Medicinrådet

# Bilag til Medicinrådets anbefaling vedrørende anifrolumab til til behandling af moderat til svær aktiv autoantistof-positiv systemisk lupus erythematosus

*Vers. 1.0*

# Bilagsoversigt

1. Ansøgers notat til Rådet vedr. anifrolumab
2. Forhandlingsnotat fra Amgros vedr. anifrolumab
3. Ansøgers endelige ansøgning vedr. anifrolumab

**Fra:** [redacted]
**Til:** [redacted]
**Emne:** Anifrolumab vurderingsrapport(udkast) SLE
**Dato:** 16. november 2022 10:00:40

---

Kære [redacted]

Tak for udkastet til Medicinrådets vurderingsrapport for anifrolumab til behandling af SLE.

Vi har ikke fundet væsentlige punkter/mangler som kan have indflydelse på [redacted] generelle konklusion. AstraZeneca er derfor overordnet enige i Medicinrådets vurdering af anifrolumab.

Vi ser frem til den endelige afgørelse.

Med venlig hilsen

[redacted]

[redacted]

---

**AstraZeneca A/S**
**Nordic Marketing Company** | Denmark | Market Access Department
World Trade Center Ballerup
Borupvang 3, DK-2750 Ballerup, Denmark
[redacted]

[redacted]

Amgros I/S
Dampfærgevej 22
2100 København Ø
Danmark

T +45 88713000
F +45 88713008

Medicin@amgros.dk
www.amgros.dk

15.11.2022

DBS/ECH

# Forhandlingsnotat

| | |
|---|---|
| Dato for behandling i Medicinrådet | 23.11.2023 |
| Leverandør | AstraZeneca |
| Lægemiddel | Saphnelo (anifrolumab) |
| Ansøgt indikation | Tillægsbehandling til behandling af voksne patienter med moderat til svær aktiv, autoantistof-positiv systemisk lupus erythematosus (SLE), uanset standardbehandling |

## Forhandlingsresultat

Amgros har opnået følgende pris på Saphnelo (anifrolumab):

*Tabel 1: Forhandlingsresultat*

| Lægemiddel | Styrke/form | Pakningsstørrelse | AIP | Forhandlet SAIP | Rabatprocent ift. AIP |
|---|---|---|---|---|---|
| Saphnelo (anifrolumab) | 300 mg/ IV | 1 stk. (koncentrat til infusionsvæske) | 7.020 | [redacted] | [redacted] |

Prisen er betinget af Medicinrådets anbefaling.

[redacted]

## Informationer fra forhandlingen

[redacted]

## Konkurrencesituationen

I dag anvendes Benlysta (belimumab) til samme indikation som Saphnelo (anifrolumab). Der er ingen behandlingsvejledning inden for SLE, da der er tale om en mindre patientpopulation.

*Tabel 2: Sammenligning af lægemiddelpriser*

| Lægemiddel | Dosering | Styrke og pakningsstørrelse | Pakningspris SAIP | Antal pakninger/år | Årlige lægemiddelomkostninger SAIP pr. år |
|---|---|---|---|---|---|
| Saphnelo (anifrolumab) | 300 mg IV hver 4. uge | 300 mg / 1 stk. | [redacted] | 13 | [redacted] |
| Benlysta (belimumab)** | Opstart: 10 mg/kg IV på dag 0, 14, 28, og efterfølgende hver 4. uge* | 400 mg / 1 stk. | [redacted] | 26 | [redacted] |
| Benlysta (belimumab)** | Opstart: 10 mg/kg IV på dag 0, 14, 28* | 400 mg / 1 stk. | [redacted] | 5 | [redacted] |
| | Efterfølgende 200 mg SC én gang ugentligt | 200 mg/ 1 stk.<br>(200 mg / 4 stk.) | [redacted] | 48<br>(9) | |
| Benlysta (belimumab)*** | 200 mg SC én gang ugentligt | 200 mg/ 1 stk. | [redacted] | 52 | [redacted] |
| Benlysta (belimumab)*** | 200 mg SC én gang ugentligt | 200 mg/ 4 stk. | [redacted] | 13 | [redacted] |

*Gns. patient vægt 71,4 kg (fra Medicinrådets vurderingsrapport)

**Vedligeholdelses behandlingen med Benlysta (anifrolumab), kan gives enten som IV hver 4. uge eller 200 mg SC én gang ugentligt (fra Medicinrådets vurderingsrapport)
***Benlysta (anifrolumab) kan gives som 200 mg SC én gang ugentligt (fra lægemidlets SPC)

## Status fra andre lande

Norge: Under evaluering [1].
Sverige: Under evaluering [2].

## Konklusion

Amgros vurderer, at det ikke muligt at få en bedre pris på nuværende tidspunkt er,

[redacted]

[1] Anifrolumab (Saphnelo) (nyemetoder.no)
[2] Hälsoekonomisk bedömning av Saphnelo vid systemisk lupus erythematosus (SLE) - Tandvårds- och läkemedelsförmånsverket TLV

Medicinrådet

# Application for the assessment of Saphnelo as an add-on therapy for moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy

Text, tables, or figures highlighted in [redacted] should be considered confidential



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# Table of contents





Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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# 1. Basic information

| Contact information | |
|---|---|
| **Name** | **Søren Clausen** |
| Title | Government Affairs & Market Access Head |
| Phone number | +45 23 61 55 84 |
| E-mail | Soren.Clausen@astrazeneca.com |
| **Name** | **Sahana Shanmugalingam** |
| Title | Pricing & Reimbursement Manager |
| Phone number | +45 31 76 50 99 |
| E-mail | sahana.shanmugalingam@astrazeneca.com |
| **Name** | **Thomas Stephens** |
| Title | Health Economist |
| Phone number | +47 401 05 991 |
| E-mail | thomas.stephens@astrazeneca.com |

| Overview of the pharmaceutical | |
|---|---|
| **Proprietary name** | Saphnelo |
| **Generic name** | Anifrolumab |
| **Marketing authorization holder in Denmark** | AstraZeneca AB SE-151 85 Södertälje Sverige |
| **ATC code** | L04AA51 |
| **Pharmacotherapeutic group** | Selective immunosuppressants |
| **Active substance(s)** | Anifrolumab |
| **Pharmaceutical form(s)** | Concentrate for solution for infusion |

| Overview of the pharmaceutical | |
|---|---|
| **Mechanism of action** | Anifrolumab is a human immunoglobulin G1 kappa monoclonal antibody that binds to subunit 1 of the type I interferon receptor (IFNAR1) with high specificity and affinity. This binding inhibits type I IFN signalling thereby blocking the biologic activity of type I IFNs. Anifrolumab also induces the internalisation of IFNAR1, thereby reducing the levels of cell surface IFNAR1 available for receptor assembly. Blockade of receptor mediated type I IFN signalling inhibits IFN responsive gene expression as well as downstream inflammatory and immunological processes. Inhibition of type I IFN blocks plasma cell differentiation and normalises peripheral T-cell subsets, restoring the balance between adaptive and innate immunity that is dysregulated in SLE. |
| **Dosage regimen** | The recommended dosage is 300 mg as an intravenous infusion over a 30-minute period every 4 weeks |
| **Therapeutic indication relevant for assessment (as defined by the European Medicines Agency, EMA)** | Saphnelo is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy |
| **Other approved therapeutic indications** | None |
| **Will dispensing be restricted to hospitals?** | Yes |
| **Combination therapy and/or co-medication** | Saphnelo is given as an adjunct therapy to standard therapy. Saphnelo has not been studied in combination with other biologic therapies and is not recommended for use in combination with biologic therapies. |
| **Packaging – types, sizes/number of units, and concentrations** | 300 mg/2 mL (150 mg/mL) in a single-dose vial |
| **Orphan drug designation** | No |



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## 2. Abbrevations

| | |
|---|---|
| **ACR** | American College of Rheumatology |
| **AHEG** | Ad Hoc Expert Group |
| **AIP** | Apotekernes indkøbspris (pharmacy purchase price) |
| **ANA** | Antinuclear antibody |
| **aPL** | Antiphospholipid antibodies |
| **AZA** | Azathioprine |
| **BEL** | Belimumab |
| **BICLA** | BILAG-based Compositive Lupus Assessment |
| **BILAG** | British Isles Lupus Assessment Group |
| **BLyS** | B lymphocyte stimulator |
| **BSA** | Body surface area |
| **CHMP** | Committee for Medicinal Products for Human Use |
| **CI** | Confidence interval |
| **CLASI** | Cutaneous Lupus Disease Area and Severity Index |
| **CNI** | Calcineurin inhibitor |
| **CNS** | Central nervous system |
| **CV(D)** | Cardiovascular (disease) |
| **CYC** | Cyclophosphamide |
| **DKK** | Danish kroner |
| **DMARD** | Disease modifying anti-rheumatic drug |
| **DRG** | Diagnosis-related group |
| **dsDNA** | Double-stranded deoxynucleic acid |
| **EAIR** | Exposure-adjusted incidence rate |
| **EMA** | European Medicines Agency |
| **EPAR** | European Public Assessment Report |
| **EULAR** | European League Against Rheumatism |
| **FACIT-F** | Functional Assessment of Chronic Illness Therapy-Fatigue |
| **GC** | Glucocorticoids (corticosteroids) |
| **GI** | Gastrointestinal |
| **HCQ** | Hydroxychloroquine |
| **HR** | Hazard ratio |



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| | |
|---|---|
| **IFN** | Interferon |
| **IFNAR1** | Type I interferon receptor |
| **IM** | Intramuscular |
| **IRR** | Incidence rate ratio |
| **ITC** | Indirect treatment comparison |
| **IV** | Intravenous |
| **KM** | Kaplan-Meier |
| **LLDAS** | Lupus Low Disease Activity State |
| **LN** | Lupus nephritis |
| **LS** | Least squares |
| **MAIC** | Matching-adjusted indirect comparison |
| **MCS** | Mental component summary (of the SF-36) |
| **mITT** | Modified intent-to-treat |
| **MMF** | Mycophenolate mofetil |
| **MTX** | Methotrexate |
| **OCS** | Oral corticosteroids |
| **OR** | Odds ratio |
| **PCS** | Physical component summary (of the SF-36) |
| **pDC** | Plasmacytoid dendritic cells |
| **PGA** | Physician's global assessment |
| **PLT** | Platelets |
| **PO** | Per os (orally) |
| **Q4W** | Every 4 weeks |
| **QoL** | Quality of life |
| **RA** | Rheumatoid arthritis |
| **RTX** | Rituximab |
| **RWE** | Real world evidence |
| **SC** | Subcutaneous |
| **SD** | Standard deviation |
| **SDI** | SLICC/ACR Damage Index |
| **SE** | Standard error |
| **SELENA** | Safety of Estrogen in Lupus National Assessment |



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| | |
|---|---|
| **SF-36(v2)** | Short Form 36 health survey (2nd version) |
| **SLE** | Systemic lupus erythematosus |
| **SLEDAI** | Systemic Lupus Erythematosus Disease Activity Index |
| **SLICC** | Systemic Lupus International Collaborating Clinics |
| **SLR** | Systematic literature review |
| **SmPC** | Summary of Product Characteristics |
| **SoC** | Standard of care |
| **SRI(4)** | SLE Responder Index (4) |
| **STC** | Simulated treatment comparison |
| **TTP** | Thrombotic thrombocytopenic purpura |
| **UK** | United Kingdom of Great Britain and Northern Ireland |
| **USA** | United States of America |



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# 3. Tables and Figures

**List of Tables**





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Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

**List of Figures**

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# 4. Summary

SLE is a heterogenous, chronic, multisystem autoimmune disease that can affect any organ and causes significant morbidity and mortality. Clinical presentation is highly variable, ranging from mild mucocutaneous manifestations to very severe life-threatening disease with multi-organ involvement. The most commonly affected organs are the skin, joints, kidneys, and lungs, as well as the cardiovascular and nervous systems. Patients with SLE experience reduced physical and mental wellbeing.

Current standard of care for SLE consists of a wide range of agents, including hydroxychloroquine (HCQ) and corticosteroids with or without immunosuppressive agents. Treatments are used in an individualised "treat to target" regimen. The goal of treatment is to achieve effective and durable disease control, prevent permanent organ damage and increase quality of life. Despite treatment with current standard of care options, some patients still have a moderate to severe, active SLE disease and could benefit from a new treatment option.

Saphnelo (anifrolumab) is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy. This application requests anifrolumab to be assessed across its whole marketing authorisations, and data is presented accordingly.

Anifrolumab is a fully human, G1 k monoclonal antibody that binds to subunit 1 of the type 1 interferon receptor (IFNAR1) and blocks the signalling of all classes of type 1 interferon. Type 1 interferons play a central role in the pathogenesis of SLE. Anifrolumab 300 mg is administered as an intravenous infusion over a 30-minute period every 4 weeks, as an adjunct therapy to standard therapy. It is a first-in-class treatment for SLE with a new mode of action and has demonstrated efficacy across the moderate to severe SLE population. Considering the heterogeneity of the disease and the individualised treat to target regimen, anifrolumab could be an alternative treatment option for Danish patients that have an active symptomatic disease, despite treatment with standard of care.

The efficacy of anifrolumab in SLE was assessed in three clinical trials; the pivotal phase 3 trial TULIP-2, supported by the phase 3 TULIP-1 and the phase 2b MUSE trials. All trials were 52-week, randomised, double-blind, placebo-controlled parallel-group studies designed to assess the efficacy and safety of anifrolumab in patients who have moderate to severe SLE despite standard therapy.

Analyses from the studies show that treatment with anifrolumab has a rapid and sustained effect on disease activity, with a numerically higher BICLA response rate observed already from week 4 (vs. standard therapy alone). In TULIP-2, patients in the anifrolumab group were 55% more likely to achieve a sustained BICLA response at any time in the study. A post hoc analysis found that BICLA responders had lower flare rates, higher rates of attainment of sustained reduction in glucocorticoids, greater improvements in patient-reported outcomes, and fewer SLE-related hospitalisations or emergency department visits.

AstraZeneca suggests that belimumab is the relevant comparator for anifrolumab in SLE patients in Denmark. Belimumab (Benlysta) is the only licensed and funded therapy for patients who still have a high degree of disease activity despite receiving treatment with standard therapy in Denmark. Although the product label for anifrolumab includes considerations for disease severity whereas belimumab's label highlights the need for a higher degree of disease activity, the patient population indicated for both treatments may overlap. AstraZeneca believes that the intravenous (IV) formulation of Benlysta is the appropriate comparator for anifrolumab given that both products are hospital-administered drugs. Belimumab 10 mg/kg, as an add-on to standard therapy, is administered as an intravenous infusion over a one hour period on days 0, 14, 28 and every 4 weeks thereafter. A scenario analysis is also considered where some patients switch to or use belimumab 200 mg instead (also as an add-on to standard therapy) administered

subcutaneously once weekly. This usage is estimated in line with the sales split per formulation of belimumab in Danish clinical practice.

An indirect treatment comparison was used to compare anifrolumab to belimumab, adjusting for differences in baseline characteristics between trials (a simulated treatment comparison) given the differences in trial populations. Based on the available data and the indirect comparison, it can be concluded that anifrolumab is at least as efficacious as belimumab with respect to reducing disease activity, whilst offering similar steroid sparing benefits. In addition, anifrolumab has demonstrated disease activity reduction in terms of overall moderate to severe organ system involvement and specific mucocutaneous disease activity reductions, not shown for belimumab.

A cost minimisation analysis was conducted comparing anifrolumab to belimumab IV as an add-on to standard therapy, given that both are hospital-administered and anifrolumab is likely to displace belimumab IV in clinical practice. The model considered time on treatment up to 5 years with costs only related to add-on biologic therapy for patients with SLE. The results showed that anifrolumab could be cost saving versus belimumab of over 16 000 DKK per patient. Scenario analyses compared to belimumab regimens combining intravenous and subcutaneous formulations show anifrolumab to have a somewhat comparable expenditure per patient. Given the overall similarity in the efficacy profiles for the average patient, it is assumed that anifrolumab will displace around half of all belimumab patients by 2027 in the budget impact analysis (an estimated 23 new patients in 2027, up from 6 in 2023) .

Generally, the current uptake of biologic treatments for SLE in Danish clinical practice is low. Due to the differentiated indication of anifrolumab, a small increase in the patient population receiving add on treatment with biologic therapy is possible, though to a large extent anifrolumab is expected to displace belimumab in clinical practice. The budgetary consequences of recommending anifrolumab for use in Danish clinical practice are expected to be modest (up to 1.4 million DKK per year within five years), whilst potentially offering benefits to a slightly broader range of patients served by currently available biologic therapies for SLE. As anifrolumab is cost saving compared to intravenous belimumab, if there is no additional growth in the biologics market following a recommendation of anifrolumab the budget impact would be minimal.



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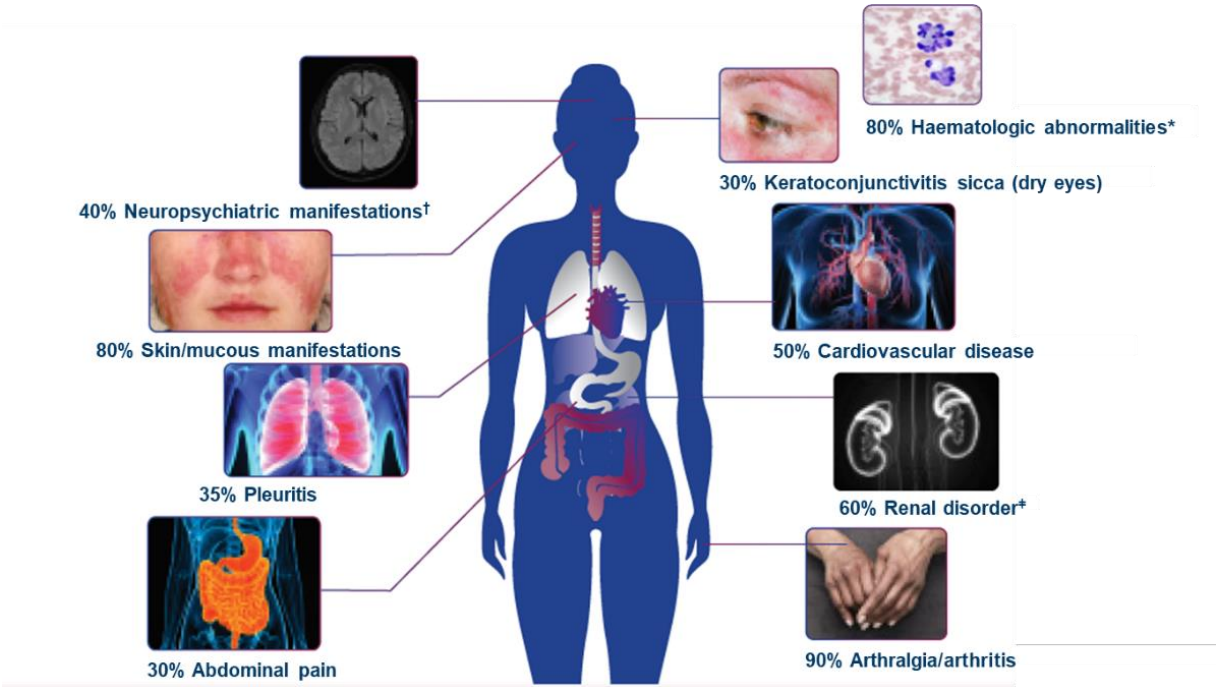
# 5. The patient population, the intervention and choice of comparator(s)

## 5.1 The medical condition and patient population

### 5.1.1 Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is a heterogenous, chronic, multisystem autoimmune disease that can affect any organ and causes significant morbidity and mortality.[1] SLE carries a high clinical burden due to wide spectrum of debilitating disease manifestations across multiple organ systems, irreversible organ damage and associated comorbidities/complications resulting from chronic systemic inflammation.[1,2] The clinical presentation of SLE is highly variable, ranging from mild mucocutaneous manifestations to severe life-threatening disease with multi-organ involvement (Figure 1).[1] Health-related quality of life in SLE patients, as measured by the EQ-5D, is lower than values reported in age- and sex-matched population norms and patients with other diseases.[3,4] Poor quality of life in patients with SLE is observed early in the disease course and persists in the long-term.[5] Despite treatment advancements in SLE, patients still experience up to a three-fold increase in risk of mortality compared to the general population.[6-8]

**Figure 1. Symptoms and manifestations of SLE**




**Sources**: [9-12]

*For example, lymphopenia, anaemia, leukopenia, thrombocytopaenia; †For example, migraines, seizures, depression, psychosis, cranial nerve lesions; ‡For example, proteinuria, haematuria, serum albumin <35g/L

Common manifestations include cutaneous and musculoskeletal symptoms, where it has been reported that up to 85% of SLE patients present with cutaneous manifestations,[12] whereas 70-95% of the patients have musculoskeletal involvement.[13] In terms of cutaneous manifestations, SLE patients may present with specific and/or non-specific skin manifestations where the specific manifestations may be acute or chronic, and can lead to permanent changes to the skin and hair loss. Acute skin involvement is often characterised by a butterfly rash (also called malar rash) which presents as a red (erythematous) rash over the cheeks and nasal bridge. Musculoskeletal involvement typically presents as arthritic symptoms and ranges in severity.[13]. Although mucocutaneous and musculoskeletal manifestations are the

most commonly observed, patients can also present with cardiovascular (CV), gastrointestinal (GI), renal, haematological, pulmonary and neuropsychiatric symptoms.[1,14] A nationwide population-based cohort study in Denmark observed a higher prevalence of comorbidities, including neuropsychiatric, cardiovascular, and venous thromboembolic diseases in patients with SLE both at diagnosis and up to 10 years prior to diagnosis.[15] The presence of these comorbidities can increase the complexity of diagnosing SLE.

The diagnosis of SLE is particularly challenging due to the heterogeneity of the disease and the wide spectrum of clinical manifestations; there is no single clinical feature or laboratory abnormality that can confirm diagnosis.[1,16] Although no official diagnostics criteria exist for SLE, classification criteria for SLE can be used to help diagnosis,[17] and several sets of criteria have been developed and refined over time.[1,18] The most recent criteria developed by the European League Against Rheumatism (EULAR) and the American College of Rheumatology (ACR) require a positive antinuclear antibody test followed by a weighted scoring across seven clinical and three immunologic domains. Patients scoring ≥10 points are classified as having SLE.[18] Although, a positive antinuclear antibody (ANA) test does not indicate the presence of SLE by itself, >98% of all SLE patients are ANA positive, 80% are positive for anti-dsDNA antibodies, and 40% have the presence of antiphospholipid antibodies.[19]

SLE is also known to affect the kidneys and can lead to hypertension, haematuria, proteinuria and chronic kidney disease.[1,11] Active and severe kidney involvement in SLE is known as lupus nephritis (LN). As the treatment paradigm for LN differs compared to other manifestations of SLE, and the clinical development programme for anifrolumab in LN is ongoing, the treatment of patients with LN is not discussed further in this submission.

### 5.1.2 Moderate to severe SLE

SLE patients can be stratified according to disease severity (mild, moderate and severe) based on the level of disease activity. Accurately assessing the level of disease activity is indicative of the patients' rates of experiencing episodic flares, organ damage, and an increased risk of mortality. Additionally, it ensures the patients receiving appropriate treatment. Several validated instruments have been developed to assess disease activity.[17,20] Current versions that are recommended and commonly used are the Systemic Lupus Erythematosus Disease Activity Index-2K (SLEDAI-2K)[21] and the British Isles Lupus Assessment Group (BILAG)-2004 index.[22] The SLEDAI-2K assesses disease activity based on the current or recent presentation of 24 clinical manifestations or serological values and provides a total score. The BILAG-2004 assess activity by the physician grading improvement in 97 clinical or laboratory items across nine organ systems which is used to develop a score for each of the organ systems on a scale of A (most active disease) to E (no previous activity). Further details on the scales can be found in Section 7.1 and Appendix D. Disease severity as defined by specified criteria on the SLEDAI-2K or BILAG-2004,[17] are presented in Table 1. Clinical trials have developed metrics of treatment response in SLE on the basis of these scales (see section 7.1 for details).

**Table 1. Defining disease severity using SLEDAI-2K and BILAG**

| | Mild | Moderate | Severe |
|---|---|---|---|
| **Clinical Description** | Clinically stable lupus with no life-threatening organ involvement, mainly manifesting as arthritis, mucocutaneous lesions and mild pleuritis | Serious manifestations, which would cause significant chronic scarring if left untreated | Organ- or life-threatening disease |
| **SLEDAI-2K Score** | <6 | 6 – 12 | >12 |
| **BILAG** | 1 BILAG B score | ≥2 BILAG B scores | ≥1 BILAG A score |

BILAG, British Isles Lupus Assessment Group; SLEDAI, SLE disease activity index

Moderate disease is defined as serious organ manifestations, which would cause significant, chronic scarring if left untreated, whereas severe disease is defined as organ- or life-threatening disease.[17,21,23] Patients can be considered to have moderate to severe disease if they have a SLEDAI-2K score ≥6 or ≥1 A or ≥2 B scores on the BILAG.[21,23] Increases in total BILAG and SLEDAI scores have been associated with increased mortality risk.[24-26] Real-world evidence studies in Sweden have found that approximately half of SLE patients had moderate-to-severe disease at diagnosis.[3,6]

The progressing organ manifestations experienced by SLE patients are linked to episodic, unpredictable flares (repeated exacerbations of disease activity that occur in one or more organ systems involving new or worse clinical signs and symptoms).[27] In patients with moderate to severe disease, flares are observed to be nearly three times as likely to occur (61% of patients had a flare in the past 12 months) compared to those with mild disease (21%).[28,29]

For every flare, the likelihood of subsequent organ damage approximately doubles.[5,30,31] Increases or higher levels of disease activity can increase organ damage in the cardiovascular, pulmonary, musculoskeletal, neuropsychiatric/central nervous system (CNS), ocular, and renal domains.[24,28,32] In terms of developing cardiovascular disease (CVD), including stroke, acute myocardial infarction, and cardiovascular death, a study in Denmark reported that SLE patients had over twice the risk of CVD compared with controls, and the risk was even more pronounced in patients ≤50 years of age.[33]

Organ damage is typically measured using the SLICC/ACR damage index (SDI) which assesses damage across 12 organs/systems. Although the SDI is distinct from disease activity measurements, higher scores from both SLEDAI and BILAG are significantly associated with increased risk of organ damage, comorbidities and mortality.[32] Hence, organ damage is commonly seen in patients with moderate to severe SLE and adds to the disability, limitations on daily activities, and in general low health-related quality of life, as well as increasing unemployment rates.[34,35] Nordic studies have identified that accrued organ damage over time is associated with increased mortality.[36,37] Specifically, a single-unit increase in SDI score is associated with a 34% increase in the risk of death.[38] In a registry-based cohort study of 3 747 Danish SLE patients, there was a significant increase in risk for all-cause mortality (HR 2.21; p<0.001) compared with controls. The risk was even more pronounced in patients ≤50 years of age (HR 2.51, p<0.001).[33]

Despite representing only a small patient group, SLE is associated with meaningful economic consequences as patients with uncontrolled moderate to severe disease are prolific users of healthcare. Danish SLE patients have an average of 0.5 hospitalizations per year, at an average of 6.4 days per stay.[39] Further, analyses on Swedish patients have shown that both disease activity and organ damage are key predictors of healthcare costs, as well as indirect costs through lost productivity and the high number of sick days taken.[40,41] The burden of increased cost associated with moderate to severe disease is greater than that for mild disease, as demonstrated by a UK retrospective cohort study which reported that average annual total healthcare costs were substantially greater, and were increasing over time.[42] The use of effective treatments in patients with active SLE can reduce the burden on the healthcare system and may help patients continue with their daily activities and work.

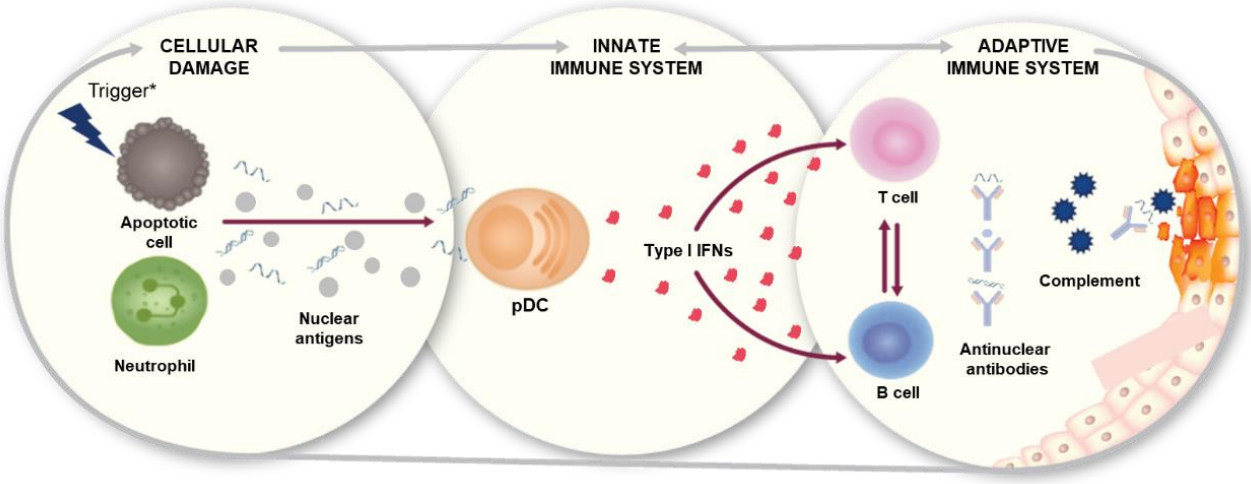
### 5.1.3 Pathophysiology

The pathophysiology of SLE involves inappropriate activation of the immune system (or immune dysregulation) following exposure to environmental factors in genetically susceptible individuals.[1] The pathogenesis of SLE involves both immune dysregulation and local inflammatory responses which lead to tissue injury.[43] In SLE, there is a defect in the removal of dead cells and remnant cellular debris causes a disturbance in immune tolerance and leads to the generation of pathogenic auto-antibodies.[1] These auto-antibodies bind to self-antigens to form immune complexes, and also activate neutrophils, the complement system, and produce cytokines, which all contribute to organ damage.[1,43,44]

A group of cytokines called type 1 interferons (IFN) are most potently produced by plasmacytoid dendritic cells, and are elevated during active SLE disease.[45] Excessive production of IFN is thought to be central to the development of the

disease and has been linked to organ damage (Figure 2).[46-48] Type I IFN bind the IFN receptor initiating a wide range of responses, including activation of immune responses (e.g., by activating antigen presenting cells and increasing the production of antibodies) and increasing the expression of self-antigens.[43,46]

**Figure 2. Pathophysiology of SLE and the role of type I IFN**




Sources: [1,49-52]

IFN, interferon; pDC, plasmacytoid dendritic cells; SLE, systemic lupus erythematosus

### 5.1.4 Patient Population

SLE predominantly affects women, approximately 85% of Danish SLE patients are female.[33,53]. Disease onset typically occurs during childbearing years,[19] though the estimated median age at diagnosis in an analysis of the Danish National Patient Registry was 47 years.[53] A cross-sectional analysis of Danish SLE patients shows a mean age of the prevalent population of 41.9 years.[33] When accounting for age at diagnosis of patients with moderate or severe disease, an UK observational study identified the mean age to be 48.2 years at diagnosis for those with moderate disease and 53.9 years for those with severe.[54]

Saphnelo is indicated for use in adult patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy. As noted above, almost all SLE patients would be considered autoantibody-positive, with >98% of patients having positive ANA, 80% are positive for anti-dsDNA antibodies, and 40% have the presence of antiphospholipid antibodies.[19] Despite estimates of between 50 and 90% of SLE patients considered to have moderate-to-severe disease globally,[54-59] analyses on Swedish datasets suggest that in the Nordics the proportion may be on the lower end of this scale at just under half of prevalent patients.[3,6] Feedback from Nordic rheumatologists suggests that this may be a result of patients having access to comprehensive, nationalised healthcare, largely centred at university hospitals.

In an analysis on a regional cohort of SLE patients in Sweden, approximately 30% (100/332) of patients would have been considered to have had moderate-to-severe, active autoantibody-positive SLE despite standard therapy at any time over a median follow-up of 8.8 years. This was based on a positive ANA or immunological disease (abnormal anti-dsDNA or anti-Smith antibodies), a clinical SLEDAI-2K score of ≥4 and a Physician's Global Assessment (PGA) ≥1, and currently on stable treatment and therefore eligible for a clinical trial of an adjunct therapy.[3] Given the dearth of Danish data on this patient group, characteristics of Swedish patients are reported in Table 2.

**Table 2. Characteristics of Swedish patients with SLE at index date***

| | All SLE patients (N = 332) | Moderate-to-severe, active, autoantibody-positive SLE despite current therapy (N = 100) |
|---|---|---|
| Female, n (%) | 284 (86%) | 84 (84%) |
| Current age (years), mean (SD) | 48.7 (17.6) | 46.0 (17.7) |
| Age at diagnosis (years), mean (SD) | 40.0 (17.7) | 34.8 (16.4) |
| Time since SLE diagnosis (years), mean (SD) | 8.67 (9.97) | 11.2 (11.1) |
| Weight (kg), mean (SD) | 69.1 (13.8) | 69.5 (13.3) |
| Caucasian ethnicity, n (%) | 293 (88%) | 83 (83%) |
| Number of ACR criteria fulfilled, mean (SD) | 4.78 (1.32) | 5.11 (1.36) |
| ACR10: Immunologic disease, n (%)† | 184 (55%) | 61 (61%) |
| ACR11: Antinuclear antibody positive, n (%) | 328 (99%) | 99 (99%) |
| Low C3 or C4 complement, n (%) | 102 (31%) | 33 (33%) |
| Clinical SLEDAI-2K score, mean (SD) | 2.39 (3.94) | 6.25 (3.40) |
| Clinical SLEDAI-2K ≥8, n (%) | 40 (12%) | 32 (32%) |
| PGA, mean (SD) | 0.60 (0.83) | 1.31 (0.62) |
| PGA ≥1, n (%) | 135 (41%) | 100 (100%) |
| SDI score, mean (SD) | 0.94 (1.58) | 1.17 (1.63) |
| Treated with hydroxychloroquine, n (%) | 207 (62%) | 70 (70%) |
| Treated with oral corticosteroids, n (%) | 222 (67%) | 83 (83%) |
| Daily prednisone-equivalent dose (mg), mean (SD)‡ | 10.6 (12.3) | 13.5 (12.4) |
| Prednisone ≥10 mg/day, n (%) | 74 (22%) | 39 (39%) |
| Treated with immunosuppressant, n (%) | 105 (32%) | 57 (57%) |
| Treated with biologic DMARD, n (%) | 12 (4%) | 18 (18%) |

* Index date is the date of inclusion into the registry for all SLE patients and the date first considered to meet the criteria of moderate-to-severe, active, autoantibody-positive SLE despite current therapy for the subgroup. † Presence of anti-dsDNA or anti-Smith antibodies. ‡ In patients currently receiving steroids

ACR, American College of Rheumatology; DMARD, disease modifying anti-rheumatic drug; PGA, Physician Global Assessment; SD, standard deviation; SDI, SLICC/ACR Damage Index; SLE, systemic lupus erythematosus

### 5.1.5 SLE in Denmark

The prevalence of SLE in Denmark appears to be increasing over time. In an 8-year prospective study conducted in Funen County, Denmark, between 1995 and 2003, the point prevalence of definite SLE was estimated to increase from 21.9 to 28.3 per 100 000 over the study period follow-up.[60] A more recent national registry-based study in Denmark estimated the 2011 point prevalence at 45.2 per 100 000 and the annual incidence at 2.35 per 100 000.[53] Table 3 shows the estimated incidence and prevalence of SLE over the past five years based on an extrapolation of the 2011 point

prevalence and the estimated incidence of SLE in Denmark from the National Patient Registry.[53] Further details on the estimation can be found in Appendix L.

**Table 3. Estimated incidence and prevalence of adult SLE over the past 5 years**

| Year | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|
| Population aged ≥18 years, 1st Jan | 4 615 690 | 4 645 697 | 4 666 625 | 5 687 050 | 4 708 372 |
| Estimated incidence of adult SLE in Denmark | 108 | 109 | 110 | 110 | 111 |
| Estimated prevalence of adult SLE in Denmark | 2 262 | 2 311 | 2 361 | 2 409 | 2 453 |

Within the marketing authorisation for Saphnelo in patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy, estimates for the proportion of patients with SLE who would meet these criteria have been derived.

Given that patient with lupus nephritis (LN) are treated under a different guideline and paradigm, and that patients with active, severe LN were excluded from the anifrolumab trials (the clinical programme for anifrolumab in LN is ongoing), it is assumed that in the near term anifrolumab will be used in patients without nephritis. The prevalence of LN in Denmark in 2011 was 6.4 per 100 000, with an annual incidence of 0.45 per 100 000.[53] Based on this it is derived that approximately 89% of SLE patients do not have concurrent nephritis at of 2022 (see Appendix L).

Whilst there are no standardised definitions of moderate to severe, active SLE, using data from a Swedish regional SLE cohort (KLURING; *Clinical Lupus Register in North-Eastern Gothia*), it is estimated that approximately 36% of current prevalent non-nephritis SLE patients would be autoantibody positive and receiving standard therapy, whilst still with moderate-to-severe, active disease.[3] This is based on 99.1% of SLE patients being considered autoantibody-positive (given a recorded history of ANA positivity or anti-dsDNA positivity), and 83.8% of autoantibody-positive patients were being treated with standard therapy in 2020 (including stable treatment with either antimalarials, corticosteroids, non-steroidal immunosuppressants, and/or biologic immunosuppressants). Of autoantibody-positive patients on standard therapy, 43.5% continue to have moderate to severe, clinically active disease (defined as a clinical SLEDAI-2K score excluding serological components of at least 4 as well as a physician's global assessment of disease activity of at least 1 on a 0 to 4 scale), indicating that 36.1% of prevalent non-nephritis SLE patients would meet the marketing authorisation for Saphnelo (99.1%*83.8%*43.5% = 36.1%). Table 4 shows the estimated patient numbers within the eligible population over the coming five years. Given that belimumab is also a treatment option for some of these patients, and rheumatologists select therapies for SLE patients on a 'treat to target' approach (see 5.2 for details), anifrolumab may not be used for all of these patients. It should also be caveated that this is only one potential method of objectively defining the moderate to severe, active autoantibody positive SLE population and is subject to some uncertainty. See section 8.7.4 for the expected uptake of anifrolumab.

**Table 4. Estimated number of patients eligible for treatment**

| Year | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| National population aged ≥18 years | 4 735 438 | 4 760 554 | 4 785 026 | 4 807 256 | 4 829 216 |
| Prevalent adult SLE patients | 2 497 | 2 540 | 2 583 | 2 625 | 2 666 |
| Patients in Denmark with moderate-to-severe, active, autoantibody-positive non-renal SLE, despite current therapy | 802 | 818 | 833 | 848 | 863 |

### 5.1.6 Patient populations relevant for this application

Given the marketing authorisation and the clinical trial evidence, the patient population considered for Saphnelo in this application is for patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy.

