IQWiG Reports – Commission No. A19-94

Belimumab (systemic lupus erythematosus in children and adolescents) –

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

Extract

[1] Translation of Sections 2.1 to 2.6 of the dossier assessment *Belimumab (systemischer Lupus erythematodes bei Kindern und Jugendlichen) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 13 February 2020). 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
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
BILAG	British Isles Lupus Assessment Group
CSR	clinical study report
dsDNA	double-stranded deoxyribonucleic acid
EULAR	European League Against Rheumatism
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
ITT	intention to treat
LOCF	last observation carried forward
NSAID	nonsteroidal anti-inflammatory drug
PGA	physician's global assessment
RCT	randomized controlled trial
SAE	serious adverse event
SELENA	Safety of Estrogens in Lupus Erythematosus – National Assessment
SFI	SELENA-SLEDAI SLE Flare Index
SGB	Sozialgesetzbuch (Social Code Book)
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SPC	Summary of Product Characteristics

2 Benefit assessment

2.1 Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SGB) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug belimumab. 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 15 November 2019.

Research question

The aim of the present report is the assessment of the added benefit of belimumab as add-on therapy in comparison with the appropriate comparator therapy (ACT) in patients aged 5 to < 18 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive test result for autoantibodies specific for double-stranded deoxyribonucleic acid [anti-dsDNA] antibodies and low complement) despite standard therapy.

For the benefit assessment, the research question presented in Table 2 resulted from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of belimumab

Research question	Therapeutic indication	ACT[a]
1	Patients aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy	Individual treatment choosing from hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, mycophenolate mofetil (in case of severe kidney involvement), taking into account the respective organ involvement, prior therapy and disease activity
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; dsDNA: double-stranded deoxyribonucleic acid; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

The company followed the G-BA's specification of the ACT.

The assessment was made by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. Randomized controlled trials (RCTs) with a minimum duration of 1 year were used for the derivation of the added benefit.

Results

Study pool

The PLUTO study is principally suitable for the present benefit assessment of belimumab. Due to the type of analyses, the results are not interpretable, however. In addition, it can be assumed that a relevant proportion of the patients did not exhibit high disease activity at study entry and thus are not part of the target population of the present benefit assessment. The results of the PLUTO study presented by the company are therefore not suitable for the derivation of the added benefit.

Characteristics of the study and of the patients

The PLUTO study was a double-blind RCT on the comparison of belimumab + individual concomitant medication versus placebo + individual concomitant medication. A total of 93 children and adolescents aged between 5 and < 18 years with active SLE under pretreatment were included in the study. According to the inclusion criteria, the disease activity of the SLE at study entry had to be ≥ 6 points on the Safety of Estrogens in Lupus Erythematosus – National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI); ≥ 50% of the patients had to have a disease activity of ≥ 8 points on the SELENA-SLEDAI. Patients had to present with a positive test result for anti-dsDNA antibodies or a low complement.

Besides analyses for the total population (= intention to treat [ITT] population) presented as supplementary information, the dossier also contained analyses for 2 subpopulations:

- ITT-ACT1 population: This corresponds to the ITT population without the patients who had received concomitant medication with drugs that are not approved in Germany (methotrexate, tacrolimus, leflunomide). It comprises 32 versus 25 patients.
- ITT-ACT2 population: This corresponds to the ITT-ACT1 population without the patients who had received mycophenolate as concomitant medication at least once during the course of the study. It comprises 21 versus 14 patients.

In the 3 sub(populations) analysed by the company, the ACT is best represented in the ITT-ACT2 population. However, it should be taken into account that the ITT population may also include patients who did not have high disease activity at study entry.

The characteristics of the patients in the ITT-ACT2 population of the PLUTO study were largely comparable between both treatment arms. About 90% of the patients included were between 12 and < 18 years of age. The proportion of women was about 90%. The mean duration of the disease was about 2.5 years, while the mean disease activity according to the SELENA-SLEDAI score was about 9.5 points. The mean prednisone dose was 8.8 mg/day in the belimumab arm and 14.6 mg/day in the comparator arm; this difference did not affect the interpretability of the study.

Provisions for the concomitant medication in the PLUTO study

In the PLUTO study, the concomitant medication for the treatment of SLE could be adapted to the individual patient according to clinical requirements. However, some changes led to the assumption of treatment failure in the patients. The patients concerned had to discontinue their participation in part A of the PLUTO study and were enrolled in part C (extension phase of the study without administration of belimumab or placebo).

The range of medications of the changes that did not lead to discontinuation of study participation was initially wide and became narrower during the course of the study; according to the company, this was in order to be able to assess the belimumab effect.

Results of the PLUTO study not interpretable on the basis of the available information

Implementation of the appropriate comparator therapy rated as treatment failure or unfavourable event

a) Type of analysis of patients with treatment optimizations outside the specified range of medication is not appropriate

Where treatment optimization beyond the range of medication described in the protocol was required, the affected patients were rated as non-responders in the analyses for dichotomous outcomes other than adverse events (AEs). For continuous outcomes, the subsequent values that were no longer recorded were replaced by the last observed value before discontinuation of study participation in part A.

This type of analysis is not appropriate, as the ACT – individual therapy – also includes dose increases or the addition of drugs from new drug categories. However, as a result of the administration of such individually optimized treatment beyond the range of medication described in the study protocol, the affected patients were included in the analyses of the PLUTO study as patients with treatment failure, and the implementation of the ACT was thus rated as an unfavourable event (treatment failure).

