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Anifrolumab (systemic lupus erythematosus) –

Addendum to Commission A22-35 (dossier assessment)[1]

Addendum

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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
BILAG	British Isles Lupus Assessment Group
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
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
OR	odds ratio
PGA	physician's global assessment
RR	relative risk
SELENA	Safety of Estrogens in Lupus Erythematosus – National Assessment
SLE	systemic lupus erythematosus
SLEDAI	Systemic Lupus Erythematosus Disease Activity Index
SLEDAI-2K	Systemic Lupus Erythematosus Disease Activity Index – Revised Version
SPC	Summary of Product Characteristics
SRI	Systemic Lupus Erythematosus Responder Index

1 Background

On 9 August 2022, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A22-35 (Anifrolumab – Benefit assessment according to §35a Social Code Book V) [1].

After submission of the dossier, on 8 June 2022, the G-BA changed the appropriate comparator therapy (ACT). As a result of the change, belimumab is the sole ACT and replaces the previously specified individualized therapy that was used as the basis for the benefit assessment for Commission A22-35 [1].

In benefit assessment A22-35 [1], the added benefit of anifrolumab as an add-on therapy for the treatment of adults with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy, was assessed in comparison with the originally specified ACT. In its dossier [2], the pharmaceutical company (hereinafter referred to as "the company") had additionally presented the results of an adjusted indirect comparison of anifrolumab with belimumab, which were not used for the assessment (see benefit assessment A22-35 [1]).

In the commenting procedure [3], the company subsequently submitted analyses of 2 further adjusted indirect comparisons of anifrolumab with belimumab.

The G-BA commissioned IQWiG to check and assess the analyses submitted by the company in the commenting procedure, taking into account the information already provided in the dossier:

- anifrolumab, total population intention to treat (ITT) (meta-analysis of the studies TULIP-1, TULIP-2 and MUSE) vs.
  belimumab total population mITT (meta-analysis of the studies BLISS-52 and BLISS-76)
- anifrolumab, subpopulation (high disease activity [positive test for autoantibodies with specificity for double-stranded DNA [anti-dsDNA antibodies] and low complement]), drugs approved only in Germany (meta-analysis of the studies TULIP-1, TULIP-2 and MUSE) vs.
  belimumab, subpopulation (high disease activity [positive test for anti-dsDNA antibodies and low complement]), drugs approved only in Germany (meta-analysis of the studies BLISS-52 and BLISS-76)

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

2 Assessment

Research question

For the benefit assessment of anifrolumab as an add-on therapy in adults with moderate to severe, active autoantibody-positive SLE, despite standard therapy, the research question presented in Table 1 results from the G-BA's change of the ACT.

Table 1: 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]	Belimumab[c]

a. Presented is the ACT specified by the G-BA.
b. In the therapeutic indication of SLE, patients with lupus nephritis represent a separate patient population. Lupus nephritis is an organ manifestation (moderate to severe renal involvement) of SLE for which specific treatment recommendations exist in differentiation from other organ manifestations. In accordance with the G-BA, it is assumed that lupus nephritis is not part of the therapeutic indication.
c. It is assumed that, within the framework of a study, the possibility of individualized standard therapy, taking into account the respective organ involvement, prior therapy and disease activity, is implemented in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SLE: systemic lupus erythematosus

Studies submitted by the company for the indirect comparisons

Benefit assessment A22-35 [1] assessed the added benefit of anifrolumab in comparison with the previously specified ACT of individualized therapy. In its dossier [2], the company additionally presented the results of an adjusted indirect comparison of anifrolumab with belimumab using placebo + standard therapy as common comparator. In the commenting procedure [3], the company subsequently submitted analyses of 2 further adjusted indirect comparisons of anifrolumab with belimumab.

The total of 3 adjusted indirect comparisons include the same studies on the intervention and comparator sides and differ in the study populations used. The study pool of the company for the 3 adjusted indirect comparisons is presented in Figure 1.

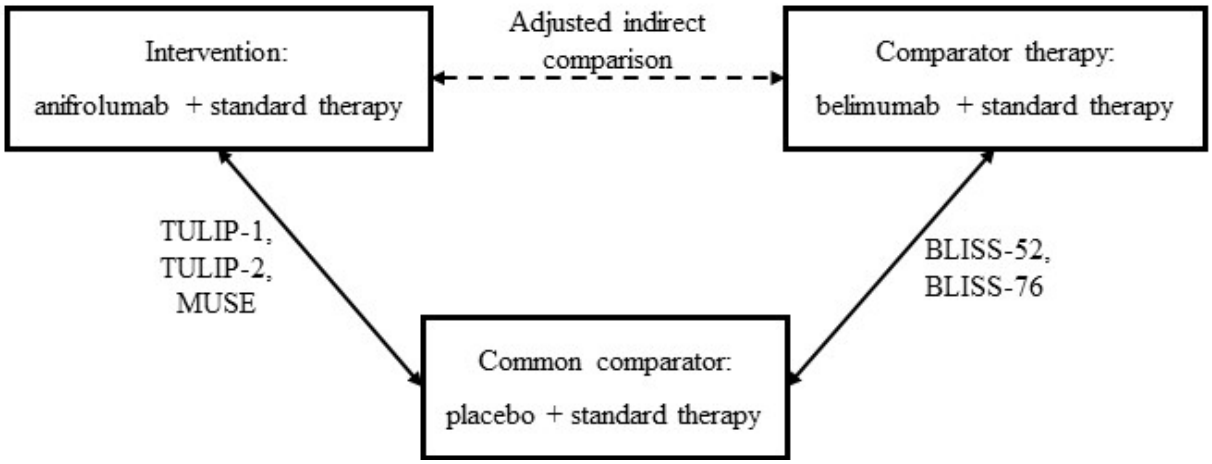

Figure 1: Study pool of the company for the adjusted indirect comparison between anifrolumab + standard therapy and belimumab + standard therapy using placebo + standard therapy as common comparator

Studies on anifrolumab: TULIP-1, TULIP-2 and MUSE

Information on study and intervention characteristics of the anifrolumab studies as well as the patient characteristics of the patient populations considered in the indirect comparisons of the studies TULIP-1, TULIP-2 and MUSE are shown in Table 4 to Table 7 in Appendix A. Dossier assessment A22-35 [1] provides a detailed characterization of the studies TULIP-1, TULIP-2 and MUSE, of the specifications regarding standard therapy and the handling of treatment adjustments.

Studies on the ACT (belimumab): BLISS-52 and BLISS-76

Information on study and intervention characteristics as well as the patient characteristics of the patient populations considered in the indirect comparisons of the studies BLISS-52 and BLISS-76 are presented in Table 4 to Table 7 in Appendix A. Both studies were already described in the benefit assessment procedure on belimumab, A12-05 [4,5], which the company referred to for the data presented.

The studies BLISS-52 and BLISS-76 are multicentre, randomized, double-blind studies with treatment durations of 52 weeks (BLISS-52) or 76 weeks (BLISS-76) comparing belimumab as an add-on therapy to standard therapy in patients diagnosed with SLE according to the American College of Rheumatology (ACR) criteria. Patients had to have clinically active (Safety of Estrogens in Lupus Erythematosus – National Assessment-Systemic Lupus Erythematosus Disease Activity Index [SELENA-SLEDAI] score ≥ 6 at screening), autoantibody-positive (antinuclear antibody titre of ≥ 1:80 and/or anti-dsDNA antibodies ≥ 30 IU/mL at 2 time points prior to randomization) disease. In addition, patients were to be on a stable medication for 30 days prior to randomization.

In the BLISS-52 study, a total of 865 patients were randomized in a 1:1:1 ratio to treatment with 1 mg/kg belimumab (N = 288), 10 mg/kg belimumab (N = 290) or placebo (N = 287). In the BLISS-76 study, a total of 819 patients were randomized in a 1:1:1 ratio to treatment with 1 mg/kg belimumab (N = 271), 10 mg/kg belimumab (N = 273) or placebo (N = 275). Randomization for all studies was stratified by SELENA-SLEDAI score at screening (6 to 9 versus ≥ 10), proteinuria level at screening (< 2 g/24 hours versus ≥ 2 g/24 hours equivalent) and family origin (African versus Native American versus other).

According to the Summary of Product Characteristics (SPC) [6] belimumab is only approved at a dose of 10 mg/kg. In the following, the respective belimumab arm with the 1 mg/kg dose is therefore not considered further for both studies. Treatment with belimumab (10 mg/kg) was administered intravenously on days 0, 14, 28 and then every 28 days until week 48 (BLISS-52) or until week 72 (BLISS-76).

Patients in both studies received standard therapy in addition to belimumab or placebo. This standard therapy also contained drugs that are not approved for the treatment of SLE in Germany.

A detailed description of the standard therapy and its possible adjustments in the studies BLISS-52 and BLISS-76 can be found in benefit assessment A12-05 [4].

The primary outcome of the studies is the SLE Responder Index (SRI) measured at week 52. Secondary outcomes were mortality, further outcomes of the morbidity and health-related quality of life categories, and adverse events (AEs).

Indirect comparisons performed by the company

The company presented a total of 3 adjusted indirect comparisons that include the same studies on the intervention and comparator sides, but differ in the respective study populations used. The populations considered by the company are shown in Table 2.

