IQWiG Reports – Commission No. A22-35

Anifrolumab (systemic lupus erythematosus) –

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

Extract

[1] Translation of Sections 2.1 to 2.5 of the dossier assessment *Anifrolumab (systemischer Lupus erythematodes) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 28 June 2022). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

Publishing details

Publisher
Institute for Quality and Efficiency in Health Care

Topic
Anifrolumab (systemic lupus erythematosus) – Benefit assessment according to §35a Social Code Book V

Commissioning agency
Federal Joint Committee

Commission awarded on
30 March 2022

Internal Commission No.
A22-35

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IQWiG thanks the medical and scientific advisor for his contribution to the dossier assessment. However, the advisor was not involved in the actual preparation of the dossier assessment. The responsibility for the contents of the dossier assessment lies solely with IQWiG.

Patient and family involvement

No feedback was received in the framework of the present dossier assessment.

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Keywords: Anifrolumab, Lupus Erythematosus – Systemic, Benefit Assessment, NCT02446912, NCT02446899, NCT01438489, NCT02794285

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[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

List of abbreviations

Abbreviation	Meaning
ACR	American College of Rheumatology
ACT	appropriate comparator therapy
AE	adverse event
anti-dsDNA	autoantibodies with specificity for double-stranded DNA
BICLA	BILAG-based Composite Lupus Assessment
BILAG	British Isles Lupus Assessment Group
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
NSAID	nonsteroidal anti-inflammatory drug
OCS	oral corticosteroids
PGA	physician's global assessment
RCT	randomized controlled trial
SAE	serious adverse event
SELENA	Safety of Estrogens in Lupus Erythematosus – National Assessment
SGB	Sozialgesetzbuch (Social Code Book)
SLE	systemic lupus erythematosus
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index – Revised Version
SRI	Systemic Lupus Erythematosus Responder Index

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 anifrolumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 30 March 2022.

Research question

The aim of the present report is the assessment of the added benefit of anifrolumab as an add-on therapy in comparison with the appropriate comparator therapy (ACT) in adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy.

The research question presented in Table 2 results from the ACT specified by the G-BA.

Table 2: Research question of the benefit assessment of anifrolumab

Therapeutic indication	**ACT**[a]
Add-on treatment in adults with moderate to severe active autoantibody-positive SLE despite standard therapy[b]	Individualized therapy taking into account the respective organ involvement, prior therapy and disease activity, choosing from the following drugs: hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, belimumab[c]
a. Presented is the ACT specified by the G-BA. b. In the therapeutic indication of SLE, patients with LN represent a separate patient population. LN is an organ manifestation (moderate to severe renal involvement) of SLE for which specific treatment recommendations exist in differentiation from other organ manifestations. The G-BA currently assumes that LN is not part of the requested therapeutic indication. c. Continuation of an inadequate therapy does not concur with the specified ACT. If conventional therapy (hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine) failed, belimumab was to be used. G-BA: Federal Joint Committee; LN: lupus nephritis; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus	

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

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

Results

The check of completeness of the study pool did not reveal any relevant study for assessing the added benefit of anifrolumab in comparison with the ACT. In contrast, the company used the

meta-analysis of the 3 RCTs TULIP-1, TULIP-2 and MUSE to assess the added benefit, and presented the extension study TULIP SLE LTE as well as an adjusted indirect comparison of anifrolumab versus belimumab via the common comparator placebo + standard therapy.

In the following, the studies included by the company are described in more detail and reasons are given why the evidence presented by the company is not suitable for assessing the added benefit.

Evidence presented by the company for the direct comparison

Studies TULIP-1, TULIP-2 and MUSE

The studies TULIP-1, TULIP-2 and MUSE are multicentre, randomized, double-blind studies with treatment durations of 52 weeks comparing anifrolumab as an add-on therapy to standard therapy against placebo + standard therapy. The studies included adults with chronic, moderate to severe autoantibody-positive SLE on stable prior therapy consisting of at least one drug or a combination of antimalarials, immunosuppressants or oral corticosteroids (OCS). Diagnosis of SLE was made based on the criteria by the American College of Rheumatology (ACR). According to the inclusion criteria, SLE disease activity at screening had to be ≥ 6 according to the Systemic Lupus Erythematosus Disease Activity Index – Revised Version (SLEDAI-2K) score and ≥ 4 according to the clinical SLEDAI-2K score. A British Isles Lupus Assessment Group (BILAG) 2004 A assessment in ≥ 1 organ system or a BILAG 2004 B assessment in ≥ 2 organ systems as well as a physician's global assessment (PGA) ≥ 1 were additionally required at screening.

