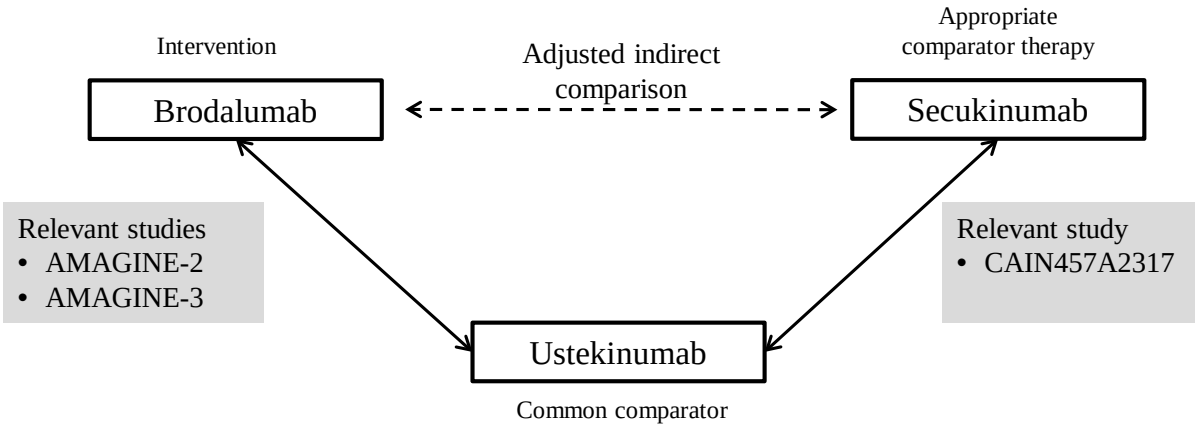

Figure 1: Data availability for the indirect comparison (research question 2)

2.2.4 Results on added benefit

2.2.4.1 Outcomes included

The following patient-relevant outcomes were to be considered in the assessment:

- Mortality
  - All-cause mortality
- Morbidity
  - remission measured with the PASI 100 (the outcomes “PASI 90” and “PASI 75” are shown as additional information, see Section 2.6.2.4.3 in the dossier assessment on brodalumab [1]).
  - symptoms of nail psoriasis recorded with the Nail Psoriasis Severity Index (NAPSI)
  - patient-reported symptoms recorded with the PSI
  - Symptoms: pain, itching, scaling
  - health status (European Quality of Life-5 Dimensions [EQ-5D] visual analogue scale [VAS])
- Health-related quality of life
  - DLQI
- Side effects
  - SAEs
  - discontinuation due to AEs
  - infections and infestations (SOC)
  - if applicable, further specific AEs (The documents on brodalumab presented and subsequently submitted by the company could not be used for the consideration of further specific AEs [see Section 2.1.2]. In addition, information on further AEs in the secukinumab study was only available for the time point 24 weeks [12]).

Table 4 shows for which outcomes data were available in the studies included.

Table 4: Matrix of outcomes – RCT, indirect comparison: brodalumab vs. ustekinumab

Study	Outcomes											
	All-cause mortality	**Remission (PASI 100)[a]**	**Symptoms of nail psoriasis (NAPSI)**	**Patient-reported symptoms (PSI)**	**Symptoms (pain)[b]**	**Symptoms (itching)[b]**	**Symptoms (scaling)[b]**	**Health status (EQ-5D VAS)**	**Health-related quality of life (DLQI 0 or 1)**	**SAEs**	**Discontinuation due to AEs**	**Infections and infestations (SOC)**
Studies with brodalumab												
AMAGINE-2	Y	Y	No[c]	Y	No[d]	No[d]	No[d]	No[d]	Y	Y	Y	Y
AMAGINE-3	Y	Y	No[c]	Y	No[d]	No[d]	No[d]	No[d]	Y	Y	Y	Y
Study with secukinumab												
Study CAIN457A2317	Y	Y	No[d]	No[d]	Y	Y	Y	Y	Y	Y	Y	Y

a: Improvement in score by 100% compared with the start of the study.
b: Recorded on a numerical scale (0–10).
c: No suitable data (see Section 2.6.2.4.3 in the dossier assessment on brodalumab [1]).
d: Outcome not recorded.
AE: adverse event; DLQI: Dermatology Life Quality Index; EQ-5D VAS: European Quality of Life-5 Dimensions visual analogue scale; NAPSI: Nail Psoriasis Severity Index; PSI: Psoriasis Symptom Inventory; RCT: randomized controlled trial; SAE: serious adverse event; SOC: System Organ Class; vs.: versus

2.2.4.2 Certainty of results

For the comparison of brodalumab with secukinumab, no study of direct comparison was available to check the consistency. In addition, there were partly heterogeneous results for the AMAGINE studies. Furthermore, it should be noted that only the analyses designated as "main analysis" in the dossier assessment were included in the indirect comparison on the brodalumab side.