Table 2: Patient populations of the 3 adjusted indirect comparisons

Intervention side (anifrolumab) **Studies TULIP-1, TULIP-2 and MUSE**		**Comparator side (belimumab)** **Studies BLISS-52 and BLISS-76**
Indirect comparison 1		
Total population	vs.	Total population
Indirect comparison 2		
Subpopulation of patients who only received drugs approved in Germany	vs.	Subpopulation of patients who only received drugs approved in Germany and have high disease activity (anti-dsDNA antibody positive, low complement C3/C4)
Indirect comparison 3		
Subpopulation of patients who only received drugs approved in Germany and have high disease activity (anti-dsDNA antibody positive, low complement C3/C4)	vs.	Subpopulation of patients who only received drugs approved in Germany and have high disease activity (anti-dsDNA antibody positive, low complement C3/C4)
anti-dsDNA antibody: autoantibody with specificity for double-stranded DNA		

Indirect comparisons presented by the company unsuitable for the benefit assessment

The adjusted indirect comparison 1 is not suitable for deriving conclusions on the added benefit of anifrolumab in comparison with belimumab, as patients are also considered who are not covered by the approval (belimumab side). For the adjusted indirect comparisons 2 and 3, there is no sufficient similarity between the subpopulations considered, so that these are also not suitable for conclusions on the added benefit of anifrolumab. This is explained below.

Adjusted indirect comparison 1

For the adjusted indirect comparison 1, the company used the total populations of the studies with anifrolumab (meta-analysis of the studies TULIP-1, TULIP-2 and MUSE) and of the studies with belimumab (meta-analysis of the studies BLISS-52 and BLISS-76) (see Table 2). However, the total population of the belimumab studies BLISS-52 and BLISS-76 includes patients with an SLE diagnosis according to ACR criteria and the presence of 2 positive tests for antinuclear antibodies, and is therefore not limited to the patient population of the approved therapeutic indication of belimumab (i.e. to patients with active, autoantibody-positive SLE with a high degree of disease activity [e.g., positive test for anti-dsDNA antibodies and low complement], despite standard therapy [6]).

In addition, the standard therapy in all 5 studies of this indirect comparison also contains drugs that are not approved for the treatment of SLE in Germany.

In addition, the check of the information retrieval led to the result that, on the comparator side of the indirect comparison, taking into account the total population (no restrictions regarding concomitant medication approved in Germany as well as disease activity based on serologic markers), there are further studies (such as BLISS-NEA [7] and EMBRACE [8]) and the study pool is potentially incomplete.

Overall, the adjusted indirect comparison 1 is therefore not suitable for deriving conclusions on the added benefit.

Adjusted indirect comparisons 2 and 3

Similarity of the study characteristics in the indirect comparison

A prerequisite for conducting an indirect comparison is sufficient similarity of the study and patient characteristics. As each of the adjusted indirect comparisons presented includes the same studies on the intervention and comparator sides, the main study and intervention characteristics are compared first, followed by the patient characteristics of the (sub)populations considered in each of the 2 indirect comparisons.

Inclusion and exclusion criteria of the studies of the indirect comparisons

The inclusion and exclusion criteria of the studies with anifrolumab and with belimumab are largely comparable. There are differences in the use of SLEDAI – Revised Version (SLEDAI-2K) in the studies with anifrolumab and of the SELENA-SLEDAI in the studies with belimumab to assess disease activity. In addition, only the anifrolumab studies defined a physician's global assessment (PGA) score ≥ 1.0 and a British Isles Lupus Assessment Group (BILAG) 2004 A score in ≥ 1 organ system or a BILAG 2004 B score in ≥ 2 organ systems as inclusion criteria. The latter is also reflected in the patient characteristics of the included patients.

Specifications regarding standard therapy in the anifrolumab and belimumab studies

Detailed information on the intervention characteristics of all studies can be found in Table 5 in Appendix A. Prior to study inclusion, patients on both sides of the indirect comparison had to receive stable standard therapy, which had to be stable for ≥ 8 weeks in the anifrolumab studies and, in contrast, for ≥ 30 days in the belimumab studies.

The specifications regarding standard therapy were notably more restrictive in the anifrolumab studies than in the belimumab studies.

For example, in the anifrolumab studies, the use of antimalarials or immunosuppressants was only possible in stable doses, and dose adjustments were not allowed, or, in the MUSE study, only possible from day 169 and only under certain circumstances. In the belimumab studies, in contrast, new antimalarials could be started or the dose of the existing medication could be increased until week 16. The dose of immunosuppressants already administered at the beginning of the study could also be increased until week 16. In addition, the belimumab studies partly allowed higher doses of immunosuppressants (for example, azathioprine ≤ 300 mg/day in belimumab studies versus ≤ 200 mg/day in anifrolumab studies).

In the anifrolumab studies, one corticosteroid burst was allowed until week 12 if disease activity increased. From week 12, no dose increases due to SLE were allowed. At the same time, all patients in the studies TULIP-1 and TULIP-2 (anifrolumab) receiving an oral corticosteroid (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 (anifrolumab) also encouraged the attempt to reduce the OCS dose to ≤ 10 mg/day after assessment of disease activity. In addition, only one prescription nonsteroidal anti-inflammatory drug (NSAID) in stable dosage was allowed.

In contrast, the belimumab studies allowed dose adjustments of corticosteroids for the treatment of SLE disease activity until week 24; from week 24, the maximum permitted dose was allowed to be 25% or 5 mg higher than the dose at baseline. The OCS dose was only reduced if disease activity improved for ≥ 8 weeks and was at the discretion of the investigator with the aim of achieving a dose of ≤ 7.5 mg/day or less after week 24. Treatment with new NSAIDs was allowed until week 44, then only for a period of less than 7 days.

In addition, there were 2 other drug groups with restricted use in the belimumab studies: angiotensin pathway antihypertensives (angiotensin converting enzyme inhibitors, angiotensin receptor blockers) and 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). No new antihypertensive (angiotensin pathway) was allowed from week 16 and no new HMG-CoA reductase inhibitor from week 24.

On both sides of the indirect comparison, adjustments in standard therapy beyond the range of medication allowed in the study protocol were considered as a treatment failure or unfavourable event.

Similarity of the patient populations in the adjusted indirect comparisons

In general, it should be noted that different versions of the SLEDAI and the BILAG were used in the anifrolumab and belimumab studies.

The anifrolumab studies used the SLEDAI-2K, and the belimumab studies used the SELENA-SLEDAI. For example, differences consist in the fact that SELENA-SLEDAI includes the additional criteria of scleritis or episcleritis and vertigo due to lupus, and in the fact that hypertension and seizure due to past irreversible central nervous system damage are defined as exclusion criteria. Furthermore, in contrast to the SLEDAI-2K, the SELENA-SLEDAI also takes into account the new onset of proteinuria [9].

The anifrolumab studies used the BILAG 2004, which includes 9 organ domains (constitutional, mucocutaneous, neuropsychiatric, musculoskeletal, cardiorespiratory, gastrointestinal, ophthalmic, renal and haematology). The belimumab studies used the classic BILAG with 8 organ domains. In contrast to the classic BILAG, the BILAG 2004 additionally includes the gastrointestinal and ophthalmic organ domains and no longer includes the organ domain of vasculitis. According to one publication, the BILAG 2004 reflects disease activity change more sensitively and reports less false-positive disease activity [9].

Adjusted indirect comparison 2

The company presented the adjusted indirect comparison 2 in its dossier. On both sides of this comparison, the company used a subpopulation of the respective studies, whose standard medication exclusively contained drugs approved in Germany. Analogous to the therapeutic indication of belimumab, the company also restricted the subpopulation on the belimumab side to a patient population with high disease activity (based on the serologic markers anti-dsDNA antibody positive and low complement C3/C4). On the intervention side (anifrolumab), the company did not make such a restriction of the study population (see Table 2).

This is reflected in differences in patient characteristics between the anifrolumab and belimumab subpopulations (see Table 6 in Appendix A). The differences in serologic markers probably result from the restriction to the subpopulation with high disease activity on the belimumab side. An important difference can be seen in the proportion of patients with one BILAG A or 2 BILAG B assessments. While 94% of patients in the anifrolumab studies had one BILAG A or 2 BILAG B assessments, the proportion in the belimumab studies was only 56%. However, it cannot be assumed that the different BILAG versions alone account for the differences in patient characteristics. Overall, patients in the anifrolumab studies had mainly organ manifestations, whereas patients in the belimumab studies were rather characterized by serologically active disease.

In addition, there were differences in disease duration and family origin of the patients, characteristics whose importance were also pointed out by the German Society for Rheumatology in its comments on the benefit assessment of anifrolumab [10].

The number of differences, in addition to the previously described differences in study characteristics, means that sufficient similarity is not given. This comparison is therefore not suitable for deriving conclusions on the added benefit.

Adjusted indirect comparison 3

For both sides of the adjusted indirect comparison 3, the company (as in the adjusted indirect comparison 2) used a subpopulation of the respective studies whose standard medication exclusively contained drugs approved in Germany. In addition, the company restricted the subpopulation on both sides of the indirect comparison to a patient population with high disease activity based on serologic markers (anti-dsDNA antibody positive and low complement C3/C4). However, as a result of this adjustment made equally on both sides of the indirect comparison, the subpopulations show further differences in patient characteristics compared with the adjusted indirect comparison 2 (see Table 7 in Appendix A). The previously described differences in BILAG and family origin remain analogous to the indirect comparison 2, but differences in disease duration are even greater than in the adjusted indirect comparison 2. In addition, the restriction based on serologic markers produced further differences in the SLEDAI and PGA scores. It cannot be estimated what influence the different versions of the SLEDAI have on this difference.