Appropriate comparator therapy not implemented in the studies TULIP-1, TULIP-2 and MUSE

Patients had to already be receiving stable standard therapy prior to study inclusion in order to be included in the studies TULIP-1, TULIP-2 or MUSE. This standard therapy could consist of one or a combination of the following drugs: antimalarials, immunosuppressants, OCS. Furthermore, a maximum of one prescription nonsteroidal anti-inflammatory drug (NSAID) at a stable dose was allowed. The dosage of antimalarials and immunosuppressants had to be kept stable until week 52, in the MUSE study until day 169. In the course of the study, the starting dose of OCS, as another component of standard therapy, was only allowed to be exceeded for burst therapy. However, the possible period and the allowed number of bursts were strongly regulated. In the studies TULIP-1 and TULIP-2, adjustments to standard therapy beyond the protocol requirements were explicitly discouraged. Administration of biologics, and thus also of belimumab, was explicitly disallowed in all 3 studies.

The possible or permitted adjustments during the study were very limited in each case and the implementation of an individualized therapy was not ensured by the strict protocol specifications. Belimumab in particular was not available to the patients as a possible treatment option in the studies. Based on the patient characteristics at baseline in the studies TULIP-1, TULIP-2 and MUSE, it can be assumed that belimumab would have been an option for a

relevant proportion of patients. During the course of the study, there is too little information on disease activity to be able to assess how many patients would have been eligible for belimumab.

As a result of the strict requirements in the study protocol and the severely limited possibilities to adjust standard therapy, as well as of the exclusion of belimumab in particular, the ACT is assessed as overall not adequately implemented in the studies because standard therapy could not be adjusted to the individual patient.

In addition, patients with treatment optimization outside the specified medication range were partly rated as patients with treatment failure. Thus, the results presented by the company on patient-relevant outcomes cannot be meaningfully interpreted due to the inappropriate analysis in which patients with treatment adjustment were considered as patients with treatment failure.

Analyses of the TULIP SLE LTE extension study presented as supplementary information are not suitable

The TULIP SLE LTE study is a multicentre, randomized, double-blind study to assess the long-term tolerability of anifrolumab (300 mg) as an add-on therapy to standard therapy in comparison with placebo + standard therapy. Patients who completed participation in the 52-week TULIP-1 or TULIP-2 study were eligible to participate in the TULIP SLE LTE extension study for a treatment duration of 156 weeks, regardless of their SLE disease severity at the time of transition to this study. Patients who had received 150 mg or 300 mg of anifrolumab in the predecessor studies TULIP-1 or TULIP-2 received blinded 300 mg of anifrolumab in the TULIP SLE LTE study. Patients who had received placebo in the studies TULIP-1 or TULIP-2 were re-randomized in a 1:1 ratio to 300 mg anifrolumab or placebo.

The company included the data from the predecessor studies TULIP-1 and TULIP-2 in the analyses of the TULIP SLE LTE study. However, the standard therapy administered in the studies TULIP-1 and TULIP-2 does not represent an adequate implementation of the ACT due to the severe limitations (see above), making the approach of including the data from these studies inappropriate. Furthermore, the baseline patient characteristics listed by the company refer to the time of randomization in the predecessor studies TULIP-1 and TULIP-2 and not to the time of entry into the TULIP SLE LTE study. It is therefore not possible to assess the disease activity of the patients at the transition to the extension study. Thus, the analyses presented are not suitable for assessing the added benefit of anifrolumab.

Indirect comparison presented by the company as supplementary evidence is not suitable for the benefit assessment

The company presented an adjusted indirect comparison between the 3 studies of anifrolumab described above (TULIP-1, TULIP-2 and MUSE) and 2 studies of belimumab (BLISS-52 and BLISS-76) as supplementary evidence.

Despite comparable inclusion criteria of the belimumab and anifrolumab studies, the company on the one hand restricted the study population on the comparator side with regard to disease

activity, but on the other hand did not restrict the study population on the intervention side with regard to disease activity, although the company itself described the therapeutic indication of anifrolumab as broader than that of belimumab. This is also reflected in the differences in patient characteristics described by the company itself. The differences in patient characteristics show that this approach means that the populations considered are not sufficiently similar for an indirect comparison. However, the consideration of a sufficiently similar patient population for which both therapies can be considered is a key prerequisite for an adjusted indirect comparison.

Furthermore, in its search for studies with belimumab, the company identified another study (LBSL02) on the comparator side, in addition to the studies BLISS-52 and BLISS-76. The company did not consider this LBSL02 study further for the indirect comparison, however. There is no comprehensible justification for the exclusion of this study in the dossier. As described in the previous benefit assessment of belimumab, the LBSL02 study was basically rated as relevant to the assessment of the added benefit of belimumab and taken into account by the G-BA as supporting evidence in the assessment of the added benefit of belimumab. The exclusion of study LBSL02 from the study pool of the indirect comparison is not appropriate without sufficient justification. Due to the exclusion of study LBSL02, the study pool of the adjusted indirect comparison is potentially incomplete on the side of belimumab.