The analyses carried out in this way probably yield results to the disadvantage of the comparator arm, since, due to the lack of additional therapies (as given in the intervention arm by the additional administration of belimumab), the patients in the comparator arm needed optimizations of their ongoing therapy outside the range of medication described in the study protocol more frequently than in the belimumab arm (related to the total population: 11% in the belimumab arm versus 23% in the comparator arm). If, in the subpopulation to be considered, the proportion of patients with a treatment adjustment rated as treatment failure was notably higher in the comparator arm than in the belimumab arm, this means that the results presented by the company for patient-relevant outcomes cannot be interpreted meaningfully.

b) Operationalization of individual outcomes is not appropriate

Some outcomes were directly operationalized using the optimization of the concomitant medication (addition/discontinuation of individual drugs and/or dose changes). This is not

appropriate and is explained using the example of the outcome “flare according to SELENA-SLEDAI SLE Flare Index (SFI)”.

According to the outcome “flare according to SFI”, a flare is defined as the occurrence of one of several components (some of which are not patient-relevant), including components that lead to events from the implementation of the ACT. This concerns the increase in the prednisone dose or the addition of new drugs. Treatment optimization required for the patient as a possible implementation of the ACT was therefore counted as an unfavourable event (flare).

Unclear proportion of patients with high disease activity in the PLUTO study

Belimumab is approved for patients with a high degree of disease activity. According to the information provided in the Summary of Product Characteristics (SPC), a high degree of disease activity is defined as a positive test result for anti-dsDNA antibodies and a low complement, for example.

The criterion mentioned as an example in the SPC was fulfilled in only about 42% of the patients in the ITT population of the PLUTO study. It cannot be inferred from the available documents whether this proportion was comparably low in the ITT-ACT2 population.

The characteristics of the patients in the ITT population and in the and ITT-ACT2 population indicate that a relevant proportion of patients did not exhibit high disease activity at study entry and thus are not part of the target population.

Results

There were no interpretable results for the assessment of belimumab as add-on therapy for the treatment of children and adolescents aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy. Hence, there was no hint of an added benefit of belimumab as add-on therapy in comparison with the ACT. An added benefit is therefore not proven.

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

Based on the results presented, probability and extent of the added benefit of the drug belimumab in comparison with the ACT are assessed as follows:

The result of the assessment of the added benefit of belimumab in comparison with the ACT is summarized in Table 3.

Table 3: Belimumab – probability and extent of added benefit

Therapeutic indication	ACT[a]	Probability and extent of added benefit
Patients aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy	Individual treatment choosing from hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, mycophenolate mofetil (in case of severe kidney involvement), taking into account the respective organ involvement, prior therapy and disease activity	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; dsDNA: double-stranded deoxyribonucleic acid; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

The assessment described above deviates from that of the company, which derived an indication of major added benefit.

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

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) “proof”, (2) “indication”, (3) “hint”, or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

2.2 Research question

The aim of the present report is the assessment of the added benefit of belimumab as add-on therapy in comparison with the ACT in patients aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g. positive test result for anti-dsDNA antibodies and low complement) despite standard therapy.

For the benefit assessment, the research question presented in Table 4 resulted from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of belimumab

Research question	Therapeutic indication	ACT[a]
1	Patients aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy	Individual treatment choosing from hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, mycophenolate mofetil (in case of severe kidney involvement), taking into account the respective organ involvement, prior therapy and disease activity
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; dsDNA: double-stranded deoxyribonucleic acid; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

As comparator therapy, the company specified individual treatment choosing from hydroxychloroquine, chloroquine, nonsteroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, azathioprine, mycophenolate mofetil (in case of severe kidney involvement), taking into account the respective organ involvement, prior therapy and disease activity. The company thus followed the G-BA's specification of the ACT.

The assessment was made by means of patient-relevant outcomes on the basis of the data presented by the company in the dossier. RCTs with a minimum duration of 1 year were used for the derivation of the added benefit. This deviates from the approach of the company, which defined a minimum duration of 24 weeks as inclusion criterion.

2.3 Information retrieval and study pool

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

Sources of the company in the dossier:

- study list on belimumab (status: 30 September 2019)
- bibliographical literature search on belimumab (last search on 30 September 2019)
- search in trial registries for studies on belimumab (last search on 30 September 2019)

To check the completeness of the study pool:

- search in trial registries for studies on belimumab (last search on 28 November 2019)

No additional relevant study was identified from the check.

2.3.1 Studies included

The study listed in the following table was included in the benefit assessment.

Table 5: Study pool – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication

Study	Study category		
	Study for approval of the drug to be assessed (yes/no)	Sponsored study[a] (yes/no)	Third-party study (yes/no)
BEL114055 (PLUTO[b])	Yes	Yes	No

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

The PLUTO study is principally suitable for the present benefit assessment of belimumab. Due to the type of analyses, the results are not interpretable, however. In addition, it can be assumed that a relevant proportion of the patients did not exhibit high disease activity at study entry and thus are not part of the target population of the present benefit assessment. The results of the PLUTO study presented by the company are therefore not suitable for the derivation of the added benefit.

To explain this, first the study design of the PLUTO study is described below, followed by a discussion of the reasons for the lack of interpretability of the results presented by the company.

2.3.2 Study characteristics and interpretability of the PLUTO study

Table 6 and Table 7 describe the study for the benefit assessment.