It should also be noted that the adjusted indirect comparison 3 could only answer a subquestion for the benefit assessment of anifrolumab, as the patient population considered on the anifrolumab side comprises a subpopulation of the approved therapeutic indication of anifrolumab.

Overall, the number of differences, in addition to the previously described differences in study characteristics (analogous to the adjusted indirect comparison 2), means that sufficient similarity is not given. This comparison is not suitable for deriving conclusions on the added benefit.

Summary assessment of the suitability of the 3 adjusted indirect comparisons presented

In summary, the adjusted indirect comparison 1 is not suitable for deriving conclusions on the added benefit of anifrolumab, in particular due to the lack of restriction to the approved therapeutic indication of belimumab on the comparator side and due to the incomplete study pool. For the reasons mentioned above, no supplementary presentation of the results of this comparison is provided.

The subpopulations of the studies considered in the adjusted indirect comparisons 2 and 3 are not sufficiently similar with regard to the study characteristics and in particular with regard to the patient characteristics to derive conclusions on the added benefit of anifrolumab on the basis of these comparisons (see Table 6 and Table 7).

Irrespective of the lack of suitability of the data provided by the company, the results for the adjusted indirect comparison 2 (Table 9 and Table 10) and comparison 3 (Table 11 and Table 12) are presented in Appendix B. Table 8 shows an overview with relevant outcomes in the included studies. Since no consistency check is possible, the certainty of results is considered low, regardless of the certainty of results at the individual study level. Therefore, the risk of bias is not assessed (as it is not decisive for the derivation of the evidence base).

For the reporting of results in Appendix B, it should be noted that the company provided no comparative presentation of the operationalizations of the outcomes and no presentation of the results at individual study level in all 3 indirect comparisons. The preparation of the 3 adjusted indirect comparisons by the company is therefore incomplete. In addition, for the indirect comparison, the company only presented analyses based on the odds ratio (OR, effect estimate and 95% confidence interval) for the binary outcomes it used. Based on the IQWiG methods, the extent cannot be determined on the basis of the OR presented [11]. The company did not conduct adjusted indirect comparisons using the relative risk (RR).

2.1 Summary

After submission of the dossier, on 8 June 2022, the G-BA changed the ACT. As a result of the change, belimumab is the sole ACT and replaces the previously specified individualized therapy that was used as the basis for the benefit assessment for Commission A22-35 [1].

Due to the G-BA's specification of belimumab as new ACT, the data subsequently submitted by the company in the commenting procedure were checked and assessed in accordance with the commission by the G-BA, taking into account the data already available in the dossier. All 3 adjusted indirect comparisons presented by the company are unsuitable for drawing conclusions on the added benefit of anifrolumab in comparison with the ACT belimumab.

The following Table 3 shows the result of the benefit assessment of anifrolumab under consideration of dossier assessment A22-35 and the present addendum.

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]	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 lupus nephritis represent a separate patient population. Lupus nephritis 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 lupus nephritis is not part of the requested therapeutic indication.
c. It is assumed that, within the framework of a study, the possibility of individualized standard therapy, taking into account the respective organ involvement, prior therapy and disease activity, is implemented in both study arms.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; SLE: systemic lupus erythematosus

The G-BA decides on the added benefit.

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Appendix A **– Characteristics of the studies and patient populations included by the company**

Table 4: Characteristics of the studies included by the company – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Anifrolumab + standard therapy vs. placebo + standard therapy						
TULIP-1	RCT, double-blind, parallel	Adults (18–70 years) with chronic, moderate to severe autoantibody-positive SLE (≥ 4 of 11 ACR criteria met) under stable prior therapy, and, at screening: ▪ SLEDAI-2K score[b] ≥ 6 ▪ "clinical" SLEDAI-2K score[b] ≥ 4 (also on day 1) ▪ BILAG-2004 A assessment in ≥ 1 organ system or BILAG-2004 B assessment in ≥ 2 organ systems ▪ PGA ≥ 1.0	Anifrolumab 150 mg + standard therapy (N = 93)[c] anifrolumab 300 mg + standard therapy (N = 180) placebo + standard therapy (N = 184) Of which subpopulation with concomitant medication approved in Germany: anifrolumab 300 mg + standard therapy (n = 127) placebo + standard therapy (n = 125) Of which subpopulation with concomitant medication approved in Germany and high disease activity[d]: anifrolumab 300 mg + standard therapy (n = 35) placebo + standard therapy (n = 35)	Screening: up to 30 days Treatment: 52 weeks Observation: 8 weeks[e]	123 centres in: Argentina, Australia, Brazil, Chile, Colombia, Germany, Hungary, Israel, Italy, New Zealand, Peru, Poland, Romania, South Korea, Taiwan, Ukraine, United Kingdom, USA 6/2015–7/2018	Primary: SRI response rate at week 52 Secondary: mortality, morbidity, health-related quality of life, AEs

Table 4: Characteristics of the studies included by the company – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
TULIP-2	RCT, double-blind, parallel	Adults (18–70 years) with chronic, moderate to severe autoantibody-positive SLE (≥ 4 of 11 ACR criteria met) under stable prior therapy, and, at screening: ▪ SLEDAI-2K score[b] ≥ 6 ▪ "clinical" SLEDAI-2K score[b] ≥ 4 (also on day 1) ▪ BILAG-2004 A assessment in ≥ 1 organ system or BILAG-2004 B assessment in ≥ 2 organ systems ▪ PGA ≥ 1.0	Anifrolumab + standard therapy (N = 181) placebo + standard therapy (N = 184) Of which subpopulation with concomitant medication approved in Germany: anifrolumab 300 mg + standard therapy (n = 119) placebo + standard therapy (n = 121) Of which subpopulation with concomitant medication approved in Germany and high disease activity[d]: anifrolumab 300 mg + standard therapy (n = 34) placebo + standard therapy (n = 31)	Screening: up to 30 days Treatment: 52 weeks Observation: 8 weeks[e]	119 centres in: Argentina, Belgium, Brazil, Bulgaria, Canada, France, Germany, Japan, Lithuania, Mexico, Russia, South Africa, South Korea, Spain, USA 7/2015–12/2018	Primary: BICLA response rate at week 52[f] Secondary: mortality, morbidity, health-related quality of life, AEs

Table 4: Characteristics of the studies included by the company – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
MUSE	RCT, double-blind, parallel	Adults (18–65 years) with chronic, moderate to severe active SLE (≥ 4 of 11 ACR criteria met) under stable prior therapy, and, at screening: ▪ SLEDAI-2K score[b] ≥ 6 ▪ "clinical" SLEDAI-2K score[b] ≥ 4 (also on day 1) ▪ BILAG-2004 A assessment in ≥ 1 organ system or BILAG-2004 B assessment in ≥ 2 organ systems ▪ PGA ≥ 1.0	Anifrolumab 300 mg + standard therapy (N = 100) anifrolumab 1000 mg + standard therapy (N = 104)[c] placebo + standard therapy (N = 103) Of which subpopulation with concomitant medication approved in Germany: anifrolumab 300 mg + standard therapy (n = 69) placebo + standard therapy (n = 75) Of which subpopulation with concomitant medication approved in Germany and high disease activity[d]: anifrolumab 300 mg + standard therapy (n = 15) placebo + standard therapy (n = 23)	Screening: up to 4 weeks Treatment: 52 weeks Observation: 8 weeks[e]	73 centres in: Brazil, Bulgaria, Colombia, Czech Republic, Hungary, India, Mexico, Peru, Poland, Romania, South Korea, Taiwan, Ukraine, USA 1/2012–4/2015	Primary: SRI response rate at week 24 Secondary: mortality, morbidity, health-related quality of life, AEs

Table 4: Characteristics of the studies included by the company – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
Belimumab + standard therapy vs. placebo + standard therapy						
BLISS-52	RCT, double-blind, parallel	Adults (≥ 18 years) with SLE diagnosis according to ACR criteria and ▪ SELENA-SLEDAI score ≥ 6 at screening ▪ positive ANA or anti-dsDNA antibody test results from 2 independent time points, at least one of which within the screening phase ▪ stable basic therapy ≥ 30 days before randomization	Belimumab 1 mg/kg BW + standard therapy (N = 288)[c] belimumab 10 mg/kg BW + standard therapy (N = 290) placebo + standard therapy (N = 287) Of which subpopulation with concomitant medication approved in Germany and high disease activity[d]: belimumab 10 mg/kg + standard therapy (n = 144) placebo + standard therapy (n = 126)	Screening: 35 days Treatment: 52 weeks Observation: 4 weeks[e]	92 centres in: Argentina, Australia, Brazil, Chile, Colombia, Hong Kong, India, Peru, Philippines, Romania, Russia, South Korea, Taiwan 5/2007–3/2010	Primary: SRI response rate at week 52 Secondary: mortality, morbidity, health-related quality of life, AEs
BLISS-76	RCT, double-blind, parallel	Adults (≥ 18 years) with SLE diagnosis according to ACR criteria and ▪ SELENA-SLEDAI score ≥ 6 at screening ▪ positive ANA or anti-dsDNA antibody test results from 2 independent time points, at least one of which within the screening phase ▪ stable basic therapy ≥ 30 days before randomization	Belimumab 1 mg/kg BW + standard therapy (N = 271)[c] belimumab 10 mg/kg BW + standard therapy (N = 273) placebo + standard therapy (N = 275) Of which subpopulation with concomitant medication approved in Germany and high disease activity[d]: belimumab 10 mg/kg + standard therapy (n = 88) placebo + standard therapy (n = 77)	Screening: 35 days Treatment: 76 weeks Observation: 4 weeks[e]	146 centres in: Austria, Belgium, Canada, Costa Rica, Czech Republic, France, Germany, Israel, Italy, Mexico, Netherlands, Poland, Puerto Rico, Romania, Slovakia, Spain, Sweden, United Kingdom, USA 2/2007–3/2010	Primary: SRI response rate at week 52 Secondary: mortality, morbidity, health-related quality of life, AEs