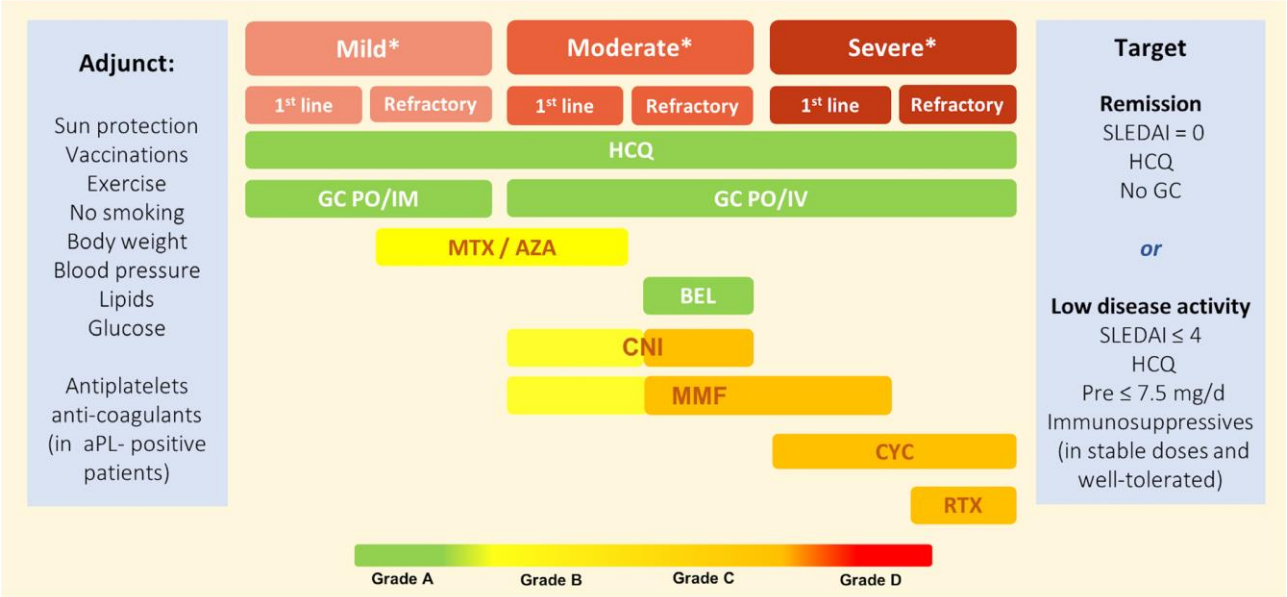
It is of note that the only other currently licensed treatment for patients with SLE in a similar population in Denmark is Benlysta. Benlysta is indicated as add-on therapy in adult patients with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti-dsDNA and low complement), despite standard therapy.

## 5.2 Current treatment options and choice of comparator(s)

### 5.2.1 Current Treatment Options

Danish SLE guidelines were last updated in 2014,[19] and are consistent with the treat-to-target approach of the 2019 European League Against Rheumatism (EULAR) recommendations for SLE. [61] The aim of treatment should be to prevent further organ damage, optimize health related quality of life by controlling the disease activity, minimize comorbidities and side effects caused by treatment, as well as ensure long term survival.[61] Figure 3 provides an overview of the 2019 EULAR recommendations for the management of non-renal SLE.

**Figure 3. 2019 EULAR recommendations for the treatment of non-renal SLE**




The figure shows the recommended drugs with the respective grading of the recommendation [61]. *Mild, constitutional symptoms/mild arthritis/rash ≤9% BSA/PLTs 50–100x103/mm3; SLEDAI ≤6; BILAG C or ≤1 BILAG B manifestation; Moderate, RA-like arthritis/rash 9–18% BSA/cutaneous vasculitis ≤18% BSA; PLTs 20–50x103/mm3/serositis; SLEDAI 7–12; ≥2 BILAG B manifestations; Severe, major organ threatening disease (nephritis, cerebritis, myelitis, pneumonitis, mesenteric vasculitis; thrombocytopaenia with platelets <20x103/mm3; TTP-like disease or acute haemophagocytic syndrome; SLEDAI >12; ≥1 BILAG A manifestation

aPL, antiphospholipid antibodies; AZA, azathioprine; BEL, belimumab; BILAG: British Isles Lupus Assessment Group disease activity index; BSA, body surface area; CNIs, calcineurin inhibitors; CYC, cyclophosphamide; GC, corticosteroids (glucocorticoids); HCQ, hydroxychloroquine; IM, intramuscular; IV, intravenous; MMF, mycophenolate mofetil; MTX, methotrexate; PLTs, platelets; Pre, prednisone; PO, per os (orally); RA, rheumatoid arthritis; RTX, rituximab; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; TTP, thrombotic thrombocytopenic purpura

Hydroxychloroquine (HCQ) is recommended for all patients with SLE, unless contraindicated. Corticosteroids can be used at doses and route of administration that depend on the type and severity of organ involvement. Prompt initiation

of immunomodulatory agents can expedite the tapering/discontinuation of corticosteroids. In patients not responding to HCQ (alone or in combination with corticosteroids) or patients unable to reduce corticosteroids below doses acceptable for chronic use, addition of immunomodulating or immunosuppressive agents such as methotrexate, azathioprine or mycophenolate should be considered. In patients with inadequate response to standard therapy (combinations of HCQ and corticosteroids with or without immunosuppressive agents), defined as residual disease activity not allowing tapering of corticosteroids and/or frequent relapses, add-on treatment with belimumab should be considered. In organ-threatening disease refractory or with intolerance/contraindications to standard immunosuppressive agents, off-label rituximab can be considered.[61] Prior to the approval of Saphnelo, only hydroxychloroquine, azathioprine, and belimumab were approved for the treatment of SLE in Denmark.[62-64] This highlights the need for further evidence-based treatments for patients across the moderate to severe disease spectrum not responding to standard therapies.

For chronic maintenance treatment, corticosteroids should be minimised to ≤7.5 mg/day (prednisone equivalent) and, when possible, withdrawn.[61] Long-term use of high systemic doses of corticosteroids (>7.5 mg/day prednisone equivalent) can cause substantial morbidity and irreversible organ damage, including osteoporosis, cataracts and fractures, Cushingoid appearance and weight gain, hyperglycaemia/diabetes, CVD, and immunosuppression.[65-68]

### 5.2.2 Choice of Comparator(s)

As the only licensed and funded therapy for active autoantibody-positive SLE, despite standard therapy in Denmark, belimumab (Benlysta®) is considered the appropriate comparator therapy for anifrolumab for this submission. Whilst anifrolumab has a different mechanism of action to belimumab, the indication for both therapies differ slightly where anifrolumab considers patients with disease severity (moderate to severe) whereas belimumab highlights patients with disease activity (high degree of activity, see section 5.2.3 below). Based on this, both therapies might fall in the same place in the treatment pathway where belimumab is expected to be displaced by anifrolumab in clinical practice as anifrolumab is not restricted to patients with high clinical or serological disease activity.

Whilst belimumab has not been previously assessed and recommended by the Danish Medicines Council, a full health economic analysis against placebo is not included in this submission. It is argued that using belimumab as a comparator meet the criteria for exception as it is an established standard treatment, with documented clinical effect, at a low cost to the Danish healthcare system. In addition, the cost-effectiveness of belimumab has previously been assessed vs. placebo (standard therapy alone) in several other countries, including England and Sweden, and was found to be cost-effective.[69,70] The clinical data from anifrolumab trials comparing anifrolumab + standard therapy to placebo + standard therapy is included for reference as well.

Belimumab has been approved and available for use in Denmark since August 2011 and is a recommended treatment in the guidelines of the Dansk Reumatologisk Selskab (from 2014),[19] implying that it is an established standard treatment in Danish clinical practice and has been for several years. The efficacy of belimumab in a patient population relevant to Denmark has been established in its European marketing authorization and its supporting data for patients with active autoantibody-positive SLE, with a high degree of disease activity, despite standard therapy. In addition, the number of patients on biologic treatment for SLE in Denmark is low. Based on sales figures for Benlysta obtained from IQVIA's databases, an estimated [redacted] doses of the IV formulation of Benlysta and [redacted] doses of the subcutaneous form were administered in 2021 (equivalent to a full year of treatment for a total of around [redacted] patients). After adjusting for time on treatment with belimumab (see details from the health economic model in section 8), [redacted] patient-years on treatment equates to approximately [redacted] patients receiving treatment at some point in a year. Therefore, the total cost of belimumab use to the Danish healthcare system is relatively low.

With respect to the low number of patients treated with belimumab in Denmark relative to the number of potentially eligible patients reported in Table 4, there are a range of potential driving factors. As noted in section 5.1.5 above, there are uncertainties in using objective measures to define eligibility for biologic therapy. In addition, the choice to initiate biologic therapy is made on a case by case basis based on the assessment of the appropriate candidate for that therapy. Factors which may specifically motivate belimumab use are unclear, though some factors which have influenced the lack of use have been identified in advisory boards AstraZeneca has held with SLE experts both in the Nordics and across the globe. Notably, there has been a lack of satisfaction with the efficacy in clinical practice, such as low response rates or delayed/slow responses. This has led to challenges in identifying appropriate candidates for treatment with regards to the clinical presentation. A treat-to-target approach is advocated in the management of SLE. Despite the label criteria for belimumab including certain biomarkers as examples (e.g., low complement and/or positive anti-dsDNA), the expert committee convened by the CHMP commented that serological measures should only be considered part of the criteria for treatment initiation and has been echoed in some treatment guidelines.[61,71,72] This lack of clarity on the appropriate candidates for therapy has led to a generally slow uptake of biologic therapies in SLE compared to other rheumatic diseases.

This uncertainty in the use of objective markers to determine candidates for biologic therapy is evident in the KLURING registry, which was used to determine potential eligibility in Table 4 above. Of the 253 patients in the register who attended the clinic between 7 September 2020 and 7 September 2021, 9 patients were treated with Benlysta.[3] Of these 9, only 7 had moderate to severe, clinically active SLE (as defined in section 5.1.5 above) out of a total of 83 patients considered to be in this subgroup. This indicates that in clinical practice the definition for biologic eligibility is not directly linked to objective measures, as 2 patients receiving belimumab were outside of this subgroup, but also the majority of patients in this subgroup were not determined to be candidates for belimumab based on the judgement of the treating physician. Therefore, objective eligibility and candidates for use are not perfectly aligned, hence the limited uptake of belimumab relative to the estimated number of eligible patients.

### 5.2.3 Description of the Comparator(s)

Belimumab (Benlysta®; ATC code L04AA26) is a human IgG1λ monoclonal antibody specific for soluble human B Lymphocyte Stimulator protein (BLyS, also referred to as BAFF and TNFSF13B). Belimumab blocks the binding of soluble BLyS, a B-cell survival factor, to its receptors on B-cells. This inhibits the survival of B-cells and reduces their differentiation into immunoglobulin-producing plasma cells.[63]

In Europe, belimumab is indicated as an add-on therapy in patients aged 5 years and older with active, autoantibody-positive SLE with a high degree of disease activity (e.g., positive anti dsDNA and low complement) despite standard therapy. The label was updated in May 2021 to include the treatment of adult patients with active lupus nephritis (in combination with background immunosuppressive therapies).[63] Belimumab is available as both an intravenous formulation (powder for concentrate for solution for infusion) and a subcutaneous formulation (solution for injection in pre-filed pen) (Table 5). The recommended dose regimen is 10 mg/kg, administered intravenously by infusion over a 1-hour period, on Days 0, 14 and 28, and at four-week intervals thereafter, or 200 mg once weekly, administered subcutaneously (dosing is not based on weight).[63] The subcutaneous formulation is only indicated for adults. Premedication including an antihistamine, with or without an antipyretic, may be administered before the infusion of belimumab.

Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after six months of treatment, if patients experiences psychiatric symptoms, or if the patient is breast-feeding.[63]

Physicians should assess the risk of depression and suicide considering the patient's medical history and current psychiatric status before treatment with belimumab and continue to monitor patients during treatment. Patients should be monitored for any symptoms suggestive of progressive multifocal leukoencephalopathy (e.g., cognitive, neurological or psychiatric symptoms).

**Table 5. Available forms of belimumab in Denmark**

| Product (Item Number) | Form | Strength | Pack Size | Manufacturer | Pharmacy Purchase Price | Pharmacy Sale Price (inc VAT) |
|---|---|---|---|---|---|---|
| Benlysta (421527) | Powder for concentrate for infusion | 120 mg | 1 | GlaxoSmithKline | 1 179.84 | 1 605.20 |
| Benlysta (422388) | Solution for injection in pre-filled pen | 200 mg | 1 | GlaxoSmithKline | 1 703.30 | 2 309.90 |
| Benlysta (166242) | Solution for injection in pre-filled pen | 200 mg | 4 | GlaxoSmithKline | 6 545.57 | 8 828.80 |
| Benlysta (458249) | Powder for concentrate for infusion | 400 mg | 1 | GlaxoSmithKline | 3 932.80 | 5 311.35 |

**Source:** medicinpriser.dk. Accessed 16 March 2022.

## 5.3 The intervention

Anifrolumab (Saphnelo) is indicated as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive systemic lupus erythematosus (SLE), despite standard therapy. Anifrolumab has been evaluated in clinical trials in patients receiving standard therapy with antimalarials (e.g., chloroquine, hydroxychloroquine, quinacrine), corticosteroids (e.g., oral prednisone), and/or immunosuppressants (e.g., azathioprine, methotrexate, mycophenolate mofetil/mycophenolic acid, and mizoribine).[73,74]

Anifrolumab has demonstrated efficacy across the indicated population, regardless of disease duration, prior biologic use, baseline serology, and baseline standard therapy.[73-78] Patients who responded to therapy also notably achieved improved outcomes in sustained glucocorticoid reduction, and skin and joint manifestations.[73,74]

The recommended dose of anifrolumab is 300 mg every four weeks. Following dilution with sodium chloride (0.9%) solution for injection, anifrolumab should be administered as an intravenous infusion over 30 minutes.[79] Treatment should be initiated and supervised by a physician experienced in the treatment of SLE. In patients with a history of infusion-related reactions, premedication (e.g., an antihistamine) may be administered before the infusion of anifrolumab.[79]

Anifrolumab modestly suppresses the levels of some cytokines, but the subsequent impact on cytochrome P450 (CYP450) metabolic activity is unknown.[79] Since the effect of anifrolumab on CYP450 is unknown, any interaction or effect on the metabolism of other medications is also unknown. In patients who are being treated with other medicines that are CYP substrates with a narrow therapeutic index, where the dose is individually adjusted (e.g., warfarin), therapeutic monitoring is recommended in case anifrolumab effects metabolism.[79] No dose adjustments are required for the elderly (≥65 years old), or patients with renal impairment or hepatic impairment. However, data on use in elderly patients are limited and no specific studies with anifrolumab 300 mg have been conducted in patients with renal or hepatic impairment.[79]

There are no established criteria on when to discontinue treatment with anifrolumab. Maximum duration of treatment with anifrolumab assessed in any active or prior clinical trial is 208 weeks,[80] though the longest follow-up published to date is 156 weeks.[81] The 2019 EULAR recommendations for management of SLE state that the goal of treatment should

be complete remission (absence of clinical activity with no use of oral corticosteroid or immunosuppressive drugs) or, if this cannot be achieved, low disease activity in all organ systems, maintained with the lowest possible dose of oral corticosteroids (see section 5.2.1).[61]

No specific diagnostic tests are required to be eligible for treatment with anifrolumab, though anifrolumab is indicated for patients with autoantibody-positive SLE. To be considered to have autoantibody-positive SLE for inclusion in clinical trials, patients had to fulfil 4 of the 11 American College of Rheumatology (ACR) revised 1982 classification criteria for SLE, including at least one of the following serological tests:

a) Positive antinuclear antibody (ANA) test at screening by immunofluorescent assay (IFA) at the central laboratory with titre ≥1:80; OR
b) Anti-dsDNA antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; OR
c) Anti-Smith antibody at screening elevated to above normal as per the central laboratory[73,74]

In clinical trials, patients were classified as having either a low or high type 1 interferon gene signature, determined by the expression of four interferon-stimulated genes: IFI27, IFI44, IFI44L, and RSAD2. Clinical efficacy of Anifrolumab was observed in both the high and low type 1 interferon gene signature groups.[74]

**Table 6. Available forms of anifrolumab in Denmark as of 18 April 2022**

| Product | Form | Strength | Pack Size | Manufacturer | Pharmacy Purchase Price | Price per Pack |
|---|---|---|---|---|---|---|
| Saphnelo | Concentrate for solution for infusion | 300 mg | 1 | AstraZeneca | 7 200.00 | 9 709.85 |

# 6. Literature search and identification of efficacy and safety studies

## 6.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted using Embase, MEDLINE®, and the Cochrane Library using the Ovid platform in order to identify phase 2 and phase 3 randomised controlled trials (RCTs) that evaluate efficacy, safety, and quality of life data of active treatments in patients with moderate to severe, active SLE. Searches were conducted up to 11 March 2021. The results were filtered according to the parameters of this report and included studies are listed below. The entire SLR can be found in appendix A.

In brief, study screening was performed using the systematic review software DistillerSR (Evidence Partners, Ontario, Canada). After the removal of duplicate citations, titles and abstracts were reviewed by two independent reviewers for study eligibility according to the pre-specified inclusion and exclusion criteria (see Table A4 in Appendix A. Literature search for efficacy and safety of intervention and comparator(s) for details). Any discrepancies between the two reviewers that could not be resolved by consensus were referred to and resolved by a third reviewer before proceeding to full-text review.

Studies that met the inclusion criteria and those that could not be excluded due to insufficient information were further reviewed at the full-text screening phase. Full-text articles were reviewed by two independent reviewers. Any discrepancies between the two reviewers that could not be resolved by consensus were referred to and resolved by a third reviewer before the article was included. Included full-text articles were further validated for inclusion during the data extraction phase.

Data extraction was performed for the studies meeting all inclusion criteria using a standardised Excel-based form to capture all relevant information. Information from the full-text articles was extracted by one reviewer and validated by a second reviewer. A third reviewer was consulted to resolve discrepancies, as necessary.

In order to localise the full SLR to the Danish case, further restrictions on the identified studies were applied. Given that belimumab is the relevant comparator (see section 5.2.2), only studies including either belimumab or anifrolumab were considered as relevant studies for this application. These included studies at the licensed doses of anifrolumab or belimumab in Denmark, and could be at any phase as long as they were randomised and included at least one of the reported endpoints from the key registration study for anifrolumab: TULIP-2. In addition, attempts were made to minimise heterogeneity between study designs and maximise their relevance to Danish clinical practice. This included considerations with regards the standard therapy used to be in line with current treatment options in Denmark, population characteristics of relevance locally and to the indicated population, and the duration of the study and timepoint for reporting of outcomes. Table 7 provides an overview of these considerations.

**Table 7. Inclusion criteria for studies relevant to the Danish case**

| | Inclusion Criteria | Exclusion Criteria |
|---|---|---|
| Population | Adult patients with moderate to severe, active autoantibody-positive SLE | • Studies including children or adolescents only<br>• Studies including a majority of patients who may be considered not representative of the Danish SLE population eligible for add on therapy (due to either demographic or clinical characteristics) |
| Intervention(s) | Add on therapies to standard therapy:<br>• Anifrolumab 300 mg IV Q4W<br>• Belimumab 10 mg/kg IV Q4W<br>• Belimumab 200 mg SC QW<br>Where standard therapy consists of antimalarials, corticosteroids, and non-steroidal immunosuppressants (as outlined in section 5.2.1) | • Any other add on therapy<br>• Where the "standard therapy" is not composed of treatments recommended for use in SLE in Denmark/Europe |
| Outcomes | • BILAG-Based Composite Lupus Assessment (BICLA) response at week 52<br>• Sustained reduction in corticosteroid dose to ≤7.5 mg/day between weeks 40 and 52<br>• Reduction of 50% or more in the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) at week 12<br>• A reduction of 50% or more in counts of both swollen joints and tender joints at week 52<br>• BILAG disease flares through week 52<br>• SLE Responder Index (SRI)-4 at week 52 | Study does not report on any of the reported outcomes of relevance |
| Study Design | Randomised clinical trial | • Single arm studies<br>• Non-randomised studies (whether prospective or retrospective) |

## 6.2 List of relevant studies

Three trials were identified evaluating the efficacy of anifrolumab at the licensed dose of 300mg Q4W: TULIP-1, TULIP-2, and MUSE. The efficacy of belimumab at the licensed doses and formulations has been assessed in five phase 3 placebo-controlled, randomised controlled trials: the initial registration studies of the IV formulation (BLISS-52[82] and BLISS-76[83]), a subsequent trial in east Asian populations (BEL113750[84]), a phase 3/4 trial to assess efficacy and safety in patients of Black African ancestry (EMBRACE[85]), and an assessment of the subcutaneous formulation (BLISS-SC[86]). All studies for anifrolumab and belimumab recruited adult patients with auto-antibody positive SLE, with the same classification criteria for SLE used between trials (see Appendix B. Main characteristics of included studies). All studies excluded those with active lupus nephritis or severe neuropsychiatric lupus.

As both anifrolumab and belimumab are add-ons to standard therapy, patients in all studies were required to be on stable (defined as no changes in dose within a specified time period) treatment with oral corticosteroids, antimalarials, and/or immunosuppressants. However, in the BEL113750 and EMBRACE studies, patients were permitted to use different background medications such as non-steroidal anti-inflammatory drugs (NSAIDs) and traditional Chinese medicine as the sole standard of care. They were therefore considered to not be relevant to the Danish case. In addition, as race and ethnicity are known risk factors for SLE,[87] as well as potential prognostic factors and treatment-effect modifiers for belimumab,[85,86,88] there is further rationale for the exclusion of these studies from indirect comparisons to avoid the introduction of unnecessary heterogeneity and potential bias.

Given that inclusion criteria were largely similar between BLISS-52, BLISS-76, BLISS-SC, TULIP-1, TULIP-2, and MUSE, these studies were considered relevant to inform indirect treatment comparisons. Scenario analyses excluding the phase 2b MUSE trial from the evidence base for anifrolumab are appended to this submission (Appendix K. Full report of the indirect treatment comparison on efficacy).

**Table 8. Relevant studies included in the assessment**

| Reference | Trial name | NCT number | Dates of study | Used in comparison of |
|---|---|---|---|---|
| Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, et al. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol. 2017 Feb;69(2):376-386. | MUSE | NCT01438489 | January 2012 – January 2014 | Anifrolumab 300mg or 1000mg in addition to standard therapy vs. placebo in addition to standard therapy for adults with active, moderate-to-severe SLE |
| Furie RA, Morand EF, Bruce IN, Manzi S, Kalunian KS, Vital EM, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol.2019 Nov;1(4):e208-e219. | TULIP-1 | NCT02446912 | June 2015 – June 2017 | Anifrolumab 150 mg or 300mg in addition to standard therapy vs. placebo in addition to standard therapy for adults with active, moderate-to-severe SLE |
| Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, et al. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 2020 Jan 16;382(3):211-221. | TULIP-2 | NCT02446899 | July 2015 – September 2018 | Anifrolumab 300mg in addition to standard therapy vs. placebo in addition to standard therapy for adults with active, moderate-to-severe SLE |
| Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, et al. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721-31. | BLISS-52 | NCT00424476 | May 2007 – March 2010 | Belimumab 1 mg/kg or 10 mg/kg in addition to standard of care vs. placebo in addition to standard of care for adults with active, autoantibody-positive SLE |

| Reference | Trial name | NCT number | Dates of study | Used in comparison of |
|---|---|---|---|---|
| Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, et al. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30. | BLISS-76 | NCT00410384 | December 2006 – March 2010 | Belimumab 1 mg/kg or 10 mg/kg in addition to standard therapy vs. placebo in addition to standard therapy for adults with active, autoantibody-positive SLE |
| Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, et al. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study. Arthritis Rheumatol. 2017 May;69(5):1016-1027. | BLISS-SC | NCT01484496 | November 2011 – October 2015 | Belimumab 200 mg (administered subcutaneously) in addition to standard therapy vs. placebo in addition to standard therapy for adults with moderate-to-severe SLE |

For detailed information about included studies, refer to Appendix B.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

# 7. Efficacy and safety

## 7.1 Efficacy and safety of anifrolumab plus standard of care compared to placebo plus standard of care for patients with moderate to severe SLE

### 7.1.1 Relevant studies

TULIP-1 and TULIP-2 were 52-week, randomised, double-blind, placebo-controlled parallel-group phase III studies designed to assess the efficacy and safety of anifrolumab in patients with moderate-to-severe SLE despite standard of care (SoC). MUSE was a phase 2b study of similar design. In both TULIP-1 and TULIP-2, patients were randomised 1:1 to receive placebo or anifrolumab 300 mg (therapeutic dose), in addition to protocol-specified SoC treatment. TULIP-1 had a third treatment arm, anifrolumab 150 mg, to provide dose-response data and to justify the 300 mg therapeutic dose. As anifrolumab 150 mg is not part of the marketing authorisation, this treatment arm will not be further discussed.

Patients received study drug infusions every 4 weeks for 48 weeks with a final assessment at week 52. At week 52 patients were either enrolled into a separate long-term extension study or were followed for a further 8 weeks. During the studies, background SoC therapies were controlled per protocol to prevent confounding of efficacy assessments. Between weeks 8 and 40, mandatory oral corticosteroid (OCS) tapering to ≤7.5 mg/day was attempted for those patients receiving ≥10 mg/day prednisone (or equivalent) at baseline, which had to be sustained through weeks 40–52.

To ensure treatment groups were balanced, randomisation was stratified by SLEDAI-2K score (<10 vs ≥10), OCS dose (prednisone [or equivalent] <10 mg/day vs ≥10 mg/day) and type 1 interferon gene signature (high vs low classification).

Identifying a reliable disease activity endpoint for SLE trials presents a significant challenge owing to the heterogeneity of disease and impact of background medication. The BILAG-Based Composite Lupus Assessment (BICLA) and the SLE responder index (SRI(4)) are validated, composite endpoints to assess overall disease activity in patients with SLE. TULIP-1 and TULIP-2 had different primary endpoints, assessing overall disease activity using BICLA and SRI(4). TULIP-2 assessed BICLA response as part of the primary endpoint and SRI(4) as the secondary endpoint; for TULIP-1, the converse applied.

**Table 9. SRI(4) and BICLA composite assessments of SLE disease activity used to evaluate treatment efficacy in clinical trials**

| SRI(4) criteria† | BICLA criteria† |
|---|---|
| 1. ≥4 point reduction in SLEDAI‡ global score | 1. At least one grade of improvement in baseline BILAG scores in all body systems with severe (BILAG A) or moderate (BILAG B) disease activity (i.e., all A scores at baseline improved to B/C/D, and all B scores improved to C or D) |
| 2. No new BILAG A (severe disease activity) or not more than one new BILAG B (moderate disease activity) organ domain score | 2. No new BILAG A or more than 1 new BILAG B scores |
| 3. No deterioration from baseline in PGA (≤10% of scale or ≤0.3 points) | 3. No worsening of total SLEDAI score from baseline |
| | 4. No significant deterioration (≤10 % worsening) in PGA |
| | 5. No treatment failure (initiation of non-protocol treatment) |

*There are small variations in the definition of SRI and BICLA endpoints across SLE clinical trials, including the anifrolumab studies; †All criteria must be met for the patient to be classed as a responder; ‡Original descriptions of the SRI score used SELENA-SLEDAI scores; however, the SLEDAI-2K score can also be used

The SRI(4) outcome is predominantly driven by the SLEDAI-2K score, which reflects an all-or-nothing score based on the presence (or absence) of an SLE manifestation or serological marker, and weighs some organ systems more than others. Complete resolution of enough clinical manifestations involved at baseline to obtain a reduction in SLEDAI-2K score of at least 4 points is required to be a responder.[89] Therefore, total resolution of manifestations in a single domain can be sufficient to constitute a treatment response. Partial resolution of a clinical manifestation would not qualify as complete resolution and therefore the patient would be considered a non-responder. For example, for a patient with at least 6 swollen and tender joints, a 50% improvement would constitute a clinically meaningful gain, but would not be classified as a response on the SLEDAI-2K. On the SLEDAI-2K, the number of swollen and tender joints must be less than 2 to be considered a responder. This would equal a 4-point improvement on the SLEDAI-2K and would be enough to consider the patient a SRI(4) responder without the resolution of any other manifestations.

In contrast, the BICLA endpoint is driven by improvement in all domains which are affected at baseline, as measured by the BILAG score, as well as no worsening of other BILAG domains, and no worsening of SLEDAI-2K or physician global assessment scores compared with baseline. The BILAG can capture important partial improvements in organ systems, and not only complete resolution of an organ manifestation, and weighs organ systems equally. Improvement in all involved organ systems at baseline is required to be a BICLA responder. Therefore, the BICLA response can represent a partial or complete response across all involved presentations of SLE and a more holistic view of the improvement, as opposed to complete improvement in a single domain where other severe manifestations may still exist. The BILAG score is intended to capture the intent-to-treat nature of manifestations of SLE across nine organ symptoms, and so the BICLA represents a stringent assessment of the reduction in need for treatment across all involved organ systems.[74,90] Returning to the example above, a patient with at least 6 swollen and tender joints who experiences a 50% improvement would have this clinically meaningful gain reflected on that organ domain on the BILAG. However, they would be required to have additional improvements in all other organ domains that were affected at baseline to be classified as a BICLA responder.

**Table 10. TULIP and MUSE primary and secondary endpoints**

| | TULIP-2 | TULIP-1 | MUSE |
|---|---|---|---|
| **Primary endpoint** | Proportion of patients who achieved BICLA response at week 52 | Proportion of patients who achieved SRI(4) response at week 52 | Proportion of patients who achieved SRI(4) response at week 24, with sustained OCS reduction (<10 mg/day and less than or equal to the dose at week 1 from week 12 through 24) |
| **Secondary endpoints** | Proportion of patients with high interferon gene signature at baseline who achieved BICLA response at week 52 | Proportion of patients with high interferon gene signature at baseline who achieved SRI(4) response at week 52 | Proportion of patients who achieved SRI(4) response at week 52, with sustained OCS reduction from week 40 to 52 |
| | Proportion of patients on ≥10 mg/day OCS at baseline who achieved a sustained dose reduction to ≤7.5 mg/day from week 40 to 52 | | |
| | Proportion of patients with a Cutaneous lupus disease area and severity index (CLASI), activity of ≥10 at baseline who achieved a ≥50% reduction in CLASI score by week 12 | | |
| | Annualised flare rate through week 52 (flare was defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B organ domains scores vs the previous visit) | | |

| | TULIP-2 | TULIP-1 | MUSE |
|---|---|---|---|
| | Proportion of patients with ≥6 swollen joints and ≥6 tender joints at baseline who achieved a reduction of ≥50% from baseline in counts of both swollen joints and tender joints at week 52 | Proportion of patients with ≥8 swollen joints and ≥8 tender joints at baseline who achieved a reduction of ≥50% from baseline in counts of both swollen joints and tender joints at week 52 | |
| | Proportion of patients who achieved SRI(4) response at week 52 | Proportion of patients who achieved BICLA response at week 52 | |
| | Individual components of SRI and BICLA; LLDAS | | |
| | Measures of organ damage i.e., SDI at week 52 | | |
| | Patient-reported health status, health-related QoL, and other patient-reported outcome measures of fatigue, pain, patient global assessment, and work productivity at week 52 | | |
| | Pharmacokinetics, immunogenicity, and pharmacodynamics of anifrolumab | | |
| **Safety** | Safety and tolerability of anifrolumab | | |

Endpoints refer to anifrolumab added to standard therapy vs. standard therapy + placebo, unless otherwise specified

For detailed study characteristics refer to appendix B. For baseline characteristics of patients included in each study refer to appendix C.

### 7.1.2 Efficacy and safety results per study

**Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-2)**

*Primary endpoint:*

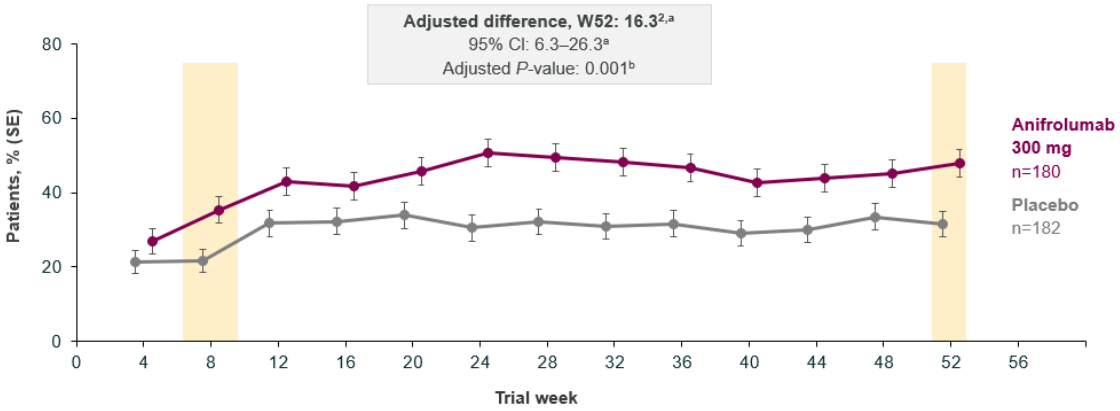
The primary efficacy endpoint for TULIP-2 was the difference in proportion of patients who achieved a BICLA response at week 52 in the anifrolumab added to SoC arm vs. SoC. [91 91 87 87 87] BICLA response was defined as (all criteria had to be met in order to achieve a positive BICLA response):

- Reduction of all severe (BILAG-2000 A) or moderately severe (BILAG-2000 B) disease activity to lower levels (BILAG-2004 B, C or D or BILAG-2004 C or D respectively; measure of clinical benefit)
- No worsening in other organ systems (defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items)
- No worsening in disease activity, as determined by the SLEDAI-2K score (no increase from baseline) and PGA score (no increase ≥0.3 points from baseline)
- No use of restricted medications beyond protocol-allowed thresholds (response not confounded by background therapy)
- No discontinuation of the study intervention.

*Result on primary endpoint:*

More patients who received anifrolumab added to SoC had a reduction in disease activity (86/180; 47.8%) compared with those who received SoC alone (57/182; 31.5%), as measured by BICLA response rates at 52 weeks, with a treatment difference of 16.3% ($p$ = 0.001).

**Figure 4. Proportion of patients with BICLA response over time in TULIP-2**




[a]The percentages of patients, the differences between the two groups, and the associated 95% CIs were adjusted for the factors which randomization was stratified using the stratified Cochran–Mantel–Haenszel method; [b]Significant following multiplicity, using a stratified Cochran–Mantel–Haenszel method. P-values adjusted per weighted Holm procedure.

*Key secondary endpoints:*

- Proportion of patients with high interferon gene signature at baseline who achieved BICLA response at week 52.
- Proportion of patients on ≥10 mg/day oral corticosteroids (OCS) at baseline who achieved a sustained dose reduction to ≤7.5 mg/day from week 40 to 52.
- Proportion of patients with a Cutaneous lupus disease area and severity index (CLASI), activity of ≥10 at baseline who achieved a ≥50% reduction in CLASI score by week 12.
- Proportion of patients with ≥6 swollen joints and ≥6 tender joints at baseline who achieved a reduction of ≥50% from baseline in counts of both swollen joints and tender joints at week 52.
- Annualised flare rate through week 52 (flare was defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B organ domains scores vs the previous visit.

*Results on key secondary endpoints:*

- In the subpopulation with a high interferon gene signature at baseline (301 of 362 patients, 83.1% of patients overall), the percentage of patients who achieved a BICLA response at week 52 was 48.0% (72 of 150) in the anifrolumab group and 30.7% (46 of 151) in the placebo group (adjusted difference, 17.3 percentage points; 95% CI, 6.5 to 28.2; adjusted $p = 0.002$). In the subpopulation with a low interferon gene signature at baseline (61 of 362 patients, 16.9% overall), the percentage of patients who achieved a BICLA response at week 52 was 46.7% and 35.5%, respectively (adjusted difference, 11.2 percentage points; 95% CI, -13.5 to 35.8).
- In patients receiving prednisone or equivalent at a dose of 10mg or more per day at baseline (47.0%, 170 of 362), a sustained reduction to 7.5mg or less per day occurred in 51.5% (45 of 87) of the anifrolumab group and 30.2% (25 of 83) in the placebo group (adjusted difference, 21.2 percentage points; 95% CI, 6.8 to 35.7; adjusted $p = 0.01$).
- In patients with at least moderately active skin disease (CLASI ≥10) at baseline, a reduction of 50% or more in the CLASI at week 12 occurred in 49.0% (24 of 49) of patients receiving anifrolumab and in 25.0% (10 of 40) receiving placebo (adjusted difference, 24.0 percentage points; 95% CI, 4.3 to 43.6; adjusted $p = 0.04$).
- The percentage of patients with six or more swollen joints and six or more tender joints at baseline who had a reduction of 50% or more in counts of both swollen joints and tender joints at 52 weeks was 42.2% (30 of 71)

in the anifrolumab group and 37.5% (34 of 90) in the placebo group (adjusted difference, 4.7 percentage points; 95% CI, -10.6 to 20.0; adjusted $p = 0.55$).

- The BILAG-2004–based annualized flare rate was 0.43 in the anifrolumab group and 0.64 in the placebo group (adjusted rate ratio, 0.67; 95% CI, 0.48 to 0.94; adjusted $p = 0.08$).

**Figure 5. Results on key secondary endpoints from TULIP-2**

| Secondary Endpoint | Placebo n/N (%) | Anifrolumab 300 mg n/N (%) | Treatment Difference Plot[a] (95% CI) | Adjusted *P*-value[b] |
|---|---|---|---|---|
| BICLA at W52, IFNGS test–high subgroup | 46/151 (30.7) | 72/150 (48.0) | 6.5, 17.3, 28.2 | 0.002 |
| Sustained glucocorticoid reduction, W40–52[c] | 25/83 (30.2) | 45/87 (51.5) | 6.8, 21.2, 35.7 | 0.01 |
| CLASI activity response, W12[d] | 10/40 (25.0) | 24/49 (49.0) | 4.3, 24.0, 43.6 | 0.04 |
| Joint count response, W52[e] | 34/90 (37.5) | 30/71 (42.2) | −10.6, 4.7, 20.0 | 0.55 |
| | | | −20, 0, 20, 40, 60 | |
| Annualized flare rate through W52[f] | 0.64 | 0.43 | 0.94, 0.67, 0.48 | 0.08 |
| | | | 1, 0.5, 0 | |
| | | | Favors placebo / Favors anifrolumab | |

The between-group difference was calculated as a rate ratio (anifrolumab/placebo).

[a]The percentages of patients, the annualized flare rates, the differences between the 2 groups, and the associated 95% CIs were adjusted for the factors for which randomization was stratified using the stratified Cochran–Mantel–Haenszel method; [b]Following multiplicity, using a stratified Cochran–Mantel–Haenszel method. P-values adjusted per weighted Holm procedure; [c]Reduction in glucocorticoid dosage to ≤7.5 mg/day,sustained from Week 40 to Week 52 in patients with baseline glucocorticoid ≥10 mg/day prednisone or equivalent; [d]CLASI response was characterized by a ≥50% reduction in CLASI activity score from baseline to Week 12 in patients with CLASI activity score ≥10 at baseline. [e]Response was characterized by ≥50% reduction in both swollen and tender joint counts from baseline to Week 52 in patients with ≥6 swollen and ≥6 tender joints at baseline. [f]Values are annualized flare rates rather than number, total number, and percent. A flare was defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items compared with the previous visit.

**Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-1)**

*Primary endpoint:*

The primary efficacy endpoint for TULIP-1 was the proportion of patients who achieved SRI(4) at week 52 in the anifrolumab plus SoC group vs. the SoC group. SRI(4) response was defined as (all criteria had to be met in order to achieve a positive SRI(4) response):

- ≥4-point reduction in SLEDAI-2K (measure of clinical benefit)
- No new organ system affected, defined by <1 new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores (no worsening of disease as assessed by BILAG-2004)
- No worsening of disease as defined by <0.3-point increase in PGA from baseline
- No use of restricted medications* beyond protocol-allowed thresholds (response not confounded by background therapy)
- No discontinuation of investigational product.

* Restricted medications included new or increased dosage of a non-steroidal anti-inflammatory drug (NSAID), new or increased dosage of antimalarial or immunosuppressant therapies, and/or increased dosage of OCS beyond the protocol-defined maximum (see section 2.1 of TULIP-1 supplementary appendix).[73] Use of these medications, although clinically appropriate, would classify a patient as a non-responder. The medication rules were revised to allow for clinically appropriate use of these medications early in the trial and a post hoc analysis of the results was conducted. Both sets of results are presented here.

*Result on primary endpoint (amended medication rules):*

The proportion of patients who achieved a SRI(4) response at week 52 were similar for anifrolumab 300 mg added to SoC (84/180; 47%) and those who received placebo added to SoC (79/184; 43%), with a treatment difference of 3.9 (*p* = 0.455).

*Result on primary endpoint (pre-specified analysis):*

The proportion of patients who achieved a SRI(4) response at week 52 were similar for anifrolumab 300 mg added to SoC (65/180; 36%) and those who received placebo added to SoC (74/184; 40%), with a treatment difference of -4.2 (*p* = 0.412).