For these reasons, the available adjusted indirect comparison had a low certainty of results.

2.2.4.3 Results

Table 5 summarizes the results on the indirect comparison of brodalumab versus secukinumab with the common comparator ustekinumab. Where necessary, calculations conducted by the Institute are provided in addition to the data from company's documents. Data on the relevant analysis date of 52 weeks were used.

In case of the presence of important heterogeneity of the brodalumab study results, the studies were not pooled.

Table 5: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: brodalumab vs. secukinumab, 52 weeks

Outcome category Outcome Comparison Study	Brodalumab or secukinumab N	 Patients with event n (%)	Ustekinumab N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
Mortality					
All-cause mortality					
Brodalumab vs. ustekinumab					
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
Secukinumab vs. ustekinumab					
CAIN457A2317	163	0 (0)	148	1 (0.7)	0.30 [0.01; 7.38]; 0.361[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					NC
Morbidity					
Remission (PASI 100)[d, e]					
Brodalumab vs. ustekinumab					
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[c]
Secukinumab vs. ustekinumab					
CAIN457A2317	163	59 (36.2)	148	39 (26.4)	1.37 [0.98; 1.93]; 0.063[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					1.65 [1.08; 2.53]; 0.021[f]
PASI 90[d, e]					
Brodalumab vs. ustekinumab					
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[c]
Secukinumab vs. ustekinumab					
CAIN457A2317	163	110 (67.5)	148	78 (52.7)	1.28 [1.06; 1.54]; 0.008[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					1.41 [1.07; 1.85][g]; 0.016[f]

(continued)

Table 5: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: brodalumab vs. secukinumab, 52 weeks (continued)

Outcome category Outcome Comparison Study	Brodalumab or secukinumab N	 Patients with event n (%)	Ustekinumab N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
PASI 75[d, e]					
Brodalumab vs. ustekinumab					
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[c]
Secukinumab vs. ustekinumab					
CAIN457A2317	163	136 (83.4)	148	100 (67.6)	1.23 [1.08; 1.41]; 0.001[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					1.24 [0.99; 1.54]; 0.056[f]
Health-related quality of life					
DLQI (0 or 1)					
Brodalumab vs. ustekinumab[e]					
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[c]
Secukinumab vs. ustekinumab[h]					
CAIN457A2317	162	100 (61.7)	148	73 (49.3)	1.25 [1.02; 1.53]; 0.029[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					1.22 [0.91; 1.63]; 0.181[f]
Side effects					
AEs (supplementary information)					
Brodalumab vs. ustekinumab					
AMAGINE-2	*97*	*82 (84.5)*	*168*	*144 (85.7)*	-
AMAGINE-3	*83*	*72 (86.7)*	*146*	*117 (80.1)*	-
Secukinumab vs. ustekinumab					
CAIN457A2317	*163*	*147 (90.2)*	*148*	*127 (85.8)*	-

(continued)

Table 5: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: brodalumab vs. secukinumab, 52 weeks (continued)