Table 4: Characteristics of the studies included by the company – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Study design	Population	Interventions (number of randomized patients)	Study duration	Location and period of study	Primary outcome; secondary outcomes[a]
a. Primary outcomes include information without consideration of the relevance for this benefit assessment. Secondary outcomes comprise exclusively data based on the information provided by the company's Module 4 A. b. The SLEDAI-2K includes points of the clinical components of arthritis, myositis, rash, alopecia, mucosal ulcers, pleurisy, pericarditis or vasculitis, and excludes points attributable to fever, lupus headache and psycho-organic syndrome. The clinical SLEDAI-2K score is without the inclusion of points attributable to any urine or laboratory results including immunologic measures. c. The arm is not relevant for the assessment and is not presented in the following tables. d. High disease activity is defined here by the presence of anti-dsDNA antibodies and low C3 or C4 level. e. Or participation in a long-term extension study directly after week 52 (in the BLISS-52 study) or week 76 (in the BLISS-76 study). f. Until amendment 5 (23 May 2019), the primary outcome was SRI at week 52. ACR: American College of Rheumatology; AE: adverse event; BICLA: BILAG-based Composite Lupus Assessment; BILAG: British Isles Lupus Assessment Group; BW: body weight; dsDNA: double-stranded deoxyribonucleic acid; n: subpopulation; N: number of randomized patients; PGA: physician's global assessment; RCT: randomized controlled trial; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index – Revised Version; SRI: SLE Responder Index					

Table 5: Characteristics of the intervention – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Intervention or comparison	Common comparator
Anifrolumab + standard therapy vs. placebo + standard therapy		
TULIP-1/ TULIP-2/ MUSE	See A22-35 [1]	
Belimumab + standard therapy vs. placebo + standard therapy		
BLISS-52	Belimumab 10 mg/kg BW on days 0, 14, 28, then every 4 weeks, IV + standard therapy[a]	Placebo on days 0, 14, 28, then every 4 weeks, IV + standard therapy[a]
	Pretreatment Required (at least one preparation, at a stable dose ≥ 30 days before randomization): ▪ corticosteroids – prednisone or equivalent ▫ as the only SLE treatment: ≥ 7.5 and ≤ 40 mg/day ▫ in combination with other drugs: ≤ 40 mg/day ▪ antimalarials or immunosuppressants or NSAIDs Not allowed ▪ B-cell targeted therapy (e.g. rituximab, other anti-CD20, anti-CD22 or anti-CD52 agents, or belimumab) ▪ abatacept or a biologic investigational agent other than B-cell targeted therapy, each within 1 year before randomization ▪ ≥ 3 courses of systemic corticosteroids for concomitant conditions (e.g. asthma or atopic dermatitis) within 1 year before randomization ▪ IV cyclophosphamide within 180 days before randomization ▪ anti-TNF therapy, interleukin-1 receptor antagonists, IV immunoglobulin, prednisone > 100 mg/day, each within 90 days before randomization ▪ use of any new immunosuppressants/immunomodulators, antimalarials, NSAIDs; HMG-CoA reductase inhibitor, angiotensin pathway antihypertensives, steroid injections, suppressive therapy for chronic infections, parenteral antibiotics within 60 days prior to randomization	
	Standard therapy ▪ Antimalarials and immunosuppressants/immunomodulators - antimalarials (chloroquine 500 mg/day, hydroxychloroquine 400 mg/day, mepacrine 100 mg/day each alone or in combination) - azathioprine ≤ 300 mg/day - mycophenolate mofetil/mycophenolic acid ≤ 4 g/day or mycophenolate sodium ≤ 2.88 g/day - methotrexate ≤ 25 mg/week - other immunosuppressants/immunomodulators: oral cyclophosphamide ≤ 2.5 mg/kg/day; 6-mercaptopurine ≤ 300 mg/day; ciclosporin ≤ 4 mg/kg/day, tacrolimus ≤ 0.2 mg/kg/day; sirolimus ≤ 2 mg/kg/day; thalidomide ≤ 200 mg/day; leflunomide ≤ 40 mg/day ▫ new antimalarial therapy could be started between day 0 and week 16; dose reduction or switch to another antimalarial in case of toxicity allowed at any time during the study; clinically indicated dose increase allowed until week 16[b] ▫ immunosuppressants/immunomodulators: therapy had to be started before study start, dose increase allowed until week 16[b]	

Table 5: Characteristics of the intervention – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Intervention or comparison	Common comparator
	▪ Corticosteroids: ▫ systemic oral, IM or IV steroids for SLE or non-SLE (prednisone or equivalent up to 40 mg/day): - day 1–week 24: increase in total steroid dose for SLE if SLE disease activity increases or use of steroids for non-SLE reasons; for relapses: increase in steroid dose according to ACR guideline - from week 24, the total steroid dose (SLE + non-SLE reasons) was allowed to be no more than 25% or 5 mg over the baseline dose[c] - week 44–52: no new increase in SLE steroids over the dose at baseline or week 44 (whichever was higher) allowed[c] - dosages higher than 40 mg/day up to ≤ 3 days allowed for non-SLE reasons - IA steroids allowed until week 44[c] ▫ reduction of the mean steroid dose if disease activity has improved for ≥ 8 weeks is at the investigator's discretion targeting a reduction to 7.5 mg/day or lower after week 24; after worsening disease activity, a 12-week period of stable or improving disease activity should be observed before considering steroid dose reduction ▪ NSAIDs: ▫ allowed as clinically indicated until week 44; no new treatment with NSAIDs for ≥ 1 week was allowed to be started after week 44[c]; switch to another NSAID due to toxicity was allowed at any time ▫ acetylsalicylic acid ≤ 1000 mg/day for the entire duration of the study; higher doses could be initiated until week 44 and continued until the end of the study; after week 44, no new treatment for ≥ 1 week[c] could be started ▫ paracetamol is recommended for non-SLE related conditions ▪ HMG-CoA reductase inhibitors: ▫ starting a new treatment after week 24 was not allowed[c]; switching to another inhibitor was allowed at any time, titration of dose to obtain therapeutic effect on lipids was allowed ▪ Antihypertensives (angiotensin pathway) ▫ starting a new treatment with ACE inhibitors or ARBs after week 16 was not allowed[c]; switching to another antihypertensive was allowed at any time, titration of dose to obtain therapeutic effect on blood pressure was allowed **Prohibited and restricted concomitant treatment[c]:** ▪ investigational products (biologic or non-biologic) ▪ TNFα inhibitors ▪ other biologics ▪ IV cyclophosphamide or IV immunoglobulins	
BLISS-76	Belimumab 10 mg/kg BW on days 0, 14, 28, then every 4 weeks, IV + standard therapy	Placebo on days 0, 14, 28, then every 4 weeks, IV + standard therapy
	Prior and concomitant treatment ▪ see BLISS-52[d]	

Table 5: Characteristics of the intervention – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Study	Intervention or comparison	Common comparator
a. At least one or a combination of: oral corticosteroids (OCS), antimalarials, immunosuppressants, NSAIDs. b. After week 16, any dose increase over the dose at baseline or week 16 (whichever was higher) or the initiation of a new antimalarial or immunosuppressant/immunomodulator therapy resulted in patients being considered as non-responders in the analysis. c. In case of non-compliance with these requirements, patients were considered non-responders in the analyses and had to terminate the study. d. Until week 52, the criteria for adjusting the standard therapy in the BLISS-76 study are the same as in the BLISS-52 study. From week 52 to week 68 and from week 68 to week 76, the regulations that were previously used for week 24 to week 44 and for week 44 to week 52 were applied again. AE: adverse event; BW: body weight; IA: intraarticular; IM: intramuscular; IV: intravenous; NSAID: nonsteroidal anti-inflammatory drug; OCS: oral corticosteroids; SLE: systemic lupus erythematosus		

Table 6: Characteristics of the study populations and study/treatment discontinuation – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) (comparison 2) (multipage table)