**Table 11. Proportion of patients with SRI(4) response at week 52 in TULIP-1**

| Endpoint[a] | Anifrolumab 300 mg n/N (%) | Placebo n/N (%) | Difference (95% CI)[c] |
|---|---|---|---|
| SRI(4) – amended medication rules[b] | 84/180 (47%) | 79/184 (43%) | **3.9** (–6.3–14.1) |
| SRI(4) – prespecified analysis | 65/180 (36%) | 74/184 (40%) | **-4.2** (–14.2–5.8) |

[a]SRI(n) response was defined as a ≥n-point reduction in SLEDAI-2K score, <1 new BILAG-2004 A or <2 new BILAG-2004 B organ domain scores, <0.3-point (10%) increase in PGA score from baseline, and no discontinuation of anifrolumab and no use of restricted medications beyond the protocol-allowed threshold, using the amended restricted medication rules to correct for inappropriately classified NSAID use; [b]Response rates, the difference in response rates, and the associated 95% CIs were adjusted for the factors for which randomization was stratified using the stratified Cochran–Mantel–Haenszel approach; [c]As the primary outcome was not significant per the prespecified analysis plan, all other comparisons were considered nonsignificant.

Inconsistency of background medication use is a major confounder in SLE clinical trials. After unmasking of data, it was recognized that the implementation of some medication rules in the efficacy endpoint definitions, particularly those regarding NSAID use, were inconsistent with the intention of the protocol. It was considered clinically inappropriate to have classified patients as non-responders if new NSAIDs or increased doses were used during a year-long study. When the amended rules were applied, the number of patients classified as non-responders (regardless of treatment) was reduced, demonstrating the effect of medication rules on assessments of efficacy.[73]

*Key secondary endpoints:*

- Proportion of patients with high interferon gene signature at baseline who achieved SRI(4) response at week 52
- Proportion of patients on ≥10 mg/day OCS at baseline who achieved a sustained dose reduction to ≤7.5 mg/day from week 40 to 52
- Proportion of patients with CLASI activity ≥10 at baseline who achieved a ≥50% reduction in score by week 12
- Proportion of patients who achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at Week 52.

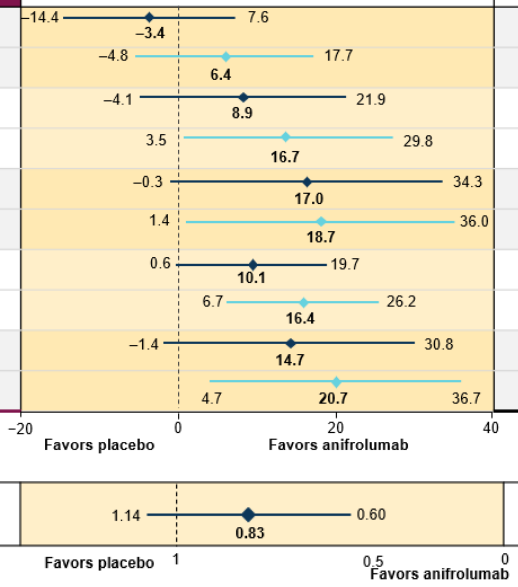
- Proportion of patients with ≥8 swollen joints and ≥8 tender joints at baseline who achieved a reduction of ≥50% from baseline in counts of both swollen joints and tender joints at week 52
- Annualised flare rate through week 52 (flare was defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B organ domains scores vs the previous visit)

*Results on key secondary endpoints:*

Although the statistical significance of secondary endpoints was not formally assessed, a greater proportion of patients who received anifrolumab achieved sustained oral corticosteroid dose reduction, BICLA response, and organ-specific measures of skin and joint responses compared with placebo. The treatment difference increased after the amended restricted medication rules were applied.[73]

**Figure 6. Results on key secondary endpoints for both the prespecified analysis and the analysis with the amended restricted medication rules**

| Secondary Endpoint | | Placebo, n/N % | Anifrolumab 300 mg n/N (%) | Treatment Difference (95% CI)[a] | Nominal *P*-value[b] |
|---|---|---|---|---|---|
| SRI(4) at W52, IFNGS test–high subgroup | Prespecified | 59/151 (39) | 53/148 (36) | −14.4, −3.4, 7.6 | 0.549 |
| | Amended | 63/151 (42) | 71/148 (48) | −4.8, 6.4, 17.7 | 0.261 |
| Sustained glucocorticoid reduction[c] | Prespecified | 33/102 (32) | 42/103 (41) | −4.1, 8.9, 21.9 | 0.180 |
| | Amended | 33/102 (32) | 50/103 (49) | 3.5, 16.7, 29.8 | 0.013 |
| CLASI activity response, W12[d] | Prespecified | 14/54 (25) | 24/58 (42) | −0.3, 17.0, 34.3 | 0.054 |
| | Amended | 14/54 (25) | 25/58 (44) | 1.4, 18.7, 36.0 | 0.034 |
| BICLA response, W52 | Prespecified | 49/184 (27) | 67/180 (37) | 0.6, 10.1, 19.7 | NE |
| | Amended | 54/184 (30) | 83/180 (46) | 6.7, 16.4, 26.2 | NE |
| Joint count response, W52[e] | Prespecified | 22/68 (32) | 33/70 (47) | −1.4, 14.7, 30.8 | NE |
| | Amended | 22/68 (32) | 37/70 (53) | 4.7, 20.7, 36.7 | NE |
| Annualized flare rate through W52[f] | | 0.72 | 0.60 | 1.14, 0.83, 0.60 | 0.258 |




Flare rate calculations did not incorporate amended restricted medication rules; therefore, values for the prespecified and amended analyses are identical.

[a]The response rates, the differences in response rates, and associated 95% CIs were adjusted for the factors for which randomization was stratified using the stratified Cochran-Mantel-Haenszel method, so with these adjustments, proportions do not always equal n/N; [b]All *P*-values are nominal except for the primary outcome. As the primary outcome was not significant per the prespecified analysis plan, all other comparisons are considered nonsignificant; [c]To ≤7.5 mg/day from W40–52 in patients with baseline dosage ≥10 mg/day prednisone or equivalent; [d]≥50% reduction in CLASI activity score from baseline to W12 in patients with CLASI activity score ≥10 at baseline; [e]≥50% reduction in both swollen and tender joints from baseline to W52 in patients with ≥8 swollen and ≥8 tender joints at baseline; [f]Values are annualized flare rates rather than number, total number, and percent. A flare was defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items compared with the previous visit. Annualized flare rate was the same in both the prespecified and amended analysis.

**A Study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus (MUSE)**

*Primary endpoint:*

Proportion of patients who achieved SRI(4) response at week 24, with sustained OCS reduction (<10 mg/day and less than or equal to the dose at week 1 from week 12 through 24). SRI(4) response was defined as meeting all of the following criteria:

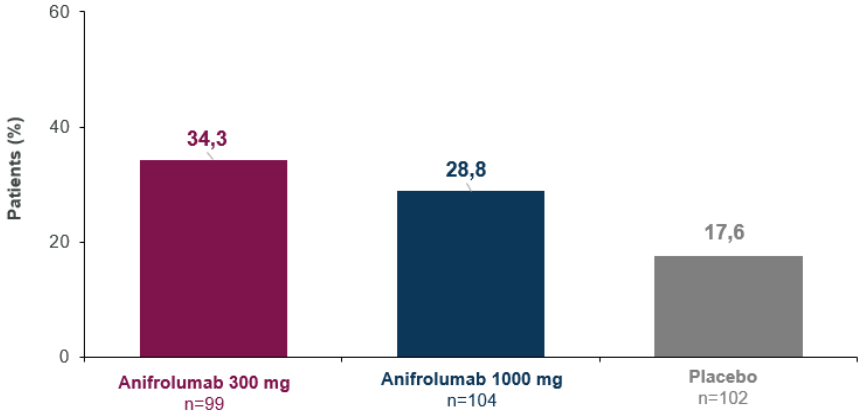
- Reduction from baseline of ≥4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)
- No new organ systems affected, defined by 1 or more British Isles Lupus Assessment Group (BILAG-2004) A or 2 or more BILAG-2004 B items
- No worsening from baseline in participants lupus disease activity. Worsening was defined as an increase of ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)
- No discontinuation of investigational product and no use of restricted medications beyond the pre-specified analysis threshold.

A target sample size of 100 patients per group was used to provide 88% power at the 0.10 alpha level to detect at least a 20% absolute improvement in SRI(4) responate at week 24 for anifrolumab relative to placebo, assuming a 40% placebo response rate. Accordingly, all results are presented with 90% confidence intervals.

*Result on primary endpoint:*

A SRI(4) response was achieved in 34.3% of patients treated with anifrolumab 300 mg and in 17.6% of patients treated with placebo ($p = 0.014$). In patients receiving anifrolumab 1000 mg, the response rate was 28.8% ($p = 0.063$). The clinical results were similar between anifrolumab 300 mg and anifrolumab 1000 mg, however a higher rate of treatment discontinuations led to a lower overall response rate. Based on the risk/benefit profile from the MUSE study the 1000 mg dose was not investigated further in the phase 3 programme and is not discussed further in this application.

**Figure 7. Proportion of patients with SRI(4) response at week 24 with sustained glucocorticoid taper in MUSE**




| | | |
|---|---|---|
| Delta[a]: | 16.7% | 11.2% |
| OR[b]: | 2.38 | 1.94 |
| 90% CI[b]: | (1.33–4.26) | (1.08–3.49) |
| *P*-value[b]: | 0.014 | 0.063 |

[a]Pairwise comparison of each anifrolumab group vs placebo group, with the requirement of a sustained glucocorticoid taper. Dropouts and patients whose medication use exceeded protocol threshold were imputed as failures; bORs, 90% CIs, and nominal P-values are from a logistic regression model for comparisons of each anifrolumab group versus placebo adjusted for randomization stratification factors.

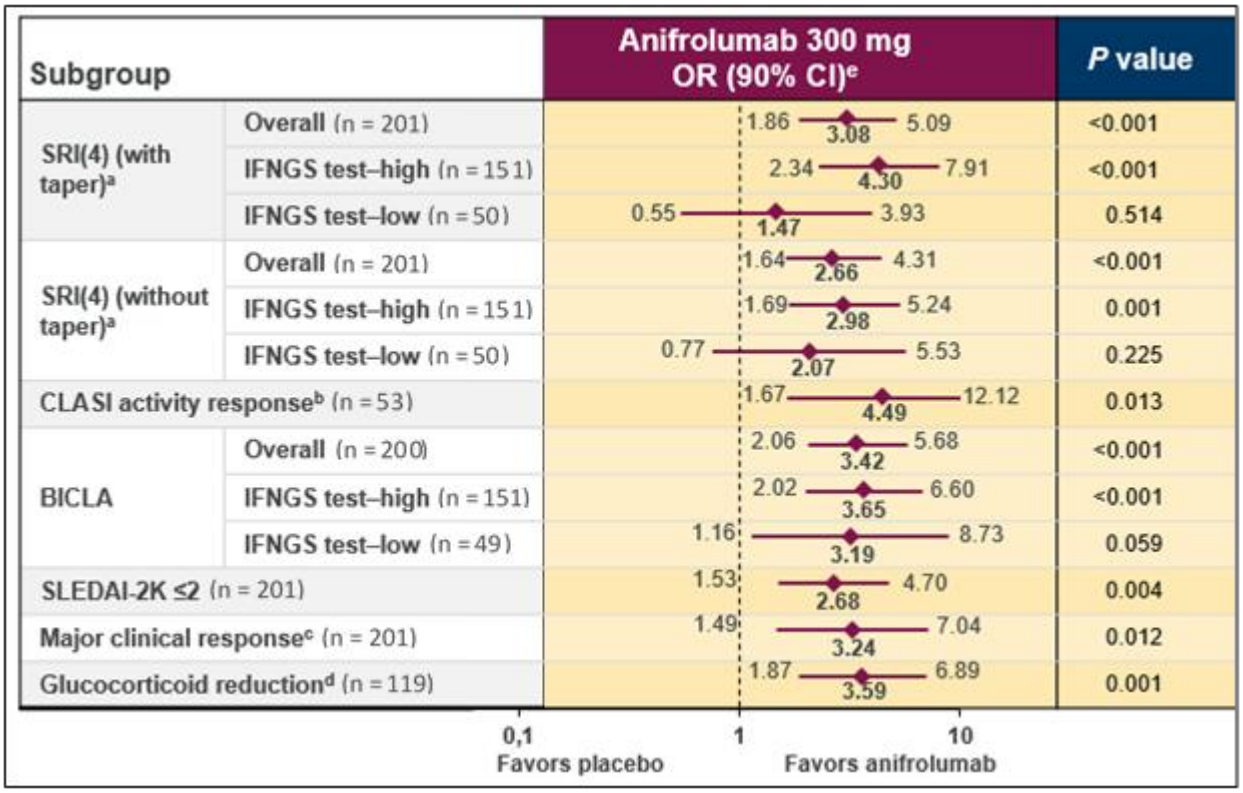
*Key secondary endpoints:*

- Proportion of patients with high interferon gene signature at baseline who achieved SRI(4) response at week 52 with a sustained OCS reduction from week 40 through 52
- Proportion of patients with a Cutaneous lupus disease area and severity index (CLASI), activity of ≥10 at baseline who achieved a ≥50% reduction in CLASI score by week 12
- Response in BILAG-based Composite Lupus Assessment (BICLA)
- Proportion of patients with a SLEDAI-2K score of ≤2
- Major clinical response defined as BILAG 2004 score of C or better in all organ domains at week 24 with maintenance of this response through week 52;
- Proportion of patients on ≥10 mg/day OCS at baseline who achieved a sustained dose reduction to ≤7.5 mg/day at week 52

*Results on key secondary endpoints:*

All secondary endpoints were met. Compared with placebo, anifrolumab treatment resulted in significantly greater rates of improvement across a broad range of composite and organ-specific disease activity measures as well as in the achievement and maintenance of low disease activity and tapering of corticosteroids.[92]

**Figure 8. Efficacy results on secondary endpoints at week 52 for anifrolumab 300mg (n=99) vs. placebo (n=102) in MUSE**




[a]Glucocorticoid taper to ≤7.5 mg/day; [b]Characterized by ≥50% improvement in CLASI activity score, among those with a CLASI activity score ≥10 at baseline; [c]Defined as a BILAG-2004 score of C or better in all organ domains at W24 and sustained through W52; [d]Defined as a reduction in glucocorticoid dosage to ≤7.5 mg/day at W52, among those taking ≥10 mg/day at baseline; [e]The ORs, 90% CIs, and P-values are from a logistic regression model adjusted for stratification factors.

### 7.1.3 Comparative analyses of efficacy and safety

**Method of synthesis**

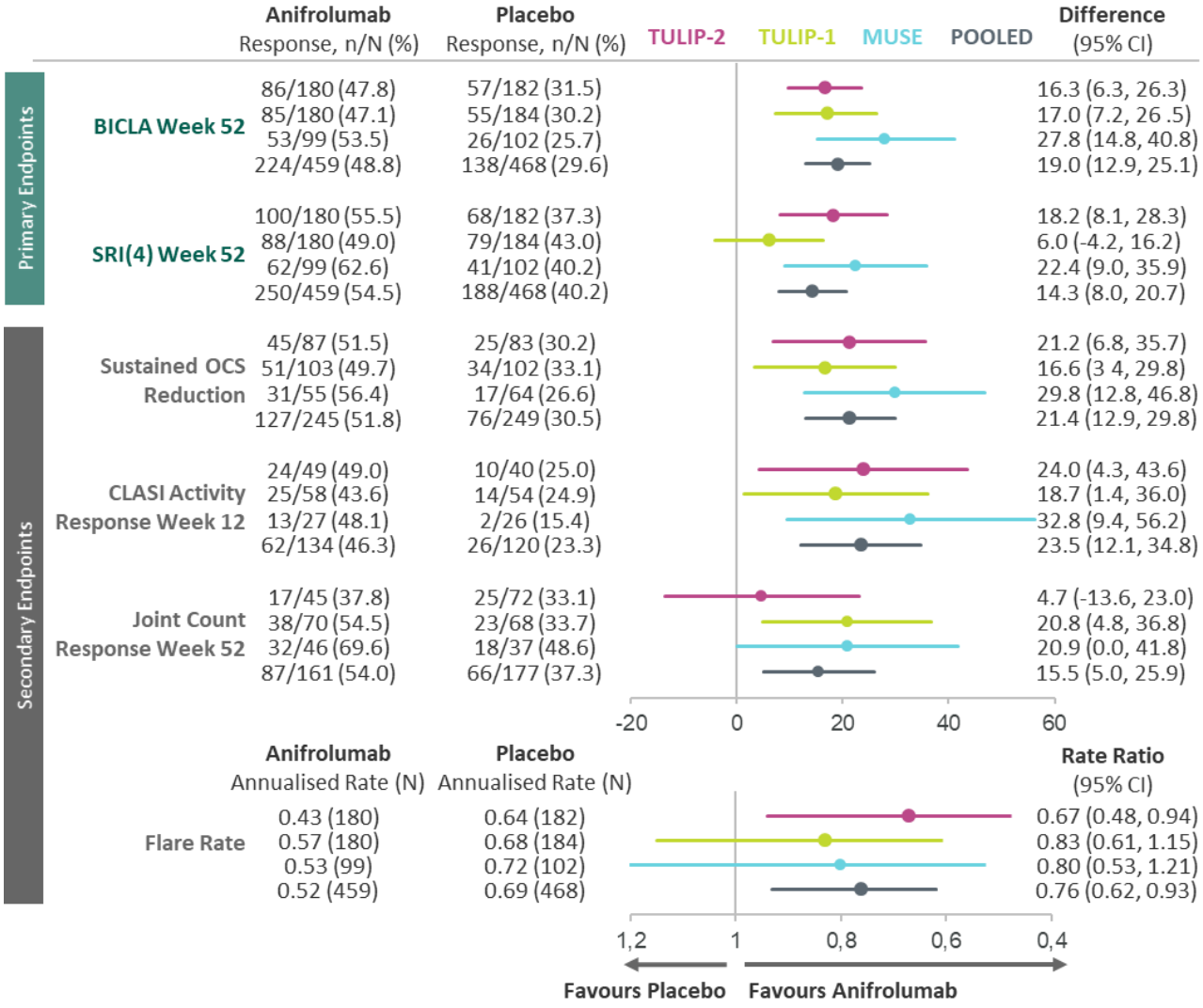
Given that the TULIP and MUSE studies were of equivalent design in terms of inclusion and exclusion criteria and assessment of the approved dose of anifrolumab, as well as collecting data on the same endpoints, a *post hoc* analysis pooling the data from both TULIP studies and MUSE has been conducted. A pooled analysis of TULIP-1 and TULIP-2 was pre-planned to strengthen observations that might not be possible within a single SLE study. The MUSE study was later added to this given its relevance to the assessment of anifrolumab's efficacy.

This approach was favoured over a meta-analysis of the studies to avoid the aggregate findings from either study being weighted based on variance of the estimates rather than considering each treated patient as a valid data point. This also means the weighting of studies is balanced across different endpoints, whereas the different variances of different endpoints across studies may lead to study results having different weights across different endpoints in a meta-analysis. However, with that in mind, the results across TULIP-1, TULIP-2, and MUSE were largely consistent. Patient characteristics of the three studies were similar (see Appendix C. Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety). The pooled analysis was conducted following the protocol applied for the TULIP-2 study.

**Results from the comparative analysis**

Across both of the pivotal phase III studies and the phase IIb MUSE study, anifrolumab in addition to standard therapy has been demonstrated to significantly reduce disease activity compared to standard therapy alone (Figure 9). This included a consistent reduction in overall disease activity, assessed by the BICLA response at week 52 (19.0% more responders in the pooled analysis) and rapid reductions in mucocutaneous disease activity as assessed by the CLASI at week 12 (23.5% more responders in the pooled analysis). This is supported by further measures of reductions in disease activity on the SRI(4) and patients with a ≥50% reduction in the number of swollen and tender joints (in patients with at least 8 swollen and 8 tender joints at baseline. Furthermore, patients treated with anifrolumab had 24% fewer severe flares (BILAG 1A/2B) over the 52 week period, despite more patients attaining significant sustained reductions in oral corticosteroid dose.

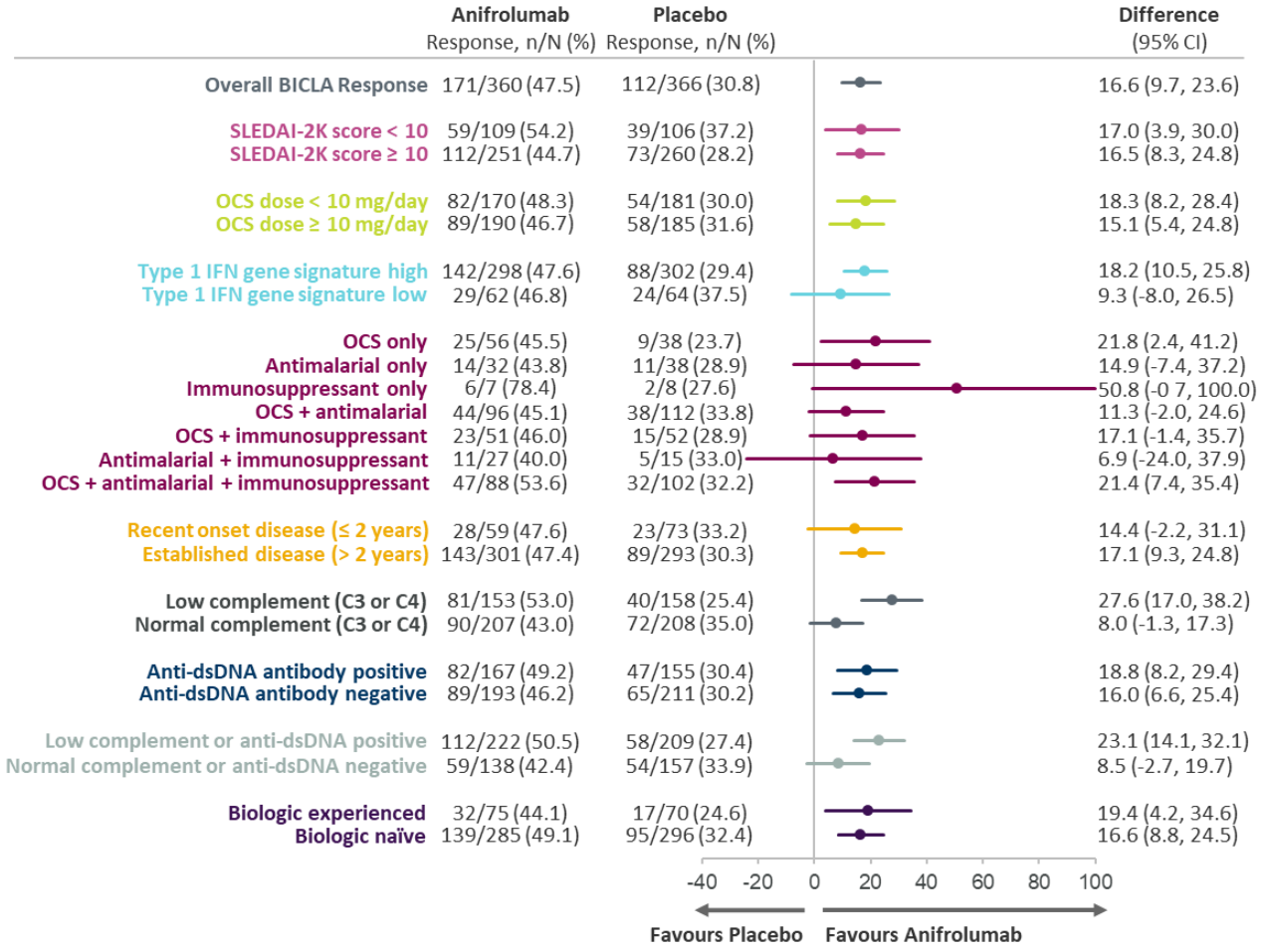
**Figure 9. Summary of main results of the pooled analysis from the TULIP and MUSE trials**




Sustained OCS reduction is a reduction to ≤ 7.5 mg/day between weeks 40 and 52 for patients receiving ≥ 10 mg/day at baseline. CLASI activity response is a 50% reduction in CLASI activity score for patients with a score ≥ 10 at baseline. Joint count response is a 50% reduction in the number of swollen and tender joints for patients with at least 8 swollen and 8 tender joints at baseline. Flares are any new BILAG 1A or 2B organ system involvement that was not present at the previous visit.

These benefits were observed across a range of subgroups. Figure 10 shows the results on the BICLA response at week 52 across different pre-defined and post hoc subgroups. As can be seen, anifrolumab was equally as efficacious in patients with high disease activity (SLEDAI-2K scores ≥ 10 at baseline) as those with more moderate activity, and was effective across steroid doses and a range of background therapies. In addition, it was equally as effective in patients with recent onset SLE and in those with established disease, and both those who had been previously treated with a biologic immunomodulator (e.g., belimumab) and those who had not. With regards to serological markers, the presence of anti-dsDNA antibodies was not associated with a difference in treatment effect, though a non-significant trend was observed for better outcomes with low C3 or C4 complement. This is in support of the association between low complement and high IFN activity levels,[93] on which the mechanism of action of anifrolumab acts, and is somewhat reflected in the comparison between patients with a high vs. low type 1 IFN gene signature.

**Figure 10. Subgroup analysis of BICLA response from a pooled analysis of the TULIP trials**



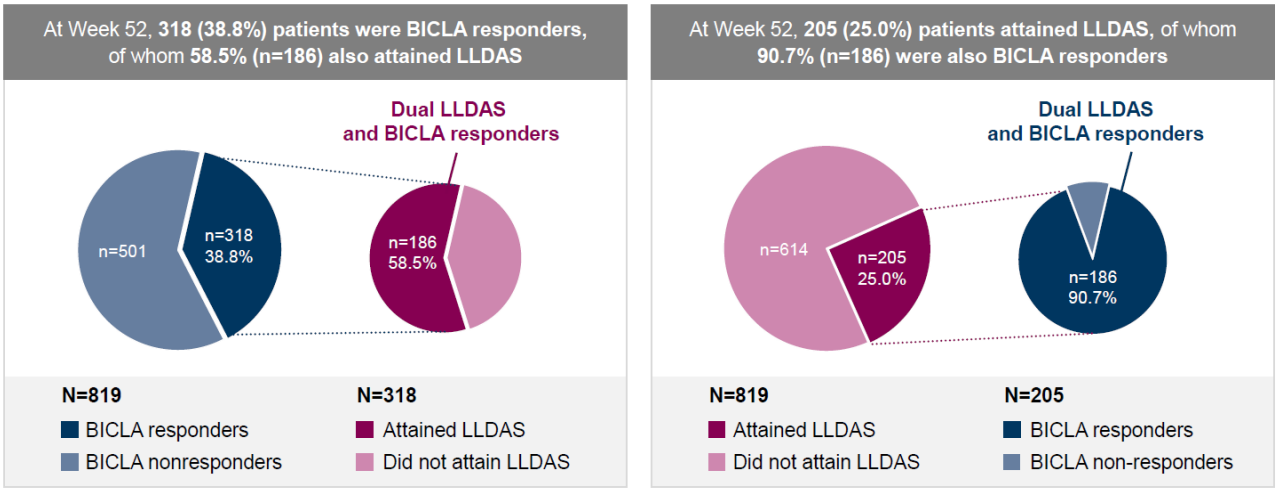

Subgroups refer to patient characteristics or treatment at study baseline. IFN, interferon; OCS, oral corticosteroids

### Lupus Low Disease Activity State (LLDAS)

LLDAS is a treat-to-target endpoint in SLE and represents a clinically meaningful outcome measure.[94,95] Attainment of LLDAS has been validated as protective from SLE flares, organ damage, mortality, and is associated with improved health-related quality of life.[26,96,97] In addition, being in a LLDAS is associated with a statistically significant reduction in healthcare costs.[98]

Pooled data from the phase 3 TULIP-1 and TULIP-2 trials have demonstrated that, at week 52, 318 (38.8%) patients were BICLA responders, of whom 58.5% (*n* = 186) also attained LLDAS.[99] Conversely, at week 52, 205 (25.0%) patients attained LLDAS, of whom 90.7% (*n* = 186) were also BICLA responders.[99] Compared with placebo, anifrolumab treatment was associated with a higher proportion of patients attaining LLDAS at multiple timepoints, shorter time to first LLDAS, more cumulative time and percentage of time spend in LLDAS, and more sustained LLDAS.[99]

**Figure 11. LLDAS attainment by BICLA responder status in the pooled TULIP trials irrespective of treatment received**




Data includes all treatment groups, including the anifrolumab 150 mg group from TULIP-1. Percentages were calculated using a stratified Cochran–Mantel–Haenszel approach, with stratification factors of SLEDAI-2K score at screening, glucocorticoid dosage at Day 1, and type I IFN gene signature at screening.

Furthermore, in the phase 2b MUSE trial, 74/159 (47%) of SRI(4) and 62/121 (51%) of BICLA responders reached LLDAS. Anifrolumab-treated patients achieved earlier LLDAS, and more spent at least half their observed time in LLDAS.[95]

**Organ Domain Data**

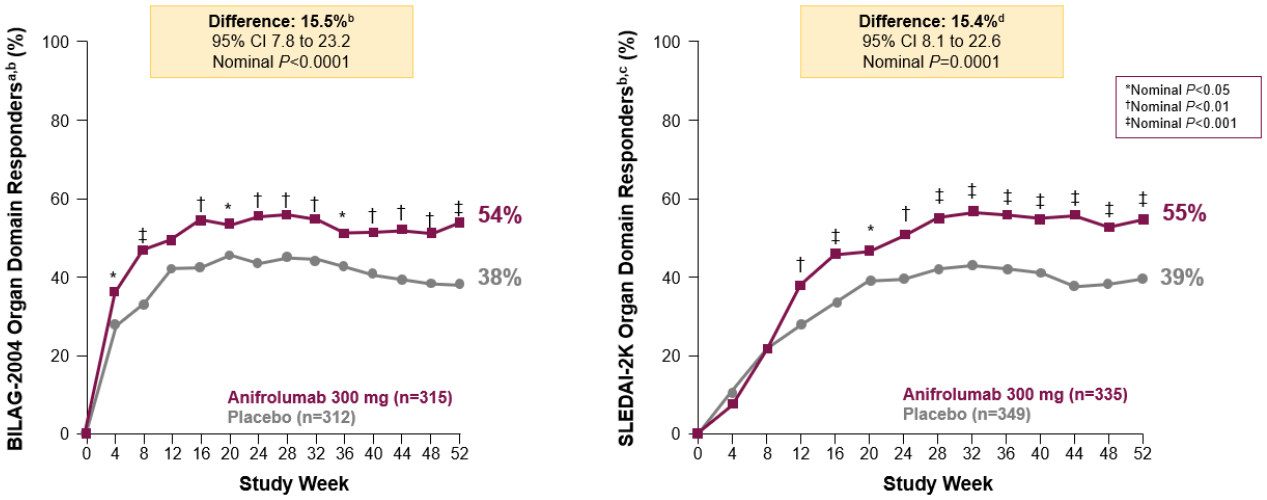
A post-hoc analysis of the TULIP-1 and TULIP-2 trials was conducted to evaluate efficacy using the BILAG and SLEDAI disease activity indices specific to each organ domain affected at baseline. BILAG-2004 response was defined as a reduction from A (severe disease) at baseline to B (moderate), C (mild), or D (no current disease) or reduction from B at baseline to C or D. SLEDAI-2K improvement was defined as a reduction in domain scores among patients with baseline scores of more than 0. A response was defined in any organ domain category: for example, a patient who improved in the musculoskeletal domain, but no others, was considered a responder in the musculoskeletal domain.

Presented below are the response data on the mucocutaneous, musculoskeletal, hematological, immunological, and vascular domains. Data on other domains (renal, cardiorespiratory, constitutional, neuropsychiatric/CNS, gastrointestinal, and ophthalmic) are not presented as fewer than 30 patients in each arm presented with symptoms on these domains at baseline on the respective scales.

*Mucocutaneous manifestations*

A greater proportion of patients on anifrolumab achieved a mucocutaneous response which was maintained over 52 weeks compared to placebo.

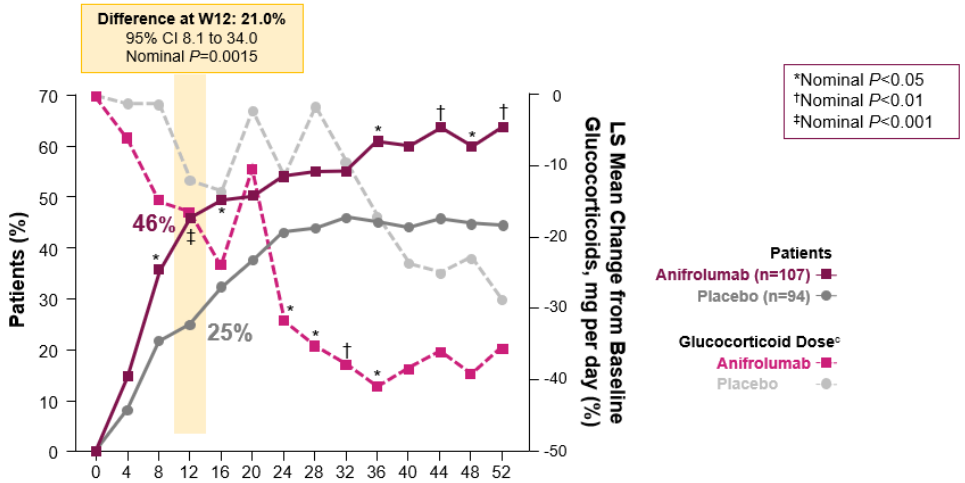
**Figure 12. Response to therapy on the mucocutaneous domains of the BILAG and SLEDAI-2K in the pooled TULIP data**




[a]BILAG-2004 responders are defined as patients with a reduction in baseline BILAG-2004 organ domain A or B score at each timepoint. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score. [d]Responder rates, treatment differences, associated 95% CIs, and *P*-values were calculated using a stratified Cochran–Mantel–Haenszel approach with stratification factors matching those in the TULIP studies.

Among patients with a baseline CLASI-A of 10 or more, anifrolumab was associated with greater mean reduction in glucocorticoid dose versus placebo across multiple timepoints. In addition to a reduction in OCS dose, patients with a baseline CLASI-A >10 treated with anifrolumab had a greater response which was maintained over time compared with placebo.

**Figure 13. CLASI response and change in steroid dose for patients with CLASI-A scores ≥10 at baseline in the pooled TULIP data**

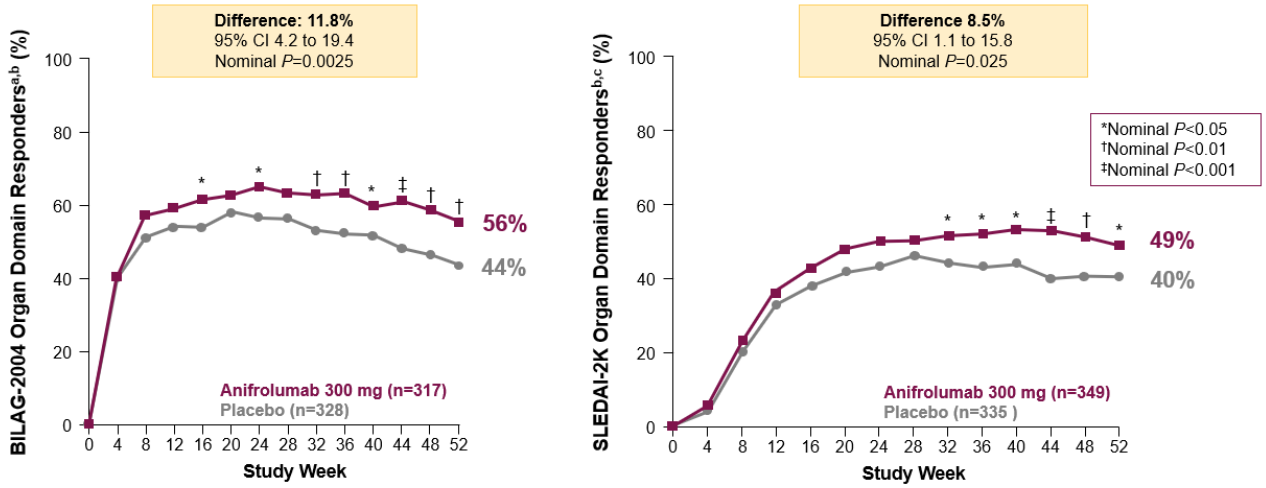



[a]CLASI response is defined as 50% or more reduction in CLASI-A from baseline for patients with a baseline CLASI-A of 10 or more. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]Percentage changes from baseline oral glucocorticoid dose are expressed as LS means. Negative LS mean values indicate a reduction in daily dose.

*Musculoskeletal manifestations*

BILAG-2004 and SLEDAI-2K musculoskeletal responses were observed in a higher proportion of patients on anifrolumab compared with placebo at 52 weeks.

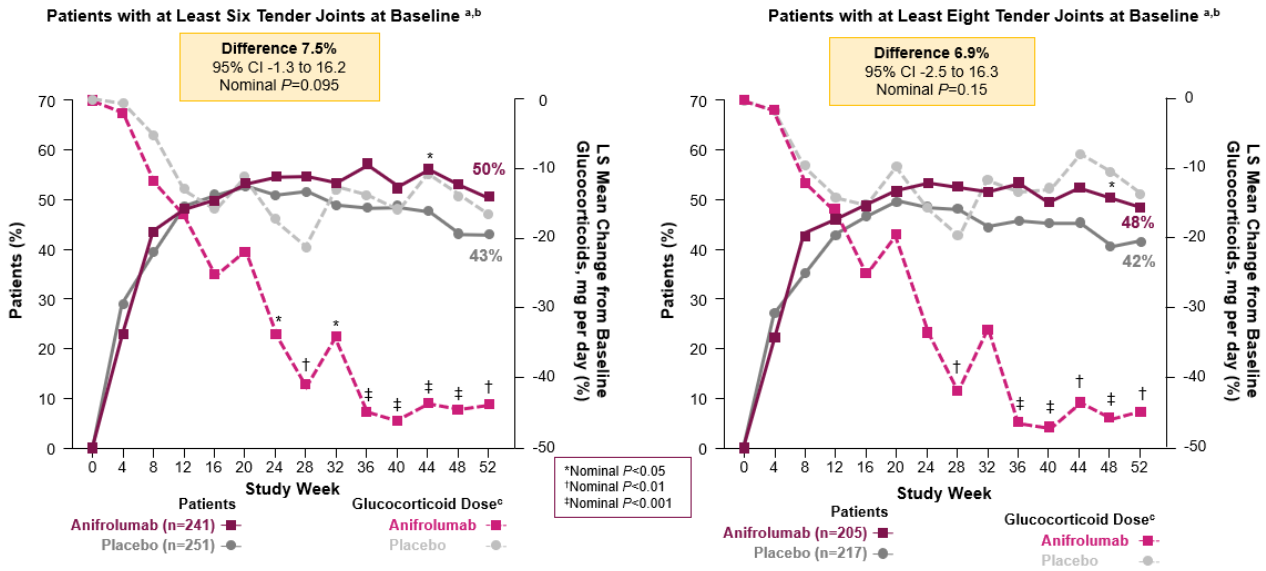
**Figure 14. Response to therapy on the musculoskeletal domains of the BILAG and SLEDAI-2K in the pooled TULIP data**




[a]BILAG-2004 responders are defined as patients with a reduction in baseline BILAG-2004 organ domain A or B score at each timepoint. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach with stratification factors matching those in the TULIP studies. [c]SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score. [d]Responder rates, treatment differences, associated 95% CIs, and *P*-values were calculated using a stratified Cochran–Mantel–Haenszel approach with stratification factors matching those in the TULIP studies

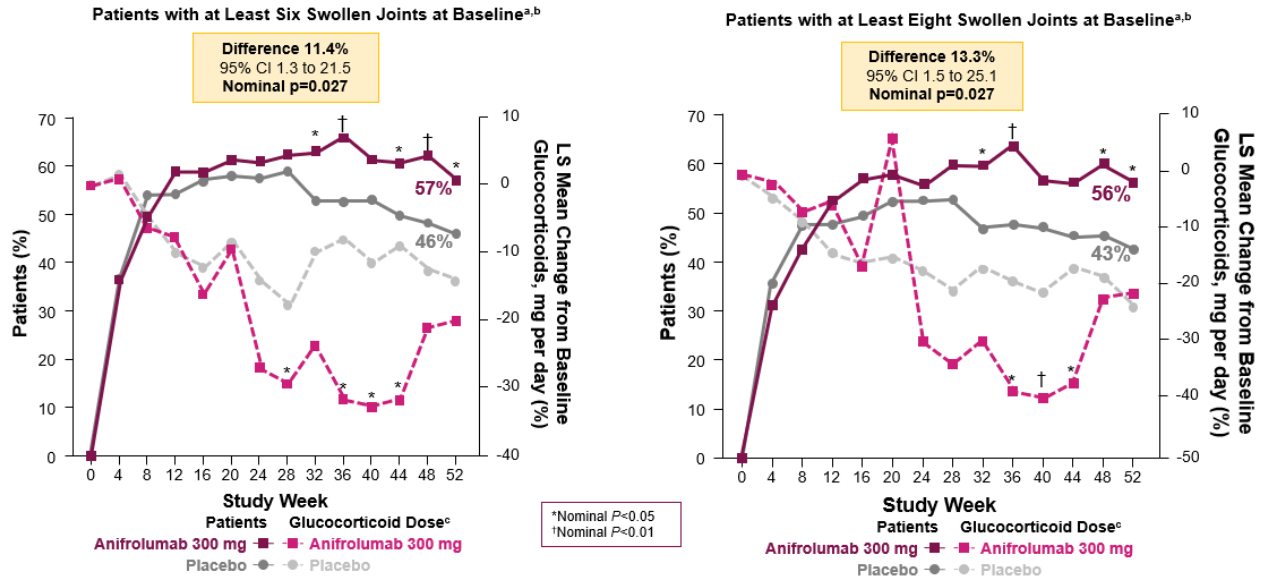
Among patients with at least six or at least eight tender or swollen joints at baseline, anifrolumab was associated with greater mean reduction in glucocorticoid dose versus placebo at multiple timepoints.