Table 6: Characteristics of the study included – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
PLUTO	RCT, double-blind, parallel	Children and adolescents aged 5–< 18 years with clinically active SLE under pretreatment and the following criteria at screening: ▪ have/had consecutively ≥ 4 of the 11 ACR criteria ▪ SELENA-SLEDAI score ≥ 6[b] ▪ positive test for ANA titre ≥ 1:80 and/or anti-dsDNA ≥ 30 IU/mL serum antibodies at 2 time points, thereof ≥ 1 at screening	Belimumab + individual concomitant medication (N = 53) placebo + individual concomitant medication (N = 40) Thereof subpopulations analysed by the company: ITT-ACT1[c] belimumab + individual concomitant medication (n = 32) placebo + individual concomitant medication (n = 25) ITT-ACT2[c] belimumab + individual concomitant medication (n = 21) placebo + individual concomitant medication (n = 14)	Screening: ≤ 35 days Part A: Treatment: 52 weeks or until treatment failure or another reason for discontinuation[d] Observation: 8 weeks[e]	29 centres in 10 countries (Argentina, Canada, Japan, Mexico, Peru, Poland, Russia, Spain, UK, USA) Study period: 9/2012–1/2018[f]	Primary: SLE Responder Index response rate Secondary: mortality, morbidity, health-related quality of life, AEs

a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes exclusively contain information on relevant available outcomes from the information provided by the company in Module 4 A of the dossier.
b. Until Amendment 3, a SELENA-SLEDAI score of ≥ 8 was an inclusion criterion; also after the change, ≥ 50% of all randomized patients had to have a SELENA-SLEDAI score of ≥ 8.
c. ITT-ACT1 population = ITT population (corresponds to total population) without the patients who received methotrexate, tacrolimus or leflunomide; ITT-ACT2 population = ITT-ACT1 population without the patients who received mycophenolate.
d. Treatment failure was defined, for example, as the administration of concomitant treatments outside a medication range described in the study protocol (see Table 7); other reasons for discontinuation included withdrawal of informed consent or toxicity.
e. Patients who completed the study treatment of 52 weeks (part A) switched, with the last day in week 52, to day 1 of an open-label extension study (part B), in which all patients were treated with belimumab + individual concomitant medication. Patients from part A or B who discontinued the study treatment with belimumab or placebo switched to a safety follow-up observation (part C) without administration of belimumab or placebo.
f. Double-blind randomized phase (part A).

ACR: American College of Rheumatology; AE: adverse event; ANA: anti-nuclear antibody; dsDNA: double-stranded deoxyribonucleic acid; ITT: intention to treat; ITT-ACT1: see footnote c; ITT-ACT2: see footnote c; n: relevant subpopulation; N: number of randomized patients; RCT: randomized controlled trial; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SLE: systemic lupus erythematosus; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; vs.: versus

Table 7: Characteristics of the intervention – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication (multipage table)

Study	Intervention	Comparison
PLUTO	Belimumab IV 10 mg/kg body weight as 1-hour infusion on days 0, 14, 28, and then every 28 days until week 48 + individual concomitant medication	Placebo IV as 1-hour infusion on days 0, 14, 28, and then every 28 days until week 48 + individual concomitant medication
	Pretreatment ▪ Stable SLE medication within ≥ 30 days prior to randomization with ≥ 1 of the following drugs: ▫ corticosteroids (prednisone or equivalent up to 0.5 mg/kg/day) ▫ immunosuppressant or immunomodulatory drugs such as methotrexate, azathioprine, leflunomide, mycophenolate, calcineurin inhibitors (e.g. ciclosporin, tacrolimus), sirolimus, oral cyclophosphamide, 6-mercaptopurine, or thalidomide ▫ antimalarial agents (e.g. hydroxychloroquine, chloroquine, mepacrine) ▫ NSAIDs ▪ No new SLE medication except corticosteroids within 60 days prior to randomization **Individual concomitant medication** ▪ Antimalarial drugs: ▫ initiation of a new drug allowed until week 16 ▫ dose reduction allowed during the entire study ▫ dose increase allowed until week 16; ▫ dose increases after week 16 beyond the dose on day 0 or week 16 (whichever was higher) resulted in discontinuation of participation in the randomized part of the study ▫ switching to a different antimalarial drug due to toxicity or unavailability was allowed during the entire study ▪ Corticosteroids including all forms of application (e.g. oral, IV, SC, calculated as average of the doses within 7 days): ▫ systemic corticosteroids to treat disease activity of the SLE - dose reduction allowed during the entire study - dose increases according to clinical need allowed without restrictions until week 24 - at week 24, the dose had to be reduced again, if necessary, so that it was no more than 25% or 5 mg above the dose at the start of treatment (whichever was higher); this dose range had to be adhered to until week 52; if this was not clinically possible, participation in the randomized part of the study was discontinued ▫ intraarticular corticosteroids - allowed between baseline and week 44 - administration between week 44 and week 52 resulted in discontinuation of participation in the randomized part of the study ▫ corticosteroids for the treatment of other diseases than SLE - unrestricted administration allowed between baseline and week 24 - week 24 to week 44: the dose could not be increased to a level higher than 25% or 5 mg above the dose at the start of treatment (whichever was higher); dose increase allowed up to 750 mg/day for 1 day and/or up to 100 mg/day for 2 to 3 days and/or up to 40 mg/day for 4 to 7 days - week 44 to week 52: no new corticosteroids except for the treatment of SLE, otherwise discontinuation of participation in the randomized part of the study	

Table 7: Characteristics of the intervention – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication (multipage table)