Results on added benefit

No suitable data are available for the assessment of the added benefit of anifrolumab as an add-on therapy in comparison with the ACT for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy. This results in no hint of added benefit of anifrolumab in comparison with the ACT; an added benefit is therefore not proven.

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

Table 3 shows a summary of the probability and extent of added benefit of anifrolumab.

[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: Anifrolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Add-on treatment in adults with moderate to severe active autoantibody-positive SLE despite standard therapy[b]	Individualized therapy taking into account the respective organ involvement, prior therapy and disease activity, choosing from the following drugs: hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, belimumab[c]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. In the therapeutic indication of SLE, patients with LN represent a separate patient population. LN is an organ manifestation (moderate to severe renal involvement) of SLE for which specific treatment recommendations exist in differentiation from other organ manifestations. The G-BA currently assumes that LN is not part of the requested therapeutic indication. c. Continuation of an inadequate therapy does not concur with the specified ACT. If conventional therapy (hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine) failed, belimumab was to be used. G-BA: Federal Joint Committee; LN: lupus nephritis; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

The G-BA decides on the added benefit.

Supplementary note on the appropriate comparator therapy

On 8 June 2022, the G-BA changed the ACT after submission of the dossier. As a result of the change, belimumab is the sole ACT and replaces individualized therapy. The present benefit assessment was based on the originally specified ACT.

2.2 Research question

The aim of the present report is the assessment of the added benefit of anifrolumab as an add-on therapy in comparison with the ACT in adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy.

The research question presented in Table 4 results from the ACT specified by the G-BA.

Table 4: Research question of the benefit assessment of anifrolumab

Therapeutic indication	**ACT**[a]
Add-on treatment in adults with moderate to severe active autoantibody-positive SLE despite standard therapy[b]	Individualized therapy taking into account the respective organ involvement, prior therapy and disease activity, choosing from the following drugs: hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, belimumab[c]
a. Presented is the ACT specified by the G-BA. b. In the therapeutic indication of SLE, patients with LN represent a separate patient population. LN is an organ manifestation (moderate to severe renal involvement) of SLE for which specific treatment recommendations exist in differentiation from other organ manifestations. The G-BA currently assumes that LN is not part of the requested therapeutic indication. c. Continuation of an inadequate therapy does not concur with the specified ACT. If conventional therapy (hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine) failed, belimumab was to be used. G-BA: Federal Joint Committee; LN: lupus nephritis; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus	

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

The assessment is conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 1 year are used for the derivation of the added benefit. This concurs with the company's inclusion criteria.

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 lists on anifrolumab (status: 2 February 2022)
- bibliographical literature search on anifrolumab (last search on 2 February 2022)
- search in trial registries/trial results databases for studies on anifrolumab (last search on 2 February 2022)
- search on the G-BA website for anifrolumab (last search on 2 February 2022)
- bibliographical literature search on the ACT (last search on 2 February 2022)

- search in trial registries/trial results databases for studies on the ACT (last search on 2 February 2022)
- search on the G-BA website for the ACT (last search on 2 February 2022)

To check the completeness of the study pool:

- search in trial registries for studies on anifrolumab (last search on 14 April 2022); for search strategies, see Appendix A of the full dossier assessment

The check did not identify any relevant studies for assessing the added benefit of anifrolumab in comparison with the ACT. The company, in contrast, identified the RCTs TULIP-1 [3-8], TULIP-2 [9-13] and MUSE [14-19], and used the meta-analysis of these studies for the benefit assessment. Furthermore, the company presented TULIP SLE LTE [20-24], the extension study of the studies TULIP-1 and TULIP-2, as supplementary information.

The company additionally presented an adjusted indirect comparison via the common comparator placebo + standard therapy for the assessment of the added benefit of anifrolumab versus belimumab as supplementary evidence.

The directly comparative data from the RCTs TULIP-1, TULIP-2, MUSE and TULIP SLE LTE presented by the company as well as the adjusted indirect comparison against belimumab are not suitable for deriving conclusions on the added benefit of anifrolumab in comparison with the ACT. In the following, the studies included by the company are described in more detail and reasons are given why the evidence presented by the company is not suitable for assessing the added benefit.

Evidence presented by the company for the direct comparison

Studies TULIP-1, TULIP-2 and MUSE

Information on study, intervention and patient characteristics of the studies TULIP-1, TULIP-2 and MUSE is presented in Table 10 to Table 12 in Appendix B of the full dossier assessment.