Study Characteristic Category	Studies with anifrolumab						Studies with belimumab			
	TULIP-1		TULIP-2		MUSE		BLISS-52		BLISS-76	
	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy
	N[a] = 127	N[a] = 125	N[a] = 119	N[a] = 121	N[a] = 69	N[a] = 75	N[a] = 144	N[a] = 126	N[a] = 88	N[a] = 77
Age [years], mean (SD)	42 (12)	41 (12)	44 (12)	41 (11)	39 (12)	41 (13)	33 (10)	34 (12)	37 (10)	35 (10)
Sex [F/M], %	91/9	94/6	91/9	90/10	94/6	92/8	98/2	94/6	93/7	91/9
Family origin, n (%)										
White	85 (67)	96 (77)	75 (63)	78 (64[b])	25 (36)	31 (41)	30 (21)	31 (25)	57 (65)	53 (69)
Black	22 (17)	14 (11)	11 (9)	18 (15)	16 (23)	8 (11)	5 (4)	2 (2)	12 (14)	10 (13)
Asian	7 (6)	3 (2)	17 (14)	16 (13)	2 (3)	10 (13)	72 (50)	56 (44)	6 (7)	3 (4)
Native Americans or Alaskans	0 (0)	1 (1)	0 (0)	0 (0)	3 (4)	0 (0)	37 (26)	37 (29)	13 (15)	10 (13)
Other	13 (10)	11 (9)	8 (7)	6 (5)	23 (33)	26 (35)	0 (0)	1 (1)	0 (0)	1 (1)
Missing	0 (0)	0 (0)	8 (7)	3 (2[b])	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Region, n (%)										
Europe	47 (37)	56 (45)	45 (38)	33 (27)	18 (26)	20 (27)	ND	ND	ND	ND
Asia-Pacific	6 (5)	2 (2)	15 (13)	14 (12)	1 (1)	9 (12)	ND	ND	ND	ND
Latin America	18 (14)	18 (14)	15 (13)	14 (12)	25 (36)	26 (35)	ND	ND	ND	ND
North America	53 (42)	46 (37)	42 (35)	54 (45)	24 (35)	20 (27)	ND	ND	ND	ND
Rest of the world	3 (2)	3 (2)	2 (2)	6 (5)	1 (1)	0 (0)	ND	ND	ND	ND
Weight, mean (SD)	76.9 (20.4)	74.2 (18.0)	72.1 (19.6)	72.1 (18.5)	70.0 (15.8)	67.4 (19.7)	ND	ND	ND	ND
BMI, mean (SD)	28.7 (7.1)	28.1 (7.0)	27.1 (6.9)	26.8 (6.7)	26.5 (5.6)	25.8 (6.6)	ND	ND	ND	ND

Table 6: Characteristics of the study populations and study/treatment discontinuation – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) (comparison 2) (multipage table)

Study Characteristic Category	Studies with anifrolumab						Studies with belimumab			
	TULIP-1		TULIP-2		MUSE		BLISS-52		BLISS-76	
	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy
	N[a] = 127	N[a] = 125	N[a] = 119	N[a] = 121	N[a] = 69	N[a] = 75	N[a] = 144	N[a] = 126	N[a] = 88	N[a] = 77
Time from SLE diagnosis to randomization [years], mean (SD)	9.3 (8.1)[b]	8.7 (7.8)[b]	11.6 (9.4)[b]	8.3 (7.5)[b]	7.9 (6.0)[b]	7.7 (7.2)[b]	5.1 (4.9)	5.9 (6.7)	7.4 (7.5)	7.0 (6.2)
SLEDAI-2K/SELENA-SLEDAI score, mean (SD)	11.2 (3.9)	11.3 (3.4)	11.3 (3.7)	11.5 (3.9)	10.9 (4.0)	11.0 (4.6)	10.8 (4.0)	10.7 (3.7)	10.4 (3.5)	10.9 (3.8)
BILAG-2004 global score, n (%)[c]										
At least one A	64 (50)	61 (49)	43 (36)	62 (51)	36 (52)	34 (45)	ND	ND	ND	ND
No A and < 2 B	4 (3)	10 (8)	7 (6)	7 (6)	5 (7)	4 (5)	60 (42)[b]	64 (51)[b]	42 (48)[b]	24 (31)[b]
No A and at least 2 B	59 (46[b])	54 (43)	69 (58)	52 (43)	28 (41)	37 (49)	ND	ND	ND	ND
BILAG 1 A or 2 B assessments[c], n (%)	123 (97)[b]	115 (92)[b]	112 (94)[b]	114 (94)[b]	64 (93)[b]	71 (95)[b]	84 (58)	62 (49)	46 (52)	53 (69)
PGA score, mean (SD)	1.9 (0.4)	1.8 (0.4)	1.7 (0.4)	1.8 (0.4)	1.8 (0.4)	1.7 (0.4)	1.4 (0.5)	1.4 (0.5)	1.4 (0.6)	1.4 (0.5)
Anti-dsDNA level, n (%)										
Negative	71 (56)	70 (56)	60 (50)	74 (61)	15 (22)	11 (15)	0 (0)	0 (0)	0 (0)	0 (0)
Positive	56 (44)	55 (44)	59 (50)	47 (39)	40 (58)	50 (67)	144 (100)	126 (100)	88 (100)	77 (100)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	14 (20)	14 (19)	0 (0)	0 (0)	0 (0)	0 (0)

Table 6: Characteristics of the study populations and study/treatment discontinuation – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) (comparison 2) (multipage table)

Study Characteristic Category	Studies with anifrolumab						Studies with belimumab			
	TULIP-1		TULIP-2		MUSE		BLISS-52		BLISS-76	
	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy
	N[a] = 127	N[a] = 125	N[a] = 119	N[a] = 121	N[a] = 69	N[a] = 75	N[a] = 144	N[a] = 126	N[a] = 88	N[a] = 77
ANA level, n (%)										
Abnormal (titre ≥ 1:80)	114 (90)	114 (91)	102 (86)	108 (89)	68 (99)	73 (97)	ND	ND	ND	ND
Normal (titre < 1:80)	9 (7)	8 (6)	9 (8)	8 (7)	1 (1)	2 (3)	ND	ND	ND	ND
Missing	4 (3)	3 (2)	8 (7)	5 (4)	0 (0)	0 (0)	ND	ND	ND	ND
Complement C3 level, n (%)										
Abnormal	44 (35)	46 (37)	48 (40)	45 (37)	20 (29)	30 (40)	ND	ND	ND	ND
Normal	83 (65)	79 (63)	71 (60)	76 (63)	49 (71)	45 (60)	ND	ND	ND	ND
Complement C4 level, n (%)										
Abnormal	24 (19)	29 (23)	30 (25)	27 (22)	17 (25)	19 (25)	ND	ND	ND	ND
Normal	103 (81)	96 (77)	89 (75)	94 (78)	52 (75)	56 (75)	ND	ND	ND	ND
Standard therapy, n (%)										
Antimalarial	92 (72)	98 (78)	75 (63)	92 (76)	53 (77)	58 (77)	95 (66)	98 (78)	54 (61)	51 (66)
Corticosteroids	106 (83[b])	103 (82)	96 (81)	96 (79)	54 (78)	63 (84)	140 (97)	122 (97)	71 (81)	65 (84)
Immunosuppressants	32 (25)	32 (26)	27 (23)	25 (21)	21 (30)	19 (25)	50 (35)	42 (33)	35 (40)	26 (34)
Dual therapy[d]	69 (54)	62 (50)	55 (46)	71 (59)	28 (41)	47 (63)	ND	ND	ND	ND
Triple therapy[e]	17 (13)	23 (18)	13 (11)	11 (9)	16 (23)	9 (12)	ND	ND	ND	ND
Treatment discontinuation, n (%)[f]	23 (18)	28 (22)	18 (15)	38 (31)	8 (12)	24 (32)	ND	ND	ND	ND
Study discontinuation, n (%)[g]	22 (17)	27 (22)	17 (14)	34 (28)	10 (14[b])	22 (29)	ND	ND	ND	ND

Table 6: Characteristics of the study populations and study/treatment discontinuation – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) (comparison 2) (multipage table)

Study Characteristic Category	Studies with anifrolumab						Studies with belimumab			
	TULIP-1		TULIP-2		MUSE		BLISS-52		BLISS-76	
	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy
	N[a] = 127	N[a] = 125	N[a] = 119	N[a] = 121	N[a] = 69	N[a] = 75	N[a] = 144	N[a] = 126	N[a] = 88	N[a] = 77

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. Institute's calculation.
c. The studies with anifrolumab used the BILAG 2004, which includes 9 organ domains. The studies with belimumab used the classic BILAG, which includes 8 organ domains. In contrast to the classic BILAG, the BILAG 2004 additionally includes the gastrointestinal and ophthalmic organ domains and no longer includes the organ domain of vasculitis.
d. Dual therapy is defined as therapy with antimalarial and/or corticosteroids and/or immunosuppressant (2 of these components).
e. Triple therapy is defined as therapy with antimalarial, corticosteroids and immunosuppressant.
f. Common reasons for treatment discontinuation in the intervention vs. control arm were:
TULIP-1: withdrawal of consent (8% vs. 8%), AEs (6% vs. 5%), lack of efficacy (2% vs. 5%)
TULIP-2: withdrawal of consent (4% vs. 12%), AEs (3% vs. 9%), lack of efficacy (2% vs. 6%)
MUSE: withdrawal of consent (4% vs. 15%), AEs (1% vs. 8%).
g. Common reasons for study discontinuation in the intervention vs. control arm were:
TULIP-1: withdrawal of consent (7% vs. 10%), AEs (6% vs. 2%), lack of efficacy (2% vs. 5%)
TULIP-2: withdrawal of consent (8% vs. 14%), AEs (1% vs. 5%)
MUSE: lost-to-follow-up (3% vs. 5%), other (12% vs. 23%).