Study	Intervention	Comparison
	▪ Other immunosuppressants or immunomodulators ▫ no new drug after randomization; if a new drug was given, discontinuation of participation in the randomized part of the study ▫ dose increase until week 16 up to specified maximum doses, e.g. azathioprine up to 300 mg/day ▫ after week 16, dose increases beyond the higher dose on day 0 or week 16 resulted in discontinuation of participation in the randomized part of the study ▫ switching to another drug due to toxicity or unavailability was allowed during the entire study ▪ NSAIDs ▫ unrestricted as-needed administration until week 44 ▫ no new drug after week 44; if a new drug was given for > 1 week, discontinuation of participation in the randomized part of the study ▫ No dose increase after week 44[a] ▫ switching to another NSAID due to toxicity or unavailability was allowed during the entire study ▫ antithrombotic doses of acetylsalicylic acid allowed during the entire study	

a. The consequences of deviations are not clearly described in the protocol; the information in the CSR suggests that participation in the randomized part of the study had to be discontinued.

CSR: clinical study report; IV: intravenous; NSAID: nonsteroidal anti-inflammatory drug; RCT: randomized controlled trial; SC: subcutaneous; SLE: systemic lupus erythematosus; vs.: versus

The PLUTO study was a double-blind RCT on the comparison of belimumab + individual concomitant medication versus placebo + individual concomitant medication. The PLUTO study consisted of 3 parts: the randomized part of the study (part A), the extension phase with the administration of belimumab (part B) for all patients who had completed part A, and the follow-up without administration of belimumab or placebo (part C) for patients who discontinued participation in part A or B. Part A of the study is completed; the study was conducted in 29 centres in 10 countries.

A total of 93 children and adolescents aged between 5 and < 18 years with active SLE under pretreatment were included in the study. Diagnosis of SLE was made based on the criteria by the American College of Rheumatology (ACR). According to the inclusion criteria, the disease activity of the SLE at study entry initially had to be ≥ 8 according to the SELENA-SLEDAI, which was reduced to ≥ 6 with Amendment 4 in order to accelerate recruitment, but ≥ 50% of the patients still had to have a disease activity of ≥ 8 points on the SELENA-SLEDAI. The presence of a positive test result for anti-dsDNA antibodies and low complement was not an inclusion criterion; it was sufficient if one of the 2 criteria was met.

Patients were stratified by age (5 to 11 years versus 12 to < 18 years) and SELENA-SLEDAI score (6 to 12 versus ≥ 13 points) and randomly allocated to the 2 treatment arms. The distribution of the patients in the ITT population (53 versus 40) is explained by the fact that inclusion and randomization took place in 3 cohorts, with the randomization ratio of belimumab versus placebo being 5:1 in 2 cohorts and 1:1 in 1 cohort.

Treatment with belimumab was largely in compliance with the recommendations of the SPC; the treatment regimen with placebo matched the treatment regimen with belimumab. The extent to which individual concomitant treatment in the sense of the ACT was implemented in the study can be seen in the Section *Provisions for the concomitant medication in the PLUTO study* below. Table 7 shows the characteristics of the randomized study treatment and of the concomitant medication.

The concomitant medication administered in the PLUTO study also included drugs that are not approved in Germany for the treatment of SLE (e.g. tacrolimus) or are only prescribable according to Appendix VI to Section K of the Pharmaceutical Directive (off-label use) [3] (mycophenolate mofetil/mycophenolic acid in lupus nephritis). To take this into account, the company used the results of 2 subpopulations for the derivation of the added benefit (designated by the company as "ITT-ACT1 population" and "ITT-ACT2 population"). The company presented the results of the total population (= ITT population with 53 versus 40 patients) as supplementary information.

With the ITT-ACT1 population and the ITT-ACT2 population, the company considered the following patient groups from the PLUTO study:

- ITT-ACT1 population: This corresponds to the ITT population without the patients who had received concomitant medication with drugs that are not approved in Germany (methotrexate, tacrolimus, leflunomide). It comprises 32 versus 25 patients.
- ITT-ACT2 population: This corresponds to the ITT-ACT1 population without the patients who had received mycophenolate as concomitant medication at least once during the course of the study. It comprises 21 versus 14 patients. The company justified the exclusion of patients with mycophenolate as concomitant medication with the fact that it was unclear whether all patients had severe kidney involvement at study entry and were thus fulfilling the criteria of Appendix VI to Section K of the Pharmaceutical Directive.

In the 3 sub(populations) analysed by the company, the ACT is best represented in the ITT-ACT2 population; hence the following considerations refer to this subpopulation. However, it should be taken into account that the ITT population may also comprise patients who did not have high disease activity at study entry. It is unclear whether and to which extent this applies to the ITT-ACT2 population; see Section *Unclear proportion of patients with high disease activity in the PLUTO study.*

Table 8 shows the characteristics of the patients in the ITT-ACT2 population of the study included.