The studies TULIP-1, TULIP-2 and MUSE are multicentre, randomized, double-blind studies with treatment durations of 52 weeks comparing anifrolumab as an add-on therapy to standard therapy against placebo + standard therapy. The studies included adults with chronic, moderate to severe autoantibody-positive SLE on stable prior therapy consisting of at least one drug or a combination of antimalarials, immunosuppressants or OCS. Diagnosis of SLE was made based on the criteria by the ACR. According to the inclusion criteria, SLE disease activity at screening had to be ≥ 6 according to the SLEDAI-2K score and ≥ 4 according to the clinical SLEDAI-2K score. A BILAG 2004 A assessment in ≥ 1 organ system or a BILAG 2004 B assessment in ≥ 2 organ systems as well as a PGA ≥ 1 were additionally required at screening.

In the TULIP-1 study, a total of 457 patients were randomly allocated in a 1:2:2 ratio to treatment with 150 mg anifrolumab (N = 93), 300 mg anifrolumab (N = 180) or placebo

(N = 184). The 150 mg anifrolumab arm is not considered further in the following, as it is not an approved dosage of anifrolumab. In the TULIP-2 study, a total of 365 patients were randomly allocated in a 1:1 ratio to treatment with 300 mg anifrolumab (N = 181) or placebo (N = 184). In the MUSE study, 307 patients were randomly allocated in a 1:1:1 ratio to treatment with 1000 mg anifrolumab (N = 104), 300 mg anifrolumab (N = 100) or placebo (N = 103). The 1000 mg anifrolumab arm is not considered further in the following, as it is not an approved dosage of anifrolumab. Randomization was stratified for all studies by SLEDAI-2K score at screening (< 10 points versus ≥ 10 points), OCS dose at week 0 (< 10 mg/day versus ≥ 10 mg/day prednisone or equivalent) and type I interferon gene signature test result at screening (high versus low).

The use of anifrolumab was in compliance with the information in the Summary of Product Characteristics [25] and thus the company considered the approved dosage of 300 mg anifrolumab. The standard therapy administered in the studies also included drugs that are not approved for the treatment of SLE in Germany (e.g. methotrexate, calcineurin inhibitor or mycophenolate mofetil/mycophenolic acid). To account for this, the company used a subpopulation for the assessment of the added benefit who received a concomitant drug approved in Germany (referred to by the company as "intention to treat [ITT] population, only drugs approved in Germany"). The company presented the results of the total population (= ITT population) as supplementary information. The exact number of patients in the subpopulation in the respective studies who received concomitant medication approved in Germany can be found in Table 10 in Appendix B of the full dossier assessment. Due to the restrictive requirements for the administration of the standard therapy, the ACT was not adequately implemented in the 3 studies. This is described in more detail in the section below "Appropriate comparator therapy not implemented in the studies TULIP-1, TULIP-2 and MUSE".

The primary outcome of the TULIP-1 study was the composite outcome of Systemic Lupus Erythematosus Responder Index (SRI(4)) at week 52 or, for the MUSE study, at day 169 (equivalent to week 24). Following the analysis of the TULIP-1 study, in the TULIP-2 study, with Amendment 5 to the study protocol (23 May 2019), the original primary outcome of response in the SRI(4) was replaced with response of the BILAG-based Composite Lupus Assessment (BICLA) at week 52. Secondary outcomes were mortality, outcomes of the morbidity and health-related quality of life categories, and adverse events (AEs).

Having completed the 52-week treatment phase, patients in the studies TULIP-1 and TULIP-2 could switch to the TULIP SLE LTE extension study. Patients who had completed the MUSE study could also switch to a single-arm open-label extension study (study 1145).

Appropriate comparator therapy not implemented in the studies TULIP-1, TULIP-2 and MUSE

Requirements for standard therapy

Patients had to already be receiving stable standard therapy prior to study inclusion in order to be included in the studies TULIP-1, TULIP-2 or MUSE. This standard therapy could consist of

one or a combination of the following drugs: antimalarials, immunosuppressants, OCS. Furthermore, a maximum of one NSAID at a stable dose was allowed.

The dose of antimalarials and immunosuppressants was to be kept stable for at least 8 weeks before study inclusion, and then the stable dose had to be maintained until week 52. In the MUSE study, the dose had to remain stable until day 169, after which a dose increase was allowed under certain circumstances (see Table 11 of the full dossier assessment). All studies allowed dose reduction only due to toxicity or AEs, and, on recovery, dose increase to the starting dose.