**Figure 15. Reduction in tender joints and change in steroid dose in the pooled TULIP data**




[a]Tender joint count responses are defined as 50% or more reduction in tender joint count, respectively, for patients with baseline counts of at least six or at least eight. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]Percentage changes from baseline oral glucocorticoid dose are expressed as LS means. Negative LS mean values indicate a reduction in daily dose.

**Figure 16. Reduction in swollen joints and change in steroid dose in the pooled TULIP data**



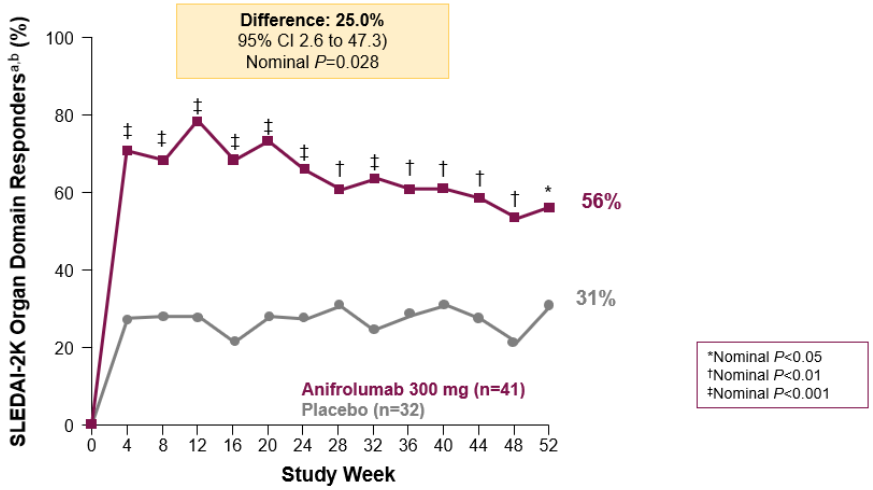

[a]Swollen joint count response was defined as 50% or more reduction in swollen joint count for patients with baseline counts of at least six or at least eight. [b]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification factors matching those in the TULIP studies. [c]Percentage changes from baseline oral glucocorticoid dose are expressed as LS means. Negative LS mean values indicate a reduction in daily dose.

*Laboratory values and investigations*

Greater proportions of patients receiving anifrolumab versus placebo had improvements at week 52 for less frequently affected SLEDAI-2K domains, such as hematology and immunology.

A higher proportion of patients receiving anifrolumab compared with placebo had improvements at week 52 in the SLEDAI hematological domain. The results for BILAG responders are not presented as only three patients in the TULIP studies were determined to have moderate (B) or severe (A) BILAG scores on the hematological domain at baseline.

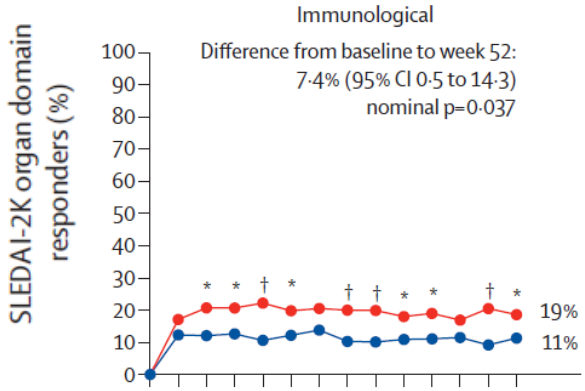
**Figure 17. Response to therapy on the haematological domain of the SLEDAI-2K in the pooled TULIP data**




[a]Proportion of patients achieving response calculated using a stratified Cochran-Mantel-Haenszel approach with stratification factors matching those in the TULIP studies. [b]SLEDAI-2K organ domain responder is defined as a reduction in baseline SLEDAI-2K organ domain score.

Patients treated with anifrolumab were significantly more likely to have immunological components of the SLEDAI-2K reduced compared to those treated with placebo. The difference was observed from week 8 until week 52.

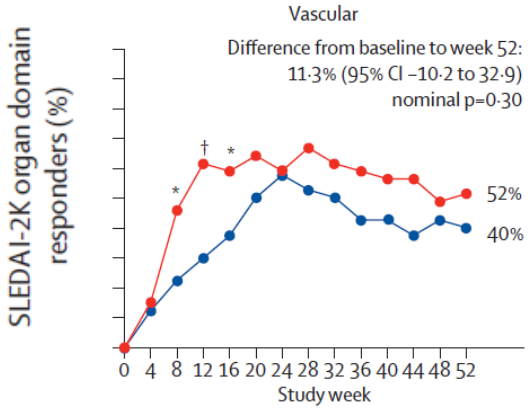
**Figure 18. Response to therapy on the immunological domain of the SLEDAI-2K in the pooled TULIP data**



*Vascular manifestations*

At week 52, there was a numerical benefit on vascular manifestations of SLE on the SLEDAI-2K for patients treated with anifrolumab. In addition, a nominally significant improvement over placebo was seen at weeks 8, 12, and 16 suggesting a faster onset of action with anifrolumab at relieving these manifestations. No specific vascular domain exists on the BILAG.

**Figure 19. Response to therapy on the vascular domain of the SLEDAI-2K in the pooled TULIP data**




**Patient Reported Outcomes**

These clinical benefits are somewhat reflected on the patient reported outcomes from the TULIP trials. Figure 20 shows the change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) score pooled across both TULIP studies estimated using a mixed model for repeated measures (MMRM) with fixed effects for baseline FACIT-F score, treatment group (anifrolumab or placebo), visit, randomisation stratification factors (interferon gene signature high/low, SLEDAI-2K score at screening, and baseline steroid dose), and an interaction term between treatment and visit, and a random intercept at the patient level. No missing values were explicitly imputed for the analysis. In the pooled analysis, patients treated with anifrolumab had a numerically greater reduction in fatigue (improvement in FACIT-F score) than those receiving placebo (Figure 20). This translated to a greater proportion of FACIT-F responders (defined as improvement of >3 points from baseline) at week 52 for anifrolumab [redacted] compared to placebo [redacted] (difference: [redacted])

Patients treated with anifrolumab also trended to have better scores on the Short Form 36 health survey (SF-36) physical component summary (PCS) and mental component summary (MCS) (Figure 21). Responders on the PCS or MCS were defined as those who achieve an improvement of >3.4 in the PCS and >4.6 in the MCS,[100] with no restricted medications beyond the protocol allowed threshold and no discontinuation from the investigational product. Response rates and confidence intervals were calculated using a stratified Cochran-Mantel-Haenszel approach, with stratification for the randomisation stratification factors as well as study (TULIP-1 or TULIP-2). Missing values on the SF-36 were imputed using the last observation carried forward (LOCF). Response rates at week 52 were numerically higher for anifrolumab compared to placebo on both the PCS and MCS. Therefore, there evidence suggests that patients treated with anifrolumab may have greater improvements in patient-reported outcomes compared with patients treated with placebo.

**Figure 20. Change from baseline in FACIT-F scores from the pooled TULIP data**

**Figure 21. Proportion of responders on the SF-36 Physical Component Summary (A) and Mental Component Summary (B) from the pooled TULIP data**

**Safety & Adverse Events**

An overview of the pooled safety data from the TULIP and MUSE studies is presented in Table 12. Patients treated with anifrolumab had a higher number of adverse events overall, including those considered to be related to treatment. However, patients treated with anifrolumab were less likely to experience a serious adverse event or one which led to treatment discontinuation. In terms of events of special interest, anifrolumab was only associated with a higher probability of developing herpes zoster, however most of these cases were predominantly cutaneous, mild or moderate in severity, and did not lead to treatment discontinuation. Overall, no significant safety signals were identified in the anifrolumab development programme and anifrolumab appeared to be well tolerated when compared to placebo.

**Table 12. Adverse events and exposure-adjusted incidence rates during the 52 weeks on study**

| Adverse Event Category | Anifrolumab (N = 459) | | Placebo (N = 466) | | EAIR Risk Difference (95% CI) |
|---|---|---|---|---|---|
| | n (%) | EAIR | n (%) | EAIR | |
| Any adverse event | 404 (88.0) | 286.9 | 377 (80.9) | 218.3 | 68.6 (33.0, 104) |
| Serious adverse event | 59 (12.9) | 13.7 | 88 (18.9) | 21.5 | -7.8 (-13.0, -2.7) |
| Death | 2 (0.4) | 0.4 | 1 (0.2) | 0.2 | 0.2 (-0.9, 1.4) |
| Adverse event leading to discontinuation of intervention | 20 (4.4) | 4.8 | 30 (6.4) | 7.4 | -2.7 (-6.1, 0.7) |
| Treatment-related adverse event | 155 (33.8) | 45.4 | 126 (27.0) | 34.8 | 10.6 (1.2, 20.0) |
| Adverse event of special interest | 69 (15.0) | 16.3 | 57 (12.2) | 13.4 | 2.9 (-1.9, 7.7) |
| • Non-opportunistic serious infections | 24 (5.2) | 5.4 | 31 (6.7) | 7.1 | -1.8 (-5.1, 1.5) |
| • Opportunistic infections | 1 (0.2) | 0.2 | 2 (0.4) | 0.4 | -0.2 (-1.4, 0.8) |
| • Anaphylaxis | 0 | 0 | 0 | 0 | 0 |
| • Malignancy | 6 (1.3) | 1.3 | 3 (0.6) | 0.7 | 0.6 (-0.8, 2.2) |
| • Herpes zoster | 28 (6.1) | 6.3 | 8 (1.7) | 1.8 | 4.5 (2.0, 7.4) |
| • Tuberculosis (including latent TB) | 6 (1.3) | 1.3 | 3 (0.6) | 0.7 | 0.6 (-0.8, 2.2) |
| • Influenza | 13 (2.8) | 2.9 | 12 (2.6) | 2.7 | 0.2 (-2.1, 3.5) |
| • Vasculitis (non-SLE) | 0 | 0 | 2 (0.4) | 0.4 | -0.4 (-1.6, 0.4) |
| • Major adverse cardiovascular events | 1 (0.2) | 0.2 | 3 (0.6) | 0.7 | -0.5 (-1.8, 0.6) |

Exposure-adjusted incidence rates reported as incidence per 100 person-years of exposure

**Summary of direct comparison results**

As the literature search was conducted including data up to March 2021, the European Public Assessment Report (EPAR) from the European Medicines Agency (EMA) was not included in the evidence base, given its publication in February 2022. However, the evidence presented here is in line with that in the EPAR, and the conclusions drawn are aligned.

In the assessment report from the Committee for Medicinal Products for Human Use (CHMP), it was concluded that the totality of evidence supports the beneficial treatment effects of anifrolumab. The difference in BICLA response observed with anifrolumab compared to placebo in the MUSE, TULIP-1, and TULIP-2 studies are clinically meaningful to the indicated patient population. Given the failure of one of the key studies on its original primary endpoint as well as the uncertainties regarding the clinical relevance of the observed treatment effect, the results were discussed within an Ad Hoc Expert Group (AHEG) comprising methodological and clinical experts on SLE. While the experts considered the failure of TULIP-1 on its original primary endpoint a notable weakness, they still considered that the total weight of evidence based on BICLA and SRI(4) responses, as well as other effects including steroid sparing, is supportive of beneficial treatment effects, and that the failure of TULIP-1 on SRI(4) would not prevent an overall conclusion that efficacy was demonstrated in the programme. This position was followed by the CHMP.

The most relevant results with regards to favourable effects include BICLA response, reduction in oral corticosteroids, and improvement in skin activity. The committee noted that the overall safety profile of anifrolumab includes an increased risk for infections (including herpes zoster) in line with the mechanism of action, as well as hypersensitivity and infusion-related events. Anifrolumab seems to be well tolerated overall, with relatively similar number of adverse events, serious adverse events, and discontinuations due to adverse events when compared to placebo.

The committee requested additional analyses in regard to sustained BICLA response, since individual patients can transition between a responder and a non-responder status from one study visit to the next. AstraZeneca provided a summary of the proportion of patients who achieved a sustained BICLA response through Week 52. There were a higher proportion of anifrolumab-treated patients who had a sustained response duration of greater than or equal to 3, 6, 9, and 12 months.

Sensitivity analyses on the BICLA and SRI(4) responses in the Phase III studies were also analysed without including the intercurrent events of "no use of restricted medication" and "no discontinuation of investigational product", if they remained in the study. These analyses showed higher overall response rates in both arms, and continued to show an added benefit of anifrolumab over placebo, though this was somewhat more modest. However, these results should be considered only indicative of real world response rates and do not necessarily reflect the incremental benefit of anifrolumab as response could be confounded by the use of other medications or treatments which influence disease activity. Based on a blinded review by physicians, patients treated with placebo were more likely to discontinue investigational product due to efficacy-related reasons than anifrolumab-treated patients, and therefore following discontinuation treatment protocols may vary which influence the week 52 response.

Overall, within the three studies anifrolumab demonstrated efficacy of a range of studied endpoints. The AHEG and CHMP concluded that the totality of evidence is supportive of a beneficial treatment effect of anifrolumab, and the treatment effect was considered clinically meaningful for patients with moderate to severe, active autoantibody-positive SLE. The overall safety of anifrolumab in treating of SLE was also concluded to be acceptable.

## 7.2 Efficacy and safety of anifrolumab compared to belimumab for adults with moderate to severe, active SLE

### 7.2.1 Relevant studies

As noted in section 7.1.1 above, the relevant studies documenting the clinical efficacy and safety of belimumab are BLISS-52, BLISS-76, and BLISS-SC.[82,83,86] Full details on these studies can be found in Appendix B. Main characteristics of included studies.

The belimumab studies were mostly similar in design and inclusion criteria, and largely aligned with that of the TULIP and MUSE trials. All three studies were randomized, double-blind, placebo-controlled parallel group phase III studies designed to assess the efficacy and safety of belimumab in patients with active SLE despite SoC. BLISS-52 and BLISS-SC were 52-weeks in duration, whereas BLISS-76 followed patients for 76 weeks but with the primary endpoint assessment at week 52.

In both BLISS-52 and BLISS-76, patients were randomised 1:1:1 to receive placebo, belimumab 1 mg/kg, or belimumab 10 mg/kg (the approved therapeutic dose) given as an intravenous infusion over 1 hour on days 0, 14, and 28, and then every 28 days until 48 or 72 weeks in BLISS-52 and BLISS-76, respectively, in addition to protocol-specified SoC treatment. To ensure treatment groups were balanced, randomisation was stratified by SLEDAI score (<10 vs ≥10), proteinuria concentration (<2 g/24 h vs ≥ 2 g/24 h), and ethnic origin (African decent or indigenous American vs other). As belimumab 1 mg/kg is not the licensed therapeutic dose of belimumab in SLE, this treatment arm will not be further discussed.

During the studies, background SoC therapies were controlled per protocol to prevent confounding of efficacy assessments. Changes to immunosuppressive drug dose were restricted after 16 weeks, and for antimalarials changes were restricted after 24 weeks in BLISS-52 and 16 weeks in BLISS-76. Corticosteroid use was not restricted during the first 24 weeks but required return to within 25% or 5 mg greater than the baseline dose, with no further increases for the remainder of the study. Unlike the TULIP studies, steroid tapering was not mandated, but investigators could taper the prednisone dose on the basis of their clinical judgment.

The primary endpoint of all three BLISS studies was the SRI(4) response at week 52. Major secondary endpoints were patients with a ≥4-point reduction in SLEDAI score at week 52, mean change in PGA score at week 24, mean change in SF-36 PCS score at week 24, and proportion of patients with an average reduction in prednisone dose of ≥25% from baseline to 7.5 mg/day or less during weeks 40 to 52.

### 7.2.2 Efficacy and safety results per study

**A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS-76)**

*Primary endpoint:*

The primary efficacy endpoint for BLISS-76 was the SRI response rate at week 52. All of the following criteria had to be met to be considered a responder:

- ≥4-point reduction in SELENA-SLEDAI* score (measure of clinical benefit)
- No new BILAG A organ domain score and no more than 1 new BILAG B score†
- No worsening (increase <0.3) in PGA versus baseline

In addition, patients were considered non-responders to treatments if they used any protocol-prohibited or protocol-restricted medications up to week 52 or if that had withdrawn from the study.

Analysis of the primary endpoint was stratified by SELENA-SLEDAI score (6–9 vs ≥10) at baseline, proteinuria concentration (<2 g/24 h vs ≥2 g/24 h) at screening, and ethnic origin (African descent or indigenous American vs. other).

* The SELENA-SLEDAI scale used in the BLISS trials is similar to the updated SLEDAI-2K used in the TULIP trials and more commonly collected in clinical practice today. Both scales have the same weighting for items and organ damage, but have different definitions for the presence of proteinuria. Proteinuria is considered present when it is 0.5 g/day or more on both scales, but on the SELENA-SLEDAI new-onset proteinuria in included even when it is less than 0.5 g/day.[101] † The BLISS trials collected results on the classic BILAG as opposed to the BILAG-2004 used in the TULIP trials. The classic BILAG focused on disease activity in eight organs or systems using a similar grading system as the BILAG-2004. The main difference is that in the BILAG-2004 ophthalmic and gastrointestinal systems were added, and the vasculitis section was removed and the items were placed in the appropriate system. In addition, features that indicated damage were removed and fatigue and migraine were excluded.[102]

*Additional efficacy endpoints potentially possible for comparison to anifrolumab:*

The following additional outcomes given as secondary or exploratory endpoints in the publications for BLISS-76 were considered potentially relevant for comparison to anifrolumab given the collection of comparable data in the TULIP studies:

- Percentage of patients with a ≥4-point reduction from baseline in SELENA-SLEDAI score at week 52
- Change in physician's global assessment at week 24
- Percentage of patients with a mean prednisone dose that was decreased ≥25% from baseline and was ≤7.5 mg/day during weeks 40-52
- Percentage of patients with a disease flare up to week 52, defined as ≥1 new BILAG A score or ≥2 new BILAG B organ domains scores
- Change in SF-36v2 PCS score at week 24

*Efficacy results:*

There were more SRI responders at week 52 in patients treated with belimumab 10 mg/kg than in those treated with placebo (43.2% vs. 33.5%, $p = 0.017$; Table 13). Further evidence on the benefits of belimumab to reduce disease activity

were mixed. Compared with patients receiving placebo, significantly more patients receiving 10 mg/kg belimumab had a ≥4-point reduction in SELENA–SLEDAI score at week 52 (46.5% vs. 35.3%; *p* = 0.006; Table 13). However, there were no significant differences in mean change in physician's global assessment score at week 24 between the placebo (-0.49) and belimumab (-0.44).

Of the subgroup of patients receiving >7.5 mg/day prednisone (or equivalent) at baseline, a greater proportion of patients receiving belimumab (17.5%) were able to reduce corticosteroids by ≥25% and to ≤7.5 mg/day between weeks 40 and 52 compared with patients receiving placebo (12.7%), but these differences were not statistically significant.

In terms of patient reported outcomes, there were no significant differences in mean change in SF-36v2 PCS score at week 24 between belimumab (+3.21) and placebo group (+3.35). SF-36v2 PCS score improvements at week 52 were +3.44 for belimumab vs. +2.85 for placebo.

Despite change from baseline in PGA and SF-36v2 scores being reported, standard errors (or confidence intervals or *p*-values from which these could be estimated) were not reported in publications and therefore an indirect comparison on these outcomes cannot be conducted.

**Table 13. Key efficacy results for belimumab from BLISS-76**

| Endpoint, n (%) | Belimumab 10 mg/kg (*n* = 273) | Placebo (*n* = 275) |
|---|---|---|
| SRI(4) response rate at week 52 | 118 (43.2) | 92 (33.5) |
| ≥4-point reduction in SLEDAI score | 127 (46.5) | 97 (35.3) |
| Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 40-52 | 21/120 (17.5) | 16/126 (12.7) |
| New BILAG 1A or 2B flare | 86 (31.5) | 94 (34.2) |
| Mean change in PGA score from baseline to week 24 | -0.44 | -0.49 |
| Mean change in SF-36 PCS score from baseline to week 24 | +3.21 | +3.35 |

**Sources**: Furie et al (2011);[83] Petri et al (2010)[103] Values are n(%) unless otherwise stated

*Key safety & tolerability outcomes:*

The overall incidence of adverse events was similar between belimumab and placebo (Table 14). Depression was reported more frequently with belimumab (6–7%) than with placebo (4%). Infusion reactions (including hypersensitivity) were also more common with belimumab than with placebo, including serious or severe reactions (Table 14).

**Table 14. Overview of safety and tolerability of belimumab from BLISS-76**

| Adverse Event Category, n (%) | Belimumab 10 mg/kg (*n* = 273) | Placebo (*n* = 275) |
|---|---|---|
| Any adverse event | 253 (92.7) | 253 (92.0) |
| Serious adverse event | 61 (22.3) | 54 (19.6) |
| Death | 1 (0.4) | 0 |
| Adverse event leading to discontinuation of intervention | 23 (8.4) | 23 (8.4) |
| Malignancies | 2 (0.7) | 1 (0.4) |

| Adverse Event Category, n (%) | Belimumab 10 mg/kg (*n* = 273) | Placebo (*n* = 275) |
|---|---|---|
| Infections | | |
| • All | 202 (74.0) | 190 (69.1) |
| • Serious infections | 20 (7.3) | 16 (5.8) |
| • Opportunistic infections | 1 (0.4) | 0 |
| Infusion reactions | | |
| • All (including hypersensitivity) | 37 (13.6) | 27 (9.8) |
| • Severe | 3 (1.1) | 1 (0.4) |
| Adverse events occurring in ≥10% of patients | | |
| • Upper respiratory tract infection | 54 (19.8) | 58 (21.1) |
| • Headache | 44 (16.1) | 38 (13.8) |
| • Urinary tract infection | 44 (16.1) | 43 (15.6) |
| • Arthralgia | 41 (15.0) | 43 (15.6) |
| • Nausea | 46 (18.6) | 27 (9.8) |
| • Diarrhoea | 33 (12.1) | 28 (10.2) |
| • Nasopharyngitis | 43 (15.8) | 24 (8.7) |
| • Sinusitis | 31 (11.4) | 28 (10.2) |
| • Pyrexia | 29 (10.6) | 21 (7.6) |
| • Bronchitis | 32 (11.7) | 21 (7.6) |

**A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (SLE) (BLISS-52)**

*Primary endpoint:*

The primary efficacy endpoint for BLISS-52 was the response rate at week 52, as assessed by the SRI. All of the following criteria had to be met to be considered a responder:

- ≥4-point reduction in SELENA-SLEDAI score (measure of clinical benefit)
- No new BILAG A organ domain score and no more than 1 new BILAG B score
- No worsening (increase <0.3) in PGA at week 52 compared to baseline

In addition, patients were considered non-responders to treatments if they used any protocol-prohibited or protocol-restricted medications up to week 52 or if that had withdrawn from the study.

Analysis of the primary endpoint was stratified by SELENA-SLEDAI score (6–9 vs ≥10) at baseline, proteinuria concentration (<2 g/24 h vs ≥2 g/24 h) at screening, and ethnic origin (African descent or indigenous American vs. other).

*Additional efficacy endpoints potentially possible for comparison to anifrolumab:*

The following secondary or exploratory endpoints in BLISS-52 were considered potentially relevant for comparison to anifrolumab given the collection of comparable data in the TULIP studies:

- Proportion of patients with ≥4-point reduction from baseline in SELENA-SLEDAI score at week 52
- Mean change in physician's global assessment at week 24
- Proportion of patients with an average reduction in prednisone dose of ≥25% from baseline to ≤7.5 mg/day during weeks 40-52

- Percentage of patients with a disease flare up to week 52, defined as ≥1 new BILAG A score or ≥2 new BILAG B organ domains scores
- Mean change in SF-36v2 PCS score at week 24

*Efficacy results:*

Significantly more people showed a response as assessed with the SRI in the belimumab 10 mg/kg group than in the placebo group at week 52 (Table 15). Supportive evidence on the reduction of disease activity showed that significantly more patients in the belimumab group achieved an improvement in the SELENA-SLEDAI score of at least 4 points at week 52 than in the placebo group (Table 15). Fewer patients treated with belimumab had disease flares as assessed by no new BILAG A and no more than 1 new BILAG B organ domain score. Belimumab 10 mg/kg also resulted in a greater mean absolute reduction in PGA score, signifying improvement at week 24, relative to placebo.

Of the patients taking prednisone at doses greater than 7.5 mg/day at baseline, reductions in dose of at least 25% to 7.5 mg/day or less during weeks 40 to 52 were numerically greater with belimumab but this was not statistically significant.

Although groups did not differ significantly in SF-36 PCS scores at week 24, the belimumab group had significant mean absolute increases at week 52 compared with placebo (Table 15).

**Table 15. Key efficacy results for belimumab from BLISS-52**

| Endpoint, n (%) | Belimumab 10 mg/kg (*n* = 290) | Placebo (*n* = 287) | Belimumab vs. Placebo Odds Ratio (95% CI) |
|---|---|---|---|
| SRI(4) response rate at week 52 | 167 (57.6) | 125 (43.6) | 1.83 (1.30, 2.59) |
| ≥4-point reduction in SLEDAI score | 169 (58.3) | 132 (46.0) | 1.71 (1.21, 2.41) |
| Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 40-52 | 38/204 (18.6) | 23/192 (12.0) | 1.75 (0.99, 3.08) |
| New BILAG 1A or 2B flare | 54 (18.6) | 86 (30.0) | 0.58 (0.41, 0.81) |
| | **LS Mean (SE)** | **LS Mean (SD)** | **Difference (95% CI)** |
| Change in PGA score from baseline to week 24 | -0.50 (0.04) | -0.35 (0.04) | -0.15 (-0.23, -0.07) |
| Change in SF-36 PCS score from baseline to week 24 | +3.34 (0.55) | 3.26 (0.54) | 0.08 (-1.00, 1.15) |
| Change in SF-36 PCS score from baseline to week 52 | +4.19 (0.60) | +2.84 (0.60) | 1.35 (0.17, 2.54) |

**Sources**: Navarra et al (2011)[82]

*Key safety & tolerability outcomes:*

The occurrence of adverse events and discontinuations were similar between belimumab and placebo (Table 16). There were marginally more serious adverse events in patients treated with belimumab, though fewer serious infections. Nearly all serious infections in both groups resulted in admission to hospital. Infusion reactions were similar between groups, though the rates of severe hypersensitivity or infusion reactions were numerically greater in belimumab treatment patients.

**Table 16. Overview of safety and tolerability of belimumab from BLISS-52**

| Adverse Event Category, n (%) | Belimumab 10 mg/kg (*n* = 290) | Placebo (*n* = 287) |
|---|---|---|
| Any adverse event | 266 (91.7) | 263 (91.6) |
| Serious adverse event | 41 (14.1) | 36 (12.5) |
| Death | 4 (1.4) | 3 (1.0) |
| Adverse event leading to discontinuation of intervention | 15 (5.2) | 19 (6.6) |
| Malignancies | 0 | 0 |
| Infections | | |
| • All | 194 (66.9) | 183 (63.8) |
| • Serious infections | 13 (4.5) | 17 (5.9) |
| • Opportunistic infections | 1 (0.3) | 0 |
| Infusion reactions | | |
| • All (including hypersensitivity) | 48 (16.6) | 49 (17.1) |
| • Severe | 3 (1.4) | 1 (0.3) |
| Adverse events occurring in ≥10% of patients | | |
| • Headache | 66 (22.8) | 76 (26.5) |
| • Upper respiratory tract infection | 36 (12.4) | 47 (16.4) |
| • Arthralgia | 33 (11.4) | 34 (11.8) |
| • Influenza | 33 (11.4) | 25 (8.7) |
| • Diarrhoea | 30 (10.3) | 20 (7.0) |
| • Hypertension | 17 (5.9) | 30 (10.5) |
| • Nausea | 23 (7.9) | 31 (10.8) |

**A Study of Belimumab Administered Subcutaneously in Subjects With SLE (BLISS-SC)**

*Primary endpoint:*

The primary efficacy endpoint in the assessment of subcutaneous belimumab in BLISS-SC was the SRI(4) response rate at week 52. All of the following criteria had to be met to be considered a responder:

- ≥4-point reduction in SELENA-SLEDAI score (measure of clinical benefit)
- No new BILAG A organ domain score and no more than 1 new BILAG B score at week 52 compared to baseline
- No worsening (increase <0.3) in PGA versus baseline

In addition, patients were considered non-responders to treatments if they used any protocol-prohibited or protocol-restricted medications up to week 52 or if that had withdrawn from the study.

Analysis of the primary endpoint was stratified by SELENA-SLEDAI score (8–9 vs. ≥10) at baseline, complement level (C3 and/or C4 low vs. other) at baseline, and race (black vs. other).

*Additional efficacy endpoints potentially possible for comparison to anifrolumab:*

The following additional endpoints collected in BLISS-SC were considered potentially relevant for comparison to anifrolumab given the collection of comparable data in the TULIP studies:

- Proportion of patients with ≥4-point reduction from baseline in SELENA-SLEDAI score at week 52
- Percentage of patients among those receiving >7.5 mg/day at baseline who experienced a mean dosage reduction of ≥25% from baseline to ≤7.5 mg/day during weeks 40-52
- Percentage of patients with a disease flare up to week 52, defined as ≥1 new BILAG A score or ≥2 new BILAG B organ domains scores
- Mean change from baseline in FACIT-Fatigue score

*Efficacy results:*

At week 52, 61.4% of belimumab patients were SRI(4) responders compared with 48.4% for placebo (OR 1.68; 95% CI 1.25, 2.25; $p = 0.0006$). All components of the SRI(4) showed statistical significance at week 52, including the proportion of patients with a ≥4-point reduction in SLEDAI score (Table 17). Fewer patients treatment with belimumab had any new BILAG flare defined as one new A score or at least two new B scores.

More patients who received belimumab were able to reduce their corticosteroid dosage by ≥25%, to ≤7.5 mg/day during weeks 40–52 as compared with placebo, although this difference did not achieve statistical significance.

Scores on the FACIT-Fatigue scale improved over time in both treatment groups. The mean change from baseline was significantly greater in the belimumab group as compared with the placebo group at weeks 8, 36, and 52 (Table 17), but not at weeks 4, 12, and 24 (data not reported). As standard errors for the change in FACIT-F score were not reported, an indirect comparison on this endpoint was deemed to not be feasible.

**Table 17. Key efficacy results for belimumab from BLISS-SC**

| Endpoint, n (%) | Belimumab 200 mg (*n* = 554) | Placebo (*n* = 279) | Belimumab vs. Placebo Odds Ratio (95% CI) |
|---|---|---|---|
| SRI(4) response rate at week 52 | 340 (61.4) | 135 (48.4) | 1.68 (1.25, 2.25) |
| ≥4-point reduction in SLEDAI score | 345 (62.3) | 137 (49.1) | NR |
| Prednisone reduced by ≥25% to ≤7.5 mg/day during weeks 40-52 | 61/335 (18.2) | 20/168 (11.9) | 1.65 (0.95, 2.84) |
| New BILAG 1A or 2B flare | 107 (19.3) | 72 (25.8) | NR |
| Mean change in FACIT-F score from baseline to week 52 | +4.4 | +2.7 | NR |

**Sources**: Stohl et al (2017)[86] Values are n(%) unless otherwise stated

*Key safety & tolerability outcomes:*

Overall, 449 patients in the belimumab group (80.8%) and 236 patients in the placebo group (84.3%) experienced at least one adverse event (Table 18). The most common types were infections and infestations. Serious adverse events were reported for 10.8% and 15.7% of patients, respectively. The most common types were infections and infestations, renal and urinary disorders, and nervous system disorders. Treatment-related adverse events were reported for 31.1% of the belimumab group and 26.1% of the placebo group. The incidence of hypersensitivity reactions was similar between treatment groups.

**Table 18. Overview of safety and tolerability of belimumab from BLISS-SC**

| Adverse Event Category | Belimumab 200 mg (*n* = 556) | Placebo (*n* = 280) |
|---|---|---|
| Any adverse event | 449 (80.8) | 236 (84.3) |
| Serious adverse event | 60 (10.8) | 44 (15.7) |
| Treatment-related adverse events | 173 (31.1) | 73 (26.1) |
| Death | 3 (0.5) | 2 (0.7) |
| Adverse event leading to discontinuation of intervention | 40 (7.2) | 25 (8.9) |
| Infections | | |
| • All | 308 (55.4) | 159 (56.8) |
| • Serious infections | 23 (4.1) | 15 (5.4) |
| • Opportunistic infections | 2 (0.4) | 1 (0.4) |
| Adverse events of special interest | | |
| • Malignancies | 2 (0.4) | 1 (0.4) |
| • Post-injection systemic reactions | 38 (6.8) | 25 (8.9) |
| • Serious delayed non-acute hypersensitivity reactions | 0 | 1 (0.4) |
| • Herpes zoster | 18 (3.2) | 13 (4.6) |
| • Sepsis | 6 (1.1) | 3 (1.1) |
| • Depression | 15 (2.7) | 10 (3.6) |
| • Serious suicidal ideation | 2 (0.4) | 0 |

### 7.2.3 Comparative analyses

**Method of synthesis**

No head-to-head studies comparing anifrolumab to belimumab have been identified, and so an indirect treatment comparison is required to assess the relative efficacy and safety.

For the analysis, the pooled data from TULIP-1, TULIP-2, and MUSE are used. A pooled analysis of the BLISS-52 and BLISS-76 studies was also used for comparison to intravenously administered belimumab. BLISS-SC was not included in the pooled data for belimumab IV, given its different route of administration and that trial inclusion criteria differed compared to the other BLISS studies. Patients in the BLISS-SC study were required to have higher disease activity at baseline, with a minimum SLEDAI score of 8 at screening in order to be eligible for the study. This is compared to a score of ≥6 in the other two BLISS studies and the anifrolumab studies, and therefore reflects a higher degree of disease activity than typically classified as moderate to severe, active SLE as covered by the indication for anifrolumab. Pharmacokinetics studies have shown that weekly SC belimumab dosed at 200 mg achieved blood levels and bioavailability similar to those achieved by a monthly 10 mg/kg IV belimumab dose, regardless of the site of injection or body size,[104-107] suggesting that a direct comparison of efficacy against SC belimumab is superfluous to requirement. Therefore, a comparison between the TULIP trials and the BLISS-SC study is only presented as a sensitivity analysis.

All listed primary and key secondary endpoints from the TULIP and BLISS trials were evaluated for comparison. Following a review of trial publications, the following outcomes were identified to be possible for comparison:

- **SRI(4) response at week 52**, defined as the proportion of patients with at least a 4-point reduction in SLEDAI score, less than one new BILAG A or less than two new BILAG B organ domain scores, less than 0.3-point increase in PGA from baseline.
- **SLEDAI ≥4-point reduction at week 52**, defined as the proportion of patients with at least a 4-point reduction in SLEDAI score from baseline.
- **Sustained prednisone dose reduction** to ≤7.5mg/day between weeks 40 and 52.
- **Patients with BILAG flare up to week 52**, defined as the proportion of patients who had experienced at least one new BILAG A or two new BILAG B organ domain scores compared to the previous visit at any time on study up to week 52.

The results on each of these four endpoints for the pooled TULIP/MUSE data and the BLISS studies are presented in Table 19.

**Table 19. Effect sizes for the pooled data used in the indirect comparisons between anifrolumab and belimumab**

| Endpoint, n (%) | Anifrolumab vs. Placebo | | Belimumab IV vs. Placebo | | Belimumab SC vs. Placebo | |
|---|---|---|---|---|---|---|
| | Anifrolumab (*n* = 459) | Placebo (*n* = 468) | Belimumab (*n* = 563) | Placebo (*n* = 562) | Belimumab (*n* = 554) | Placebo (*n* = 279) |
| SRI(4) response at week 52 | 250 (54.5) | 188 (40.2) | 285 (50.6) | 217 (38.6) | 340 (61.4) | 135 (48.4) |
| SLEDAI ≥4-point reduction at week 52 | [redacted] | [redacted] | 296 (52.6) | 229 (40.7) | 345 (62.3) | 137 (49.1) |
| Prednisone reduced to ≤7.5mg/day in weeks 40-52† | 127/245 (51.8) | 76/249 (30.5) | 59/324 (18.2) | 39/318 (12.3) | 61/335 (18.2) | 20/168 (11.9) |
| Patients with BILAG new 1A or 2B flare up to week 52 | [redacted] | [redacted] | 140 (24.9) | 180 (32.0) | 107 (19.3) | 72 (25.8) |

† The definition of steroid reduction differed between the trials, with this reflecting a reduction to ≤7.5mg/day for patients with a dose ≥10mg/day at baseline in the TULIP/MUSE trials, and a reduction of ≥25% to below ≤7.5mg/day for patients with a dose >7.5mg/day at baseline in the BLISS trials

It should be noted that the definition of sustained steroid dose reduction differed between the anifrolumab and belimumab trials. In the TULIP and MUSE trials, the definition of steroid reduction reflecting a reduction to ≤7.5mg/day for patients with a dose ≥10mg/day at baseline, whereas in the BLISS trials this was a reduction of ≥25% to below ≤7.5mg/day for patients with a dose >7.5mg/day at baseline. For patients on a dose ≥10mg/day at baseline in TULIP trials constituted the same level of response, whereas in the BLISS trials patients on doses between 7.5 and 10mg/day could be classified as responders. This is assumed to have a negligible impact on the results as only 4 patients across the pooled TULIP trials were receiving a dose between 7.5 and 10mg/day at baseline (see Appendix C). An alternative analysis on the TULIP data to assess steroid dose reduction in patients receiving >7.5 mg/day at baseline was not conducted as the trial design and protocol stipulated that an attempt to taper steroid dose was only required for patients on doses of 10 mg/day or more at baseline.