Table 8: Characteristics of the ITT-ACT2 population – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication (multipage table)

Study Characteristics Category	**Belimumab + individual concomitant medication Nª = 21**	**Placebo +individual concomitant medication Nª = 14**
PLUTO		
Age [years], mean (SD)	14 (2.7)	15 (1.9)
Age [years] n (%)		
< 12	3 (14.3)	1 (7.1)
≥ 12	18 (85.7)	13 (92.9)
Sex [F/M], %	90/10	93/7
Family origin n (%)		
Caucasian	12 (57.1)	9 (64.3)
Asian	2 (9.5)	1 (7.1)
Black/African American	1 (4.8)	0 (0.0)
Alaskan/Native American	6 (28.6)	4 (28.6)
Region n (%)		
Europe and North America	5 (23.8)	6 (42.9)
Rest of the world	16 (76.2)	8 (57.1)
Body weight [kg], mean (SD)	55.4 (17.5)	53.6 (13.4)
BMI [kg/m^2] mean (SD)	23.0 (4.9)	21.3 (4.3)
Disease duration: time between first diagnosis and randomization [months], mean (SD)	2.3 (2.4)	2.8 (1.9)
Disease activity SELENA-SLEDAI score n (%)		
< 13	20 (95.2)	12 (85.7)
≥ 13	1 (4.8)	2 (14.3)
Disease activity SELENA-SLEDAI score		
Mean (SD)	8.9 (2.5)	9.9 (3.6)
Median (min, max)	8.0 (4, 14)	10.0 (4, 18)
25% quantile; 75% quantile	8.0; 10.0	8.0; 12.0
PGA n (%)		
0–1	1 (4.8)	3 (21.4)
> 1–2.5	20 (95.2)	11 (78.6)
> 2.5	0 (0.0)	0 (0.0)
Paediatric SDI score n (%)		
0	17 (81.0)	12 (85.7)
1	3 (14.3)	1 (7.1)
> 1	1 (4.8)	1 (7.1)

Table 8: Characteristics of the ITT-ACT2 population – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication (multipage table)

Study Characteristics Category	**Belimumab + individual concomitant medication N[a] = 21**	**Placebo +individual concomitant medication N[a] = 14**
Organ involvement according to BILAG n (%)		
≥ 1 organ system with grade A or ≥ 2 organ systems with grade B	11 (52.4)	9 (64.3)
≥ 1 organ system with grade A	0 (0.0)	3 (21.4)
≥ 1 organ system with grade B	19 (90.5)	12 (85.7)
No organ system with grade A or B	2 (9.5)	1 (7.1)
Mean prednisone dose (SD)	8.8 (4.2)	14.6 (10.9)
Treatment discontinuation, n (%)	ND	ND
Study discontinuation, n (%)	ND	ND

a. Number of patients in the ITT-ACT2 subpopulation of the PLUTO study; the ITT-ACT2 corresponds to the ITT population without the patients who received methotrexate, tacrolimus, leflunomide or mycophenolate.

ACT: appropriate comparator therapy; BILAG: British Isles Lupus Assessment Group; F: female; ITT: intention to treat; M: male; n: number of patients in the category; N: number of patients in the relevant subpopulation; ND: no data; PGA: physician's global assessment; RCT: randomized controlled trial; SD: standard deviation; SDI: Systemic Lupus International Collaborating Clinics/American College of Rheumatology (SLICC/ACR) Damage Index; SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment – Systemic Lupus Erythematosus Disease Activity Index; vs.: versus

The characteristics of the patients in the ITT-ACT2 population of the PLUTO study were largely comparable between both treatment arms. About 90% of the patients included were between 12 and < 18 years of age. The proportion of women was about 90%. The mean duration of the disease was about 2.5 years, while the mean disease activity according to the SELENA-SLEDAI score was about 9.5 points. The mean prednisone dose was 8.8 mg/day in the belimumab arm and 14.6 mg/day in the comparator arm; this difference did not affect the interpretability of the study.

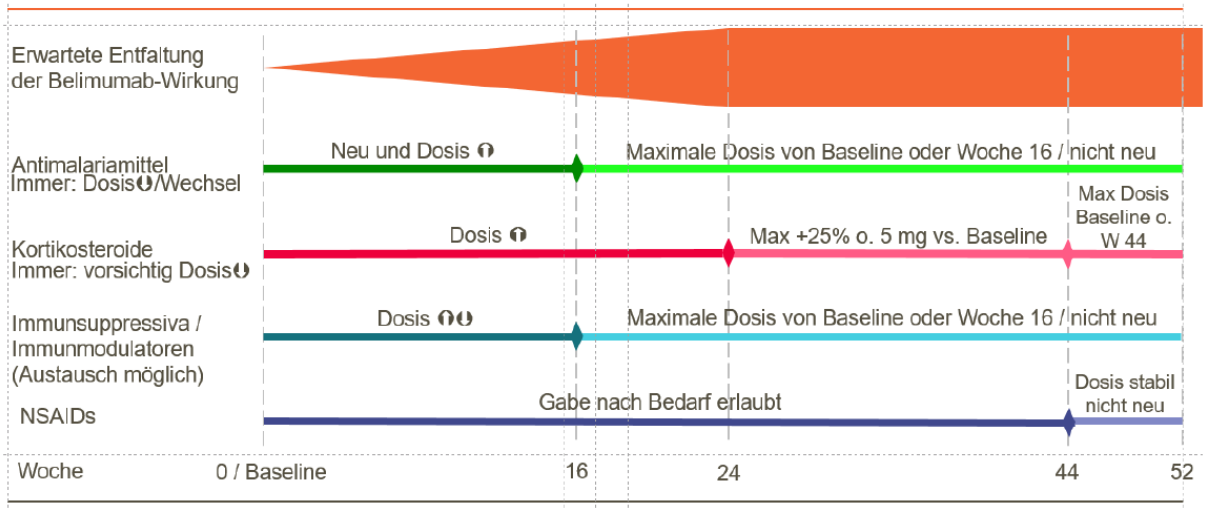
It cannot be inferred from the patient characteristics that a clear majority of patients had a high level of disease activity, as specified in the scientific information, at study entry (see Section *Unclear proportion of patients with high disease activity in the PLUTO study*).