AE: adverse event; ANA: antinuclear antibody; BILAG: British Isles Lupus Assessment Group; BMI: body mass index; dsDNA: double-stranded deoxyribonucleic acid; F: female; ITT: intention to treat; M: male; max: maximum; min: minimum; N: number of randomized patients in the subpopulation; PGA: physician's global assessment; RCT: randomized controlled trial; SD: standard deviation; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index – Revised Version

Table 7: Characteristics of the study populations and study/treatment discontinuation – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) (comparison 3) (multipage table)

Study Characteristic Category	Studies with anifrolumab						Studies with belimumab			
	TULIP-1		TULIP-2		MUSE		BLISS-52		BLISS-76	
	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy
	N[a] = 35	N[a] = 35	N[a] = 34	N[a] = 31	N[a] = 15	N[a] = 23	N[a] = 144	N[a] = 126	N[a] = 88	N[a] = 77
Age [years], mean (SD)	36 (10)	37 (11)	40 (11)	37 (10)	37 (11)	39 (14)	33 (10)	34 (12)	37 (10)	35 (10)
Sex [F/M], %	86/14	86/14	88/12	84/16	93/7	96/4	98/2	94/6	93/7	91/9
Family origin, n (%)										
White	24 (69)	25 (71)	18 (53)	20 (65)	7 (47)	10 (44)	30 (21)	31 (25)	57 (65)	53 (69)
Black	3 (9)	5 (14)	2 (6)	3 (10)	3 (20)	2 (9)	5 (4)	2 (2)	12 (14)	10 (13)
Asian	5 (14)	1 (3)	7 (21)	4 (13)	0 (0)	5 (22)	72 (50)	56 (44)	6 (7)	3 (4)
Native Americans or Alaskans	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	37 (26)	37 (29)	13 (15)	10 (13)
Other	3 (9)	4 (11)	4 (12)	2 (7)	5 (33)	6 (26)	0 (0)	1 (1)	0 (0)	1 (1)
Missing	0 (0)	0 (0)	3 (9)	2 (7)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Time from SLE diagnosis to randomization [years], mean (SD)	9.8 (8.6)	9.6 (6.6)	12.9 (9.9)	8.5 (6.4)	10.0 (5.4)	7.1 (7.3)	5.1 (4.9)	5.9 (6.7)	7.4 (7.5)	7.0 (6.2)
SLEDAI-2K/SELENA-SLEDAI score, mean (SD)	13.4 (4.4)	14.1 (3.4)	13.0 (3.6)	14.6 (4.2)	14.2 (5.1)	13.4 (5.7)	10.8 (4.0)	10.7 (3.7)	10.4 (3.5)	10.9 (3.8)
BILAG 1 A or 2 B assessments, n (%)[b]	35 (100)	31 (89)	31 (91)	29 (94)	13 (87)	21 (91)	84 (58)	62 (49)	46 (52)	53 (69)
PGA score, mean (SD)	2.0 (0.4)	1.9 (0.4)	1.8 (0.4)	1.8 (0.4)	2.0 (0.4)	1.8 (0.4)	1.4 (0.5)	1.4 (0.5)	1.4 (0.6)	1.4 (0.5)

Table 7: Characteristics of the study populations and study/treatment discontinuation – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation, high disease activity [positive test for anti-dsDNA and low complement], only drugs approved in Germany) (comparison 3) (multipage table)

Study Characteristic Category	Studies with anifrolumab						Studies with belimumab			
	TULIP-1		TULIP-2		MUSE		BLISS-52		BLISS-76	
	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Anifrolumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy	Belimumab + standard therapy	Placebo + standard therapy
	N[a] = 35	N[a] = 35	N[a] = 34	N[a] = 31	N[a] = 15	N[a] = 23	N[a] = 144	N[a] = 126	N[a] = 88	N[a] = 77
Anti-dsDNA level, positive, n (%)	35 (100)	35 (100)	34 (100)	31 (100)	15 (100)	23 (100)	144 (100)	126 (100)	88 (100)	77 (100)
Complement C3 level, low, n (%)	33 (94)	32 (91)	30 (88)	29 (94)	13 (87)	21 (91)	ND	ND	ND	ND
Complement C4 level, low, n (%)	17 (49)	18 (51)	19 (56)	17 (55)	10 (67)	9 (39)	ND	ND	ND	ND
Standard therapy, n (%)										
Antimalarial	24 (69)	25 (71)	22 (65)	24 (77)	9 (60)	17 (74)	95 (66)	98 (78)	54 (61)	51 (66)
Corticosteroids	29 (83)	34 (97)	28 (82)	27 (87)	13 (87)	17 (74)	140 (97)	122 (97)	71 (81)	65 (84)
Immunosuppressants	9 (26)	14 (40)	11 (32)	8 (26)	6 (40)	8 (35)	50 (35)	42 (33)	35 (40)	26 (34)
Treatment discontinuation, n (%)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND
Study discontinuation, n (%)	ND	ND	ND	ND	ND	ND	ND	ND	ND	ND

a. Number of randomized patients. Values that are based on other patient numbers are marked in the corresponding line if the deviation is relevant.
b. The studies with anifrolumab used the BILAG 2004, which includes 9 organ domains. The studies with belimumab used the classic BILAG, which includes 8 organ domains. In contrast to the classic BILAG, the BILAG 2004 additionally includes the gastrointestinal and ophthalmic organ domains and no longer includes the organ domain of vasculitis.

BILAG: British Isles Lupus Assessment Group; dsDNA: double-stranded deoxyribonucleic acid; F: female; number of patients in the category; N: number of randomized patients in the subpopulation; PGA: physician's global assessment; RCT: randomized controlled trial; SD: standard deviation; SELENA: Safety of Estrogens in Lupus Erythematosus – National Assessment; SLE: systemic lupus erythematosus; SLEDAI-2K: Systemic Lupus Erythematosus Disease Activity Index – Revised Version

Appendix B **– Results**

B.1 Matrix of outcomes

Table 8: Matrix of outcomes – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Comparison / **Study**	**Outcomes**																	
	All-cause mortality[a]	**Systemic Lupus Erythematosus Responder Index (SRI)[b]**	**BILAG relapses**	**PtGA VAS[c]**	**Joint status (swollen joints[d], tender joints[d])**	**Skin symptoms (CLASI)[c]**	**SLICC/ACR Damage Index (SDI)[c]**	**Physical functioning (HAQ)[c]**	**Pain[e]**	**Fatigue (FACIT-Fatigue)**	**Health status (EQ-5D VAS)**	**Health-related quality of life (SF-36v2)**	**Health-related quality of life (Lupus QoL)**	**Columbia Suicide Severity Rating Scale (C-SSRS)[c]**	**Personal Health Questionnaire Depression Scale-8 (PHQ-8)[c]**	**Relapses according to modified SELENA flare index**	**SAEs**	**Discontinuation due to AEs**
Anifrolumab + standard therapy vs. placebo + standard therapy																		
TULIP-1	●	●	●	●	●	●	●	–	●	●	●	●	●	●	●	●	●	●
TULIP-2	●	●	●	●	●	●	●	–	●	●	●	●	●	●	●	●	●	●
MUSE	●	●	●	●	●	●	●	●	●	●	●	●	●	–	–	–	●	●
Belimumab + standard therapy vs. placebo + standard therapy																		
BLISS-52	●	●	●	–	–	–	–[f]	–	–	●	●	●	–	–	–	●	●	●
BLISS-76	●	●	●	–	–	–	–[f]	–	–	●	●	●	–	–	–	●	●	●
Indirect comparison	Yes	No[g]	No[h]	No[i]	No[i]	No[i]	No[i]	No[i]	No[i]	Yes	Yes	Yes	No[i]	No[i]	No[i]	No[j]	Yes	Yes

Table 8: Matrix of outcomes – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Comparison / Study	All-cause mortality[a]	Systemic Lupus Erythematosus Responder Index (SRI)[b]	BILAG relapses	PtGA VAS[c]	Joint status (swollen joints[d], tender joints[d])	Skin symptoms (CLASI)[c]	SLICC/ACR Damage Index (SDI)[c]	Physical functioning (HAQ)[c]	Pain[e]	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	Health-related quality of life (Lupus QoL)	Columbia Suicide Severity Rating Scale (C-SSRS)[c]	Personal Health Questionnaire Depression Scale-8 (PHQ-8)[c]	Relapses according to modified SELENA flare index	SAEs	Discontinuation due to AEs
Outcomes																		

a. Deaths were recorded within the framework of the AEs.
b. The SRI is composed of the reduction in SLEDAI-2K or SELENA-SLEDAI ≥ 4 points and no new BILAG A or ≤ 1 new BILAG B organ assessment in comparison with baseline and no worsening in PGA (maximum increase of < 0.3 points from baseline on a 3-point scale) and no permanent discontinuation of study treatment and no treatment with drugs for restricted use beyond the dose limits allowed by the protocol. The anifrolumab studies also recorded the outcome of BILAG-based Composite Lupus Assessment (BICLA), which differs from the SRI only in 2 included components. As the BICLA was not recorded in the belimumab studies, and is therefore only available on one side of the indirect comparison, patient relevance was not conclusively assessed.
c. For some outcomes that are only available on side of the indirect comparison, patient relevance was not conclusively assessed.
d. Based on 28 joints.
e. The outcome of pain was recorded by NRS in the TULIP-1 and TULIP-2 studies and by VAS in the MUSE study.
f. No data available for the relevant subpopulation
g. Different versions of BILAG and SLEDAI were used (BILAG 2004 or SLEDAI-2K in the anifrolumab studies vs. classic BILAG or SELENA-SLEDAI in the belimumab studies). The extent to which the differences in BILAG or SLEDAI influence the results and how great the influence of these differences is on the results of the SRI cannot be assessed conclusively. In addition, the studies differ in the strictness of their specifications regarding dose adjustments in the standard therapy (see above), resulting in different thresholds at which a patient was considered a non-responder. This leads to different operationalizations of the outcome.
h. Different versions of the BILAG (BILAG-2004 [studies on anifrolumab] vs. classic BILAG [studies on belimumab]) were used. Whether and to what extent the differences in BILAG influence the results cannot be assessed conclusively.
i. Not feasible because results are not available for at least one side of the indirect comparison.
j. The indirect comparison is not feasible due to different operationalizations on the intervention and comparator side. In the studies on belimumab, the outcome was directly operationalized using the optimization of the concomitant medication (addition of individual drugs and/or dose changes). This is not appropriate.
●: outcome not recorded
–: outcome not recorded