As noted in section 7.2.2 above, the BLISS trials also used the SELENA-SLEDAI and classic BILAG as components in the SRI(4) response, as opposed to the SLEDAI-2K and the BILAG-2004 as were used in the TULIP and MUSE studies. No formal adjustments were made to assess the impact of this on results, given the alternative items collected in the BILAG-2004 and the differences between SELENA-SLEDAI and SLEDAI-2K values were not recorded for the TULIP/MUSE studies. However, unpublished exploratory analyses on the BLISS trials show that SRI(4) response rates were not especially sensitive to the use of the SLEDAI-2K. In BLISS-52, the SRI(4) response rate at week 52 using the SLEDAI-2K (vs. base case using SELENA-SLEDAI) were 57.9% (57.6%) and 42.9% (43.6%) in the belimumab 10 mg/kg and placebo groups,

respectively.[108] In the BLISS-76 trial, the response rates using SLEDAI-2K (or SELENA-SLEDAI) were 43.6% (43.2%) for belimumab 10 mg/kg and 33.8% (33.5%) for placebo.[109] As can be seen, response rates using the SLEDAI-2K do not differ significantly from the base case results using the SELENA-SLEDAI. No such analysis comparing outcomes using the different BILAG scales had been conducted on the BLISS or TULIP trials. It has been commented that the BILAG-2004 reflects disease activity change more sensitively and reports less false-positive disease activity than the classic BILAG index,[101] and therefore one must accept this differences as a limitation of the analysis. The outcomes included in the analysis fail to include the primary endpoint for TULIP-2 (BICLA response), as well as several other key endpoints from the TULIP trials, where anifrolumab was shown to have a statistically or clinically significant improvement over standard therapy alone (see section 7.1.2). These includes the CLASI score, the rate of BILAG flares (as opposed to just patients experiencing a flare), and the reduction in the number of swollen or tender joints. This is due to the lack of reporting these outcomes in belimumab trials. Post hoc analysis of the BLISS trials showed that there were modest rates of improvement in patients with BILAG A or B scores at baseline treated with belimumab compared to placebo in terms of musculoskeletal (Δ10.2%) and mucocutaneous (Δ8.5%) organ involvement.[110] However, comprehensive assessment of skin and joint symptomology in patients treated with belimumab in randomized trials has not been published and therefore it is not possible to conduct a conclusive indirect treatment comparison of anifrolumab vs. belimumab on these outcomes.

Despite similar inclusion criteria, patients in the anifrolumab studies were older at baseline, more likely to be of Caucasian race, have a higher SLEDAI score and more likely to have ≥1 BILAG A score or ≥2 BILAG B scores compared to patients enrolled in the three BLISS studies. However, there were much higher proportions of patients in the BLISS studies with anti-dsDNA antibodies and/or low complement, which are known treatment-effect modifiers for belimumab leading to the label recommendation for this product. Background standard of care therapies also differed between the studies, with higher doses of steroids used in the BLISS trials, and differing distributions of the concomitant immunosuppressants used. A full comparison of baseline characteristics can be found in Appendix C. Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety.

As several of these factors were considered to be potential treatment-effect modifiers based on clinical opinion and published literature, an adjusted indirect comparison was conducted. Pairwise indirect comparisons between anifrolumab and belimumab were performed using an anchored simulated treatment comparison (STC), using the placebo arm of trials for both drugs as the common comparator. Adjusted indirect treatment comparisons, such as STCs, are effective in accounting for cross-trial imbalances in patient characteristics that may otherwise cause biased comparative estimates, thus providing a methodologically robust alternative to unadjusted indirect comparisons when heterogeneity exists between studies. The STC method was favoured over a matching-adjusted indirect treatment comparison (MAIC) as accounting for all relevant treatment-effect modifiers led to an imbalanced distribution of weights and reduced the effective sample size to unacceptable levels to permit robust comparisons. More details on the STC methods and a full technical report can be found in appendices F and K, respectively. In brief, potential treatment effect modifiers were identified based on published literature in conjunction with clinical experts. Ranking of the impact of these parameters of the relative efficacy of anifrolumab compared to placebo was determined via a quantitative assessment between effect estimates when adjusting for one potential modifier at a time compared to an unadjusted model. In the base case, all potential modifiers were adjusted for in analyses. Scenario analyses excluding parameters one-by-one from that with the lowest ranked effect on the outcome to the highest ranked effect were also considered to assess influence on outcome due to potential overfitting of models. Parameters included in the base case adjustment (in highest to lowest rank order with respect to impact on SRI(4) response at week 52) were:

- Proportion of patients with at least 1 BILAG A or 2 BILAG B scores at baseline
- Race
- Positive anti-dsDNA at baseline

- Low C3 complement at baseline
- Low C4 complement at baseline
- Treated with non-steroidal immunosuppressant at baseline (azathioprine)
- SLEDAI score at baseline
- Age
- Treated with non-steroidal immunosuppressant at baseline (methotrexate)
- Oral corticosteroid dose >7.5 mg/day at baseline
- Treated with non-steroidal immunosuppressant at baseline (mycophenolate)
- Sex
- ANA positive
- Treated with antimalarials are baseline

The effect of each individual effect modifier on the relative efficacy between anifrolumab and belimumab can be found in Appendix K. Full report of the indirect treatment comparison on efficacy.

As less information is known on what could constitute a treatment-effect modifier with regards to the safety of biologic immunomodulatory drugs for SLE, only an unadjusted analysis (Bucher indirect comparison) of the relative safety between anifrolumab and belimumab is presented.

**Results from the comparative analysis**

The probability of patients meeting the all-or-nothing response criteria of an SRI(4) response at week 52, and its key efficacy component of a reduction of at least 4 points on the SLEDAI, suggests an efficacy benefit for anifrolumab relative to IV belimumab after adjustment for baseline characteristics (Table 20). There were also small, non-significant trends for a more favourable outcome for anifrolumab with regards to proportion of patients experiencing a new disease flare over the course of 52 weeks, as assessed on the BILAG, and the probability of meeting steroid sparing goals, though meaningful differences between anifrolumab and IV belimumab cannot be established.

Results were largely consistent in the sensitivity analysis vs. BLISS-SC compared to patients with a higher disease activity at baseline (SLEDAI ≥8), with a trend for better response rates on the SRI(4) and SLEDAI reduction after 52 weeks with anifrolumab compared to SC belimumab (Table 21). Anifrolumab-treated patients appear less likely to experience a new BILAG flare. An adjusted comparison of steroid dose reduction was not conducted between anifrolumab and SC belimumab as patient baseline characteristics for the subgroup of patients eligible for this endpoint from the BLISS-SC trial have not been published.

Results were not particularly sensitive to the number of parameters included for adjustment, particularly once adjusting for BILAG A or B scores at baseline where point estimates for the odds ratio for SRI(4) response ranged from [redacted] to [redacted] after adjustment. As may be expected, in some scenarios excluding variables resulted in a marginally lower AIC, however the base case results were retained and presented below as adjustment for all variables did not appear to meaningfully result in overfitting (see Appendix K. Full report of the indirect treatment comparison on efficacy).



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

**Table 20. Indirect treatment comparison of efficacy between anifrolumab (TULIP/MUSE) and intravenous belimumab (BLISS-76/BLISS-52)**

| Endpoint | Anifrolumab vs. Placebo, Odds Ratio (95% CI) | | | | Belimumab IV vs. Placebo, Odds Ratio (95% CI) | | Anifrolumab vs. Belimumab IV, Odds Ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | | | |
| SRI(4) response at week 52 | *n* = 927 | 1.84 (1.41, 2.39) | *n* = 889 | [redacted] | *n* = 1125 | 1.63 (1.29, 2.07) | [redacted] |
| SLEDAI ≥4-point reduction at week 52 | *n* = 927 | 1.76 (1.36, 2.28) | *n* = 888 | [redacted] | *n* = 1125 | 1.61 (1.27, 2.04) | [redacted] |
| Prednisone reduced to ≤7.5mg/day in weeks 40-52† | *n* = 494 | 2.04 (1.55, 2.69) | *n* = 471 | [redacted] | *n* = 642 | 1.59 (1.03, 2.47) | [redacted] |
| Patients with BILAG new 1A or 2B flare up to week 52 | *n* = 927 | 0.69 (0.52, 0.91) | *n* = 889 | [redacted] | *n* = 1125 | 0.70 (0.54, 0.91) | [redacted] |

† The definition of steroid reduction differed between the trials, with this reflecting a reduction to ≤7.5mg/day for patients with a dose ≥10mg/day at baseline in the TULIP/MUSE trials, and a reduction of ≥25% to below ≤7.5mg/day for patients with a dose >7.5mg/day at baseline in the BLISS trials

**Table 21. Sensitivity analysis of the indirect treatment comparison of efficacy between anifrolumab (TULIP/MUSE) and subcutaneous belimumab (BLISS-SC)**

| Endpoint | Anifrolumab vs. Placebo, Odds Ratio (95% CI) | | | | Belimumab SC vs. Placebo, Odds Ratio (95% CI) | | Anifrolumab vs. Belimumab SC, Odds Ratio (95% CI) |
|---|---|---|---|---|---|---|---|
| | Unadjusted | | Adjusted | | | | |
| SRI(4) response at week 52 | *n* = 927 | 1.84 (1.41, 2.39) | *n* = 927 | [redacted] | *n* = 833 | 1.68 (1.25, 2.25) | [redacted] |
| SLEDAI ≥4-point reduction at week 52 | *n* = 927 | 1.76 (1.36, 2.28) | *n* = 926 | [redacted] | *n* = 833 | 1.71 (1.28, 2.29) | [redacted] |
| Prednisone reduced to ≤7.5mg/day in weeks 40-52† | *n* = 494 | 2.04 (1.55, 2.69) | N/A | N/A | *n* = 503 | 1.65 (0.95, 2.84) | N/A |
| Patients with BILAG new 1A or 2B flare up to week 52 | *n* = 927 | 0.69 (0.52, 0.91) | *n* = 927 | [redacted] | *n* = 833 | 0.69 (0.49, 0.97) | [redacted] |

† The definition of steroid reduction differed between the trials, with this reflecting a reduction to ≤7.5mg/day for patients with a dose ≥10mg/day at baseline in the TULIP/MUSE trials, and a reduction of ≥25% to below ≤7.5mg/day for patients with a dose >7.5mg/day at baseline in BLISS-SC

There were more adverse events overall in the BLISS trials of IV belimumab compared to anifrolumab trials, but relative to placebo there were slightly more events in patients receiving anifrolumab (Table 22). This translates to a trend for an increased risk of adverse events with anifrolumab compared to belimumab in the indirect comparison. However, there is a significantly reduced risk of serious adverse events with anifrolumab compared to IV belimumab. This same trend is observed for the comparison in infections, where patients treated with anifrolumab were marginally more likely to have an infection in the trial, but this was less likely to be serious infection when compared with belimumab. Anifrolumab patients were also less likely to experience a psychiatric event – an established risk with belimumab.[111] The risk of treatment discontinuation or death due to adverse events, and the development of malignancies, appears to be similar between the add-on biologics for SLE. The observed safety profile for anifrolumab also appears to be largely similar to that of SC belimumab (Table 22).

**Table 22. Indirect treatment comparison of safety and tolerability between anifrolumab and belimumab**

| Adverse Event Category | Anifrolumab vs. Placebo | | | Belimumab IV vs. Placebo | | | Anifrolumab vs. Belimumab IV | Belimumab SC vs. Placebo | | | Anifrolumab vs. Belimumab SC |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Anifrolumab n (%) | Placebo n (%) | OR (95% CI) | Belimumab n (%) | Placebo n (%) | OR (95% CI) | OR (95% CI) | Belimumab n (%) | Placebo n (%) | OR (95% CI) | OR (95% CI) |
| | *N = 459* | *N = 466* | | *N = 563* | *N = 562* | | | *N = 556* | *N = 280* | | |
| Any adverse event | 404 (88.0) | 377 (80.9) | 1.73 (1.20, 2.50) | 519 (92.2) | 516 (91.8) | 1.05 (0.68, 1.62) | 1.65 (0.94, 2.90) | 449 (80.8) | 236 (84.3) | 0.78 (0.53, 1.15) | 2.22 (1.30, 3.77) |
| Serious adverse event | 59 (12.9) | 88 (18.9) | 0.63 (0.44, 0.91) | 102 (18.1) | 90 (16.0) | 1.16 (0.85, 1.58) | 0.55 (0.34, 0.88) | 60 (10.8) | 44 (15.7) | 0.65 (0.43, 0.99) | 0.98 (0.56, 1.69) |
| Treatment-related adverse event | 155 (33.8) | 126 (27.0) | 1.38 (1.04, 1.82) | 206 (36.6) | 233 (41.5) | 0.81 (0.64, 1.04) | 1.69 (1.17, 2.44) | 173 (31.1) | 73 (26.1) | 1.28 (0.93, 1.77) | 1.07 (0.70, 1.65) |
| Treatment discontinuations due to any reason | 74 (16.1) | 121 (26.0) | 0.55 (0.40, 0.76) | 113 (20.1) | 131 (23.3) | 0.83 (0.62, 1.10) | 0.66 (0.43, 1.02) | 93 (16.7) | 66 (23.6) | 0.65 (0.46, 0.93) | 0.84 (0.52, 1.36) |
| Adverse event leading to discontinuation of intervention | 20 (4.4) | 30 (6.4) | 0.66 (0.37, 1.18) | 38 (6.7) | 42 (7.5) | 0.90 (0.57, 1.41) | 0.74 (0.35, 1.55) | 40 (7.2) | 25 (8.9) | 0.79 (0.47, 1.33) | 0.84 (0.38, 1.83) |
| Adverse events leading to death | 2 (0.4) | 1 (0.2) | 2.04 (0.18, 22.52) | 5 (0.9) | 3 (0.5) | 1.67 (0.40, 7.02) | 1.22 (0.07, 20.05) | 3 (0.5) | 2 (0.7) | 0.75 (0.13, 4.54) | 2.70 (0.13, 54.21) |
| Selected adverse events of special interest:† | | | | | | | | | | | |
| All infections | 330 (71.9) | 271 (58.2) | 1.84 (1.40, 2.42) | 396 (70.3) | 373 (66.4) | 1.20 (0.93, 1.55) | 1.53 (1.06, 2.22) | 308 (55.4) | 159 (56.8) | 0.95 (0.71, 1.26) | 1.95 (1.31, 2.90) |
| • Serious infections | 24 (5.2) | 32 (6.9) | 0.75 (0.43, 1.29) | 33 (5.9) | 33 (5.9) | 1.00 (0.61, 1.64) | 0.75 (0.36, 1.57) | 23 (4.1) | 15 (5.4) | 0.76 (0.39, 1.49) | 0.98 (0.41, 2.32) |
| Malignancies | 6 (1.3) | 3 (0.6) | 2.04 (0.51, 8.22) | 2 (0.4) | 1 (0.2) | 2.00 (0.18, 22.12) | 1.02 (0.06, 16.43) | 2 (0.4) | 1 (0.4) | 1.01 (0.09, 11.16) | 2.03 (0.13, 32.67) |
| Psychiatric Disorders | 34 (7.4) | 44 (9.4) | 0.77 (0.48, 1.22) | 78 (13.9) | 58 (10.3) | 1.40 (0.97, 2.01) | 0.55 (0.30, 0.99) | 35 (6.3) | 32 (11.4) | 0.52 (0.31, 0.86) | 1.47 (0.74, 2.93) |

† These refer to the subset of adverse events of special interest (by System Organ Class) for anifrolumab or belimumab specified as being an important identified or potential risk in the European Public Assessment Report Risk Management Plans

**Summary of indirect comparison results**

Results from the indirect treatment comparison method suggest that anifrolumab is at least equally efficacious as belimumab with regards to objective measures of disease activity as used in clinical trials, such as the SRI(4), SLEDAI score, and BILAG flares. There may be an added benefit of anifrolumab over belimumab given the improvements in disease activity as assessed by the adjusted SRI(4) response and SLEDAI scores. However, the inability to conduct an indirect treatment comparison on the BICLA response hinders the ability to make broader conclusions on the relative disease control. The BICLA reflects a stringent requirement for the reduction in treatment need and improvement in disease activity across all involved organ systems, which is perhaps more akin to response measures in clinical practice than the SRI(4). Hence it is assumed that anifrolumab can offer at least the same reduction in disease activity in clinical practice as belimumab, though potentially with a more rapid onset where anifrolumab met the endpoint for early reductions in mucocutaneous in the 50% reduction in CLASI activity at week 12, but belimumab did not meet the endpoint for change in PGA score at week 24.

With regards to the proportion of patients with a sustained reduction in steroid dose, the indirect treatment comparisons demonstrated at least as good results for anifrolumab as for belimumab. Importantly, the definition of sustained steroid sparing differed between anifrolumab and belimumab trials with regards to the baseline dose of steroids taken and the per protocol application of the dose tapering. Irrespective of this difference in definition, anifrolumab has demonstrated significant steroid sparing in both pivotal trials, unlike belimumab. Therefore, anifrolumab is likely to offer at least the same steroid sparing abilities whilst controlling disease activity as belimumab.

Adjusting for the identified treatment effect modifiers may be important when considering the relative efficacy of anifrolumab vs. belimumab, as they influence the relative efficacy of anifrolumab over placebo. Because STCs account for between-study differences that may cause bias in unadjusted estimate, results from an unadjusted ITC alone cannot fully explore the possible relative effects between anifrolumab and belimumab (unadjusted comparisons can be found in the appendix to this submission). While the STC was able to adjust for important baseline and study characteristics, there have been some remaining differences in patients and study characteristics between TULIP-1 and TULIP-2 and the pooled BLISS data that cannot be accounted for due to the lack of reporting.

The results of the naïve comparison on safety suggest that anifrolumab largely has a comparable safety and tolerability profile compared to belimumab. However, anifrolumab has the potential to offer some benefits in terms of a reduced incidence of serious adverse events (notably serious infections) and psychiatric disorders compared with the IV formulation of belimumab. A higher relative incidence of adverse events was observed with anifrolumab, though one must interpret this indirect comparison with caution. As this analysis was not adjusted for baseline characteristics or background therapies, it is unclear to what extent these factors may influence comparisons on safety. Higher doses of steroids and different background immunosuppressive therapies may influence adverse event rates, and patients with higher disease activity may be more prone to experiencing SLE-related events.

Based on the indirect treatment comparison, overall it can be concluded that anifrolumab is at least as effective as belimumab when considering objective measures of disease activity, and is likely to have a comparable safety profile with a potentially reduced risk of serious adverse events.

# 8. Health economic analysis

As the results of the indirect comparison suggest that anifrolumab is likely to be, at a minimum, equally as efficacious as belimumab, with a comparable tolerability profile and no additional safety concerns, a cost-minimisation analysis is sufficient to assess the relative economic impact. This approach is considered to be conservative as anifrolumab may potentially offer some benefits in terms of better disease activity control and a reduced risk of serious adverse events, as well as unmeasured benefits in terms of skin manifestations (CLASI) and BICLA response that were not captured in belimumab trials.

Belimumab is available as both an intravenous (IV) infusion and a subcutaneous (SC) injection. The SC formulation has only been used in Denmark since September 2020, and only around [redacted] of patient days on treatment are administered with the SC formulation, based on sales figures (Figure 22). This implies that the IV formulation is still the predominant route of administration in Danish clinical practice for the majority of patients. Given that anifrolumab is also administered intravenously, it is most likely to displace IV belimumab in clinical practice, on the grounds that self-administering medication may be preferential for some patients, and therefore forms the main economic comparator in this analysis.

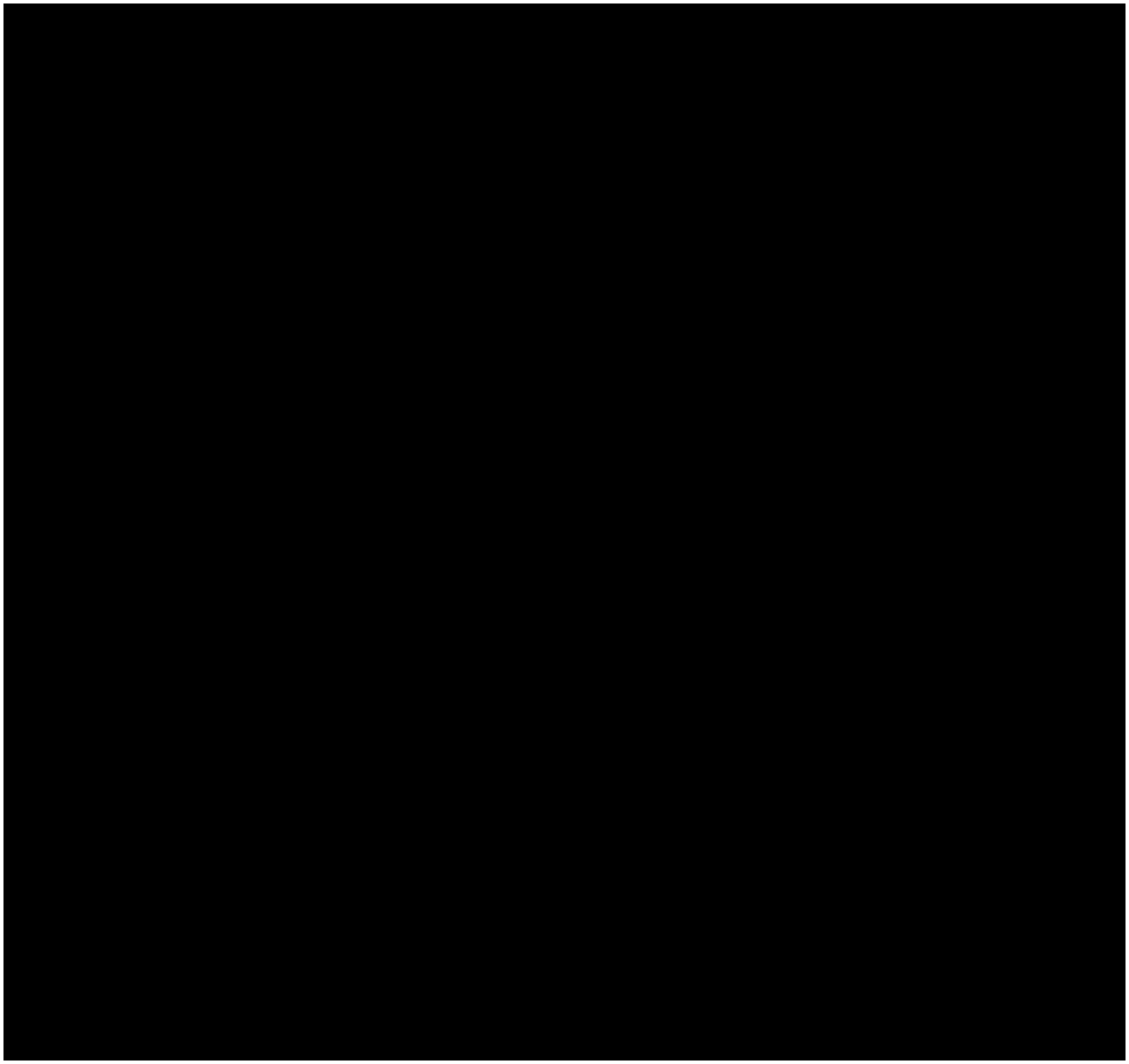
**Figure 22. Proportion of estimated patient days on treatment on intravenous belimumab, based on packs sold per month**

Based on feedback from rheumatologists, some patients who respond to treatment with intravenous belimumab may be transitioned onto subcutaneous belimumab for longer-term maintenance therapy. Therefore a scenario analysis is considered where the comparator is a blended mix of IV and SC belimumab, where all patients start on the IV formulation and a subset will later transition onto SC. As can be seen in [redacted], following the introduction of subcutaneous belimumab a drop in the number of monthly patients is observed in the capital region and southern Denmark, and to a lesser extent in Zealand, potentially indicating patients being transitioned from one formulation to the other. For the purposes of the cost minimization analysis, it is estimated that around 20% of patients continuing on treatment may transition on to the subcutaneous formulation.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

**Figure 23. Estimated users (3-month averages) of belimumab in the year preceding and following the introduction of subcutaneous belimumab in Denmark by hospital/regions prescribing belimumab in practice**



Dotted black line indicates month subcutaneous belimumab was first sold in Denmark

In addition, upon request from Medicinrådet a further scenario is considered where some patients are assumed to start subcutaneous belimumab from their first day of treatment, in a weighted combination with a proportion of patients starting IV belimumab. An estimate of the proportion of patients starting treatment with each formulation has been derived based on historical sales figures for belimumab and estimates of the time on treatment/discontinuation rate from the economic model (Table 23). Based on the nine month period from September 2021 to June 2022, it is estimated that 20 patients initiated belimumab therapy in Denmark, of which 10 were with the subcutaneous formulation. Therefore, a 50/50 weight split in applied in the analysis.



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**Table 23. Estimated patients starting intravenous and subcutaneous belimumab**

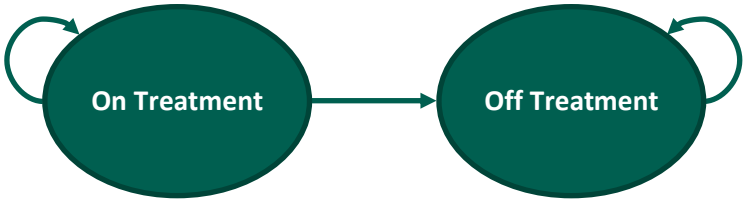
| | 03.19-08.19 | 09.19-02.20 | 03.20-08.20 | 09.20-02.21 | 03.21-08.21 | 09.21-02.22 | 03.22-06.22 |
|---|---|---|---|---|---|---|---|
| **Fully adherent patients on IV** | | | | | | | |
| **Actual patients on IV** | | | | | | | |
| • **New patients** | | | | | | | |
| • **Continuing patients** | | | | | | | |
| **Fully adherent patients on SC** | | | | | | | |
| **Actual patients on SC** | | | | | | | |
| • **New patients** | | | | | | | |
| • **Patients switched from IV** | | | | | | | |
| • **Continuing patients** | | | | | | | |

## 8.1 Model

### 8.1.1 Model structure

SLE is a chronic condition and patients are likely to require some treatment over the lifetime. However, there are no established guidelines with respect to the sequencing of add-on therapies if a patient has persistent disease activity despite treatment with standard therapy, though anifrolumab has demonstrated equal efficacy in both patients with previous biologic exposure and biologic naïve patients.[76] In addition, as SLE is a heterogenous and relapsing/remitting disease where physicians "treat-to-target", the specific treatment requirements over time can vary. Therefore, periods of treatment with add-on therapy and the associated clinical decisions with that treatment are somewhat independent of other periods of treatment. As such, using a lifetime horizon to determine differences in costs between anifrolumab and belimumab cannot be reliably calculated, and instead estimating the differences in cost between these two therapies for a single period of treatment may be a more valid assessment. Accordingly, the model is based on a simple structure of "On Treatment" or "Off Treatment" (Figure 24). Other key economic drivers within SLE, such as disease flares, organ damage, and steroid use, are not incorporated into the model on the basis of the indirect treatment comparison where there were no significant differences on the observed outcomes on these domains.

**Figure 24. Model structure for cost-minimisation analysis**




### 8.1.2 Time horizon, cycle length, and discounting

To determine a reasonable time horizon, consideration was given to the time on treatment. There are no formal discontinuation criteria for anifrolumab and belimumab, though discussions with Nordic and Danish rheumatologists have highlighted that patients will eventually discontinue therapy, either due to adverse events or lack of effect in the short-term, physician/patient choice, or eventual loss of effect or disease remission in the long-term. As anifrolumab has a similar efficacy and safety profile to belimumab, it is assumed that overall time on treatment for these products would be similar. As the dosing schedules for IV belimumab involves an additional loading dose during the first cycle compared to anifrolumab, as well as some patients potentially switching to the subcutaneous formulation in the future,

a five year time horizon has been deemed sufficient to capture all relevant differences in costs between anifrolumab and belimumab.

A cycle length of one week is applied in the analysis, corresponding to the shortest interval between doses of any treatment given in the model (subcutaneous belimumab). No half cycle correction has been applied as treatment costs are assumed to be incurred at the start of a cycle.

Discounting was applied as recommended in the methods guide of the Danish Medicine Council to be based on the current socio-economic discount rate from the Danish Ministry of Finance. Within the relevant time horizon for this analysis, this equates to 3.5% per year.[112]

### 8.1.3 Perspective

The analysis considers a limited societal perspective where all relevant treatment-related costs have been included. These include costs of drug acquisition, treatment administration, training visits in the use of the subcutaneous belimumab autoinjector, and relevant patient costs for receiving/collecting medications. Costs related to adverse events have not been included in the analysis as they were deemed to have a negligible impact on costs: no significant safety signals have been identified for anifrolumab, and no single serious adverse event occurred in more than 2% of patients in either the pooled anifrolumab data nor the pooled belimumab data. Therefore, the demands on the Danish healthcare system for the management of adverse events related to anifrolumab or belimumab are expected to be minimal and unlikely to influence cost-effectiveness findings. This is considered a conservative assumption as the results of the indirect comparison presented in section 0 suggest that anifrolumab may have a marginally more favourable safety profile overall, in terms of the incidence of all serious adverse events. A summary of the model scope is presented in Table 24.

**Table 24. Model scope**

| | Scope | Rationale |
|---|---|---|
| **Population** | Patients with moderate to severe, active autoantibody-positive SLE, despite receiving standard therapy | In line with the European marketing authorization for Saphnelo (anifrolumab) |
| **Intervention** | Anifrolumab 300 mg, administered as an intravenous infusion, every four weeks | As per the Summary of Product Characteristics for Saphnelo |
| **Comparator(s)** | • Belimumab 10 mg/kg, administered as an intravenous infusion, on Days 0, 14, 28, and at four-week intervals thereafter<br>• Belimumab 200 mg once weekly, administered subcutaneously | Benlysta (belimumab) is the only currently approved treatment indicated as an add-on therapy for adult patients with active autoantibody-positive SLE, despite standard therapy |
| **Outcome(s) and economic factors included** | • Drug acquisition costs<br>• Drug administration costs<br>• Training costs<br>• Patient costs<br>• Time on treatment | In line with the limited societal perspective as stipulated in the methods guide of the Danish Medicines Council |
| **Time horizon** | Five years | Assumed to be sufficient to capture all relevant differences in costs between anifrolumab and belimumab |
| **Cycle length** | One week | Minimal interval between doses of any included treatment |

## 8.2 Relationship between the parameters used in the model and relevance for Danish clinical practice

### 8.2.1 Presentation of input data used in the model and how they were obtained

The clinical parameters used in the model are used to estimate the time on treatment. In the base case, time on treatment has been estimated based on potential reasons for discontinuation and the rates of these reasons observed in clinical trials. Reasons for discontinuation are assumed to be: adverse events, non-response to treatment, death, or physician/patient choice due to eventual loss of effect or disease remission in the long-term. Accordingly, this is split into two phases: discontinuation during the first year due to non-response and adverse events, and discontinuation during subsequent years. In a scenario analysis, discontinuations during the first year are modelled based on the discontinuation rates observed during the 52 weeks of the TULIP and MUSE trials. Each of these aspects are discussed in the sections below. Table 25 gives an overview of the clinical inputs in the model.

**Table 25. Input data used in the model**

| Variable | Results in Source | Source | Input Value in Model | How Input Value is Derived |
|---|---|---|---|---|
| **Anifrolumab: SLEDAI response at week 52** | 252 / 459 (54.9%) | mITT population of pooled TULIP and MUSE data | 54.9% | As observed in trial data |
| **Belimumab: SLEDAI response at week 52** | Anifrolumab vs. Belimumab IV: OR 2.20 (95% CI 1.10, 4.40) | Indirect treatment comparison (see section 0) | 54.9% | Assumed equal to anifrolumab as overall efficacy analyses suggest anifrolumab is at least as efficacious as belimumab |
| **Anifrolumab: Timepoint from which non-responders are tapered off** | N/A | N/A | 24 weeks | Assumption based on clinical feedback that non-responders will begin to be tapered off treatment after ~6 months |
| **Belimumab: Timepoint from which non-responders are tapered off** | 6 months | Benlysta SmPC[63] | 24 weeks | Given 1-week cycle length, 24 weeks assumed appropriate proxy |
| **Anifrolumab: Discontinuations due to adverse events** | 20 / 459 (4.4%) | Safety population of pooled TULIP and MUSE data | 4.4% | As observed in trial data |
| **Belimumab: Discontinuations due to adverse events** | Anifrolumab vs. Belimumab IV: OR 0.74 (95% CI 0.35, 1.55) | Indirect treatment comparison (see section 0) | 4.4% | Assumed equal to anifrolumab as belimumab appears non-inferior to anifrolumab with regards to safety |

| Variable | Results in Source | Source | Input Value in Model | How Input Value is Derived |
|---|---|---|---|---|
| **Discontinuation rate up to week 52 in TULIP and MUSE trials** | 74/459 (16.1%) | Safety population of pooled TULIP and MUSE data | [redacted]% per cycle/week ([redacted]% per year) | Fitted exponential distribution to the patient level data |
| **Long-term discontinuation rate** | Discontinue Y1: 33/218<br>Discontinue Y2: 19/185<br>Discontinue Y3: 27/166 | MUSE Open Label Extension[81] | [redacted]% per cycle/week ([redacted]% per year) | Fitted exponential distribution to the patient level data |
| **Mortality in SLE** | Danish SLE patients vs. General Population:<br>Aged ≤50 yrs: HR 2.51 (95% CI 2.09, 3.01)<br>Aged >50 yrs: HR 2.08 (95% CI 1.88, 2.29) | SLE patients in the Danish patient register[33] | ~0.01% per week/cycle<br>(0.4 – 0.5% per year within time horizon) | Hazard ratios for mortality applied to Danish lifetables based on sex and time-dependent age distributions (see Table 26), obtained from Danmarks Statistik[113] |

### 8.2.2 Relationship between the clinical documentation, data used in the model and Danish clinical practice

#### 8.2.2.1 Patient population

The patient population in the economic model are patients with active, autoantibody-positive SLE on standard therapy who are considered eligible for add-on biologic therapy due to clinical or serological markers of disease activity. This is assumed to align with the labelled indication for anifrolumab as an add-on therapy for the treatment of adult patients with moderate to severe, active autoantibody-positive SLE despite standard therapy, and be reflected by the characteristics of patients randomized at European sites into the TULIP clinical trials (Table 26). These patients were similar in age (41.3 years) and sex (92.8% female) to the overall population from the pooled TULIP and MUSE studies, but had slightly lower weight (73.1 kg).

In Danish clinical practice, the estimated age at diagnosis of SLE is 46.7 years and 86% of diagnosed cases are female, suggesting that Danish patients are somewhat older and include more males than those included in the trials. There are considerations as to whether overall incident cases of SLE are representative of the moderate to severe population on standard therapy. However, the impact of these differences is minimal in the model as age and sex only influence treatment discontinuation due to mortality, which accounts for only a small fraction of modelled discontinuations.

There is a paucity of evidence on the weight of Danish SLE patients, and so the average weight of adult females in Denmark is reported, as more SLE patients are female. The average Danish female has a very marginally higher weight than the European patients in the TULIP trials, and Danish males was higher still (84 kg). It is therefore possible that the costs of weighted drugs (e.g., IV belimumab) could be higher in Denmark than modelled if the population as a whole are representative of SLE patients. This is explored in a scenario analysis.

**Table 26. Patient characteristics used in the economic analysis**

| Characteristic | Source Used for Parameter | Value Used in the Model | Value in Danish Clinical Practice |
|---|---|---|---|
| **Age (years), mean (SD)** | Patients randomised to TULIP-1 or TULIP-2 at European sites | 40.7 (11.73) | 46.7 (17.07)†[53] |
| **Female (%)** | Patients randomised to TULIP-1 or TULIP-2 at European sites | 92.4% | 85.7%[53] |
| **Weight (kg), mean (SD)** | Patients randomised to TULIP-1 or TULIP-2 at European sites | 69.7 (16.05) | 70.2 (N/A)[114] |

† Derived from the median and interquartile range reported using the formulae published by Wan et al. (2014)[115]

#### 8.2.2.2 Intervention

The intervention included in the model is anifrolumab 300 mg, administered as an intravenous infusion over 30 minutes, every 4 weeks as per the licensed indication in Europe. This is how anifrolumab is expected to be given in Denmark, and aligns with the clinical data obtained from the TULIP and MUSE studies. Table 27 gives an overview of anifrolumab, its use in the model, and the applicability to Danish clinical practice.

**Table 27. Overview of the use of anifrolumab and the relevance to Danish clinical practice**

| Intervention | Clinical Documentation | Approach Used in the Model | Expected Outcome in Danish Clinical Practice |
|---|---|---|---|
| **Posology** | 300 mg, administered as an intravenous infusion over a 30-minute period, every 4 weeks (Saphnelo SmPC)[79] | As per SmPC | As per SmPC |
| **Time on treatment** | No data has yet been published regarding the duration of treatment of anifrolumab | Derived from occupancy of the "On Treatment" state in the model to a mean of [redacted] months in the base case. See section 8.3 below for details. | Expected to be comparable to that as modelled |
| **Criteria for discontinuation** | No formal criteria for the discontinuation of anifrolumab have been established, though discontinuation is recommended if breast feeding and anifrolumab is not recommend during pregnancy.[79] | Treatment discontinuation has been determined based on adverse events, lack of initial response to therapy, and observed long-term discontinuation rates on anifrolumab from the MUSE Open Label Extension study, as well as all-cause mortality | Decisions to discontinue treatment in clinical practice are expected to be made based on adverse events, lack of effect, subsequent loss of effect, achieving a state of remission no longer requiring add-on therapy, or other factors influencing patient and physician choices. |
| **The pharmaceutical's position in Danish clinical practice** | Anifrolumab has been evaluated in patients with moderate to severe, active autoantibody-positive SLE, despite standard therapy in clinical trials. This is reflected in the EU marketing | The model is based on clinical trial data from anifrolumab trials and therefore is believed to reflect the marketing authorization and approved product positioning of | The use of anifrolumab in Denmark is expected to be in line with the marketing authorization, for patients with active disease despite standard therapy who are considered |

| Intervention | Clinical Documentation | Approach Used in the Model | Expected Outcome in Danish Clinical Practice |
|---|---|---|---|
| | authorization where it is expected to be positioned as an add-on therapy for patients who have previously received treatment with antimalarials, oral corticosteroids, and conventional non-steroidal immunosuppressants but have persistent active disease. | anifrolumab as an add-on treatment after standard therapy in patients with active SLE. | candidates for add-on therapy with an appropriate biologic. This position in the patient pathway in Danish clinical practice is currently only occupied by belimumab. |

#### 8.2.2.3 Comparators

As described in section 5.2 and above, the comparator for the economic analysis is belimumab, as belimumab is the only currently licensed and available treatment in Denmark for patients with active autoantibody-positive SLE, despite standard therapy. Belimumab in Denmark is primarily given as an intravenous infusion over 1 hour at a dose of 10 mg/kg.[63] The recommended dosing schedule in the summary of product characteristics and from the Dansk Reumatologisk Selskab is on Day 0, 14 and 28, and every 4 weeks thereafter.[63,116] Accordingly, this is the dosing and administration schedule applied in the model.

**Table 28. Overview of the use of belimumab and the relevance to Danish clinical**

| Intervention | Clinical Documentation | Approach Used in the Model | Outcome in Danish Clinical Practice |
|---|---|---|---|
| **Posology** | IV: 10 mg/kg, administered as an IV infusion over a 1 hour period, on Days 0, 14, and 28, and every 4 weeks thereafter[63,116]<br><br>SC: 200 mg, administered as an injection, once weekly[63] | As per SmPC | As per SmPC |
| **Time on treatment** | One study has been identified showing time on treatment on belimumab in the real world, with 66.5% of patients on remaining on therapy at 6 months, 54.8% at 12 months, and 50.8% at 18 months[117] | Derived from occupancy of the "On Treatment" state in the model to a mean of [redacted] months in the base case. See section 8.3 below for details. | Expected to be comparable to that as modelled |
| **Criteria for discontinuation** | Discontinuation of treatment with belimumab should be considered if there is no improvement in disease control after six months of treatment, if patients experiences psychiatric symptoms, or if the patient is pregnant/breast-feeding.[63] No formal criteria for the eventual discontinuation of belimumab | Treatment discontinuation has been determined based on adverse events, lack of initial response to therapy, and observed long-term discontinuation rates of anifrolumab from the MUSE Open Label Extension study (assuming comparability to anifrolumab on the eventual loss | Decisions to discontinue treatment in clinical practice are expected to be made based on adverse events, lack of effect, subsequent loss of effect, achieving a state of remission no longer requiring add-on therapy, or other factors influencing patient and physician choices. |

| Intervention | Clinical Documentation | Approach Used in the Model | Outcome in Danish Clinical Practice |
|---|---|---|---|
| | have been established, however guidance from the Dansk Reumatologisk Selskab states that in the case of persistent remission without the use of steroids, attempts to reduce treatment can be made | of effect or desire to discontinue), as well as all-cause mortality | |
| **The pharmaceutical's position in Danish clinical practice** | Beliumumab has been evaluated in patients with active autoantibody-positive SLE, despite standard therapy in clinical trials, and has EU marketing authorization for patients with a high degree of disease activity as an add-on therapy for patients who have previously received treatment with antimalarials, oral corticosteroids, and conventional non-steroidal immunosuppressants but have persistent active disease. | The position of belimumab is considered to be the same as that which anifrolumab is anticipated to occupy. Therefore, belimumab is given for an appropriate treatment period as an add-on therapy after a patient has had an insufficient response to standard therapy. | According to guidance from the Dansk Reumatoligsk Selskab, belimumab should be used within its indication in patients with clinical and serological activity, and initiated subject to conference with rheumatologists.[19,116] As a therapy for more complicated disease, it is reserved for after an insufficient response to standard therapy or where therapy can only be controlled at high doses of oral corticosteroids. |

As a scenario, it is assumed that a proportion of patients switch to the subcutaneous formulation of belimumab for maintenance therapy. The summary of product characteristics states that subcutaneous formulation should be administered at a dose of 200 mg, once weekly.[63] As no guidance is available from the Dansk Reumatologisk Selskab on the use of subcutaneous belimumab, it is assumed to be in line with the SmPC. Table 28 gives an overview of the application of belimumab in the analysis.