Provisions for the concomitant medication in the PLUTO study

In the PLUTO study, the concomitant medication for the treatment of SLE could be adapted to the individual patient according to clinical requirements. However, some changes led to the assumption of treatment failure. The patients concerned had to discontinue their participation in part A of the PLUTO study and were enrolled in part C (extension phase of the study without administration of belimumab or placebo).

The medication range of the changes that did not lead to discontinuation of study participation (part A) was initially wide and became narrower during the course of the study (see Figure 1 and Table 7). The company justified this with the fact that with the slow onset of the effect of belimumab, expected after several months, the aim was to bring the corticosteroid dosage in both study arms closer to the initial range and then to keep the concomitant medication stable in order to be able to assess the effect of belimumab.

Figure 1 presents the provisions for the administration of the concomitant medication in the PLUTO study.



Translation of terms in Figure 1:
Erwartete Entfaltung der Belimumab-Wirkung – Expected onset of belimumab effect; Antimalariamittel – Antimalarial agents; Immer: Dosis ↓/Wechsel – Always: dose ↓/change; Neu und Dosis ↑ – New and dose ↑; Maximale Dosis von Baseline oder Woche 16 / nicht neu – maximum dose from baseline or week 16 / not new; Kortikosteroide – corticosteroids; Immer: vorsichtig Dosis ↓ – Always: cautious dose ↓; Dosis ↑ – Dose ↑; Max. Dosis Baseline o. W44 – Maximum dose baseline or W44; Immunsuppressiva/Immunomodulatoren (Austausch möglich) – Immunosuppressants/immunomodulators (exchange possible); Gabe nach Bedarf erlaubt – As-needed administration allowed; Dosis stabil nicht neu – Stable dose not new; Woche – Week

Figure 1: Provisions for the concomitant medication in the PLUTO study (figure from Module 3 A)

Results of the PLUTO study not interpretable on the basis of the available information

It can be inferred from the information provided in the previous section that treatment optimization in the sense of the implementation of the ACT was not withheld from the patients. Due to the data recording and the type of analysis, the results are not interpretable, however.

Implementation of the appropriate comparator therapy partly rated as treatment failure or unfavourable event

a) Type of analysis of patients with treatment optimizations outside the specified range of medication is not appropriate

As described above, patients in the randomized part of the PLUTO study were rated as patients with treatment failure if treatment optimization beyond the medication range described in the protocol was required. These patients were rated as non-responders in the analyses for dichotomous outcomes except AEs. In the analyses for continuous outcomes, the subsequent values that were no longer recorded were replaced by the last observed value before discontinuation of study participation in part A (last observation carried forward [LOCF]).

This type of analysis is not appropriate. For example, the ACT provides for individual treatment using different drugs. This may require the optimization of the patients' ongoing treatment in the course of the study, e.g. by increasing the dosage or adding a drug from a new drug category. The patients who received these treatment adjustments were thus treated in the sense of the ACT. However, as a result of the administration of such individually optimized treatment beyond the range of medication described in the study protocol, the affected patients were included in the analyses of the PLUTO study as patients with treatment failure. The implementation of the ACT was thus rated as unfavourable event (treatment failure).

It can be assumed that the analyses carried out in this way were to the disadvantage of the comparator arm. The reason for this assessment is that, due to the lack of additional therapies (as given in the intervention arm by the additional administration of belimumab), the patients in the comparator arm needed optimizations of their ongoing therapy outside the range of medication described in the study protocol more frequently than in the belimumab arm. If, in the subpopulation to be considered, the proportion of patients with a treatment adjustment rated as treatment failure was notably higher in the comparator arm than in the belimumab arm, this means that the results presented by the company for patient-relevant outcomes cannot be interpreted meaningfully.

Information on the number of patients from both study arms for whom treatment optimization beyond the medication range described in the study protocol was rated as treatment failure is only available for the ITT population. In this population, the proportions of 11% versus 23% (6 patients in the belimumab arm versus 9 patients in the comparator arm) were relevant and differed between the study arms.

However, a subpopulation of the ITT population was considered for the present benefit assessment (ITT-ACT2 population under consideration of the disease activity). It is unclear how high the proportions in this subpopulation were in the 2 treatment arms. If the differences between the arms were of a similar magnitude as in the ITT population, the results, as described above, would not be interpretable. Depending on the size of the proportions in the treatment arms, the problem may be reduced or even exacerbated. In order to assess this, it is necessary to know the sizes of the proportions in the subpopulation to be considered.

b) Operationalization of individual outcomes is not appropriate

Some outcomes were directly operationalized using the optimization of the concomitant medication (addition/discontinuation of individual drugs and/or dose changes). This is not appropriate and is explained using the example of the outcome "flare according to SFI". The added benefit determined by the company for the ITT-ACT2 population was mainly based on this outcome. Due to the operationalization, the results of this outcome are not interpretable, however.

According to the outcome "flare according to SFI", a flare is defined as the occurrence of at least one of several components[4] (some of which are not patient-relevant), including components that lead to events from the implementation of the ACT. This concerns the increase in the prednisone dose or the addition of new drugs (e.g. hydroxychloroquine, azathioprine, cyclophosphamide).

For example, an increase in the prednisone dose to up to 0.5 mg/kg per day was considered a mild/moderate flare, and an increase in the prednisone dose to above 0.5 mg/kg per day was considered a severe flare. Treatment optimization required for the patient (dose increase of prednisone as a possible implementation of the ACT) was therefore counted as an unfavourable event (mild/moderate or severe flare).