Table 8: Matrix of outcomes – RCT, indirect comparison: anifrolumab + standard therapy vs. belimumab + standard therapy (multipage table)

Comparison / Study	Outcomes																	
	All-cause mortality[a]	Systemic Lupus Erythematosus Responder Index (SRI)[b]	BILAG relapses	PtGA VAS[c]	Joint status (swollen joints[d], tender joints[d])	Skin symptoms (CLASI)[c]	SLICC/ACR Damage Index (SDI)[c]	Physical functioning (HAQ)[c]	Pain[e]	Fatigue (FACIT-Fatigue)	Health status (EQ-5D VAS)	Health-related quality of life (SF-36v2)	Health-related quality of life (Lupus QoL)	Columbia Suicide Severity Rating Scale (C-SSRS)[c]	Personal Health Questionnaire Depression Scale-8 (PHQ-8)[c]	Relapses according to modified SELENA flare index	SAEs	Discontinuation due to AEs
ACR: American College of Rheumatology; AE: adverse event; BICLA: BILAG-based Composite Lupus Assessment; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index; FACIT: Functional Assessment of Chronic Illness Therapy; HAQ: Health Assessment Questionnaire; NRS: numeric rating scale; PGA: physician's global assessment; PtGA: patient global assessment; QoL: quality of life; RCT: randomized controlled trial; SAE: serious adverse event; SF-36v2: Short Form 36 version 2; SLE: systemic lupus erythematosus; SLEDAI-2K: SLE Disease Activity Index – Revised Version; SLICC: Systemic Lupus Erythematosus International Collaborating Clinics; SRI: SLE Responder Index; VAS: visual analogue scale																	

B.2 Results of comparison 2

Table 9: Results (mortality, side effects, dichotomous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Anifrolumab + standard therapy or belimumab + standard therapy**		**Placebo + standard therapy**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**OR [95% CI]; p-value**
Mortality					
All-cause mortality[a]					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1	127	1 (0.8)	125	0 (0)	–[b]
TULIP-2	119	0 (0)	121	0 (0)	–
MUSE	69	0 (0)	75	0 (0)	–
Total					–[b]
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	
Total					–[b]
Indirect comparison using common comparators:					
Anifrolumab + standard therapy vs. belimumab + standard therapy					–[b]
Side effects					
AEs (supplementary information)					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1	127	114 (89.8)	125	93 (74.4)	–
TULIP-2	119	103 (86.6)	121	104 (86.0)	–
MUSE	69	59 (85.5)	75	59 (78.7)	–
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	

Table 9: Results (mortality, side effects, dichotomous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category Outcome Comparison Study	Anifrolumab + standard therapy or belimumab + standard therapy		Placebo + standard therapy		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p-value
SAEs					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1	127	14 (11.0)	125	20 (16.0)	0.65 [0.31; 1.35]; 0.250
TULIP-2	119	10 (8.4)	121	26 (21.5)	0.34 [0.15; 0.73]; 0.006
MUSE	69	14 (20.3)	75	15 (20.0)	1.02 [0.45; 2.30]; 0.965
Total					0.60 [0.38; 0.94]; 0.024[c]
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	
Total					1.31 [0.79; 2.19]; ND[d]
Indirect comparison using common comparators[e]:					
Anifrolumab + standard therapy vs. belimumab + standard therapy					0.46 [0.23; 0.90]; ND
Discontinuation due to AEs					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1	127	8 (6.3)	125	4 (3.2)	2.03 [0.60; 6.93]; 0.257
TULIP-2	119	3 (2.5)	121	10 (8.3)	0.29 [0.08; 1.07]; 0.063
MUSE	69	2 (2.9)	75	6 (8.0)	0.34 [0.07; 1.76]; 0.200
Total					0.67 [0.30; 1.47]; 0.317[c]
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	
Total					0.77 [0.30; 1.51]; ND[d]
Indirect comparison using common comparators[e]:					
Anifrolumab + standard therapy vs. belimumab + standard therapy					0.87 [0.31; 2.45]; ND

a. Deaths were recorded within the framework of the AEs. The follow-up period during which AEs were recorded was 84 days in the studies TULIP-1 and TULIP-2 and 28 days in the MUSE study. For comparability of the studies, only AEs up to 28 days after the end of the study were considered for all 3 studies for the meta-analysis. In the TULIP-1 study, one additional death occurred in the placebo arm after the observation period of 28 days.
b. Due to very low proportions of events, the effect estimation for the anifrolumab studies is not informative. The company did not provide any corresponding data for the belimumab studies, but it is assumed that there is an analogous picture for this outcome. Therefore, the effect estimation is not presented at all.
c. Meta-analysis based on individual patient data; generalized linear model (GLM) with the covariates of treatment and study.
d. Meta-analysis: fixed-effect model, inverse variance method.
e. Indirect comparison according to Bucher [12].

Table 9: Results (mortality, side effects, dichotomous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Anifrolumab + standard therapy or belimumab + standard therapy**		**Placebo + standard therapy**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**OR [95% CI]; p-value**
AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; OR: odds ratio; RCT: randomized controlled trial; SAE: serious adverse event					

Table 10: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category **Outcome**	**Anifrolumab + standard therapy or belimumab + standard therapy**			**Placebo + standard therapy**			**Group difference**
Comparison **Study**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**MD [95% CI]; p-value[b]**
Morbidity							
Health status (EQ-5D VAS)[c]							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1	ND	54.6 (20.1)	14.9 (23.0)	ND	52.6 (22.0)	12.1 (27.4)	1.52 [−2.79; 5.83]; 0.487 SMD[d]: 0.08 [−0.18; 0.34]
TULIP-2	ND	60.7 (19.3)	5.2 (24.7)	ND	53.6 (21.8)	5.4 (25.7)	2.77 [−1.51; 7.05]; 0.203 SMD[d]: 0.15 [−0.12; 0.41]
MUSE	ND	51.0 (20.7)	19.0 (23.9)	ND	56.6 (20.4)	11.0 (24.6)	2.83 [−2.51; 8.16]; 0.297 SMD[d]: 0.16 [−0.17; 0.49]
Total							SMD[d, e]: 0.17 [−0.01; 0.35]; ND
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD[f]: 0.13 [−0.09; 0.35]
Indirect comparison using common comparators[g]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**SMD:** **0.04 [−0.24; 0.33]**

Table 10: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category **Outcome**	**Anifrolumab + standard therapy or belimumab + standard therapy**			**Placebo + standard therapy**			**Group difference**
Comparison **Study**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**MD [95% CI]; p-value[b]**
Fatigue (FACIT-Fatigue)[c]							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1	ND	24.5 (11.8)	7.4 (10.8)	ND	27.3 (11.5)	5.1 (11.6)	1.68 [−0.35; 3.70]; 0.105 SMD[d]: 0.19 [−0.07; 0.44]
TULIP-2	ND	28.3 (12.2)	4.2 (10.7)	ND	23.4 (10.7)	4.5 (10.6)	0.00 [−1.92; 1.91]; 0.998 SMD[d]: 0.0 [−0.26; 0.26]
MUSE	ND	26.1 (11.5)	6.0 (10.4)	ND	26.2 (13.4)	6.3 (12.0)	1.08 [−1.60; 3.76]; 0.428 SMD[d]: 0.12 [−0.20; 0.45]
Total							SMD[d, e]: 0.11 [−0.08; 0.29]
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD[f]: 0.26 [0.07; 0.45]
Indirect comparison using common comparators[g]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**SMD:** **−0.16 [−0.42; 0.11]**

Table 10: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category **Outcome**	**Anifrolumab + standard therapy or belimumab + standard therapy**			**Placebo + standard therapy**			**Group difference**
Comparison **Study**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**MD [95% CI]; p-value[b]**
Health-related quality of life							
SF-36v2[c]							
Physical Component Summary (PCS)							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1	ND	37.5 (9.1)	4.0 (8.1)	ND	37.6 (8.8)	5.1 (8.7)	0.08 [−1.54; 1.70]; 0.921 SMD[d]: 0.01 [−0.24; 0.27]
TULIP-2	ND	39.3 (8.2)	3.3 (7.8)	ND	37.4 (9.8)	3.3 (7.3)	0.40 [−1.04; 1.84]; 0.582 SMD[d]: 0.06 [−0.20; 0.33]
MUSE	ND	35.2 (8.9)	6.7 (7.7)	ND	35.3 (11.1)	6.2 (10.1)	−0.33 [−2.46; 1.81]; 0.761 SMD[d]: −0.05 [−0.37; 0.28]
Total							SMD[d, e]: −0.01 [−0.19; 0.17]
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD[f]: 0.17 [−0.02; 0.36]
Indirect comparison using common comparators[g]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**SMD:** **−0.18 [−0.44; 0.08]**