#### 8.2.2.4 Relative efficacy outcomes

As noted above, one of the primary reasons anticipated for discontinuation is that if a patient fails to show a benefit of treatment within a given time frame, they will be weaned off therapy. This is in line with guidance on the use of belimumab and feedback from rheumatologists.[63,116] Accordingly, estimates on the level of response were required. Objective estimates of the relative efficacy of anifrolumab and belimumab from the indirect treatment comparison at a fixed time point (at which non-response could be reliably determined) were the SRI(4) at week 52 and the proportion of patients with at least a 4-point reduction in SLEDAI score at week 52. As the SRI(4) is not often used as a measure of response in clinical practice, but SLEDAI scores are somewhat more routinely calculated and collected by rheumatologists, the reduction in SLEDAI score was considered to be more representative of a response metric that may be applied in Danish clinical practice. Therefore, all patients who did not achieve a SLEDAI reduction of at least 4-points compared to baseline by week 52 are assumed to discontinue and no longer receive treatment.

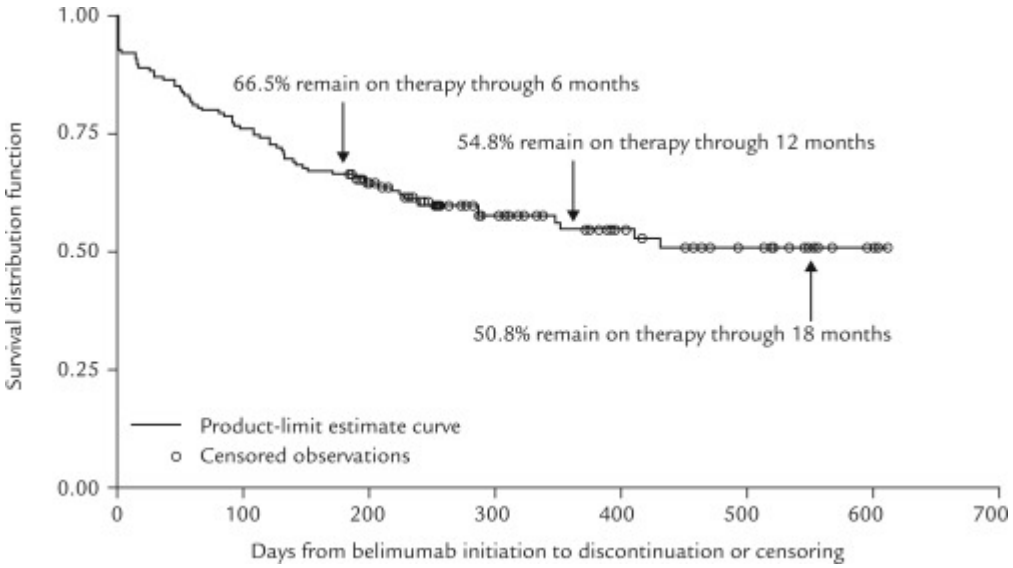
In the pooled TULIP and MUSE data, 54.9% of patients responded and therefore 45.1% are assumed to discontinue (including some earlier discontinuations due to adverse events). As the overall efficacy of belimumab is similar to that of anifrolumab, in the base case it is assumed that an equal proportion of patients to anifrolumab will continue on therapy beyond 52 weeks. A scenario analysis is also applied based on the differential odds ratio of response observed

in the ITC. Note that this analysis is only informative of costs and fails to account for the additional efficacy benefit of improved disease control with anifrolumab.

As a second scenario to inform discontinuations over the first year in the analysis, the observed discontinuation rate on anifrolumab 300 mg from the pooled TULIP and MUSE trials was used. Of the 459 patients treated with anifrolumab at the licensed dose in these studies, 74 discontinued up to prior to week 52. [redacted]. A further scenario was considered using data from a cohort of 155 newly initiated belimumab users between March 2011 and July 2012 in the USA based on medical insurance claims.[117] The data reported time from first infusion and discontinuation of belimumab. Discontinuation was defined as having a gap of at least 105 days between consecutive administrations of belimumab, and was censored for death, loss of insurance eligibility, or end of follow-up. Figure 26 shows the Kaplan Meier curve for discontinuation. The proportion of patients remaining on treatment each week over the first 52 weeks as reported on the Kaplan Meier plot were used in the scenario analysis to determine time on treatment for belimumab and anifrolumab. A relative discontinuation rate of anifrolumab, based on the results of the ITC (OR 0.66), was applied as a scenario.

**Figure 25. Kaplan-Meier curve of anifrolumab 300 mg discontinuations in TULIP and MUSE and fitted exponential curve**

**Figure 26. Time from belimumab initiation to discontinuation or censoring in a US administrative claims database analysis (n = 155)**




Source: Ke et al (2015)[117]

**Table 29. Overview of response data used for discontinuation in the model**

| Efficacy Outcome | Clinical Documentation | Value Used in the Model |
|---|---|---|
| **Anifrolumab: SLEDAI response (≥4-point reduction) at week 52** | Pooled TULIP & MUSE data: [redacted] / 459 ([redacted]) | [redacted], as per the trial data |
| **Belimumab: SLEDAI response (≥4-point reduction)at week 52** | Pooled BLISS data: 296 / 563 (52.6%)<br>Anifrolumab vs. Belimumab IV (STC): OR 2.20 (95% CI 1.10, 4.40) | [redacted], assuming comparable efficacy to anifrolumab |
| **Anifrolumab: Discontinuation rate during first year** | Pooled TULIP & MUSE data: 74 / 459 (16.1%) | [redacted]% per cycle/week |
| **Belimumab: Discontinuation rate during first year** | Pooled BLISS data: 113 / 563 (20.1%)<br>Ke et al (2015): 45.2%<br>Anifrolumab vs. Belimumab IV (ITC): OR 0.66 (95% CI 0.43, 1.02) | 0.3% per cycle/week, assuming comparable time on treatment to anifrolumab, or based on the Kaplan Meier curve for scenarios using the US RWE |

**Table 30. Summary of the relevance of SLEDAI response to Danish clinical practice**

| Efficacy Outcome | Clinical Documentation & Measurement | Relevance of Outcome to Danish Clinical Practice | Relevance of measurement method for Danish clinical practice |
|---|---|---|---|
| **SLEDAI response (≥4-point reduction) at week 52** | • ≥4-point reduction in SLEDAI-2K score compared to baseline<br>• No discontinuation of investigational product<br>• No use of medications beyond protocol allowed threshold (see section 7.1.2 above for details) | Guidelines from the Danish Reumatologisk Selskab recommend completing the SLEDAI before starting treatment with belimumab and it is included in the DANBIO registry.[19,116] It is therefore plausible that the SLEDAI is one of the clinical measures used in Danish clinical practice to evaluate response or non-response to treatment. | As noted in section 7.1.1 above, an improvement on the SLEDAI is defined by the complete resolution of symptoms within a given domain. Therefore, a SLEDAI response is an objective assessment of reductions in disease activity that can be relevant to practice, given the collection of SLEDAI scores in clinical practice. However, physicians may also use subjective or holistic measures of improvement, including reporting by patient, to assess response. Therefore, the SLEDAI score can be considered indicative of response assessments in practice, but potentially not in 100% of cases.<br><br>By definition, discontinuation of investigational product is representative of discontinuation. The use of restricted medications outside of the trial protocol may not necessarily be grounds for discontinuation in terms of non-response in Danish clinical practice, where dose escalations may be clinically mandated. Post hoc analysis reported in the EPAR shows that excluded the restricted medication rules from the pooled TULIP trials increased SRI(4) response rates in the anifrolumab arm from 52.2% to 62.5%, and therefore it is possible that fewer patients would discontinue due to non-response at week 52 in clinical practice.[118] |
| **Discontinuation rate during first year** | All cause discontinuation of anifrolumab 300 mg in the pooled data from the TULIP and MUSE trials, or US RWE on discontinuation of belimumab during the first 12 months of treatment | The overall observed discontinuations in the randomized trials is not expected to be of particular relevance to Danish clinical practice as the trials were designed to assess efficacy after 52 weeks and therefore there is a protocol-driven mandate to keep patients on therapy to this time, whereas in practice decisions may be made to discontinue patients earlier. This analysis is therefore only included as a scenario to represent the completeness of data. The | As all types of treatment discontinuation were captured in the trials, this is assumed to be equivalent to all types of treatment discontinuation that may occur in Danish clinical practice. |

| Efficacy Outcome | Clinical Documentation & Measurement | Relevance of Outcome to Danish Clinical Practice | Relevance of measurement method for Danish clinical practice |
|---|---|---|---|
| | | scenario using US RWE may represent considerations on discontinuations in practice, though given the data is over 10 years old and recorded at a time when there was limited real world experience with belimumab, as well as the definition of discontinuation used, some caution is advised in its interpretation. | |

#### 8.2.2.5 Adverse reaction outcomes

As noted above, specific adverse events have not been included in the model as they are unlikely to influence costs given no serious adverse event occurred in more than 2% of patients in either anifrolumab or belimumab treated patients. Discontinuations due to adverse events are considered in the economic model with respect to duration of treatment.

As presented in Table 22 (see section 0 above), 4.4% of patients receiving anifrolumab 300 mg in the supportive safety pool (TULIP-1, TULIP-2, and MUSE) discontinued due to adverse events during follow. In the economic model, all discontinuations due to adverse events are assumed to occur after the first two doses of a product on the assumption that a lack of tolerability would be evident early. To estimate discontinuations due to adverse events for belimumab, the indirect comparison of safety suggested no significant differences in the probability of discontinuation due to adverse events (odds ratio for anifrolumab vs. belimumab: 0.74; 95% CI 0.35, 1.55). Therefore, an equal probability of discontinuation due to adverse events is assumed.

**Table 31. Adverse reaction outcomes included in model**

| Outcome | Clinical documentation | Value Used in the Model |
|---|---|---|
| **Discontinuation due to adverse events** | • Anifrolumab: Anifrolumab 300 mg supportive safety pool<br>• Belimumab: indirect treatment comparison of safety (see Table 22) | • Anifrolumab: 4.4%<br>• Belimumab: 4.4% (on assumption of comparable tolerability) |

### 8.3 Extrapolation of relative efficacy

No extrapolation of relative efficacy data is required in the model, as the efficacy of anifrolumab is assumed to be at least as good of that of belimumab (see section 0) and a cost-minimisation analysis has been conducted assuming a comparable efficacy. Therefore, for longer-term outcomes, in terms of the long-term treatment discontinuation rate, this is assumed equal between treatment and only the absolute discontinuation rate of anifrolumab has been extrapolated.

Discontinuation rates in the long-term are assumed to be due to subsequent changes in the disease state, such as eventual loss of effect or disease remission which no longer requires add on therapy, or further aspects of physician/patient choice such as further adverse events. All of these factors were not well captured in the randomised TULIP, MUSE, or BLISS studies. Therefore, discontinuation rates for year 2 onwards have been derived from the open label extension (OLE) of the MUSE study, where patients were followed for up to three years after enrolment.[81]

The MUSE OLE included 218 patients, of which 153 had received anifrolumab in the randomised phase of MUSE. During the 156 weeks of follow-up, 79 patients discontinued treatment with anifrolumab. The most common reasons for discontinuation were patient withdrawal of consent (*n* = 31) and adverse events (*n* = 15), though most of these adverse events were not considered to be related to anifrolumab by the investigator. In addition, 7 patients discontinued treatment due to the study sponsor closing the site and 1 patient relocated to an area without a study site in which to continue treatment. For the purposes of estimating the discontinuation rate, these patients were assumed to be censored for discontinuation at the recorded discontinuation date, rather than considered a discontinuation event, as these are not issues expected if anifrolumab is to be funded nationally in Denmark. The Kaplan-Meier survivor plot for persistence on treatment in Figure 27.

To estimate the discontinuation rate in the MUSE OLE study, parametric survival curves were fitted to the patient level data. This method was used to estimate the average rate of discontinuation during follow-up using maximum likelihood estimation with consideration to the timing of discontinuation and censoring events, as opposed to attempting to extrapolate the data over a longer time horizon. This method was considered preferable to a naïve estimation of the probability of discontinuation over given period based on the number of discontinuations after 156 weeks (i.e., 71 of 218 patients [32.6%] of patients discontinued after 156 weeks, equivalent to 12.3% per year). It also permits statistical testing of potential covariates on the discontinuation rate which may bias assumptions.

**Figure 27. Persistence on anifrolumab treatment in the MUSE Open Label Extension**

**Note:** most patients are censored for discontinuation around month 36 given the end of study, though the last patient followed up at 36.7 months discontinued treatment, hence why the curve converges to zero. [redacted] patients were censored due to closure of study site or relocating to an area where a study site was not available to continue treatment.

In the MUSE OLE, 29.8% of patients had no prior exposure to anifrolumab and 33.5% has received anifrolumab 1000 mg in the randomised phase. In addition, all patients in the MUSE OLE initially received 1000 mg and then were subsequently switched to 300 mg once the risk/benefit profile from the randomised phase had been evaluated. [redacted]. As neither factor influenced discontinuation rates, data from the full population across the whole follow-up of MUSE OLE were used to extrapolate discontinuation rates.

Fitting of the parametric curve to the observed data was done with consideration to the guidelines from the Danish Medicines Council.[119] Common parametric functional forms (exponential, Weibull, Gompertz, log-logistic, lognormal, and generalised gamma) were fitted to the data (Figure 28). Visual fit to the within trial data was comparable between all evaluated model fits. Given the five year time horizon of the model, and that the first year discontinuation rate is derived from other sources, Figure 28 also shows the extrapolation of each fit out to 4 years. Within this extrapolated period, no meaningful differences in time on treatment was observed between fits. Based on the AIC/BIC criteria, no single fit was demonstrated to provide a better fit to the data (ΔAIC < 5; see Appendix G). Therefore, it was deemed appropriate to assume a Markov structure without time-dependent transition probabilities and apply to exponential distribution in the model, given this had the lowest BIC.

**Figure 28. Fitted parametric curves for time on treatment compared to the Kaplan-Meier curve from MUSE OLE**

Based on the fitted estimate to the exponential distribution, the average annual probability of discontinuation was [redacted]% (equivalent to [redacted]% per cycle). As there is no evidence over differential long-term tolerability and efficacy of anifrolumab and belimumab, this is assumed to be equal on the basis of the somewhat similar efficacy and safety profile observed in the short-term. Therefore, the average annual probability of discontinuation of [redacted]% is applied to both treatments in the model.

In addition to the long-term effects, an interpolation of the relative efficacy data has been conducted in order to estimate when patients may discontinue treatment during the first year of treatment. Feedback from Danish rheumatologists is that they will begin assessing for response and phasing non-responders off treatment from around six months onwards. In the base case it is therefore assumed that the proportion of patients on treatment will gradually decline from week 24 up to week 52, with only the responders continuation beyond week 52. This assumption is applied to both the anifrolumab and belimumab arms, as shown in Figure 29.



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**Figure 29. Modelled time on treatment for anifrolumab and belimumab in the economic analysis**

However, anecdotal clinical feedback has highlighted that patients can typically be slow to respond to belimumab and some physicians may prefer to wait 9-12 months before discontinuing therapy. Conversely, the rapid onset of effect of anifrolumab has been highlighted as a potential benefit by clinicians, as demonstrated by the statistically significant early responses such as CLASI response at week 12. Accordingly, scenario analyses are considered varying the time at which response (and non-response) can start be evaluated, ranging from 12 (3 months) to 40 weeks (9 months) for anifrolumab, and 40 (9 months) to 52 weeks (12 months) for belimumab.

For the comparison to belimumab where responders are assumed to switch from IV to SC, it was assumed that the switch would happen at the same rate and at the same timepoints as for non-responders to discontinue, on the assumption that grounds for the lack of response at that time that would justify discontinuation would also mean that the response at the time is sufficient to justify switching. Figure 30 shows the transition and discontinuation of patients on the different IV formulation of belimumab over time, assuming up to 20% of patients would be candidates for a switch of formulation.



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**Figure 30. Distribution of patients on different formulations of belimumab over time**

### 8.3.1 Validation of time on treatment assumptions

There is a paucity of the long-term evidence on the duration of use of anifrolumab and belimumab. Only one published study has been identified reporting on the time to discontinuation of belimumab in a real-world setting.[117] In this study, any SLE patient who had been prescribed belimumab between March 2011 and July 2012 with at least 6 months of pre-belimumab recorded medical and pharmacy history and at least 6 months of follow-up (regardless of duration of belimumab treatment) from the HealthCore Integrated Research Database in the US were included. A total of 155 patients were identified with a median follow-up after belimumab initiation of 372 days. Figure 31 compares the Kaplan-Meier curve of time to discontinuation from this study with the modelled estimates. As can be seen, the proportion of patients on treatment at 12 (RWE 54.8% vs. model [redacted]%) and 18 (RWE 50.8% vs. model [redacted]%) months are consistent between the study data and the model. However, the model assumes patients will stay on treatment for longer during the first year, with the proportion of patients on treatment after 6 months being 66.5% in the US data but [redacted]% in the model. As reasons for discontinuation were not provided in the US data, the rationale for a higher discontinuation rate than assumed in the model cannot be determined. In the study, approximately 7% of patients discounted belimumab after the first infusion, in line with the modelled assumption that some patients will discontinue early due to adverse events.

**Figure 31. Comparison of the modelled time on treatment curve for belimumab compared to a retrospective administrative claims database evaluation of the utilisation of belimumab in the USA**

**Source**: Ke et al (2015)[117]

## 8.4 Documentation of health-related quality of life (HRQoL)

Health-related quality of life data are not applicable to the submitted model given that it is a cost-minimisation analysis.

## 8.5 Resource use and costs

Included costs in the analysis are those of drug acquisition, drug administration, and patient costs, in line with the scope reported in section 8.1.

### 8.5.1 Drug acquisition costs

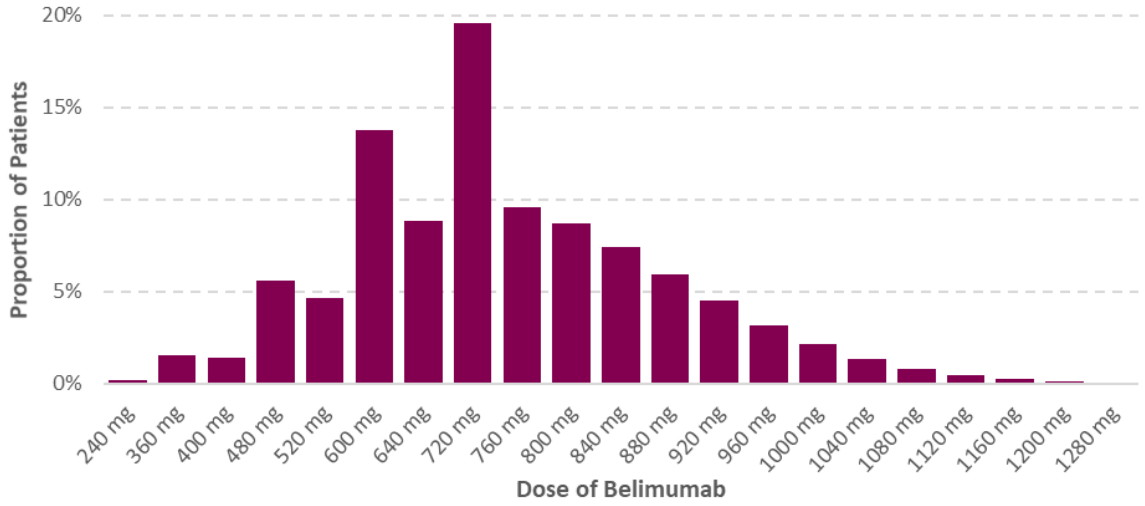
Following the recommended dosing schedules of anifrolumab and belimumab, as reported in their respective summaries of product characteristics, a cost per administration was estimated. The unit costs of belimumab used in the model are at the pharmacy purchase price (Apotekernes indkøbspris, AIP), obtained from medicinpriser.dk on 1 March 2022. Where multiple items or pack sizes were available for the same product, that with the cheapest AIP per unit was used. For anifrolumab, this is based on the price submitted to medicinpriser.dk that would be available on 18$^{th}$ of April.

Anifrolumab is given at a dose of 300 mg once every four weeks. As anifrolumab is provided in single packs of vials containing 300 mg, the cost per administration is determined to be at the pharmacy purchase price for a single pack of anifrolumab (Table 32). The costs was applied in the model starting from day 0 and every four cycles thereafter (i.e., every four weeks) for the proportion of patients remaining on treatment at that timepoint as determined by the time on treatment curve.

Intravenous belimumab is given at a dose of 10 mg/kg and is available in vial sizes of 120 mg and 400 mg. To derive a representative estimate of the average cost per dose, the weight of 1000 patients was simulated using a mean of 69.7 kg and a standard deviation of 16.1, as observed in European patients enrolled in the TULIP trials. For each of these patients, the cheapest combination of vials that could provide the minimum required dose of 10 mg/kg was derived. This method is assumed to more accurately describe the amount of drug wastage in clinical practice, as opposed to

assuming all patients would require the dose based on the average weight. Figure 32 shows the distribution of doses of belimumab modelled for these patients. Based on this, the average cost per administration of belimumab was estimated at 7 150.22 DKK (Table 32). This cost is applied on days 0, 14, and 28, and every four weeks thereafter for the proportion of patients remaining on treatment at that timepoint as determined by the time on treatment curve, in line with the recommended dosing of belimumab.

**Figure 32. Modelled doses of belimumab given to 1000 simulated SLE patients**




For patients switching to subcutaneous belimumab, the recommended dosing schedule is one single injection of 200 mg belimumab once per week, and therefore only one single unit is given. The pre-filled pen (autoinjector) of belimumab is available in single packs or packs of four in Denmark. The cost per unit is marginally lower in the four pack and therefore this value is applied in the model at 1 639.39 DKK per injection (Table 32). To more accurately account for the costs of drug acquisition and consider potential wastage, since subcutaneous belimumab must be collected from hospitals it is assumed patients would be given three months of belimumab with which they can treat themselves at home. Accordingly, at the date the patient is first switched to subcutaneous belimumab they are assumed to be given 12 injections and then return to collect 12 more 12 weeks later, with only those still remaining on treatment (as per the time on treatment curve) returning to collect the next round of prescriptions.

**Table 32. Drug acquisition costs applied in the model**

| Drug (Item No) | Dose per unit | Units per pack | Price per pack (DKK; AIP) | Dose per admin | Units per admin | Cost per admin (DKK; AIP) | Average cost per week (DKK; AIP) |
|---|---|---|---|---|---|---|---|
| **Saphnelo (469003)** | 300 mg | 1 | 7 200.00 | 300 mg | 1 | 7 200.00 | 1 800.00 |
| **Benlysta (421527)** | 120 mg | 1 | 1 179.84 | 10 mg/kg | Based on distribution of patient weights | 7 150.22 | 1 787.56 |
| **Benlysta (458249)** | 400 mg | 1 | 3 932.80 | | | | |
| **Benlysta (422388)** | 200 mg | 1 | 1 703.30 | 200 mg | 1 | 1 636.39 | 1 636.39 |
| **Benlysta (166242)** | 200 mg | 4 | 6 545.57 | | | | |

**Note:** average cost per week is only indicative of costs in model as costs are applied on administration days where belimumab IV is subject to one additional loading dose and belimumab SC is assumed to be dispensed with 12 doses at a time.

### 8.5.2 Drug administration costs

The cost of intravenous drug administration was estimated using the Interaktiv DRG webpage,[120] assuming that a 41 year old female with a scheduled attendance of less than 12 hours with a primary diagnosis code of SLE with organ or system involvement (ICD-10: M32.1) and a supplementary procedure code of medication administration by intravenous infusion (BWAA62).

It is recommended that patients prescribed the subcutaneous formulation receive proper training in the use of the autoinjector.[63] For the training visits, a similar query was run in Interaktiv DRG but assuming a supplementary procedure codes of medication administration by subcutaneous injection (BWAA31) and training of patient in a manual task (BVDY02). Both queries produced the same results with the cost of an outpatient visit for an adult with a musculoskeletal condition (08MA98 - MDC08 1-dagsgruppe, pat. mindst 7 år) at 1 645 DKK per visit.

**Table 33. Drug administration and training costs applied in the model**

| Healthcare resource | Resource use | Cost per unit (DKK) |
|---|---|---|
| **Drug administration by intravenous infusion** | Per infusion of anifrolumab or belimumab | 1 645.00 |
| **Training in the use of subcutaneous autoinjector (inc. first administration)** | Once per patient upon switching to SC formulation | 1 645.00 |

### 8.5.3 Patient costs

Patient costs applied in the model consider the costs of time and transport required to receive drug administration or collect prescriptions. Based on the unit costs provided in the Danish Medicines Council's catalogue of unit costs, the costs of transport are assumed to be 140 DKK per visit, with patient time at 181 DKK per hour.[121]

Patient time for intravenous infusions of anifrolumab and belimumab was assumed to be composed of travel time to/from the hospital, the duration of the infusion, and the duration of post-infusion monitoring. Travel time to the hospital was assumed to be 30 minutes in each direction (1 hour total). Anifrolumab is infused over a 30-minute period, whereas belimumab is infused over one hour. In addition, belimumab is subject to additional monitoring due to the risks of infusion and hypersensitivity reactions,[63] and the Dansk Reumatologisk Selskab state that patients should be under observation for at least 2 hours.[116] As this additional monitoring is not required for anifrolumab, the duration of monitoring of anifrolumab was assumed equal to that in the TULIP-2 trial protocol at 1 hour.[74] Therefore, total patient time per infusion for anifrolumab is estimated to be 150 mins (452.50 DKK per infusion), and 240 mins for belimumab (724.00 DKK per infusion).

For belimumab SC, patients are assumed to have to travel to hospital for their initial training visit in the use of the autoinjector, with the same 30 minutes travel time in each direction. As the training includes multiple components such as storing and disposing of the pens, preparing for the injection, waiting for it to come to room temperature, as well as the actual injection process, 30 minutes was assumed for training, as well as an additional 30 minutes of monitoring for any immediate injection site reactions. Therefore the training visit is assumed to take a total of 120 minutes of patient time (362.00 DKK). For subsequent visits to the hospital to collect prescriptions, only 60 minutes of travel time are included, as well as 5 minutes to go to the pharmacy (65 minutes; 196.10 DKK). These were applied every 12 weeks in line with the acquisition costs of SC belimumab.

As all patients are assumed to have control visits with their treating physician as the same interval, regardless of therapy, no other visit costs to the patient are considered.

**Table 34. Patient costs applied in the model**

| Process | Resource Use | | | |
|---|---|---|---|---|
| | Anifrolumab | Belimumab IV | Belimumab SC (1st) | Belimumab SC (2+) |
| **Travel time to hospital** | 60 mins | 60 mins | 60 mins | 60 mins |
| **Duration of drug administration** | 30 mins | 60 mins | 30 mins | N/A |
| **Duration of monitoring** | 60 mins | 120 mins | 30 mins | N/A |
| **Time to attend pharmacy** | N/A | N/A | N/A | 5 mins |
| **Total time** | 150 mins | 240 mins | 120 mins | 65 mins |
| **Patient time costs @ 181 DKK/hour** | 452.50 DKK | 724.00 DKK | 362.00 DKK | 196.10 DKK |
| **Transport costs** | 140.00 DKK | 140.00 DKK | 140.00 DKK | 140.00 DKK |
| **Total patient costs** | 592.50 DKK | 864.00 DKK | 502.00 DKK | 336.10 DKK |

## 8.6 Results

### 8.6.1 Base case overview

An overview of the specifications used in the base case are presented in Table 35. In summary, anifrolumab 300 mg IV is compared to belimumab 10 mg/kg IV over a five year time horizon in a cost minimization analysis that only include costs related to add-on biologic therapy for patients with SLE. The analysis considers possible criteria for discontinuation.

**Table 35. Base case overview**

| Parameter or Setting | Modelled Approach |
|---|---|
| **Comparator** | Belimumab |
| **Type of analysis** | Cost minimization |
| **Type of model** | Two-state Markov model |
| **Time horizon** | 5 years |
| **Treatment line** | Post-standard therapy (subsequent treatment lines are not included) |
| **Measurement and valuation of health effects** | Not included |
| **Included costs** | • Drug acquisition (pharmaceutical) costs<br>• Drug administration (hospital )costs<br>• Patient costs |

| Parameter or Setting | Modelled Approach |
|---|---|
| **Dosage of pharmaceuticals** | • Anifrolumab: 300 mg IV Q4W<br>• Belimumab: 10 mg/kg IV on days 0, 14, and 28 and Q4W thereafter (average patient weight 69.7 kg) |
| **Drug wastage** | Included |
| **Criteria for discontinuation** | • Adverse events<br>• Non-response (assumed to be assessed between weeks 24 and 52)<br>• All-cause discontinuation after week 52<br>• All-cause mortality |
| **Average time on treatment** | Derived from the model as 30.5 for both treatments |

### 8.6.2 Base case results

In the base case, anifrolumab was found to be cost saving compared to belimumab IV. Despite the marginally addition cost of anifrolumab per administration (~50 DKK), this is significantly outweighed by the additional loading dose required with belimumab at the start of treatment. This loading dose is also associated with increased drug administration costs, and contributes to the greater disparity in patient costs observed. The patient costs for belimumab are also inflated due to the increased infusion and monitoring time required compared to anifrolumab.

**Table 36. Base case results**

| Per patient | Anifrolumab (DKK) | Belimumab (DKK) | Difference (DKK) |
|---|---|---|---|
| **Total costs** | [redacted] | [redacted] | - 16 321 |
| **Drug acquisition costs** | [redacted] | [redacted] | - 5 247 |
| **Drug administrative costs** | [redacted] | [redacted] | - 1 573 |
| **Patient time and transport costs** | [redacted] | [redacted] | - 9 501 |

## 8.7 Sensitivity analyses

### 8.7.1 Deterministic sensitivity analyses

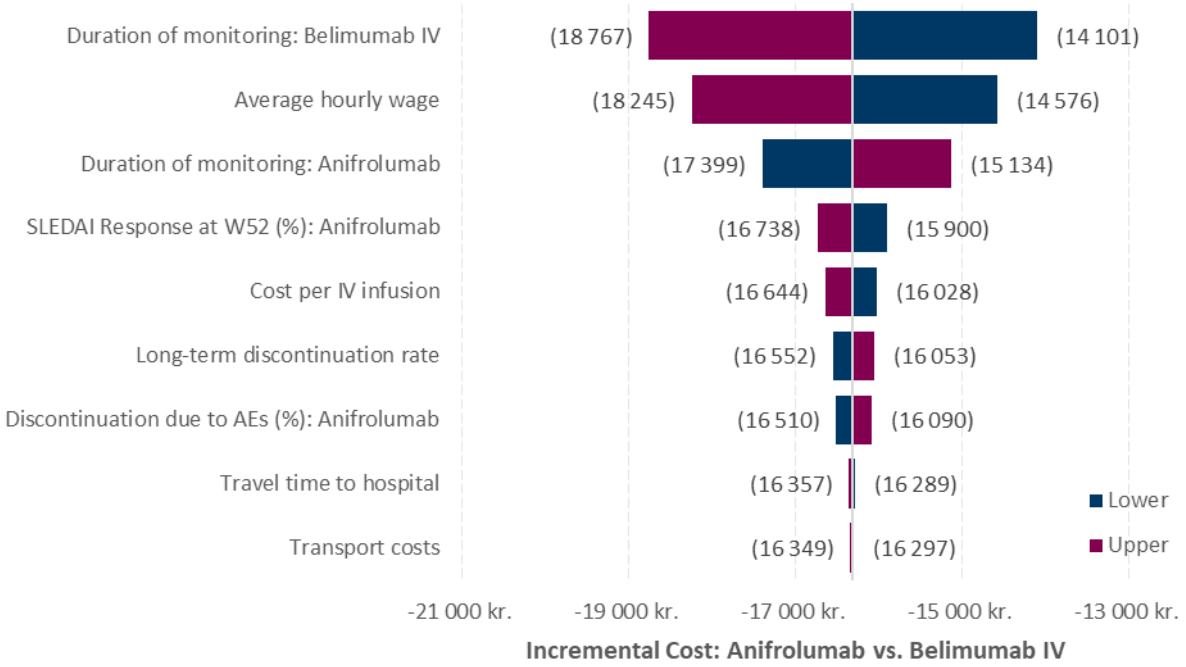
The results of the one-way deterministic sensitivity analysis comparing anifrolumab to IV belimumab are presented in Figure 33 (only parameters with a difference > 0 DKK from the base case are shown). In this analysis, key parameters were sampled to upper and lower confidence limits. Where standard errors were not reported in the original source or estimates for estimating confidence limits (i.e., unit costs and patient time), these were assumed to be 10% of the mean value. All confidence limits were sampled from appropriate distributions for each parameter (e.g., gamma for costs and time, beta for proportions, normal for (log) rates). Note that despite weight being a key parameter for estimating costs of belimumab, this was not sampled as results are applied from a distribution. Varying assumptions on weight are applied in a scenario analysis below.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

As can be seen, in all sampled analyses anifrolumab is still cost saving compared to belimumab. The parameters which had the greatest impact on incremental costs were the duration of monitoring (2 hours for belimumab and 1 hour for anifrolumab in the base case) and the average hourly wage. However, the additional loading dose of belimumab means that it still has an overall higher cost burden.

**Figure 33. Tornado diagram of one-way sensitivity analysis results**




As well as the one-way sensitivity analysis, a number of scenario analyses have been conducted (Table 37). In the majority of explored scenarios, anifrolumab remained cost saving compared to IV belimumab. If Danish SLE patients have a similar weight to the general population, the costs of belimumab are expected to increase. In addition, over 5 years approximately 10 000 DKK per patient of wastage is produced due to the weighted dose of belimumab. Should early and late response for anifrolumab and belimumab, respectively, have an influence on treatment duration, the cost savings of anifrolumab treatment could be even greater. Results were not particularly sensitive to changes in time horizon or different parameterizations of discontinuation during first year (using the pooled TULIP/MUSE data at [redacted]% or US RWE), unless belimumab and anifrolumab are assumed to have different treatment durations as a result of differential efficacy or safety.

If significantly fewer patients respond to belimumab compared to anifrolumab, to the extent estimated in the simulated treatment comparison reported in 0 above (odds ratio 0.45), the response rate in the belimumab arm would be [redacted]% compared to [redacted]% for anifrolumab and the base case for belimumab. Therefore, it is assumed that there are a greater number of patients discontinuing and as a consequence the proportion of patients on treatment with anifrolumab and its relative cost are expected to increase. However, this scenario fails to account for the clinical and economic benefits of an improved response rate. For example, SLEDAI score is a significant predictor of prolonged hospitalization in Danish SLE patients[39] and costs of healthcare in UK patients with active, autoantibody-positive disease,[122] as well as being a predictor of health related quality of life.[3] In addition, disease activity is associated with an increased risk of organ damage,[24,25,123] which itself has a detrimental effect on quality of life and can dramatically increase hospitalizations and healthcare costs.[3,39-41] Therefore, whilst in the base case it is assumed that anifrolumab is similar in effectiveness to belimumab, if it is a superior treatment it may still be cost-effective.

**Table 37. Deterministic scenario analyses results**

| Parameter | Base Case | Scenario | Rationale | Incremental Cost (DKK) |
|---|---|---|---|---|
| **Base Case** | - | - | - | - 16 321 |
| **Patient weight (kg), mean (SD)** | 69.1 (16.1) | 71.2 (14.2) | Weighted combination of average for Danish adults[114] | - 20 566 |
| **Time horizon** | 5 years | 2 years | One additional dose is given during first year of belimumab treatment | - 13 256 |
| | | 10 years | | - 18 944 |
| **Drug wastage** | Included (based on distribution of weights) | Excluded (all patients receive average dose) | To explore economic loss due to wastage in practice | - 6 634 |
| **Start of response assessment: anifrolumab** | 24 weeks | 12 weeks | Some patients may be early responders | - 22 547 |
| | | 40 weeks | Physicians may prefer to wait for response assessment with a new treatment like anifrolumab | - 7 985 |
| **Start of response assessment: belimumab** | 24 weeks | 40 weeks | Anecdotal evidence on delayed response with belimumab may require longer periods of follow-up to confirm non-response | - 24 854 |
| | | 52 weeks | | - 29 228 |
| **Response at week 52: belimumab** | Equal to anifrolumab (OR = 1.00 / [redacted]%) | Based on ITC (OR = 0.45 / [redacted]%) | If there is a lower response rate to belimumab, treatment discontinuations may be higher than with anifrolumab | 61 725 |
| **Discontinuation due to adverse events: belimumab** | Equal to anifrolumab (OR = 1.00 / 4.4%) | Based on ITC (OR = 1.11 / 4.8%) | If there are more adverse events with belimumab, treatment discontinuations may be higher than with anifrolumab | - 15 945 |
| **Discontinuation rate during first year: both arms** | Based on adverse events and non-response | As observed in the TULIP / MUSE trials | Exploration of other reasons for discontinuation | - 17 473 |
| | | Using US RWE with equal duration between arms | To assess the sensitivity of considering all causes of discontinuation that may occur in clinical practice | - 15 435 |
| | | Using US RWE for belimumab and relative discontinuation for anifrolumab (OR = 0.66) | To ascertain the potential impact on costs if anifrolumab has a preferential efficacy or safety profile leading to a longer time on treatment | 28 479 |

| Parameter | Base Case | Scenario | Rationale | Incremental Cost (DKK) |
|---|---|---|---|---|
| **Price of belimumab** | Published pharmacy purchase price | -10% from AIP | For comparison to potential discounted net prices of belimumab to the Danish healthcare system | 7 208 |
| | | -20% from AIP | | 30 738 |

### 8.7.2 Probabilistic sensitivity analyses

No probabilistic sensitivity analysis is presented as the model is a cost-minimisation analysis, meaning a cost-effectiveness acceptability curve would be non-informative.

### 8.7.3 Scenario compared with a formulation switch of belimumab

The comparison with belimumab including a formulation switch followed the same parameterization as the base case (as reported in Table 35), with the exception of the comparator treatment used. All patients are assumed to start on IV belimumab and then, between weeks 24 and 52, 20% of patients remaining on treatment (responders) would gradually transition onto the subcutaneous formulation. The results of this analysis are presented in Table 38. Compared to this treatment approach, anifrolumab would still be cost saving in terms of drug acquisition and patient costs, leading to providing an overall cost saving of over 4000 DKK. However, there is an additional costs of drug administration of anifrolumab over the 5 year time horizon of 5 700 DKK.

**Table 38. Scenario analysis compared to belimumab with a formulation switch at treatment response**

| Per patient | Anifrolumab (DKK) | Belimumab (DKK) | Difference (DKK) |
|---|---|---|---|
| **Total costs** | [redacted] | [redacted] | - 4 105 |
| **Drug acquisition costs** | [redacted] | [redacted] | - 3 696 |
| **Drug administrative costs** | [redacted] | [redacted] | 5 702 |
| **Patient time and transport costs** | [redacted] | [redacted] | - 6 111 |

The sensitivity of the results were tested in a selection of scenario analyses. These analyses show that the results are rather sensitive to time horizon and the proportion of patients switching to the SC formulation, as for longer time horizons or more patients switching, the costs of administering anifrolumab in hospitals becomes relatively higher.