In addition, for the interpretation of this outcome, it is not clear from the available documents how many events were rated as flares only because the prednisone dose was increased. An appropriate analysis of the number of flares therefore requires the information on how many of the flares observed in the study were based on characteristic symptoms of the outcome "flare according to SFI" introduced by the company and not solely on the increase in prednisone dose (or other treatment-related components of this outcome).

Since the other components of the outcome "flare according to SFI" cited by the company were not decisive for the argumentation, no comments are made on their patient relevance.

Unclear proportion of patients with high disease activity in the PLUTO study

Belimumab is approved for patients with a high degree of disease activity. According to the information provided in the SPC, a high degree of disease activity is defined as a positive test result for anti-dsDNA antibodies and a low complement, for example [4].

[4] The PLUTO study investigated 2 severity grades of flares: mild/moderate flares and severe flares. Both operationalizations contain almost the same components: increase in prednisone dosage, change in SELENA-SLEDAI score, change in PGA, deterioration of defined symptoms, addition of new drugs. Differences between mild/moderate and severe flares resulted from the threshold values, the type of new drugs used for the treatment of SLE, the symptoms and the hospital admissions.
Module 4 A contained discrepant information regarding the definitions of "mild/moderate" and "severe" flares. The information in Module 4 A (Table 4-6) concurred with the information in the study protocol.

Arguments of the company are unfounded

In its information on the consideration of disease activity, the company stated that the criteria mentioned in the approval of belimumab were examples. According to the company, a high degree of disease activity can also be determined on the basis of other criteria, such as a general need of corticosteroids and/or a SELENA-SLEDAI score ≥ 10.

From the company's point of view, the criterion of high disease activity was met in all patients in the PLUTO study because 88 of 93 (94.6%) of the patients were receiving a corticosteroid at a mean dose of 10.44 mg/day at study entry. According to the company, this dose is beyond an acceptable range and is not in compliance with any guideline or remission criterion. It considered it unlikely that the remaining 5 (5.4%) patients did not meet any other criterion for high disease activity.

The arguments of the company are unfounded. On the one hand, it can be inferred neither from the European League Against Rheumatism (EULAR) guideline [5], nor from other scientific literature (e.g. [6,7]) that the administration of corticosteroids alone indicates a high degree of disease activity in patients. The company also did not present any guidelines or publications from which its assessment can be inferred.

On the other hand, the consideration of the mean corticosteroid dose alone does not allow the conclusion that almost all patients in the study were receiving a high dose. This conclusion also requires considering the measures of dispersion, for example. Data from the clinical study report (CSR) of the PLUTO study show that more than 20% of the patients in the ITT population were receiving a prednisone dose ≤ 7.5 mg/day at study entry. According to the EULAR guideline [5] a prednisone dose of ≤ 7.5 mg/day is compatible with low disease activity.

The sole consideration of the corticosteroid use of the patients in the PLUTO study is therefore not sufficient to draw conclusions on the presence of high disease activity.

High disease activity of patients not evident from available data

An exploratory search was carried out to check which further criteria are used in addition to the example in the SPC (positive test result for anti-dsDNA antibodies and low complement) to determine high disease activity. The following possible criteria of high disease activity were identified, but none of them can be considered the gold standard:

- SLEDAI score > 10 (EULAR guideline 2019 [5])
- organ involvement according to British Isles Lupus Assessment Group (BILAG); at least one grade A assessment (EULAR guideline 2019 [5] and Mikdashi 2015 [6])
- physician's global assessment (PGA) ≥ 2.1 (Barr 1999 [7])

Table 9 shows how these criteria are distributed between the 2 treatment arms of the ITT population of the PLUTO study.

Table 9: Criteria for the assessment of disease activity at the start of treatment in the PLUTO study – RCT, direct comparison: belimumab + individual concomitant medication vs. placebo + individual concomitant medication

			Belimumab + individual concomitant medication		**Placebo + individual concomitant medication**	
Criterion	**Analysis population**	**Statistical parameter**	**N**	**Result**	**N**	**Result**
Positive test result for anti-dsDNA antibodies and low complement[a]	ITT	n (%)	53	22[b] (41.5)	40	17[b] (42.5)
	ITT-ACT2[c]	n (%)	21	ND	14	ND
SELENA-SLEDAI > 10 [5]	ITT	n (%)	53	ND	40	ND
	ITT-ACT2[c]	n (%)	21	ND	14	ND
SELENA-SLEDAI	ITT	Mean (SD)	53	10.3 (3.3)	40	10.4 (3.6)
		Median		10.0		10.0
		1st quartile		8.0		8.0
		3rd quartile		12.0		12.0
SELENA-SLEDAI ≥ 8	ITT	n (%)	53	46 (86.8)	40	33 (84.6)
SELENA-SLEDAI ≥ 13	ITT	n (%)	53	10 (18.9)	39	6 (15.4)
SELENA-SLEDAI	ITT-ACT2[c]	Mean (SD)	21	8.9 (2.5)	14	9.9 (3.6)
SELENA-SLEDAI ≥ 8	ITT-ACT2[c]	n (%)	53	ND	40	ND
SELENA-SLEDAI ≥ 13	ITT-ACT2[c]	n (%)	21	1 (4.8)	14	2 (14.3)
BILAG grade A in ≥ 1 organ system [5,6]	ITT	n (%)	53	4 (7.5)	40	6 (15.0)
	ITT-ACT2[c]	n (%)	21	0 (0.0)	14	3 (21.4)
PGA ≥ 2.1 [7]	ITT	n (%)	53	ND	40	ND
	ITT-ACT2[c]	n (%)	21	ND	14	ND
PGA	ITT	Mean (SD)	53	1.3 (0.4)	40	1.4 (0.4)
PGA > 1 to ≤ 2.5	ITT	n (%)	53	44 (83.0)	40	31 (77.5)
PGA > 2.5	ITT	n (%)	53	0	40	0
PGA	ITT-ACT2[c]	Mean (SD)	21	1.4 (0.3)	14	1.4 (0.4)
PGA > 1 to ≤ 2.5	ITT-ACT2[c]	n (%)	21	20 (95.2)	14	11 (78.6)
PGA > 2.5	ITT-ACT2[c]	n (%)	21	0	14	0

a. Cited as an example in the SPC of belimumab [4].
b. Institute's calculation.
c. See Section 2.3.1 for the definition of the ITT-ACT2 population.