Outcome category Outcome Comparison Study	Brodalumab or secukinumab N	 Patients with event n (%)	Ustekinumab N	 Patients with event n (%)	Group difference RR [95% CI]; p-value
SAEs					
Brodalumab vs. ustekinumab					
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)	148	3 (2.1)	4.10 [1.09; 15.45]; 0.024[a]
Total					Heterogeneity: p = 0.02; I^2 = 80%
Secukinumab vs. ustekinumab					
CAIN457A2317	163	13 (8.0)	148	12 (8.1)	0.98 [0.46; 2.09]; > 0.999[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					
AMAGINE-2 and CAIN457A2317					0.63 [0.18; 2.20]; 0.469[f]
AMAGINE-3 and CAIN457A2317					4.18 [0.91; 19.25]; 0.066[f]
Discontinuation due to AEs					
Brodalumab vs. ustekinumab					
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[c]
Secukinumab vs. ustekinumab					
CAIN457A2317	163	6 (3.7)	148	5 (3.4)	1.09 [0.34; 3.50]; 0.922[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					1.14 [0.23; 5.76][i]; 0.875[f]
Infections and infestations					
Brodalumab vs. ustekinumab					
AMAGINE-2	97	66 (68.0)	168	95 (56.5)	1.20 [0.99; 1.46]; 0.071[a]
AMAGINE-3	83	44 (53.0)	146	81 (55.5)	0.96 [0.74; 1.23]; 0.797[a]
Total					1.09 [0.74; 1.27]; 0.532[c]
Secukinumab vs. ustekinumab					
CAIN457A2317	163	99 (60.7)	148	94 (63.5)	0.96 [0.80; 1.14]; 0.648[a]
Adjusted indirect comparison[b]:					
Brodalumab vs. secukinumab					1.14 [0.85; 1.51]; 0.371[f]

(continued)

Table 5: Results (mortality, morbidity, health-related quality of life, side effects) – RCT, indirect comparison: brodalumab vs. secukinumab, 52 weeks (continued)

a: Institute's calculation (unconditional exact test, CSZ method according to [9]).
b: Adjusted indirect comparison according to Bucher [11].
c: Institute's calculation, meta-analysis with fixed effect (Mantel-Haenszel method).
d: Improvement in score by 100% or 90% or 75% versus start of study.
e: In this analysis, missing values were imputed as non-response (NRI analysis).
f: Institute's calculation: p-value from effect estimate and CI under normal distribution assumption.
g: Institute's calculation of the indirect comparison as the results presented by the company were not plausible when considering the results from the individual studies.
h: LOCF analysis of the FAS population for which one value at baseline and at least one value in the course of the study were available.
i: Institute's calculation of the indirect comparison as the company's event rates from the AMAGINE-2 study for the indirect comparison are not comprehensible and deviated from those of the dossier assessment [1].
AE: adverse event; CI: confidence interval; CSZ: convexity, symmetry, z score; FAS: full analysis set; LOCF: last observation carried forward; n: number of patients with (at least one) event; N: number of analysed patients; NC: not calculated; NRI: non-responder imputation; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; vs.: versus

Mortality

All-cause mortality

In the AMAGINE studies, 2 deaths were reported under ustekinumab. In the CAIN457A2317 study, 1 death occurred under ustekinumab. Due to this overall very small number of events, no indirect comparison was conducted.

Morbidity

Remission (PASI 100)

The indirect comparison showed a statistically significant difference in favour of brodalumab for the outcome "remission" measured with the PASI 100.

Health-related quality of life

DLQI

The indirect comparison showed no statistically significant difference between brodalumab and secukinumab for the proportion of patients with a DLQI score of 0 or 1 at week 52.

Side effects

SAEs

The meta-analysis of the AMAGINE studies showed unexplained heterogeneity without effects in the same direction for the outcome "SAEs". Hence no common estimate was calculated. Consequently, an indirect comparison based on the overall study pool could not be meaningfully calculated and interpreted. The indirect comparisons, in which only one of the studies AMAGINE-2 and AMAGINE-3 was considered in each case, showed no statistically significant differences between brodalumab and secukinumab.

Discontinuation due to AEs

The indirect comparison showed no statistically significant difference between brodalumab and secukinumab for the outcome "discontinuation due to AEs".

Specific adverse events

Infections and infestations

The indirect comparison showed no statistically significant difference between brodalumab and secukinumab for the outcome "infections and infestations".

2.2.5 Overall conclusion on added benefit

Hereinafter it is explained which effects the indirect comparison of brodalumab with secukinumab subsequently submitted by the company with its comment had on the overall conclusion on the added benefit of brodalumab in patients with moderate to severe plaque psoriasis with inadequate response to other systemic treatments or who are not candidates for such treatments. Table 6 compares the results from the direct comparison with results from the indirect comparison.

Table 6: Comparison of the effects from the direct comparison of brodalumab with ustekinumab and the indirect comparison of brodalumab with secukinumab

Direct comparison		**Indirect comparison**
Positive effects	**Negative effects**	
Indication of an added benefit, extent "non-quantifiable": remission (PASI 100)	-	PASI 100 – statistically significant difference in favour of brodalumab (RR: 1.65; 95% CI: [1.08; 2.53]; p = 0.021)
Hint of an added benefit – extent: "non-quantifiable": health-related quality of life (DLQI 0 or 1)	-	-
AE: adverse event; CI: confidence interval; DLQI: Dermatology Life Quality Index; PASI: Psoriasis Area and Severity Index; RR: relative risk		

In summary, the direct comparison of brodalumab with ustekinumab results in 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.