Table 10: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category **Outcome**	**Anifrolumab + standard therapy or belimumab + standard therapy**			**Placebo + standard therapy**			**Group difference**
Comparison **Study**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**N[a]**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[b] (SD)**	**MD [95% CI]; p-value[b]**
Mental Component Summary (MCS)[c]							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1	ND	42.9 (11.7)	3.7 (10.5)	ND	45.1 (11.5)	1.4 (10.1)	0.74 [−1.07; 2.55]; 0.422 SMD[d]: 0.09 [−0.17; 0.35]
TULIP-2	ND	44.9 (11.8)	1.9 (10.8)	ND	41.9 (10.9)	2.0 (11.8)	1.22 [−0.72; 3.16]; 0.217 SMD[d]: 0.14 [−0.12; 0.41]
MUSE	ND	38.0 (11.2)	4.2 (11.2)	ND	37.7 (12.6)	5.2 (11.4)	0.82 [−1.73; 3.37]; 0.525 SMD[d]: 0.10 [−0.23; 0.42]
Total							SMD[d, e]: 0.10 [−0.08; 0.28]
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD[f]: 0.19 [−0.15; 0.52]
Indirect comparison using common comparators[g]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**SMD:** **−0.09 [−0.47; 0.29]**

Table 10: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 2) (multipage table)

Outcome category Outcome	Anifrolumab + standard therapy or belimumab + standard therapy			Placebo + standard therapy			Group difference
Comparison Study	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SD)	N[a]	Values at baseline mean (SD)	Mean change in the course of the study mean[b] (SD)	MD [95% CI]; p-value[b]

a. Number of patients considered in the analysis for the calculation of the effect estimation; the values at the start of the study (possibly at other time points) may be based on other patient numbers.
b. MMRM with the covariables of treatment, visit, stratification factors, baseline value, and interaction between treatment and visit. Effect relates to the entire period.
c. Higher (increasing) values mean an improvement in symptoms or quality of life; positive effects mean an advantage for anifrolumab + standard therapy or belimumab + standard therapy. In the indirect comparison, positive effects mean an advantage for anifrolumab + standard therapy and negative effects mean a disadvantage for anifrolumab + standard therapy.
d. Unclear which formula was used to calculate the SMD.
e. Discrepancies between the information provided by the company within Module 4 A for the meta-analytical summary of the anifrolumab studies are either due to different time reference (entire study period vs. time point week 52) or due to the model used (ANCOVA model with or without repeated measures).
f. Meta-analysis: fixed-effect model (inverse variance method).
g. Indirect comparison according to Bucher [12].

CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; MD: mean difference; MMRM: mixed-effects model with repeated measures; N: number of analysed patients; RCT: randomized controlled trial; SD: standard deviation; SF-36v2: Short Form 36 version 2; SMD: standardized mean difference; VAS: visual analogue scale

B.3 Results of comparison 3

Table 11: Results (mortality, side effects, dichotomous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 3) (multipage table)

Outcome category **Outcome** **Comparison** **Study**	**Anifrolumab + standard therapy or belimumab + standard therapy**		**Placebo + standard therapy**		**Group difference**
	N	**Patients with event n (%)**	**N**	**Patients with event n (%)**	**OR [95% CI]; p-value**
Mortality					
All-cause mortality[a]					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1				ND	
TULIP-2				ND	
MUSE				ND	
Total	84	0 (0)	89	0 (0)	–
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	
Total					–[b]
Indirect comparison using common comparators:					
Anifrolumab + standard therapy vs. belimumab + standard therapy					–[b]
Side effects					
AEs (supplementary information)					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1				ND	
TULIP-2				ND	
MUSE				ND	
Total	84	75 (89.3)	89	73 (82.0)	–
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	

Table 11: Results (mortality, side effects, dichotomous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 3) (multipage table)

Outcome category Outcome Comparison Study	Anifrolumab + standard therapy or belimumab + standard therapy		Placebo + standard therapy		Group difference
	N	Patients with event n (%)	N	Patients with event n (%)	OR [95% CI]; p-value
SAEs					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1				ND	
TULIP-2				ND	
MUSE				ND	
Total	84	9 (10.7)	89	24 (27.0)	0.34 [0.15; 0.79]; 0.018[c]
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	
Total					1.31 [0.79; 2.19]; ND[d]
Indirect comparison using common comparators[e]:					
Anifrolumab + standard therapy vs. belimumab + standard therapy					0.26 [0.10; 0.70]; ND
Discontinuation due to AEs					
Anifrolumab + standard therapy vs. placebo + standard therapy					
TULIP-1				ND	
TULIP-2				ND	
MUSE				ND	
Total	84	5 (6.0)	89	5 (5.6)	1.13 [0.30; 4.20]; 0.858[c]
Belimumab + standard therapy vs. placebo + standard therapy					
BLISS-52				ND	
BLISS-76				ND	
Total					0.77 [0.30; 1.51]; ND[d]
Indirect comparison using common comparators[e]:					
Anifrolumab + standard therapy vs. belimumab + standard therapy					1.47 [0.33; 6.42]; ND

a. Deaths were recorded within the framework of the AEs.
b. No events occurred in the anifrolumab studies. The company did not provide any corresponding data for the belimumab studies, but it is assumed that there is an analogous picture for this outcome. Therefore, the effect estimation is not presented at all.
c. Meta-analysis: fixed-effect model (Mantel-Haenszel method).
d. Meta-analysis: fixed-effect model (inverse variance method).
e. Indirect comparison according to Bucher [12].

AE: adverse event; CI: confidence interval; n: number of patients with (at least one) event; N: number of analysed patients; ND: no data; OR: odds ratio; RCT: randomized controlled trial; SAE: serious adverse event

Table 12: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 3) (multipage table)

Outcome category **Outcome**	**Anifrolumab + standard therapy or belimumab + standard therapy**			**Placebo + standard therapy**			**Group difference**
Comparison **Study**	**N**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[a] (SE)**	**N**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[a] (SE)**	**MD [95% CI]; p-value**
Morbidity							
Health status (EQ-5D VAS)[b]							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1					ND		
TULIP-2					ND		
MUSE					ND		
Total	77	ND	13.3 (3.0)	83	ND	5.2 (3.0)	8.07 [2.60; 13.54]; 0.004[a] SMD: 0.30 [−0.02; 0.61][c]
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD: 0.13 [−0.09; 0.35][d]
Indirect comparison using common comparators[e]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**SMD: 0.17 [−0.21; 0.55][e]**
Fatigue (FACIT-Fatigue)[b]							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1					ND		
TULIP-2					ND		
MUSE					ND		
Total							ND
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD: 0.26 [0.07; 0.45][d]
Indirect comparison using common comparators[e]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**ND**

Table 12: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 3) (multipage table)

Outcome category **Outcome**	**Anifrolumab + standard therapy or belimumab + standard therapy**			**Placebo + standard therapy**			**Group difference**
Comparison **Study**	**N**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[a] (SE)**	**N**	**Values at baseline mean (SD)**	**Mean change in the course of the study mean[a] (SE)**	**MD [95% CI]; p-value**
Health-related quality of life							
SF-36v2[b]							
Physical Component Summary (PCS)							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1					ND		
TULIP-2					ND		
MUSE					ND		
Total	79	ND	4.0 (1.1)	84	ND	2.9 (1.1)	1.1 [−0.96; 3.16]; 0.292[a] SMD: 0.11 [−0.20; 0.42][c]
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD: 0.17 [−0.02; 0.36][d]
Indirect comparison using common comparators[e]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							**SMD: 0.06 [−0.42; 0.30][e]**
Mental Component Summary (MCS)							
Anifrolumab + standard therapy vs. placebo + standard therapy							
TULIP-1					ND		
TULIP-2					ND		
MUSE					ND		
Total	79		ND	84		ND	–
Belimumab + standard therapy vs. placebo + standard therapy							
BLISS-52					ND		
BLISS-76					ND		
Total							SMD: 0.19 [−0.15; 0.52][d]
Indirect comparison using common comparators[e]: **Anifrolumab + standard therapy vs. belimumab + standard therapy**							–

Table 12: Results (morbidity, health-related quality of life, continuous) – RCT, indirect comparison: anifrolumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) vs. belimumab + standard therapy (subpopulation with high disease activity, only drugs approved in Germany) (comparison 3) (multipage table)

Outcome category Outcome	Anifrolumab + standard therapy or belimumab + standard therapy			Placebo + standard therapy			Group difference
Comparison Study	N	Values at baseline mean (SD)	Mean change in the course of the study mean[a] (SE)	N	Values at baseline mean (SD)	Mean change in the course of the study mean[a] (SE)	MD [95% CI]; p-value

a. IPD meta-analysis, model with repeated measures with fixed effects for treatment, visit, stratification factors, baseline value, and interaction between treatment and visit. Effect relates to the entire period.
b. Higher (increasing) values mean an improvement in symptoms or quality of life; positive effects mean an advantage for anifrolumab + standard therapy or belimumab + standard therapy. In the indirect comparison, positive effects mean an advantage for anifrolumab + standard therapy and negative effects mean a disadvantage for anifrolumab + standard therapy.
c. To calculate the SMD, the company calculated a pooled SD using the approximate SD per treatment arm (from SE of the LSM estimators). As these are supplementary presentations, the Institute does not perform its own calculations for the SMD based on an estimation of the pooled SD from CI and MD.
d. Calculated from meta-analysis with random effects according to DerSimonian and Laird. For both studies, the meta-analysis considered the respective observed effect for the change at week 52 in comparison with baseline (each adjusted for values at baseline).
e. Indirect comparison according to Bucher [12].

CI: confidence interval; FACIT: Functional Assessment of Chronic Illness Therapy; IPD: individual patient data; LSM: least squares mean; MD: mean difference; N: number of analysed patients; ND: no data; RCT: randomized controlled trial; SD: standard deviation; SE: standard error; SF-36v2: Short Form 36 version 2; SMD: standardized mean difference; VAS: visual analogue scale