Criteria for high disease activity according to the sources are presented in **bold**.

ACT: appropriate comparator therapy; BILAG: British Isles Lupus Assessment Group; dsDNA: double-stranded deoxyribonucleic acid; ITT: intention to treat; n: number of patients with event; N: number of patients considered; PGA: physician's global assessment; RCT: randomized controlled trial; SD: standard deviation; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SLEDAI: Systemic Lupus Erythematosus Disease Activity Index; SPC: Summary of Product Characteristics; vs.: versus

The criteria of high disease activity mentioned in the sources identified above are presented in **bold** in Table 9. When assessing disease activity, it must be taken into account that the various criteria may correlate with one another (see, for example, van Vollenhoven 2012 [8]).

The criterion mentioned as an example in the SPC (positive test result for anti-dsDNA antibodies and low complement) was fulfilled in only about 42% of the patients in the ITT population of the PLUTO study. It cannot be inferred from the available documents whether this proportion was comparably low in the ITT-ACT2 population.

For the other criteria, such as a SELENA-SLEDAI score > 10 or a PGA ≥ 2.1, no data on the respective proportions of patients are available for either the ITT or the ITT-ACT2 population. However, the information on the median provided in Table 9 shows that < 50% of the ITT population had a SELENA-SLEDAI score of > 10. The joint consideration of the mean PGA value and the distribution of patients with a PGA value of PGA > 1 to ≤ 2.5 or PGA > 2.5 suggests that only a small proportion of patients fulfilled the criterion of high disease activity (PGA value > 2.1).

Overall, the proportion of patients with high disease activity in the ITT or ITT-ACT2 population of the PLUTO study can only be estimated to a limited extent. However, the available data suggest that a relevant proportion of the patients did not exhibit high disease activity at study entry and thus are not part of the target population.

To be able to assess the influence of non-high disease activity on the results, information on the proportion of patients with high disease activity and additional subgroup analyses for this characteristic would have to be available.

Summary

For the reasons stated above (type of analyses; implementation of the ACT resulted in an unfavourable event; unclear proportion of patients that concur with the target population), the results of the PLUTO study presented by the company are not interpretable and thus not suitable for the derivation of an added benefit of belimumab as add-on therapy in comparison with the ACT in the therapeutic indication to be assessed.

2.4 Results on added benefit

There were no interpretable results for the assessment of belimumab as add-on therapy for the treatment of children and adolescents aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy. Hence, there was no hint of an added benefit of belimumab as add-on therapy in comparison with the ACT. An added benefit is therefore not proven.

2.5 Probability and extent of added benefit

The result of the assessment of the added benefit of belimumab in comparison with the ACT is summarized in Table 10.

Table 10: Belimumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Patients aged 5 to < 18 years with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test result for anti-dsDNA antibodies and low complement) despite standard therapy	Individual treatment choosing from hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, mycophenolate mofetil (in case of severe kidney involvement), taking into account the respective organ involvement, prior therapy and disease activity	Added benefit not proven
a. Presentation of the respective ACT specified by the G-BA. ACT: appropriate comparator therapy; dsDNA: double-stranded deoxyribonucleic acid; G-BA: Federal Joint Committee; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

The assessment described above deviates from that of the company, which derived an indication of major added benefit.

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

2.6 List of included studies

GlaxoSmithKline. Pediatric lupus trial of belimumab plus background standard therapy (PLUTO): study results [online]. In: ClinicalTrials.gov. 03.09.2018 [Accessed: 05.12.2019]. URL: https://clinicaltrials.gov/ct2/show/results/NCT01649765.

GlaxoSmithKline. Pediatric lupus trial of belimumab plus background standard therapy (PLUTO): study details [online]. In: ClinicalTrials.gov. 03.09.2018 [Accessed: 05.12.2019]. URL: https://ClinicalTrials.gov/show/NCT01649765.

GlaxoSmithKline. A multi-center, randomized parallel group, placebo-controlled double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of belimumab, a human monoclonal anti-BLyS antibody, plus standard therapy in pediatric patients with systemic lupus erythematosus (SLE): double-blind endpoint analysis (part A); study BEL114055; clinical study report [unpublished]. 2018.

GlaxoSmithKline. A multi-center, randomized parallel group, placebo-controlled double-blind trial to evaluate the safety, efficacy, and pharmacokinetics of belimumab, a human monoclonal anti-BLyS antibody, plus standard therapy in pediatric patients with systemic lupus erythematosus (SLE): double-blind endpoint analysis (part A); study BEL114055; Zusatzanalysen [unpublished]. 2019.

References for English extract

Please see full dossier assessment for full reference list.

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

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The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a19-94-belimumab-sle-benefit-assessment-according-to-35a-social-code-book-v.12798.html.