The results of the indirect comparison do not raise doubts about the results of the direct comparison. On the one hand, the markedly lower certainty of results of the indirect comparison versus the direct comparison from 2 RCTs (see Section 2.2.4.2) has to be considered. On the other, in contrast to the direct comparison, the indirect comparison showed a statistically significant effect in favour of brodalumab only in one outcome, i.e. remission (PASI 100). The

adjusted indirect comparison showed no difference between brodalumab and secukinumab for further outcomes (all-cause mortality, DLQI [0 or 1], side effects considered).

Overall, the indirect comparison subsequently submitted by the company did not change the conclusion on the added benefit of brodalumab from dossier assessment A17-42.

2.3 Summary

The data subsequently submitted by the company in the commenting procedure did not change the conclusion on the added benefit of brodalumab from dossier assessment A17-42.

The following Table 7 shows the result of the benefit assessment of brodalumab under consideration of dossier assessment A17-42 and the present addendum.

Table 7: 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 G-BA decides on the added benefit.

3 References

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Appendix A – Results of the sensitivity analyses for the outcome "PSI"

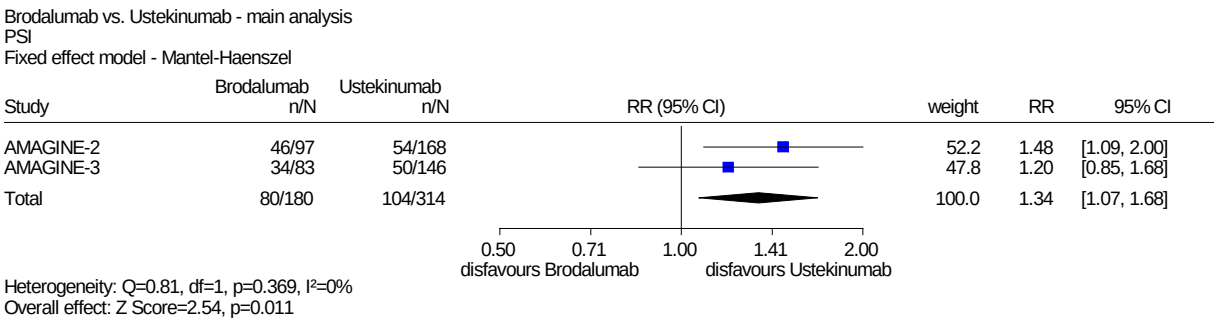

Figure 2: Meta-analysis (fixed-effect model according to Mantel-Haenszel) for the outcome "PSI"

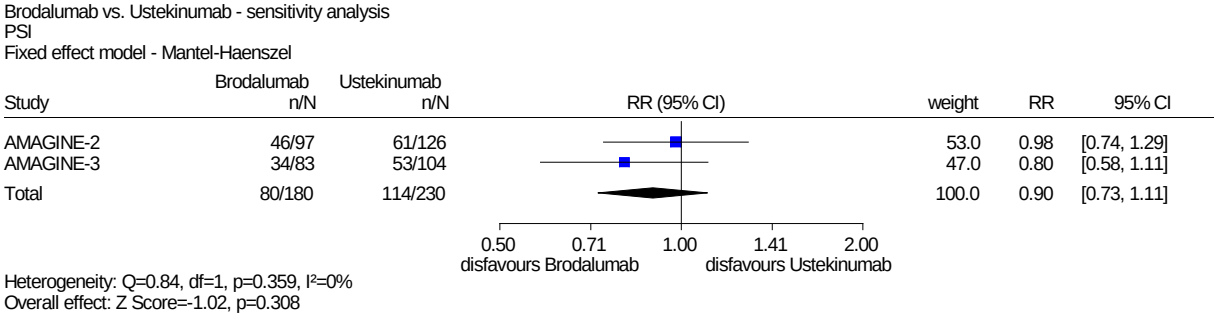

Figure 3: Meta-analysis (fixed-effect model according to Mantel-Haenszel) for the outcome "PSI", sensitivity analysis (see Section 2.6.2.2 of dossier assessment A17-42)