Another component of standard therapy were OCS, the dosage of which had to be stable at least during the 2 weeks before randomization. In the course of the study, the starting dose was only allowed to be exceeded for burst therapy. In the studies TULIP-1 and TULIP-2, one burst for SLE or another condition (e.g., asthma or COPD exacerbation) was allowed in the first 12 weeks after randomization; after 14 days, the OCS dose of the burst therapy had to be returned to the level of the starting dose. From week 12 to week 40, only one burst was allowed for other diseases, but not for SLE. No further increase in OCS dose was allowed after week 40. In addition, all patients receiving an OCS dose ≥ 10 mg/day at the time of randomization had to attempt to reduce the OCS dose to ≤ 7.5 mg/day from week 8 to week 40. The MUSE study, in comparison, allowed one burst for SLE or other conditions from day 1 to 71 and one burst from day 169 to 281. After assessment of disease activity, the MUSE study also encouraged the attempt to reduce the OCS dose to ≤ 10 mg/day.

Furthermore, NSAIDs could be administered in the 3 studies. However, the use of a prescription NSAID was only allowed at a stable dose from screening until week 52, and no other NSAID was allowed at the same time. The dose was only allowed to be reduced for reasons of toxicity. Non-prescription NSAIDs for the treatment of pain were allowed to be taken at the approved dose for up to 1 week. In patients with previous infusion-related reactions, premedication with an antihistamine or paracetamol was allowed.

Administration of biologics, and thus also of belimumab, was explicitly disallowed in all 3 studies.

In the studies TULIP-1 and TULIP-2, adjustments to standard therapy beyond the protocol requirements were explicitly discouraged. Using disallowed medications (e.g. belimumab) or exceeding the maximum allowed dosage of immunosuppressants or corticosteroids either led to the immediate discontinuation of the study medication (anifrolumab or placebo) or required clarification with the monitor about the further procedure. However, patients were to be encouraged to remain in the study despite discontinuation of the study medication, and data recording was to be continued. In the MUSE study, the use of medications that were not permitted or restricted (e.g. belimumab) led to discontinuation of the study medication. After discontinuation of the study medication, further data recordings only took place at 2 follow-up visits, at which mainly data on side effects were recorded for these patients. In all 3 studies,

changes in standard therapy could ultimately lead to the affected patients being included in the analyses as patients with treatment failure (non-responders).

Standard therapy is not an implementation of the appropriate comparator therapy

From the specifications for standard therapy described in the previous section, it is clear that the possible or permitted adjustments during the studies were very limited in each case and the strict specifications in the protocol did not ensure the implementation of individualized therapy. Belimumab in particular was not available to the patients as a possible treatment option in the studies. However, the G-BA explicitly cited belimumab as a treatment option of individualized therapy in the ACT, noting that belimumab should be used if conventional therapy (hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine) fails. Belimumab is indicated as add-on therapy in patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive test for autoantibodies with specificity for double-stranded DNA [anti-dsDNA antibodies] and low complement) despite standard therapy [26]. Based on the baseline patient characteristics in the studies TULIP-1, TULIP-2 and MUSE, it can be assumed that belimumab would have been an option for a relevant proportion of patients (e.g. in the TULIP-1 study: positive anti-dsDNA level at 44%, abnormal complement C3 level at 37%, abnormal complement C4 level at 23% in the comparator arm; see Table 12 in Appendix B of the full dossier assessment for information on TULIP-2 and MUSE). During the course of the study, there is too little information on disease activity to be able to assess how many patients would have been eligible for belimumab.

As a result of the strict requirements in the study protocol and the severely limited possibilities to adjust standard therapy, as well as of the exclusion of belimumab in particular, the ACT is assessed as overall not adequately implemented in the studies because standard therapy could not be adjusted to the individual patient.

Adjustments to standard therapy partly rated as treatment failure or unfavourable event

In addition, adjustments to standard therapy were partly considered as treatment failure or unfavourable event. This is explained below.

Patients with treatment optimization outside the specified medication range were rated as patients with treatment failure for all binary efficacy outcomes planned in the study. It is not clear from the dossier how the patients were dealt with in the analyses of binary outcomes carried out post hoc for Module 4 A. This type of analysis is not appropriate. The ACT provides for individualized therapy using different drugs. This may require 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 optimized treatment beyond the range of medication described in the study protocol, the affected patients were included in the analyses as patients with treatment failure. An adjustment to standard therapy in the sense 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 it can be assumed that, due to the lack of additional therapies (as given in the intervention arm by the additional administration of anifrolumab), the patients in the comparator arm needed optimization of their ongoing therapy outside the range of medication described in the study protocol more frequently than in the intervention 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 intervention 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 of the studies TULIP-1 and TULIP-2. In this population of the 2 studies, the proportion differed between the study arms by about 17% versus 25% (anifrolumab arm versus comparator arm). Data for the subpopulation of patients treated with drugs approved in Germany are not available. No information at all is available for the MUSE study.