**Table 39. Additional scenario analyses compared to belimumab with a formulation switch at treatment response**

| Parameter | Base Case | Scenario | Rationale | Incremental Cost (DKK) |
|---|---|---|---|---|
| **Base Case** | - | - | - | - 4 105 |
| **Time horizon** | 5 years | 2 years | To assess the impact of the change in formulation on costs if patients remain on treatment for many years | - 9 267 |
| | | 10 years | | 251 |
| | 20% | 10% | | - 10 213 |

| Parameter | Base Case | Scenario | Rationale | Incremental Cost (DKK) |
|---|---|---|---|---|
| **Proportion of patients switching to SC** | | 50% | To assess the impact if the proportion of patients switch formulation changes | 14 220 |
| **Frequency of SC belimumab prescription collection** | Every 12 weeks | Every 4 weeks | Only one pack is dispensed per visit to minimize wastage for those discontinuing treatment (but more frequent collections) | - 4 116 |
| **Start of response assessment: belimumab** | 24 weeks | 52 weeks | Assume patients don't switch formulation until confirmed response at 52 weeks | - 17 706 |
| **Price of belimumab** | Published pharmacy purchase price | -10% from AIP | For comparison to potential discounted net prices of belimumab to the Danish healthcare system | 19 270 |
| | | -20% from AIP | | 42 645 |

### 8.7.4 Scenario compared with a weighted combination of belimumab IV and SC

The comparison with the weighted combination intravenous and subcutaneous belimumab is presented in Table 40. Compared to when half of patients starting treatment with belimumab begin on the subcutaneous formulation, anifrolumab treatment is associated with an addition cost of just over 30 000 DKK across five years. Most of this additional cost is associated with the costs of hospital administration of anifrolumab where half of patients treated with belimumab are assumed to self-administer their medication.

**Table 40. Scenario analysis compared to a 50/50 weighted combination of belimumab IV and SC**

| Per patient | Anifrolumab (DKK) | Belimumab (DKK) | Difference (DKK) |
|---|---|---|---|
| **Total costs** | [redacted] | [redacted] | 32 736 |
| **Drug acquisition costs** | [redacted] | [redacted] | 5 266 |
| **Drug administrative costs** | [redacted] | [redacted] | 24 671 |
| **Patient time and transport costs** | [redacted] | [redacted] | 2 799 |

The sensitivity of these results were explored in scenario analyses (Table 41). Longer time horizons favour belimumab, given the lower acquisition and administration costs of the subcutaneous formulation of belimumab. Given that anifrolumab is more likely to displace the intravenous formulation of belimumab in clinical practice, given some patients/physicians may have a preference for the ease of administration of a subcutaneous product, a scenario was explored where only 20% of patients are assumed to start subcutaneous belimumab and 80% are on the intravenous formulation. In this scenario, the costs of the anifrolumab and belimumab were comparable (3000 DKK more of anifrolumab over 5 years).

**Table 41. Additional scenario analyses compared to a weighted combination of belimumab IV and SC**

| Parameter | Base Case | Scenario | Rationale | Incremental Cost (DKK) |
|---|---|---|---|---|
| **Base Case** | - | - | - | 32 736 |
| **Time horizon** | 5 years | 2 years | To assess the impact of the change in formulation on costs if patients remain on treatment for many years | 15 661 |
| | | 10 years | | 46 952 |
| **Proportion of patients starting on SC treatment** | 50% | 20% | To assess the impact if the proportion of patients starting SC belimumab changes | 3 301 |
| | | 80% | | 62 170 |
| **Frequency of SC belimumab prescription collection** | Every 12 weeks | Every 4 weeks | Only one pack is dispensed per visit to minimize wastage for those discontinuing treatment (but more frequent collections) | 31 916 |
| **Start of response assessment: belimumab** | 24 weeks | 52 weeks | Assume patients don't switch formulation until confirmed response at 52 weeks | 20 705 |
| **Price of belimumab** | Published pharmacy purchase price | -10% from AIP | For comparison to potential discounted net prices of belimumab to the Danish healthcare system | 55 215 |
| | | -20% from AIP | | 77 693 |

# 9. Budget impact analysis

The budget impact analysis considers the estimated additional expenditure to the Danish healthcare system as a consequence of a recommendation of anifrolumab as an add-on treatment for moderate to severe SLE. Within this analysis it is assumed that available add-on treatments are anifrolumab and belimumab, with belimumab being available to patients in either the subcutaneous formulation, the IV formulation, or where a subset of patients may start on the IV formulation and later switch to the subcutaneous formulation. The budget impact estimates are derived from the current size of the biologics market for SLE and the expected growth of this market over the coming years. The budget impact analysis start in the year 2023, assuming that this is the first year following a recommendation for anifrolumab in Denmark. Note that anifrolumab has been available for use in Denmark since 18 April 2022 and some patients first received treatment shortly thereafter. It is therefore assumed that there will be some use of anifrolumab in Denmark both prior and irrespective of the recommendation.

**Number of patients**

As reported in section 5.1.5, 36.1% of prevalent SLE patients without nephritis are assumed to have moderate to severe, active autoantibody-positive disease despite receiving standard therapy, based on a regional cohort study in Sweden.[3] Based on the forecasted prevalence of non-nephritis SLE in Demark (see Appendix L), this is estimated to be between 802 and 863 prevalent patients in Denmark over the next five years (Table 4). However, as outlined in section 5.2.1, SLE is managed with a treat-to-target approach. Therefore, whilst this many patients may be eligible for biologic add-on treatment based on aggregate clinical criteria, not all will be considered candidates for biologic therapy.

To derive estimates of the number of candidates for biologic therapy in Danish clinical practice, consideration has been given to historical sales of belimumab in Denmark. Based on the modelled dose and duration of treatment from the cost-minimization analysis, how many patients initiated treatment with belimumab between 2016 and 2021 was back calculated from the sales volume (Table 42). Forecasts of how many patients may begin treatment with belimumab for SLE over the coming years were done by fitting a Poisson regression model to the data, considering patients potentially eligible to start treatment as the exposure and calendar year as the predictor. The number of patients eligible to start treatment with belimumab was assumed to be those meeting the label criteria who were not already being treated with belimumab. Based on the same Swedish cohort analysis deriving the number of eligible patients for anifrolumab, 76% of patients with active, autoantibody-positive SLE despite standard therapy also had high clinical or serological disease activity which could make them potential candidates for belimumab.[3] In addition, since 30 April 2021 belimumab has been approved for use in LN and so these patients were also included from this date onwards when fitting the model, but were excluded when forecasting patients who may specifically start belimumab for the treatment of non-renal SLE.

**Table 42. Treatment with belimumab in Denmark between 2016 and 2022**

| | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022† |
|---|---|---|---|---|---|---|---|
| **Volume of IV belimumab sold (mg)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Estimated patient years of treatment | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Volume of SC belimumab sold (mg)** | 0 | 0 | 0 | 0 | [redacted] | [redacted] | [redacted] |
| Estimated patient years of treatment | 0 | 0 | 0 | 0 | [redacted] | [redacted] | [redacted] |
| **Total patient years on belimumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated patients treated with belimumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Of which are new patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| Of which are continuing patients | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Estimated patients eligible to start belimumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

† Figures are up to 26 June 2022 and adjusted for exposure time accordingly

Using the parameters of the fitted model, an estimated number of patients potentially eligible to start treatment with biologic therapy (assuming no changes to the market) was estimated up to the end of the time horizon of the budget impact model. This assumes a growth in the number of biologics treated patients in Denmark following historical patterns. Should anifrolumab be recommended for patients with moderate to severe SLE, in the base case it is assumed that there will be an additional modest growth in the biologics market beyond that expected if just belimumab was available. As anifrolumab is not restricted to patients with high clinical or serological disease activity, an assumption was applied to how much the market may grow for patients who do not have high disease activity. As noted above, 76% of moderate to severe patients also had high disease activity in a Swedish study,[3] or conversely the total moderate to severe population is estimated to be 32% larger (1/0.76) than just those with high disease activity. Given that biologic treatment is likely to be reserved for a subset of patients, it is assumed that the biologics market may grow into half of these other patients over the next five years (i.e., 16% greater by 2027) and all these additional patients would receive anifrolumab. In addition, anifrolumab is likely to displace belimumab in clinical practice. Given that the efficacy profiles for anifrolumab and belimumab may be similar in the average patient, it is assumed that anifrolumab will displace half of all belimumab patients within three years of launch, growing from a quarter of patients in the first year. However, as

anifrolumab is a hospital administered drug it is assumed that it is likely to displace more of IV belimumab than subcutaneous belimumab. In the budget impact analysis it is assumed that 65% of future belimumab treated patients would start treatment on the subcutaneous formulation compared to the 50% starting on this formulation today (as described in 8 above). Of those patients starting treatment on the IV formulation, 20% of these patients will switch from the IV formulation to the subcutaneous formulation on response as in the cost minimization analysis. Table 43 shows the expected number of patients per treatment if anifrolumab is recommended for moderate to severe, non-nephritis SLE, integrating all of these assumptions.

**Table 43. Number of patients expected to start treatment per year over the next five-years if anifrolumab is recommended**

| | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Anifrolumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (IV Only)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (Formulation Switch)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (SC Only)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total patients starting biologic add-on therapy** | 21 | 25 | 29 | 35 | 41 |

**Note:** total biologic patients may be equal to the sum of each treatment due to rounding

If anifrolumab is not recommended for moderate to severe SLE, its uptake is expected to be lower. However, as SLE is a treat-to-target disease, the new mechanism of action may offer particular benefits for some patients. Some rheumatologists treating SLE in Denmark have noted an interest in using it regardless of it receiving national funding. [redacted]. Based on feedback from the treating physician, these patients had a high clinical need for alternative treatment that was not being met by other currently available treatments, such as prolonged periods not in remission or persistent high use of steroids. Accordingly, a more modest uptake of anifrolumab is expected should it not receive a recommendation, with uptake in this scenario only for patients with a high clinical need for an alternative therapy to belimumab. It has been commented that patients with moderate to severe mucocutaneous, musculoskeletal, or haematological manifestations may be candidates for type I interferon receptor blockade in SLE.[124] In the TULIP trials, 10% of patients had cytopenias defined by the presence of the haematological domain of the SLEDAI-2K, 28% of patients had moderate to skin manifestations as defined by a CLASI activity score ≥ 10, and 49% had at least six swollen and tender joints, indicating lupus arthritis. It is estimated in the base case that [redacted]% of new patients starting a biologic therapy would be treated with anifrolumab in the case it is not recommended. [redacted]. This estimate of the market share is varied between 0% and [redacted]% in scenario analysis. This proportion is assumed to be constant over time. The remainder of forecasted biologics patients (assuming no additional growth in the biologics market) are assumed to receive belimumab, of which 50% continue to receive the subcutaneous formulation from the start of treatment as observed in recent months. Of those patients starting on the IV formulation, 20% are assumed to switch to the subcutaneous formulation on response. Table 44 reports the estimated patient numbers for each treatment.

**Table 44. Number of patients expected to start treatment per year over the next five-year if anifrolumab is NOT recommended**

| | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Anifrolumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (IV Only)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (Formulation Switch)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (SC Only)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Total patients starting biologic add-on therapy** | 20 | 23 | 26 | 30 | 35 |

**Note:** total biologic patients may be equal to the sum of each treatment due to rounding

### Expenditure per patient

The costs per patient per year are derived from the cost minimization model, based on the undiscounted costs of drug acquisition and drug administration (patient costs excluded), following the time on treatment curve for each year after treatment initiation. Therefore, patients starting treatment in the first year of the budget impact model (2023) will accrue all five years of costs within the budget impact time horizon, but those starting treatment later will accrue fewer years of costs. Future changes in pharmaceutical list prices (AIP) are expected with regards to the price cap agreement with an annual -2.5% reduction. These price reductions are not reflected in the analysis as the current agreement will expire in February 2023, and it is unclear whether the same reduction rate would continue in a new agreement. The impact of this is expected to be limited, given the somewhat similar costs of treatment with anifrolumab and belimumab presented in section 8.6.2 above.

**Table 45. Costs per patient per year**

| Costs per year after treatment initiation (DKK) | Year 1 | Year 2 | Year 3 | Year 4 | Year 5 |
|---|---|---|---|---|---|
| **Anifrolumab** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (IV Only)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (Formulation Switch)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |
| **Belimumab (SC Only)** | [redacted] | [redacted] | [redacted] | [redacted] | [redacted] |

Note: Year 3 costs for Belimumab (SC Only) are higher than Year 2 costs due to the timing of packs dispensed based on the assumption patients collect their medication every 12 weeks

### Budget impact

The estimated budget impact of recommending anifrolumab for moderate to severe SLE ranges from approximately 90 000 DKK in 2023 up to 1.4 million DKK in 2027 (Table 46). The growth in expenditure relates to a modest increase in drug expenditure (Δ 950 000 DKK by 2027), but also further drug administration costs (Δ 425 000 DKK by 2027).

**Table 46. Expected budget impact of recommending anifrolumab for moderate to severe SLE**

| Costs (DKK) | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Anifrolumab is recommended** | 2 016 445 | 3 475 856 | 5 148 218 | 6 944 477 | 8 972 355 |
| Of which is drug acquisition costs | 1 780 104 | 3 036 810 | 4 477 974 | 5 992 069 | 7 721 989 |
| Of which is drug administration costs | 236 341 | 439 047 | 670 244 | 952 408 | 1 250 365 |
| **Anifrolumab is NOT recommended** | 1 928 111 | 3 203 190 | 4 586 988 | 5 981 754 | 7 599 798 |
| Of which is drug acquisition costs | 1 711 748 | 2 847 326 | 4 089 145 | 5 328 983 | 6 774 095 |
| Of which is drug administration costs | 216 363 | 355 864 | 497 843 | 652 772 | 825 703 |
| **Budget impact of the recommendation** | 88 334 | 272 666 | 561 230 | 962 723 | 1 372 557 |

As can be seen from the scenario analyses on the budget impact explored in Table 47, the budget impact and additional expenditure largely comes from the anticipated growth in the biologics market, with some small additional expenditure relative to that of subcutaneous belimumab. The average costs per patient are largely similar for biologic therapy. If there is no additional growth (beyond that currently expected) in the biologics market, recommending anifrolumab has a minimal additional cost compared to the current scenario. Therefore, should more future patients be treated with anifrolumab compared to IV belimumab, this could be cost saving to the Danish healthcare system, whilst also offering additional health benefits and disease control to some patients who may not be considered appropriate candidates for treatment with belimumab. It should be noted that the growth in the market is uncertain.

**Table 47. Scenario analyses on the budget impact of recommending anifrolumab in moderate to severe SLE**

| Budget impact (DKK) | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Base case** | 88 334 | 272 666 | 561 230 | 962 723 | 1 372 557 |
| **Lower limit of estimated anifrolumab-eligible population size** | 66 250 | 202 088 | 426 480 | 735 073 | 1 052 265 |
| **Upper limit of estimated anifrolumab-eligible population size** | 106 000 | 331 059 | 701 791 | 1 212 182 | 1 724 921 |
| **No use of anifrolumab if not recommended** | 48 920 | 232 049 | 519 507 | 946 886 | 1 322 974 |
| **Use of anifrolumab is double the base case when not recommended** | 127 748 | 313 284 | 602 953 | 978 560 | 1 422 139 |
| **No expansion of biologics-treated population due to recommendation** | 6 550 | 38 195 | 95 141 | 162 730 | 251 863 |
| **Relative increase based on all patients without high disease activity** | 170 118 | 507 138 | 1 027 320 | 1 762 716 | 2 493 250 |

| Budget impact (DKK) | 2023 | 2024 | 2025 | 2026 | 2027 |
|---|---|---|---|---|---|
| **Up to 40% of future potential belimumab patients displaced** | 79 187 | 244 593 | 514 061 | 886 828 | 1 267 270 |
| **Up to 60% of future potential belimumab patients displaced** | 97 480 | 300 739 | 608 399 | 1 038 618 | 1 477 843 |

There are likely to be additional cost savings to the healthcare system overall as a result of the efficacy of anifrolumab. Should the biologics market expand as a result of the recommendation of anifrolumab, patients treated with anifrolumab have lower disease activity, flares, and steroid use compared to patients treated with standard therapy alone. This would lead to direct medication cost savings on the acquisition of oral corticosteroids, but also steroid use is significantly associated with both acute and chronic adverse events and organ damage.[6,9,67,125] These events all have cost implications for health care, with an estimated additional $784 per year (in 2010 USD) in steroid related adverse events for those on steroids compared to those not taking steroids for SLE. Each 1-point increase on the SLICC/ACR Organ Damage Index (SDI) was shown to increase direct health care costs of SLE in Sweden by 35%.[41]

Anifrolumab was also shown to reduce the incidence of severe disease flares by 30% compared to standard therapy alone. The costs of managing a severe flare have been estimated at £610 in the UK in 2010 and 49 434 SEK in Sweden in 2021.[6,122] Disease activity is also associated with increased hospitalizations in Danish SLE patients.[39] Therefore, the introduction of anifrolumab may present meaningful cost savings to the healthcare as a result of better disease control and less reliance on steroids, however the specific scale of these savings has not been quantified in this analysis.

## 10. Discussion on the submitted documentation

SLE is a systemic heterogenous disease that can affect any organ system in the body and can result in a wide spectrum of debilitating disease manifestations. SLE carries a high clinical burden due to these manifestations, as well as irreversible organ damage and associated comorbidities/complications in the longer-term,[1,2] and there is a high unmet need for treatments in patients who do not respond to standard therapy.

The beneficial effect of anifrolumab has been demonstrated across all three randomised clinical studies, including consistent results in BICLA response at week 52. BICLA responders have a clinically meaningful improvement in all moderate to severe manifestations affected at baseline. This is associated with lower flare rates, higher rates of attainment of sustained reduction in glucocorticoids, greater improvements in patient-reported outcomes, and fewer SLE-related hospitalisations or emergency department visits.[90] In addition, anifrolumab was directly associated with a significant improvement on outcomes that are observed in clinical practice, such as steroid reduction, improvement in skin activity, and improvement in flares. These results are important for clinicians and patients because both corticosteroids and flares are associated with long-term organ damage.[66,68]

Results from the indirect comparison suggest that anifrolumab may offer an added benefit over belimumab given the improvements in disease activity as assessed by the SRI(4) and SLEDAI. However, the heterogeneity between trial populations means this result is subject to adjustment for baseline characteristics. It is therefore assumed that anifrolumab is at least as efficacious as belimumab with regards to objective measures of disease activity in clinical trials, with some potential additional benefit with the findings on the BICLA, CLASI, joint count, and patient-reported outcomes for anifrolumab, on which no results or non-significant results have been published for belimumab.

There is a recognized lack of a gold standard efficacy measurement in SLE given the heterogeneity of SLE and composite endpoints do not translate perfectly into clinical practice. Disease activity measurements differ in the type of response they detect.[20] Treatment goals of remission or low disease activity as stated in the EULAR recommendations have not yet been formalised into a response metric that is acceptable to regulators. The SRI(4) reflects an all-or-nothing response based on the complete resolution of symptoms in enough involved organ systems at baseline to obtain a reduction of 4-points in disease activity. The BICLA reflects a reduction in disease activity across all involved organ systems based on an intent-to-treat principle (i.e., if disease activity is fully or partially reduced in the organ system, less treatment will be required). This may be more indicative of response in clinical practice. Given the clinical relevance of BICLA, and its ability to detect a range of clinically meaningful improvements, it was included in all anifrolumab trials. Following the analysis of TULIP-1, clinically meaningful results on the secondary endpoints (including BICLA response) were identified by the clinical community and suggested that anifrolumab was a potentially efficacious treatment. Therefore, to ensure that adequate emphasis was placed on efficacy outcomes that were considered clinically relevant and could potentially represent meaningful improvements for SLE patients, it was decided to switch the primary endpoint of TULIP-2 to the BICLA response and have SRI(4) as a secondary endpoint. Both endpoints still formed part of the efficacy assessment as they provide complementary measures of global disease activity. However, BICLA response as a primary endpoint consequently allowed for significance testing of secondary endpoints that translate to clinical practice such as steroid sparing, reduction in skin manifestations, flare rates, and joint involvement.

Type 1 IFN is elevated in active SLE and initiates activation of immune responses, increasing the expression of self-antigens.[43,46] Two monoclonal antibodies that act to neutralize IFN-α, which is only one class of type 1 IFN, have previously failed clinical trials in SLE.[126,127] Anifrolumab is different and works upstream on the Type 1 IFN receptor, thereby inhibiting signalling of all classes of Type 1 IFN. Anifrolumab restores the balance between adaptive and innate immunity that is dysregulated in SLE and other autoimmune disorders.[79] It has been shown to be effective at reducing disease activity in patients with moderate to severe SLE in randomised trials, unlike other compounds that target the

IFN pathway. Anifrolumab is currently being evaluated in other autoimmune disorders that are characterized by activation of the IFN system.

As the efficacy of anifrolumab in practice is expected to be at least as good as that of belimumab, the economic value of anifrolumab was assessed in a cost minimisation analysis compared to belimumab. Given that anifrolumab is a hospital administered product, it is assumed that in clinical practice it is most likely to displace intravenously administered belimumab and so was compared to this formulation in the primary analysis. Anifrolumab was found to be cost saving compared to IV belimumab. This can be attributed to the fewer administrations required and the reduced patient burden in terms of time with each administration, resulting in lower drug costs, hospital costs, and patient costs. There are further economic benefits with anifrolumab, as it assists in the economic efficiency of procurement. On average, ~4% of belimumab procured would go to wastage, equating to 277 DKK per infusion or nearly 10 000 DKK of wastage per patient over five years. If anifrolumab is more efficacious than belimumab in clinical practice, it could offer further cost savings in terms of reduced hospitalisations and lower costs of managing future organ damage caused by increased disease activity.

Anifrolumab was found to be associated with a similar cost to belimumab in scenario analyses where either some patients responding to treatment are assumed to switch to the subcutaneous formulation, or where a proportion of patients begin treatment with the subcutaneous formulation from day 0, though there were some cases of cost savings or additional expenditure related to drug acquisition and patient costs depending on the proportion of patients assumed to use each comparator therapy. Drug administration costs across the duration of treatment were higher, based on the DRG costs of administration. However, belimumab has a longer infusion time and is expected to require longer monitoring than anifrolumab. If the administration cost were microcosted to reflect the true administration burden of anifrolumab and belimumab, this incremental cost may be reduced.

The estimated budget impact of recommending anifrolumab for eligible patients in Denmark is modest. The additional expenditure to the healthcare service is thought to not exceed 1.4 million DKK per year over the next five years. The results of this analysis are somewhat uncertain with respect to the forecasted uptake of anifrolumab. Given its novel mechanism of action, and presenting as an effective new treatment option for a patient group with high unmet need, anifrolumab may offer more value to a wider group of patients than currently served by biologic therapies available in Denmark, and may therefore lead to a small expansion of the biologics market. However, the costs per patient are comparable to those of belimumab and therefore the cost impact of displacing belimumab in any potential future biologic-treated patient is limited, with the potential for cost savings over IV belimumab. There are also some potential additional unmeasured cost savings as a result of better disease control for patients not previously receiving biologics, including fewer steroid related adverse events, and reduced reliance on off-label medications. There may also be a societal economic gain, as many patients with SLE are of working age and may therefore have the possiblity to return to work with properly tailored treatment. In TULIP-2, [redacted]% more patients treated with anifrolumab were in employment by week 52 compared to placebo. In TULIP-1, patients in the anifrolumab 300mg group showed greater improvements compared with patients in the placebo group at week 52 in terms of work hours missed (mean change [redacted] vs [redacted]) and work productivity loss [redacted]% vs [redacted]%).

Despite currently available treatment options for moderate to severe SLE, including belimumab and other conventional immunosuppressive regimens or cortiocosteroids, disease activity persists in some of these patients which can increase the risk of future organ damage and mortality. Reliance on cortiocosteroids is also associated with a greater side effect burden and organ damage.[65-68] There is therefore still a need for effective, steroid-sparing therapies. Anifrolumab (added to standard therapy) demonstrated early and sustained improvements in SLE disease activity as well as significant, sustained reduction in OCS and significant, clinically-meaningful early and sustained response in skin disease with no major safety signals.[73,74,92]

## 11. List of experts

No experts have formally been consulted in the development of the submission. However, AstraZeneca has had previous held advisory boards and interviews to gain greater insights on the SLE disease space, which have included Danish rheumatologists specializing in SLE in Denmark. As no specific statements have been given with respect to points made in this submission, they have opted to remain anonymous.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

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# Appendix A. Literature search for efficacy and safety of intervention and comparator(s)

**Objective of the literature search:** To conduct a systematic literature review (SLR) of efficacy, safety, and quality of life (QoL) data to inform an indirect treatment comparison (ITC) feasibility assessment, and any potential ITCs to compare different treatments in adults with moderately to severely active SLE.

**Databases:** A systematic search of Embase, MEDLINE®, and the Cochrane Library using the OVID platform was conducted by an information specialist and peer-reviewed by another senior information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist. Phase 2 and 3 randomized controlled trials (RCTs) investigating approved therapies for the treatment of adult patients with moderate to severely active SLE while receiving SOC treatment were included. Publication dates from database inception through March 11, 2021 are included in this report. Conference abstracts were limited to the most recent two years. Conference proceedings, bibliographies of previously published SLRs, and the ClinicalTrials.gov website were searched to ensure inclusion of all relevant clinical trials. Study selection was performed in duplicate and standardized data extraction templates were used to collect data on study and patient characteristics and outcomes of interest.

**Table A1. Bibliographic databases included in the literature search**

| Database | Platform | Relevant period for the search | Date of search completion |
|---|---|---|---|
| **Embase** | Ovid | 1974 until 10.03.2021 | 11.03.2021 |
| **MEDLINE** | Ovid | 1946 until 10.03.2021 | 11.03.2021 |
| **Cochrane Library** | Ovid | 2005 until 03.03.2021 | 11.03.2021 |

**Table A2. Registers included in the search**

| Database | Platform | Search strategy | Date of search |
|---|---|---|---|
| **US NIH registry & results database** | https://clinicaltrials.gov | See below | 22.03.2021 |
| **Cochrane Central Register of Controlled Clinical Trials** | EBM Reviews / Ovid | See below | 11.03.2021 |

**Table A3. Conference material included in the literature search**

| Conference | Source of abstracts | Search strategy | Words/terms searched |
|---|---|---|---|
| **American College of Rheumatology and the Association for Rheumatology Health Professionals Annual Meeting** | Embase / Conference website | Included in search strategy below and by manual search | See below |
| **Annual European Congress of Rheumatology** | Embase / Conference website | Included in search strategy below and by manual search | See below |

| Conference | Source of abstracts | Search strategy | Words/terms searched |
|---|---|---|---|
| **International Congress on Systemic Lupus Erythematosus** | Embase / Conference website | Included in search strategy below and by manual search | See below |
| **Canadian Rheumatology Association and Arthritis Health Professions Association Annual Scientific Meeting** | Embase / Conference website | Included in search strategy below and by manual search | See below |

### Search strategy

**Database(s):** EBM Reviews - Cochrane Central Register of Controlled Trials February 2021, EBM Reviews - Cochrane Database of Systematic Reviews 2005 to March 3, 2021, EBM Reviews - Database of Abstracts of Reviews of Effects 1st Quarter 2016, Embase 1974 to 2021 March 10 , Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily 1946 to March 10, 2021

**Table A4. Inclusion & Exclusion Criteria**

| Criteria | Include | Exclude |
|---|---|---|
| **Population** | Adults (≥18 years) with moderately to severely active systemic lupus erythematosus (SLE) while receiving standard of care (SOC) treatment | • Nonadults (≤18 years)<br>• Cutaneous (discoid) lupus erythematosus, druginduced lupus, neonatal lupus<br>• Lupus nephritis<br>• Neuropsychiatric lupus<br>• Animals, in vitro studies<br>• Any other disease areas; healthy volunteers<br>• Pregnant women |
| **Intervention** | Interferon-alpha inhibitor<br>Anifrolumab | |
| **Comparators** | Antimalarial<br>• Hydroxychloroquine<br>Protease Inhibitor<br>• Tofacitinib<br>Immunosuppressants/Cytotoxic drugs<br>• Azathioprine<br>• Cyclophosphamide<br>• Cyclosporine/ciclosporin/cyclosporin Leflunomide<br>• Methotrexate<br>• Mizoribine<br>• Mycophenolate mofetil (MMF)<br>• Mycophenolate sodium<br>• Tacrolimus | • Treatments not related to SLE<br>• Medical devices<br>• Nonpharmacological interventions |



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| Criteria | Include | Exclude |
|---|---|---|
| | Corticosteroids/Steroids<br>• IV corticosteroids<br>• Oral corticosteroids (low and high doses)<br>• Prednisone<br>• Methylprednisolone<br>Immunomodulatory<br>• Dapirolizumab pegol<br>• Lupuzor<br>• Rontalizumab<br>• Ustekinumab<br>• Laquinimod<br>B cell modulators<br>• Rituximab<br>• Belimumab (IV or SC)<br>• Atacicept<br>T cell modulator<br>• Abatacept | |
| **Outcomes** | Efficacy<br>• Improvement in disease activity<br>• Steroid tapering<br>• Flare reduction<br>• Improvement in skin disease<br>• Fatigue<br>• Pain<br>Safety<br>• Infections (including serious, opportunistic, and herpes zoster)<br>• Malignancies | Outcomes not related to SLE (e.g., outcomes related to another population or disease) |
| **Study Design** | • Phase 2, phase 3, and phase 2/3 randomized controlled trials (RCTs), including published studies, conference abstracts/posters, and grey literature<br>• Open label extension trials of RCTs<br>• Systematic reviews, meta-analyses, and network meta-analyses[a] | • Phase 1, phase 1/2 and phase 4 RCTs<br>• Non-RCTs<br>• Single-arm studies<br>• Study protocols<br>• Opinion pieces, commentaries, letters, editorials, case reports<br>• Economic/cost-effectiveness evaluations<br>• Narrative reviews (ie, nonsystematic) |
| **Location** | Global | None; all countries/regions with available data should be included |
| **Language** | English only[b] | Non-English |
| **Date** | Database inception to present (ie, no data restriction) | None |

[a]Systematic reviews, meta-analyses, network meta-analyses, and the bibliographies of these records were reviewed and cross-referenced with the included study lists to ensure that no primary studies were missed.
[b]Search captured all languages, but non-English citations were excluded during screening.
Abbreviations: BILAG = British Isles Lupus Assessment Group; IV = intravenous; PGA = Physician's Global Assessment; RCT = randomized controlled trial; SC = subcutaneous; SLE = systemic lupus erythematosus; SLEDAI = Systemic Lupus Erythematosus Disease Activity Index; SOC = standard of care.

**Table A5. Original search syntax (including journal articles and conference abstracts indexed in Embase)**

| # | Searches | Results |
|---|---|---|
| 1 | Lupus Erythematosus, Systemic/ | 75769 |
| 2 | (systemic adj1 lupus erythemato*).tw,kf. | 98424 |
| 3 | (disseminated adj1 lupus erythemato*).tw,kf. | 1444 |
| 4 | (disseminatus adj1 lupus erythemato*).tw,kf. | 267 |
| 5 | disseminated lupus.tw,kf. | 1069 |
| 6 | (SLE and lupus).tw,kf. | 6207 |
| 7 | (erythemato* adj2 visceral*).tw,kf. | 182 |
| 8 | lupoviscerit#s.tw,kf. | 0 |
| 9 | libman sacks.tw,kf. | 491 |
| 10 | or/1-9 [SLE] | 127816 |
| 11 | exp Child/ not (Adolescent/ or exp Adult/) | 1850667 |
| 12 | exp Infant/ not (Adolescent/ or exp Adult/) | 1160356 |
| 13 | 10 not (11 or 12) [CHILD-, INFANT-ONLY REMOVED] | 123970 |
| 14 | exp Animals/ not (exp Animals/ and Humans/) | 13120941 |
| 15 | 13 not 14 [ANIMAL-ONLY REMOVED] | 99759 |
| 16 | (editorial or news or newspaper article).pt. | 1183319 |
| 17 | (letter not (letter and randomized controlled trial)).pt. | 1852070 |
| 18 | 15 not (16 or 17) [OPINION PIECES REMOVED] | 93505 |
| 19 | limit 18 to systematic reviews [Limit not valid in Embase; records were retained] | 38914 |
| 20 | meta analysis.pt. | 85751 |
| 21 | exp meta-analysis as topic/ | 53001 |
| 22 | (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kf. | 292877 |
| 23 | (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kf. | 346131 |
| 24 | exp Technology assessment, biomedical/ | 22268 |
| 25 | (cochrane or health technology assessment or evidence report).jw. | 38573 |
| 26 | (network adj (MA or MAs)).tw,kf. | 16 |
| 27 | (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kf. | 13569 |
| 28 | indirect* compar*.tw,kf. | 4176 |
| 29 | (indirect treatment* adj1 compar*).tw,kf. | 547 |
| 30 | (mixed treatment* adj1 compar*).tw,kf. | 1180 |
| 31 | (multiple treatment* adj1 compar*).tw,kf. | 287 |
| 32 | (multi-treatment* adj1 compar*).tw,kf. | 4 |
| 33 | simultaneous* compar*.tw,kf. | 1886 |
| 34 | mixed comparison?.tw,kf. | 41 |
| 35 | or/20-34 | 627909 |
| 36 | 18 and 35 | 1470 |
| 37 | 19 or 36 [REVIEWS] | 39109 |
| 38 | (controlled clinical trial or randomized controlled trial).pt. | 542943 |

| # | Searches | Results |
|---|---|---|
| 39 | clinical trials as topic.sh. | 182885 |
| 40 | Randomized Controlled Trials as Topic/ | 194480 |
| 41 | (randomi#ed or randomi#ation? or randomly or RCT? or placebo*).tw,kf. | 1944805 |
| 42 | ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kf. | 340091 |
| 43 | trial.ti. | 401724 |
| 44 | or/38-43 | 2457124 |
| 45 | 18 and 44 [RCTS] | 2989 |
| 46 | open label.tw,kf. | 97333 |
| 47 | 18 and 46 [OPEN LABEL STUDIES] | 251 |
| 48 | 37 or 45 or 47 [REVIEWS, RCTS, OPEN-LABEL STUDIES] | 40753 |
| 49 | 48 use ppez [MEDLINE RECORDS] | 2833 |
| 50 | systemic lupus erythematosus/ | 117107 |
| 51 | (systemic adj1 lupus erythemato*).tw,kw. | 99094 |
| 52 | (disseminated adj1 lupus erythemato*).tw,kw. | 1059 |
| 53 | (disseminatus adj1 lupus erythemato*).tw,kw. | 260 |
| 54 | disseminated lupus.tw,kw. | 1071 |
| 55 | (SLE and lupus).tw,kw. | 62729 |
| 56 | (erythemato* adj2 visceral*).tw,kw. | 183 |
| 57 | lupoviscerit#s.tw,kw. | 0 |
| 58 | libman sacks.tw,kw. | 482 |
| 59 | or/50-58 [SLE] | 139590 |
| 60 | exp juvenile/ not exp adult/ | 1566499 |
| 61 | fetus/ not exp adult/ | 167649 |
| 62 | 59 not (60 or 61) [CHILD-, INFANT-, FETUS-ONLY REMOVED] | 134923 |
| 63 | exp animal experimentation/ or exp animal model/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ | 41356500 |
| 64 | exp human/ or exp human experimentation/ or exp human experiment/ | 33205212 |
| 65 | 63 not 64 | 8152466 |
| 66 | 62 not 65 [ANIMAL-ONLY REMOVED] | 127464 |
| 67 | editorial.pt. | 980319 |
| 68 | letter.pt. not (letter.pt. and randomized controlled trial/) | 1847475 |
| 69 | 66 not (67 or 68) [OPINION PIECES REMOVED] | 119202 |
| 70 | meta-analysis/ | 225541 |
| 71 | systematic review/ | 160784 |
| 72 | meta analysis (topic)/ | 36672 |
| 73 | (meta-analy* or metanaly* or metaanaly* or met analy* or integrative research or integrative review* or integrative overview* or research integration or research overview* or collaborative review*).tw,kw. | 295500 |
| 74 | (systematic review* or systematic overview* or evidence-based review* or evidence-based overview* or (evidence adj3 (review* or overview*)) or meta-review* or meta-overview* or meta-synthes* or rapid review* or "review of reviews" or technology assessment* or HTA or HTAs).tw,kw. | 348993 |
| 75 | biomedical technology assessment/ | 21161 |
| 76 | (cochrane or health technology assessment or evidence report).jw. | 38573 |
| 77 | (network adj (MA or MAs)).tw,kw. | 16 |



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| # | Searches | Results |
|---|---|---|
| 78 | (NMA or NMAs or MTC or MTCs or MAIC or MAICs).tw,kw. | 13618 |
| 79 | indirect* compar*.tw,kw. | 4228 |
| 80 | (indirect treatment* adj1 compar*).tw,kw. | 551 |
| 81 | (mixed treatment* adj1 compar*).tw,kw. | 1202 |
| 82 | (multiple treatment* adj1 compar*).tw,kw. | 290 |
| 83 | (multi-treatment* adj1 compar*).tw,kw. | 4 |
| 84 | simultaneous* compar*.tw,kw. | 1886 |
| 85 | mixed comparison?.tw,kw. | 42 |
| 86 | or/70-85 | 681024 |
| 87 | 69 and 86 | 2581 |
| 88 | randomized controlled trial/ or controlled clinical trial/ | 1193427 |
| 89 | exp "clinical trial (topic)"/ | 259591 |
| 90 | Randomized Controlled Trials as Topic/ | 194480 |
| 91 | (randomi#ed or randomi#ation? or randomly or RCT? or placebo*).tw,kw. | 1946875 |
| 92 | ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw,kw. | 340244 |
| 93 | trial.ti. | 401724 |
| 94 | or/88-93 | 2689641 |
| 95 | 69 and 94 [RCTS] | 5137 |
| 96 | open label.tw,kf. | 97333 |
| 97 | 69 and 96 [OPEN LABEL STUDIES] | 378 |
| 98 | 87 or 95 or 97 [REVIEWS, RCTS, OPEN-LABEL STUDIES] | 7411 |
| 99 | 98 use emed [EMBASE RECORDS] | 5198 |
| 100 | 49 or 99 [BOTH DATABASES] | 8031 |
| 101 | limit 100 to yr="2010-current" | 5296 |
| 102 | remove duplicates from 101 | 4078 |
| 103 | 100 not 101 | 2735 |
| 104 | remove duplicates from 103 | 2067 |
| 105 | 102 or 104 [TOTAL UNIQUE RECORDS] | 6145 |
| **106** | **105 use ppez [MEDLINE UNIQUE RECORDS]** | **2825** |
| **107** | **105 use emed [EMBASE UNIQUE RECORDS]** | **3320** |



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**Figure A1. Systematic selection of studies**