Overall, the studies TULIP-1, TULIP-2 and MUSE are not suitable for drawing a conclusion on the added benefit of anifrolumab in comparison with the ACT due to the inadequate implementation of the ACT. Moreover, the results presented by the company on patient-relevant outcomes cannot be meaningfully interpreted due to the inappropriate analysis in which patients with treatment adjustment were considered as patients with treatment failure.

Additional evidence provided by the company for the direct comparison – extension study TULIP SLE LTE

Information on study and intervention characteristics of the TULIP SLE LTE study is presented in Table 10 and Table 11 in Appendix B of the full dossier assessment.

The TULIP SLE LTE study is a multicentre, randomized, double-blind study to assess the long-term tolerability of anifrolumab (300 mg) as an add-on therapy to standard therapy in comparison with placebo + standard therapy. Patients who completed participation in the 52-week TULIP-1 or TULIP-2 study were eligible to participate in the TULIP SLE LTE extension study for a treatment duration of 156 weeks, regardless of their SLE disease severity at the time of transition to this study.

In the TULIP SLE LTE study, a total of 556 patients were randomly allocated in a ratio of about 4:1 to treatment with 300 mg anifrolumab (N = 443) or placebo (N = 113). Patients who had received 150 mg or 300 mg of anifrolumab in the predecessor studies TULIP-1 or TULIP-2 received blinded 300 mg of anifrolumab in the TULIP SLE LTE study. Patients who had received placebo in the studies TULIP-1 or TULIP-2 were re-randomized in a 1:1 ratio to 300 mg anifrolumab or placebo. The primary outcome of the study were AEs (including mortality). For this study, the company also presented results for the subpopulation of patients

treated with drugs approved in Germany (ITT population, only drugs approved in Germany) and additionally presented results for the ITT population. According to information provided in Module 4 A, the final analysis of the study was not yet available at the time of dossier preparation; therefore the company presented data from an interim analysis (19 March 2020).

Analyses of the TULIP SLE LTE study presented as supplementary information are not suitable

For the TULIP SLE LTE study, the company presented analyses for the following 2 treatment arms: 300 mg anifrolumab (patients who had been randomized to the 300 mg anifrolumab arms in the 2 predecessor studies, TULIP-1 and TULIP-2, and continued to receive 300 mg anifrolumab in the TULIP SLE LTE study) and placebo (patients who had been randomized to the placebo arms in the 2 predecessor studies, TULIP-1 and TULIP-2, and were re-randomized to placebo in the TULIP SLE LTE study, as well as patients who had been randomized to the placebo arms in the 2 predecessor studies, TULIP-1 and TULIP-2, until the time of re-randomization to 300 mg anifrolumab). The company thus included the data from the studies TULIP-1 and TULIP-2 in the analyses of the TULIP SLE LTE study. However, as described above, the standard therapy administered in the studies TULIP-1 and TULIP-2 does not represent an adequate implementation of the ACT due to the severe limitations (see above), making the approach of including the data from these studies inappropriate. Furthermore, the baseline patient characteristics listed by the company refer to the time of randomization in the predecessor studies TULIP-1 and TULIP-2 and not to the time of entry into the TULIP SLE LTE study. It is therefore not possible to assess the disease activity of the patients at the transition to the extension study. Although the company provided information on AEs and serious AEs (SAEs) in Appendix 4 G of the dossier, broken down by the individual therapy sequences represented in the TULIP SLE LTE study without including the predecessor studies TULIP-1 and TULIP-2, data on the other outcomes recorded are missing for the individual therapy sequences represented. Thus, the analyses presented are not suitable for assessing the added benefit of anifrolumab.

Furthermore, it is questionable whether the ACT was adequately implemented in the TULIP SLE LTE study. Compared with the predecessor studies TULIP-1 and TULIP-2, the specifications for standard therapy were less restricted (see Table 11 of the full dossier assessment), but the use of belimumab was still not permitted and led to immediate discontinuation of the study medication. The implementation of the adjustments to the standard therapy allowed in the study protocol was at the discretion of the investigator. In particular, it was allowed to adjust drug doses or add new drugs. In addition, the use of corticosteroids as burst therapy was possible once in the first 12 weeks and then every 6 months.

However, due to missing patient characteristics (e.g. anti-dsDNA antibodies, complement C3 or C4, SLEDAI-2K) at baseline and missing data on disease activity during the study, it is not possible to assess whether belimumab would have been suitable for only a negligible proportion of patients in the TULIP SLE LTE study.

Overall, due to the inappropriate consideration of the predecessor studies TULIP-1 and TULIP-2 and the missing information on patient characteristics at the start of the TULIP SLE LTE study, the analyses of the evidence presented by the company as supplementary information for the direct comparison are not suitable for drawing a conclusion on the added benefit of anifrolumab.

Indirect comparison presented by the company as supplementary evidence is not suitable for the benefit assessment

Since, according to the company in Module 4 A, in the actual health care setting, belimumab can also be used on a patient-specific basis in patients with high disease activity, an adjusted indirect comparison between anifrolumab and belimumab, in each case as an add-on therapy to standard therapy, supplements the data basis presented in the dossier, according to the company. For the adjusted indirect comparison, the company used the 3 studies of anifrolumab described above (TULIP-1, TULIP-2 and MUSE) as well as 2 studies of belimumab (BLISS-52 and BLISS-76). Figure 1 is a schematic representation of the adjusted indirect comparison presented by the company as supplementary information.

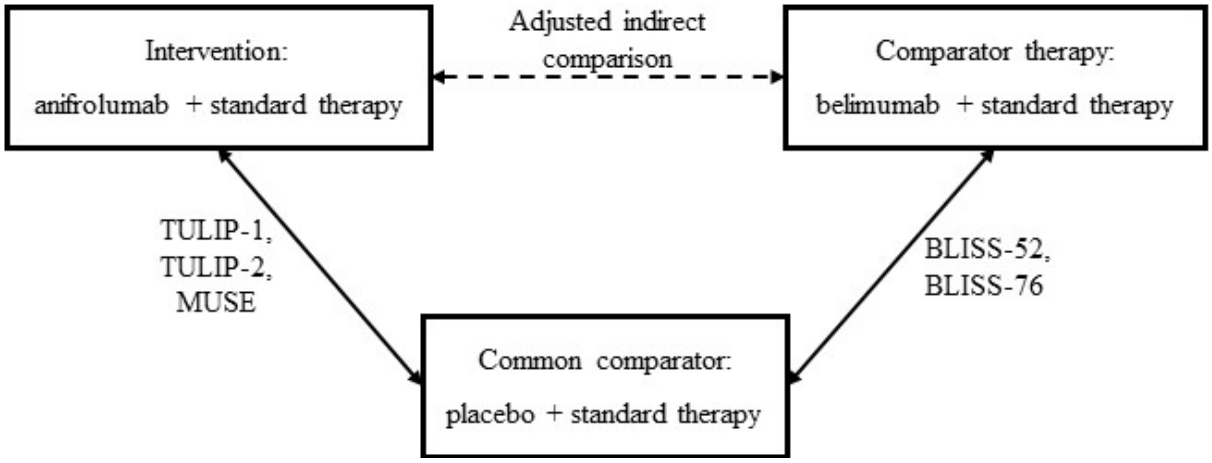

Figure 1: Study pool of the company for the adjusted indirect comparison between anifrolumab + standard therapy and belimumab + standard therapy using placebo + standard therapy as common comparator

The 2 studies included by the company on the belimumab side of the adjusted indirect comparison, BLISS-52 and BLISS-76, included patients with an SLE diagnosis according to the ACR criteria and clinically active (Safety of Estrogens in Lupus Erythematosus – National Assessment [SELENA] SLEDAI score of ≥ 6 at screening), autoantibody-positive disease (antinuclear antibody titre of ≥ 1:80 and/or anti-dsDNA ≥ 30 IU/mL at 2 time points prior to randomization). In addition, patients were to be on a stable medication for 30 days prior to randomization. From the BLISS studies, the company used a subpopulation of patients with high disease activity, defined as anti-dsDNA-positive and low complement (C3 or C4) at baseline, who were treated with drugs approved in Germany, for the assessment. In the dossier,

it referred to this subpopulation of the BLISS studies as “active SLE with medication approved in Germany”; it corresponds to the subpopulation that was used by the G-BA in the previous benefit assessment procedure for belimumab to assess the added benefit [27].

As described above, the anifrolumab studies also included patients on stable prior therapy with autoantibody-positive SLE disease, characterized by SLEDAI-2K score of ≥ 6, at least 1 BILAG A or 2 BILAG B organ assessments and PGA ≥ 1. Despite comparable inclusion criteria of the belimumab and anifrolumab studies, the company restricted the population of the anifrolumab studies for the adjusted indirect comparison only with regard to treatment with drugs approved in Germany, but not with regard to disease activity, although the company itself described the therapeutic indication of anifrolumab as broader than that of belimumab. This is also reflected, for example, in the differences described by the company itself in Module 4 A between the proportions of patients with anti-dsDNA antibodies (approximately 48% versus 100% [anifrolumab versus belimumab studies]) and low complement (approximately 37% versus 100% [anifrolumab versus belimumab studies]). The company did not present a more detailed similarity test in the dossier, for example with regard to the similarity of the standard therapy or the handling of patients with adjustments to standard therapy in the analyses. The described procedure of the company, despite comparable inclusion criteria, to restrict the study population on the comparator side with regard to disease activity on the one hand and not to make any restrictions in this respect on the intervention side on the other hand, is not appropriate. The differences in patient characteristics described above show that this approach means that the populations considered are not sufficiently similar for an indirect comparison. A key prerequisite for an adjusted indirect comparison is, in particular, the consideration of a sufficiently similar patient population for which both therapies can be considered.

Furthermore, in its search for studies with belimumab, the company identified another study (LBSL02 [28]) on the comparator side, in addition to the studies BLISS-52 [29] and BLISS-76 [30]. However, the company did not consider the LBSL02 study further for the indirect comparison because, according to the company, it did not include any relevant data for the joint assessment with the studies BLISS-52 and BLISS-76 in the context of an indirect comparison of anifrolumab versus belimumab. The company stated that the LBSL02 study differed from the BLISS studies with regard to the included patient population, the basic medication and the definition of the primary outcomes. The dossier does not contain a comprehensible justification for the exclusion of this study, e.g. with regard to what exactly the differences in the patient population or the concomitant medication were. As described in the previous benefit assessment of belimumab [31], the LBSL02 study was basically rated as relevant to the assessment of the added benefit of belimumab. The G-BA also considered this study as supporting evidence in the assessment of the added benefit of belimumab [27]. The exclusion of study LBSL02 from the study pool of the indirect comparison is not appropriate without sufficient justification. Due to the exclusion of study LBSL02, the study pool of the adjusted indirect comparison is potentially incomplete on the side of belimumab. Furthermore, the completeness of the study pool on the comparator side was not systematically checked.

Overall, as a result of the different restrictions of the company regarding disease activity between the anifrolumab and belimumab study populations and the exclusion of the LBSL02 study on the belimumab side of the adjusted indirect comparison, the adjusted indirect comparison presented by the company is not used for the assessment.

Summary

The evidence presented by the company for the direct comparison, consisting of the 3 studies TULIP-1, TULIP-2 and MUSE, does not fulfil the criteria of an individualized therapy due to the very limited options for adjusting standard therapy and the exclusion of belimumab as a possible therapy option and therefore does not represent an adequate implementation of the ACT. Thus, the 3 studies are not suitable for drawing a conclusion on the added benefit of anifrolumab in comparison with the ACT. Moreover, the results presented on patient-relevant outcomes cannot be meaningfully interpreted due to the inappropriate analysis in which patients with treatment adjustment were considered as patients with treatment failure.

The evidence presented by the company as supplementary information for the direct comparison, the extension study TULIP SLE LTE, is not suitable for drawing a conclusion on the added benefit of anifrolumab due to the inappropriate consideration of the studies TULIP-1 and TULIP-2 in the analyses and the missing information on patient characteristics. Furthermore, it is questionable whether the ACT was sufficiently implemented.

The adjusted indirect comparison presented by the company as supplementary evidence is also not used for the present benefit assessment. On the one hand, the company restricted the patient population of the belimumab studies more than that of the anifrolumab studies with regard to disease activity. The differences in patient characteristics described above show that this approach means that the populations considered are not sufficiently similar for an indirect comparison. On the other hand, the company did not adequately justify the exclusion of the LBSL02 study on the comparator side.

2.4 Results on added benefit

No suitable data are available for the assessment of the added benefit of anifrolumab as an add-on therapy in comparison with the ACT for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy. This results in no hint of added benefit of anifrolumab in comparison with the ACT; an added benefit is therefore not proven.

2.5 Probability and extent of added benefit

Table 5 summarizes the result of the assessment of added benefit of anifrolumab in comparison with the ACT.

Table 5: Anifrolumab – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Add-on treatment in adults with moderate to severe active autoantibody-positive SLE despite standard therapy[b]	Individualized therapy taking into account the respective organ involvement, prior therapy and disease activity, choosing from the following drugs: hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine, belimumab[c]	Added benefit not proven
a. Presented is the ACT specified by the G-BA. b. In the therapeutic indication of SLE, patients with LN represent a separate patient population. LN is an organ manifestation (moderate to severe renal involvement) of SLE for which specific treatment recommendations exist in differentiation from other organ manifestations. The G-BA currently assumes that LN is not part of the requested therapeutic indication. c. Continuation of an inadequate therapy does not concur with the specified ACT. If conventional therapy (hydroxychloroquine, chloroquine, NSAIDs, glucocorticoids, azathioprine) failed, belimumab was to be used. G-BA: Federal Joint Committee; LN: lupus nephritis; NSAID: nonsteroidal anti-inflammatory drug; SLE: systemic lupus erythematosus		

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

The G-BA decides on the added benefit.

Supplementary note on the appropriate comparator therapy

On 8 June 2022, the G-BA changed the ACT after submission of the dossier. As a result of the change, belimumab is the sole ACT and replaces individualized therapy. The present benefit assessment was based on the originally specified ACT.

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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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