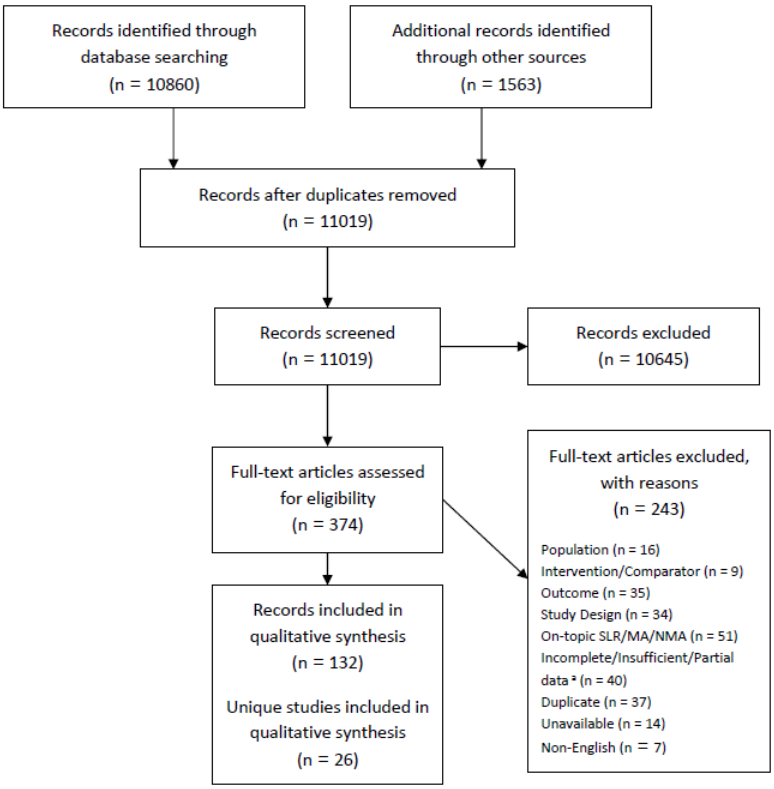


**Table A6. Overview of study design for studies included in the technology assessment/analysis:**

| Trial (Name: Identifier) | Intervention arms | Eligibility criteria | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Current treatments | Prior treatments | SLE severity | Age | SLEDAI (type: score) | BILAG score | Antibodies | Lupus Nephritis | Neuropsychiatric SLE |
| MUSE: NCT01438489 | • Anifrolumab IV 300 mg<br>• Anifrolumab IV 1000 mg<br>• Placebo | Stable SOC[a] required | NR | Moderate to severe | 18-65 | SLEDAI-2K: ≥6 | Organ domain score: ≥1A or ≥2B | Required to have:<br>• Antinuclear<br>• Anti-dsDNA<br>• Anti-sm | Excluded | Excluded |
| MUSE OLE: NCT01753193 | • Anifrolumab IV 300 mg | Stable SOC[a] required | NR | Moderate to severe | 18-65 | SLEDAI-2K: ≥6 | Organ domain score: ≥1A or ≥2B | Required to have:<br>• Antinuclear<br>• Anti-dsDNA Anti-sm | Excluded | Excluded |
| ADDRESS II: NCT01972568 | • Atacicept SC 75 mg<br>• Atacicept SC 150 mg<br>• Placebo | Select SOC[b] permitted | NR | Moderate to severe | ≥18 | SLEDAI-2K: ≥6 | NR | Required to have:<br>• Antinuclear<br>• Anti-dsDNA<br>• Anti-sm | Excluded | Excluded |
| ADDRESS II LTE: NCT02070978 | • Atacicept SC 75 mg<br>• Atacicept SC 150 mg | Select SOC[b] permitted | NR | Moderate to severe | ≥18 | SLEDAI-2K: ≥6 | NR | Required to have:<br>• Antinuclear<br>• Anti-dsDNA Anti-sm | Excluded | Excluded |
| BLISS-52: NCT00424476 | • Belimumab IV 1 mg/kg<br>• Belimumab IV 10 mg/kg<br>• Placebo | Stable SOC[c] required | NR | NR | ≥18 | SELENA-SLEDAI: ≥6 | NR | Required to have:<br>• Antinuclear<br>• Anti-dsDNA | Excluded | Excluded |
| BLISS-76: NCT00410384 | • Belimumab IV 1 mg/kg<br>• Belimumab IV 10 mg/kg<br>• Placebo | Stable SOC[c] required | NR | NR | ≥18 | SELENA-SLEDAI: ≥6 | NR | Required to have:<br>• Antinuclear<br>• Anti-dsDNA | Excluded | Excluded |

| Trial (Name: Identifier) | Intervention arms | Eligibility criteria | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Current treatments | Prior treatments | SLE severity | Age | SLEDAI (type: score) | BILAG score | Antibodies | Lupus Nephritis | Neuropsychiatric SLE |
| BEL112233: NCT00724867 | • Belimumab IV 1 mg/kg; Belimumab IV 10 mg/kg | NR | NR | NR | ≥18 | SELENA-SLEDAI: ≥6 | NR | Required to have: • Antinuclear • Anti-dsDNA | Excluded | NR |
| BLISS-SC: NCT01484496 | • Placebo; Belimumab IV 10 mg/kg | Select SOC[d] permitted | NR | Moderate to severe | ≥18 | SELENA-SLEDAI: ≥8 | NR | Required to have: • Antinuclear • Anti-dsDNA | Excluded | NR |
| BEL113750: NCT01345253 | • Belimumab IV 10 mg/kg • Placebo | Stable SOC[e] required | Prior B cell targeted therapy was excluded | Active | ≥18 | SELENA-SLEDAI: ≥8 | NR | Required to have: • Antinuclear | Excluded | Excluded |
| BEL114333: NCT01597622 | • Belimumab IV 10 mg/kg | Stable SOC[e] required | Prior B cell targeted therapy was excluded | Active | ≥18 | SELENA-SLEDAI: ≥8 | NR | Required to have: • Antinuclear | Excluded | Excluded |
| APRIL-SLE: NCT00624338 | • Atacicept SC 75 mg • Atacicept SC 150 mg • Placebo | Stable SOC[f] required | NR | Moderate to severe | NR | NR | A or B[g] | Required to have: • Antinuclear • Anti-dsDNA | Excluded | Excluded |
| EXPLORER: NCT00137969 | • Rituximab IV 1000 mg • Placebo | Stable SOC[h] required | Prior CAMPATH-1H antibody or B cell targeted treatments were excluded | Moderate-to-severely active extra-renal | 16-75 | NR | ≥1A or ≥2B | Required to have: • Antinuclear | NR | NR |
| ROSE: NCT00962832 | • Rontalizumab IV 750 mg • Rontalizumab SC 300 mg • Placebo | Stable SOC[i] permitted | Prior B cell targeted therapy was excluded | Active | 18-65 | NR | ≥1A or ≥2B | Required to have: • Antinuclear | Excluded | Excluded |
| Zimmer, 2013 | • Lupuzor SC 200 mg q2w • Lupuzor SC 200 mg q4w • Placebo | Stable SOC[j] permitted | Select SOC permitted with appropriate washout period[k] | Moderately active | 18-68 | SELENA-SLEDAI: ≥6 | ≥1A was excluded | Required to have: • Antinuclear | NR | NR |
| NCT00119678 | • Abatacept IV 10 mg/kg • Placebo | Stable SOC[l] permitted | Excluded[m] | Moderate to severe | ≥18 | NR | A or B | NR | Excluded | Excluded |
| Yahya, 2013 | • Mycophenolate sodium 360/720 mg • SOC[n] | NR | Recent biologic therapy[o] was excluded | Active | ≥18 | SLEDAI: ≥11 | NR | NR | Excluded | NR |
| Fortin, 2008 | • Methotrexate 7.5-20 mg/week • Placebo | Stable SOC[r] required | Excluded[s] | At least moderately active | ≥18 | NR | NR | NR | Excluded | Excluded |
| Kalunian, 2013 | • Mycophenolate mofetyl • SOC[t] | NR | NR | NR | NR | NR | NR | NR | Excluded | NR |
| Griffiths, 2010 | • Ciclosporin **(oral)** 1.0-3.5 mg/kg/day • Azathioprine 0.5-2.5 mg/kg/day | At least 15 mg/d prednisolone | NR | Severe | NR | NR | NR | NR | NR | NR |
| Mackworth-Young, 1988 | • Methylprednisolone IV 1g • Placebo | Oral prednisolone ≥40 mg per day | NR | Moderate to severe | 14-65 | NR | NR | NR | NR | NR |

| Trial (Name: Identifier) | Intervention arms | Eligibility criteria | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Current treatments | Prior treatments | SLE severity | Age | SLEDAI (type: score) | BILAG score | Antibodies | Lupus Nephritis | Neuropsychiatric SLE |
| EMBRACE: NCT01632241 | • Belimumab IV 10 mg/kg<br>• Placebo | Stable SOC[u] required | Excluded[v] | Active | ≥18 | SELENA-SLEDAI: ≥8 | NR | Required to have one of:<br>• Antinuclear<br>• Anti-dsDNA | Excluded | NR |
| NCT02804763 | • Dapirolizumab pegol IV 6 mg/kg<br>• Dapirolizumab pegol IV 24 mg/kg<br>• Dapirolizumab pegol IV 45 mg/kg<br>• Placebo | Stable SOC [w] required | Restricted[x] | Moderate to severe | ≥18 | SLEDAI-2K: ≥6 | Organ domain score: ≥1A or ≥2B | Required to have anti-nuclear with either history of anti-dsDNA or extractable nuclear antigen | Excluded | Excluded |
| TULIP-1: NCT02446912 | • Anifrolumab IV 150 mg<br>• Anifrolumab IV 300 mg<br>• Placebo | Stable SOC[y] required | Restricted[z] | Moderate to severe | 18-70 | SLEDAI-2K: ≥6 | Organ domain score: ≥1A or ≥2B | Required to have one of:<br>• Antinuclear<br>• Anti-dsDNA<br>• Anti-sm | Excluded | Excluded |
| TULIP-2: NCT02446899 | • Anifrolumab IV 300 mg<br>• Placebo | Stable SOC[y] required | Restricted[z] | Moderate to severe | 18-70 | SLEDAI-2K: ≥6 | Organ domain score: ≥1A or ≥2B | Required to have:<br>• Antinuclear<br>• Anti-dsDNA<br>• Anti-sm | Excluded | Excluded |
| NCT02349061 | • Ustekinumab IV 6 mg/kg; Ustekinumab SC 90 mg; Placebo<br>• Placebo; Ustekinumab SC 90 mg | Stable SOC [aa] required | Excluded[bb] | Moderate to severe | 18-75 | SLEDAI-2K: ≥6 | Organ domain score: ≥1A or ≥2B | Required to have current or history of:<br>• Antinuclear<br>• Anti-dsDNA<br>• Anti-sm | Excluded | Excluded |
| NCT02962960 | • Anifrolumab SC 300 mg<br>• Placebo SC 300 mg<br>• Anifrolumab SC 150 mg<br>• Placebo SC 150 mg | Stable SOC [cc] required | Restricted [dd] | At least moderately active skin disease | 18-70 | NR | NR | Required to have one of:<br>• Antinuclear<br>• Anti-dsDNA<br>• Anti-sm | Excluded [ee] | Excluded |

[a] Patients were receiving treatment with at least one of the following: oral prednisone (≤40 mg/day or equivalent), azathioprine (≤200 mg/day), an antimalarial, mycophenolate mofetil/mycophenolic acid (≤2.0 gm/day), or methotrexate (≤25mg/week).
[b] Permitted immunosuppressant or immunomodulatory therapies included: azathioprine ≤2.5mg/kg/day, 6-mercaptopurine ≤1.5 mg/kg/day, mycophenolate (as MMF ≤3 g/day or MPS ≤2160 mg/day), methotrexate ≤25 mg/week, sulfasalazine ≤3g/day, or leflunomide ≤20 mg/day.
[c] Stable treatment could include prednisone (or equivalent) alone (7.5–40 mg/day) or combined (0–40 mg/day) with antimalarial drugs, nonsteroidal anti-inflammatory drugs, and/or immunosuppressive therapies.
[d] Corticosteroids, antimalarials, NSAIDs, and immunosuppressives allowed alone or in combination. Biologics and intravenous cyclophosphamide were not permitted.
[e] Permitted SLE treatments: corticosteroids (all doses reported as prednisone or equivalent), antimalarials, NSAIDS or any other immunosuppressive or immunomodulatory therapy.
[f] Permitted SLE treatments: azathioprine (≤3 mg/kg/day), hydroxychloroquine (≤400 mg/day), chloroquine (≤250 mg/day) or methotrexate (≤25 mg/week) for 2 months prior to screening.
[g] Excluding a single B score in haematology.
[h] Background SOC treatment with either azathioprine 100–250 mg/day, MMF; 1–4 gm/day, or methotrexate 7.5–27.5 mg/ week.
[i] Permitted background treatments included NSAIDs, antimalarials, ACE inhibitors, angiotensin receptor-blocking agents, osteoporosis therapies and statins.
[j] Permitted treatments and dosing as follows: oral corticosteroids with the weekly cumulative dose under the equivalent of 80 mg of prednisone or 72 mg of budesonide; antimalarial drugs, methotrexate, leflunomide, mycophenolate mofetil or azathioprine must have started them ≥3 months before study entry. Angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists must have been receiving stable doses for ≥4 weeks before baseline assessment. All doses must have been stable during the 4 weeks before study entry.
[k] Patients who had previously taken corticosteroids, antimalarial drugs, methotrexate, mycophenolate mofetil or azathioprine must have received the last dose ≥4 weeks before study entry. Patients who had previously taken leflunomide must have received the last dose ≥8 weeks before study entry unless they underwent an adequate cholestyramine wash-out.
[l] Permitted background treatments were NSAIDs, azathioprine, MMF, chloroquine, hydroxychloroquine, or methotrexate, as well as proteinuria therapies (ie, angiotensin-converting enzyme inhibitors or angiotensin receptor–blocking agents).
[m] Patients were excluded if they had received any investigational drug within 28 days of study entry or had taken abatacept or rituximab at any time previously, had received corticosteroids for an SLE flare for >14 days before randomization, had undergone treatment of the entry flare episode at any time with a prednisone dosage ≥30 mg/day (or equivalent).
[n] SOC was identified as azathioprine or dapsone.
[o] Recent biologic therapy was defined as rituximab or anti-CD20 in the past 24 months, or anti-tumor necrosis factor therapy in the last 12 months.
[p] SOC included antimalarials and oral corticosteroids (up to 80 mg/wk prednisone equivalent) at stable doses for ≥ 4 weeks before study treatment.
[q] Adults were included.
[r] Must be on stable dose of NSAIDs, prednisone, or antimalarial drugs for minimum of 4 weeks prior to study enrollment.

**Table A7. List of included studies**

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| 1 | MUSE | NCT01438489 | 393 | *Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K et al. (2017) Anifrolumab, an Anti-Interferon-alpha Receptor Monoclonal Antibody, |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| | | | | in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis rheumatol 69 (2): 376-386. |
| 2 | | | 8 | Morand EF, Trasieva T, Berglind A, Illei GG, Tummala R (2018) Lupus Low Disease Activity State (LLDAS) attainment discriminates responders in a systemic lupus erythematosus trial: post-hoc analysis of the Phase IIb MUSE trial of anifrolumab. Annals of the Rheumatic Diseases Feb 02 |
| 3 | | | 3327 | Merrill J, Furie R, Werth V, Khamashta M, Drappa J et al. (2016) Anifrolumab reduces disease activity in multiple organ domains in moderate to severe systemic lupus erythematosus (SLE). Clinical and Experimental Rheumatology Conference: (4 Supplement 99): S4. |
| 4 | | | 3404 | Merrill JT, Furie R, Werth VP, Khamashta M, Drappa J et al. (2016) The effect of anifrolumab on cutaneous manifestations and arthritis in moderate to severe systemic lupus erythematosus (SLE) using categorical SLEDAI-2K responses and continuous measures of activity as outcome measures. Arthritis and Rheumatology Conference: (Supplement 10): 2569-2570. |
| 5 | | | 3863 | Furie R, Merrill JT, Werth VP, Khamashta M, Kalunian K et al. (2015) Anifrolumab, an anti-interferon alpha receptor monoclonal antibody, in moderate to severe systemic lupus erythematosus (SLE). Arthritis and Rheumatology Conference: 67 (Suppl 10): |
| 6 | | | 3396 | Morand E, Berglind A, Sheytanova T, Tummala R, Illei G (2016) Utility of the lupus low disease activity state definition in discriminating responders in the phase IIB muse trial of anifrolumab in systemic lupus erythematosus. Arthritis and Rheumatology Conference: (Supplement 10): 2575-2576. |
| 7 | | | ACR398 | Furie R, Kalunian K, Merrill J, Abreu G, Tummala R. Lupus Disease Activity After Cessation of Anifrolumab Treatment During the Phase 2b MUSE Trial Follow-up Period. Arthritis Rheumatol. 2020; 72 (suppl 10). |
| 8 | MUSE Extension Study | NCT01753193 | G4 | Chatham WW, Furie R, Saxena A, Brohawn P, Schwetje E et al. Long-term safety and efficacy of anifrolumab in adults with systemic lupus erythematosus: results of a phase 2 open-label extension study. Arthritis & Rheumatology: |
| 9 | ADDRESS II | NCT01972568 | 59 | *Merrill JT, Wallace DJ, Wax S, Kao A, Fraser PA et al. (2018) Efficacy and Safety of Atacicept in Patients with Systemic Lupus Erythematosus: Results of a Twenty-Four-Week, Multicenter, |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| | | | | Randomized, Double-Blind, Placebo-Controlled, Parallel-Arm, Phase IIb Study. Arthritis rheumatol 70 (2): 266-276. |
| 10 | | | 2967 | Merrill JT, Wallace DJ, Vazquez-Mateo C, Kao AH, Fleuranceau-Morel P et al. (2017) Safety profile in sle patients treated with atacicept in a phase IIb study (address II) and its extension study. Arthritis and Rheumatology Conference: (Supplement 10). |
| 11 | | | 2988 | Morand EF, Merrill JT, Kao AH, Vazquez-Mateo C, Wax S et al. (2017) Attainment of low disease activity by patients with systemic lupus erythematosus starting with high disease activity in a 24-week, randomized, placebo-controlled, phase iib study of atacicept (address II). Arthritis and Rheumatology Conference: (Supplement 10). |
| 12 | | | 6231 | Merrill JT, Wallace DJ, Wax S, Kao A, Fraser P et al. (2016) Efficacy and safety of atacicept in patients with systemic lupus erythematosus: results of a 24-week randomized, placebo-controlled, phase IIb study. Arthritis and rheumatology Conference: ACR/ARHP 68: 4377-4379. |
| 13 | | | U-1329 | Merril JT, Morand E, Wallace D.J, Kao A, Vazquez-Mateo C, Chang P, Fleuranceau-Morel P, Isenberg DA. (2018) Sri response, attainment of low disease activity and safety in patients with systemic lupus treated with atacicept in a phase iib study (address ii). Lupus Science and Medicine 5 (Supplement 1): A26-A27. |
| 14 | | | U-1416 | Morand E, Merrill JT, Isenberg DA, Kao AH, Vazquez-Mateo C, Wax S, Chang P, Pudota K, Aranow C, Wallace D. (2018) Attainment of low disease activity and remission in systemic lupus erythematosus patients with high disease activity in the atacicept phase IIb address II study and its long-term extension. Annals of the R heumatic Diseases 77 (Supplement 2): 174-175. |
| 15 | | | U-2468 | Wallace, D. J., Isenberg, D. A., Kao, A., Vazquez-Mateo, C., Fleuranceau-Morel, P., Chang, P., Merril, J. T. (2018) Reduction of systemic lupus flares by atacicept in a randomised, placebocontrolled, phase iib study (address ii) and its extension study. Lupus Science and Medicine 5 (Supplement 1): A25-A26. |
| 16 | | | U-1417 | Morand, E., Merrill, J. T., Isenberg, D. A., Kao, A. H., Vazquez-Mateo, C., Wax, S., Chang, P., Pudota, K., Aranow, C., Wallace, D. J. (2018) Attainment of low disease activity and remission in sle patients who started with high disease activity in the atacicept phase IIb address II study and its long-term extension. Arthritis and Rheumatology 70 (Supplement 9): 1900-1902. |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| 17 | | | U-1418 | Morand, E., Merrill, J. T., Isenberg, D. A., Kao, A. H., Vazquez-Mateo, C., Wax, S., Chang, P., Pudota, K., Aranow, C., Wallace, D. J. (2019) Attainment of low disease activity and remission with atacicept in patients with systemic lupus erythematosus and high disease activity in the phase iib address II study and its long-term extension. Lupus Science and Medicine 6 (Supplement 1): A156-A157. |
| 18 | | | U-1425 | Morand Ef, Isenberg D. A. Wallace D. J. Kao A. H. Vazquez-Mateo C. Chang P. Pudota K. Aranow C. Merrill J. T. (2020) Attainment of treat-to-target endpoints in SLE patients with high disease activity in the atacicept phase 2b ADDRESS II study. Rheumatology (Oxford, England) |
| 19 | BLISS-52 | NCT00424476 | 1422 | *Navarra SV, Guzman RM, Gallacher AE, Hall S, Levy RA et al. (2011) Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet 377 (9767): 721-731. |
| 20 | | | 5269 | Gladman DD, Kang YM, Tsai ST, Lichauco JJ, Bojinca M et al. (2010) Belimumab, A BLyS-specific inhibitor, significantly improved physical functioning, fatigue, and other health-related quality of life (HRQoL) measures in patients with seropositive systemic lupus erythematosus (SLE): BLISS-52 study. Lupus Conference: 19 (Suppl 1): 154-155. |
| 21 | | | 5293 | Navarra S, Bae SC, Hall S, Guzman R, Gallacher A et al. (2010) Belimumab, A BLyS-specific inhibitor, reduced disease activity, flares, and steroid use in patients with seropositive systemic lupus erythematosus (SLE): BLISS-52 study. Lupus Conference: 19 (Suppl 1): 12-13. |
| 22 | | | U-996 | Jolly M, Annapureddy N. Arnaud L. Devilliers H. (2019) Changes in quality of life in relation to disease activity in systemic lupus erythematosus: post-hoc analysis of the BLISS-52 Trial. Lupus 28 (14): 1628. |
| 23 | BLISS-76 | NCT00410384 | 1329 | *Furie R, Petri M, Zamani O, Cervera R, Wallace DJ et al. (2011) A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis and Rheumatism 63 (12): 3918-3930. |
| 24 | | | 5124 | van Vollenhoven RF, Zamani O, Wallace D, Tegzova D, Petri M et al. (2011) Belimumab reduced disease activity in patients with SLE: BLISS-76. Lupus Conference: 20 (4): 349. |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| 25 | | | 5345 | Petri M, van Vollenhoven RF, Zamani O, Furie RA, Tegzova D et al. (2010) Belimumab, a BLyS-specific inhibitor, reduces disease activity and severe flares in seropositive systemic lupus erythematosus (SLE) patients: BLISS-76 study. International Journal of Rheumatic Diseases Conference: 13 (Suppl 1): 111-112. |
| 26 | Pooled analyses of BLISS-52 and BLISS-76 | NCT00424476 NCT00410384 | 458 | Schwarting A, Dooley MA, Roth DA, Edwards L, Thompson A et al. (2016) Impact of concomitant medication use on belimumab efficacy and safety in patients with systemic lupus erythematosus. Lupus 25 (14): 1587-1596. |
| 27 | | | 503 | van Vollenhoven RF, Petri M, Wallace DJ, Roth DA, Molta CT et al. (2016) Cumulative Corticosteroid Dose Over Fifty-Two Weeks in Patients with Systemic Lupus Erythematosus: Pooled Analyses From the Phase III Belimumab Trials. Arthritis rheumatol 68 (9): 2184-2192. |
| 28 | | | 4534 | van Vollenhoven RF, Petri M, Wallace DJ, Roth D, Molta CT et al. (2013) Corticosteroid use across 52 weeks of belimumab therapy in patients with systemic lupus erythematosus: Combined analyses from the bliss trials. Arthritis and Rheumatism Conference: 65 (Suppl 10): S672. |
| 29 | | | 952 | Strand V, Levy RA, Cervera R, Petri MA, Birch H et al. (2014) Improvements in health-related quality of life with belimumab, a B-lymphocyte stimulator-specific inhibitor, in patients with autoantibody-positive systemic lupus erythematosus from the randomised controlled BLISS trials. Annals of the Rheumatic Diseases 73 (5): 838-844. |
| 30 | | | 1266 | van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN et al. (2012) Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Annals of the Rheumatic Diseases 71 (8): 1343-1349. |
| 31 | | | 4048 | Furie R, Petri MA, Strand V, Gladman DD, Zhong ZJ et al. (2014) Clinical, laboratory and health-related quality of life correlates of Systemic Lupus Erythematosus Responder Index response: A post hoc analysis of the phase 3 belimumab trials. Lupus Science and Medicine 1 (1). |
| 32 | | | 5072 | Furie RA, Zhong ZJ, Freimuth W, Petri M (2011) Clinical and laboratory correlates in responders (by the systemic lupus erythematosus responder index) in phase 3 belimumab clinical trials. Arthritis and Rheumatism Conference: 63 (10 Suppl 1). |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| 33 | | | 4565 | D'Cruz D, Gladman D, Navarra SV, Sanchez-Guerrero J, Manzi S et al. (2013) Post-HOC british isles lupus assessment group index musculoskeletal organ domain analysis of systemic lupus erythematosus patients in phase 3 belimumab trials. Lupus Conference: 22 (1): 106. |
| 34 | | | 4834 | Petri MA, van Vollenhoven RF, Levy, Sr., Navarra SV, Cervera R et al. (2012) Baseline laboratory characteristics from the combined placebo groups in the phase 3 belimumab trials are predictive of severe flare at 52 weeks. Arthritis and Rheumatism Conference: 64 (Suppl 10): S266-S267. |
| 35 | | | 4835 | van Vollenhoven RF, Petri MA, Levy RA, Navarra SV, Buyon JP et al. (2012) Predictors of systemic lupus erythematosus flares: Baseline disease activity and demographic characteristics from the combined placebo groups in the phase 3 belimumab trials. Arthritis and Rheumatism Conference: 64 (Suppl 10): S266. |
| 36 | | | 4859 | Doria A, Petri M, Sanchez-Guerrero J, Tegzova D, Ginzler EM et al. (2012) Early clinically meaningful improvement in SLE patients treated with belimumab. International Journal of Rheumatic Diseases Conference: 15 (Suppl 1): 73. |
| 37 | | | 1230 | Manzi S, Sanchez-Guerrero J, Merrill JT, Furie R, Gladman D et al. (2012) Effects of belimumab, a B lymphocyte stimulator-specific inhibitor, on disease activity across multiple organ domains in patients with systemic lupus erythematosus: combined results from two phase III trials. Annals of the Rheumatic Diseases 71 (11): 1833-1838. |
| 38 | | | 5044 | Manzi S, Gladman D, Navarra S, Sanchez-Guerrero J, D'Cruz D et al. (2011) Post hoc british isles lupus assessment group index mucocutaneous organ domain item analysis of systemic lupus erythematosus patients treated in phase 3 belimumab clinical trials. Arthritis and Rheumatism Conference: 63 (10 Suppl 1). |
| 39 | | | 5042 | Strand V, Cooper S, Zhong ZJ, Dennis G (2011) Responders in the phase 3 belimumab clinical trials in patients with systemic lupus erythematosus reported improvements in fatigue and health-related quality of life at week 52. Arthritis and Rheumatism Conference: 63 (10 Suppl 1). |
| 40 | | | 5062 | van Vollenhoven RF, Petri M, Cervera R, Kleoudis C, Zhong ZJ et al. (2011) Factors associated with belimumab treatment benefit: Results |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| | | | | from phase 3 studies in patients with systemic lupus erythematosus. Arthritis and Rheumatism Conference: 63 (10 Suppl 1). |
| 41 | | | 1127 | Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase A et al. (2013) Effect of belimumab treatment on renal outcomes: results from the phase 3 belimumab clinical trials in patients with SLE. Lupus 22 (1): 63-72. |
| 42 | | | 5068 | Dooley MA, Houssiau F, Aranow C, D'Cruz DP, Askanase AD et al. (2011) Effect of belimumab treatment on renal outcomes: Results from phase 3 belimumab clinical trials in patients with systemic lupus erythematosus. Arthritis and Rheumatism Conference: 63 (10 Suppl 1). |
| 43 | | | 5109 | van Vollenhoven RF, Gallacher A, Navarra S, Ginzler EM, Dooley MA et al. (2011) Belimumab reduced corticosteroid use in patients with SLE: Results from phase 3 BLISS-52 and BLISS-76 studies. Lupus Conference: 20 (4): 426. |
| 44 | | | 5122 | van Vollenhoven RF, Petri M, Cervera R, Kleoudis C, Roth D et al. (2011) Efficacy of belimumab in active SLE patients with low complement as well as positive anti-dsDNA or receiving corticosteroids: BLISS-52/BLISS-76. Lupus Conference: 20 (4): 351. |
| 45 | | | 1134 | Wallace DJ, Navarra S, Petri MA, Gallacher A, Thomas M et al. (2013) Safety profile of belimumab: pooled data from placebo-controlled phase 2 and 3 studies in patients with systemic lupus erythematosus. Lupus 22 (2): 144-154. |
| 46 | | | U-2526 | Wilkinson C, Henderson R. B. Jones-Leone A. R. Flint S. M. Lennon M. Levy R. A. Ji B. Bass D. L. Roth D. (2020) The role of baseline BLyS levels and type 1 interferon-inducible gene signature status in determining belimumab response in systemic lupus erythematosus: a post hoc meta-analysis. Arthritis research & therapy 22 (1): |
| 47 | | | U-797 | Gomez A, Soukka S. Johansson P. Akerstrom E. Emamikia S. Enman Y. Chatzidionysiou K. Parodis I. (2020) Use of antimalarial agents is associated with favourable physical functioning in patients with systemic lupus erythematosus. Journal of clinical medicine 9 (6): 1. |
| 48 | | | U-1951 | Parodis I, Gomez A. Emamikia S. Chatzidionysiou K. (2019) Established organ damage reduces belimumab efficacy in systemic lupus erythematosus. Annals of the rheumatic diseases 78 (7): 1006. |
| 49 | | | U-58 | Oon, S., Huq, M., Golder, V., Ong, P.X., Morand, E.F. (2019) Lupus Low Disease Activity State (LLDAS) discriminates responders in the BLISS-52 |

| | Trial Name | NCT# | RefID | Citations |
|---|---|---|---|---|
| | | | | and BLISS-76 phase III trials of belimumab in systemic lupus erythematosus. Lupus Low Disease Activity State (LLDAS) discriminates responders in the BLISS-52 and BLISS-76 phase III trials of belimumab in systemic lupus erythematosus |
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## Table A8. Excluded references

| Studies excluded at full-text review | n = 243 |
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### Quality assessment

Risk of bias was assessed for 19 eligible RCTs at the study level using the NICE Quality appraisal checklist of quantitative intervention studies. The table below reports the summary internal and external validity scores for each assessed study.

| Questions | 5.1 Are the study results internally valid (i.e. unbiased)? | 5.2 Are the findings generalisable to the source population (i.e. externally valid)? |
|---|---|---|
| Response options | (++/+/–/NR/NA) | (++/+/–/NR/NA) |
| MUSE: NCT01438489 | ++ | ++ |
| ADDRESS II: NCT01972568 | + | ++ |
| BLISS-52: NCT00424476 | ++ | ++ |
| BLISS-76: NCT00410384 | ++ | ++ |
| BLISS-SC: NCT01484496 | ++ | + |
| BEL113750: NCT01345253 | + | ++ |
| APRIL-SLE: NCT00624338 | + | ++ |
| EXPLORER: NCT00137969 | + | ++ |
| ROSE: NCT00962832 | ++ | ++ |
| Zimmer 2013 | + | + |
| NCT00119678 | + | ++ |
| Yahya 2013 | + | - |
| Fortin 2008 | + | ++ |
| Griffiths 2010 | + | + |
| Mackworth-Young 1988 | - | - |
| TULIP-1: NCT02446912 | ++ | ++ |
| TULIP-2: NCT02446899 | ++ | ++ |
| NCT02349061 | ++ | ++ |
| NCT02962960 | + | ++ |

### Unpublished data

The indirect treatment comparison presented in this dossier includes anifrolumab data from clinical study reports of randomised controlled trials. Not all of these outcomes have been published but were necessary to include in order to match the outcomes presented for belimumab.

Data specific to time on treatment was used from the clinical study report of the MUSE open-label extension study for the economic model.

Disease state data from two Swedish registry-based real world evidence studies, Health-Related Quality of Life in Patients with Systemic Lupus Erythematosus (SLE) in Sweden (KLURING) and Observational Population Based Study of Disease Burden, Treatment Pattern, Comorbidities and Healthcare Resource Utilization of Systemic Lupus Erythematosus Patients in Sweden (SLURP), were used in this dossier and are referenced as data on file. A manuscript for each study is in development and should be published by the end of 2022.

# Appendix B. Main characteristics of included studies

| **Trial name:** Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-2) | **NCT number:** NCT02446899 |
|---|---|
| **Objective** | The purpose of this study is to evaluate the efficacy and safety of an intravenous treatment regimen of anifrolumab versus placebo in adult participants with moderately to severely active, autoantibody-positive systemic lupus erythematosus (SLE). |
| **Publication** | Morand EF, Furie R, Tanaka Y, Bruce IN, Askanase AD, Richez C, Bae SC, Brohawn PZ, Pineda L, Berglind A, Tummala R; TULIP-2 Trial Investigators. Trial of Anifrolumab in Active Systemic Lupus Erythematosus. N Engl J Med. 2020 Jan 16;382(3):211-221. |
| **Study type and design** | Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial. Enrolled patients were randomly assigned 1:1 to receive intravenous infusions of placebo or anifrolumab (300 mg) every 4 weeks for 48 weeks. Randomization was stratified according to the SLEDAI-2K score at screening (<10 or ≥10), baseline glucocorticoid dose (<10 mg per day or ≥10 mg per day of prednisone or equivalent), and type I interferon gene signature (high or low). |
| **Sample size (n)** | 365 patients underwent randomization (181 to anifrolumab and 184 to placebo).<br><br>The modified intention-to-treat population included patients who underwent randomization and received at least one dose of anifrolumab or placebo (180 to anifrolumab and 182 to placebo). |

**Main inclusion and exclusion criteria**

Inclusion Criteria:

1. Aged 18 through 70 years at the time of screening
2. Diagnosis of paediatric or adult SLE with a diagnosis of SLE according to the ACR 1982 revised criteria ≥24 weeks prior to signing the Informed Consent form (ICF)
3. Currently receiving at least 1 of the following:
    a. Where prednisone is the single standard of care medication (ie, the subject is not concurrently receiving any medication listed in inclusion criterion 3(c)), a dose of oral prednisone ≥7.5 mg/day but ≤40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to Day 1. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation
    b. Where prednisone is not the single standard of care medication (ie, the subject is concurrently receiving at least one medication listed in inclusion criterion 3(c), a dose of oral prednisone (≤40 mg/day) (or prednisone equivalent) for a minimum of 2 weeks prior to signing of the ICF. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation.
    c. Any of the following medications administered for a minimum of 12 weeks prior to signing the informed consent, and at a stable dose for a minimum of 8 weeks prior to signing the informed consent and through Day 1:
    (i) Azathioprine ≤200 mg/day (ii) Antimalarial (eg, chloroquine, hydroxychloroquine, quinacrine) (iii) Mycophenolate mofetil ≤2 g/day or mycophenolic acid ≤1.44 g/day (iv) Oral, subcutaneous (SC), or intramuscular methotrexate ≤25 mg/week (v) Mizoribine ≤150 mg/day
4. Fulfils at least 4 of the 11 ACR modified 1982 classification criteria for SLE, at least 1 of which must be:
    a. Positive antinuclear antibody (ANA) test at screening by immunofluorescent assay (IFA) at the central laboratory with titre ≥1:80; OR
    b. Anti-dsDNA antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; OR
    c. Anti-Smith (anti-Sm) antibody at screening elevated to above normal as per the central laboratory
5. At Screening, Disease Activity Adjudication Group confirmation of:
SLEDAI-2K Criteria: SLEDAI-2K score ≥6 points and "Clinical" SLEDAI-2K score ≥4 points. The "Clinical" SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures.
6. Must not have active or latent TB on either chest radiograph or by quantiferon gold test
7. Day 1 "Clinical" SLEDAI-2K score ≥4 points
8. OCS dose stable for at least 2 weeks prior to randomisation
9. Stable SLE SOC treatment at the time of randomisation
10. Women of child-bearing potential must have a negative serum β-hCG test at and negative urine pregnancy test at randomisation prior to administration of investigational product

Exclusion Criteria:

1. Receipt of any investigational product (small molecule or biologic agent) within 4 weeks or 5 half-lives prior to signing of the ICF, whichever is greater
2. Receipt of any of the following: Intra-articular, intramuscular or IV glucocorticosteroids within 6 weeks prior to Day 1
3. History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome.
4. Active severe or unstable neuropsychiatric SLE
5. Active severe SLE-driven renal disease
6. Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE or SSc.
7. History of, or current, inflammatory joint or skin disease other than SLE
8. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than 2 weeks within the last 24 weeks prior to signing the ICF

| **Trial name:** Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-2) | **NCT number:** NCT02446899 |
|---|---|
| | 9. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the subject to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at screening. Subjects refusing HIV testing during the screening period will not be eligible for study participation<br>10. Confirmed positive test for hepatitis B or hepatitis C<br>11. Any severe herpes infection at any time prior to Week 0 (Day 1)<br>12. Opportunistic infection requiring hospitalisation or intravenous antimicrobial treatment within 3 years prior to randomization<br>13. History of cancer, apart from:<br>a. Squamous or basal cell carcinoma of the skin that has been successfully treated<br>b. Cervical cancer in situ that has been successfully treated |
| **Intervention** | Anifrolumab 300 mg every 4 weeks for 48 weeks. There were 181 patients randomly assigned to receive anifrolumab. |
| **Comparator(s)** | Placebo intravenous injections every 4 weeks for 48 weeks. There were 184 patients randomly assigned to receive placebo. |
| **Follow-up time** | 52 weeks |
| **Is the study used in the health economic model?** | Yes |

**Primary, secondary and exploratory endpoints**

Primary Endpoint:

Proportion of patients who achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at week 52 [Time Frame: Baseline; Week 52]

*Composite endpoint BICLA was defined by meeting all of the following criteria:*

- Reduction of all baseline British Isles Lupus Assessment Group (BILAG)-2004 A to B/C/D and baseline BILAG-2004 B to C/D, and no BILAG-2004 worsening in other organ systems, as defined by ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B
- No worsening from baseline in Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K), where worsening is defined as an increase from baseline of >0 points in SLEDAI-2K
- No worsening from baseline in participants' lupus disease activity, where worsening is defined by an increase ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)
- No discontinuation of investigational product
- No use of restricted medications beyond the protocol allowed threshold before assessment

Key Secondary Endpoints:

1. Proportion of patients who achieved the BICLA Response at week 52 in the IFN Test-High Sub-group [Time Frame: Baseline; Week 52]
2. Proportion of patients who achieved and maintained an Oral Corticosteroids (OCS) dose of ≤7.5 mg/Day at week 52 in the sub-group of patients with baseline OCS ≥10 mg/Day [Time Frame: Week 40; Week 52]

   *Maintained OCS reduction was defined by meeting all of the following criteria:*

   a. Achieve an OCS dose of ≤7.5 mg/day prednisone or equivalent by Week 40
   b. Maintain an OCS dose ≤7.5 mg/day prednisone or equivalent from Week 40 to Week 52
   c. No discontinuation of investigational product
   d. No use of restricted medications beyond the protocol allowed threshold before assessment
3. Proportion of patients with a ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) Activity Score at Week 12 in the sub-group of patients with baseline CLASI Activity Score of ≥10 [Time Frame: Baseline; Week 12]

   *50% reduction in CLASI activity score compared to baseline was defined by meeting all of the following criteria:*

   a. Achieve ≥50% reduction of CLASI activity score at Week 12 compared to baseline
   b. No discontinuation of investigational product
   c. No use of restricted medications beyond the protocol allowed threshold before assessment
4. Proportion of patients with a ≥50% reduction in Joint Counts at Week 52 in the sub-group of participants with ≥6 Swollen and ≥6 Tender Joints at baseline [Time Frame: Baseline; Week 52]

   *50% reduction in the number of swollen and tender joints compared to baseline was defined by meeting all of the following criteria:*

   a. Achieve ≥50% reduction from baseline in the number of swollen and tender joints, separately
   b. No discontinuation of investigational product



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c. No use of restricted medications beyond the protocol allowed threshold before assessment

5. Annualised Flare Rate Through 52 Weeks [Time Frame: Baseline to Week 52]

   A flare was defined as either 1 or more new British Isle Lupus Assessment Group (BILAG-2004) A or 2 or more new BILAG-2004 B items compared to the previous visit. The occurrence of a new flare was checked for each available visit versus the previous available visit up to Week 52. If no new flares occurred, the number of flares was set to 0. Otherwise all flares were counted leading to the maximum number of flares of 13. The annualized flare rate was calculated as the number of flares divided by the flare exposure time in days multiplied with 365.25 (1 year). The flare exposure time is the time up to Week 52 (date of BILAG-2004 assessment at Week 52) or up to the date of last available BILAG-2004 assessment.

Other Secondary Endpoints:

1. Proportion of patients who achieved a Systemic Lupus Erythematosus (SLE) Responder Index ≥4 (SRI[4]), as well as SRI[5], SRI[6], SRI[7], and SRI[8] at Week 52.

   *SRI(4) response was defined as meeting all of the following criteria:*

   - Reduction from baseline of ≥4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)*
   - No new organ systems affected, defined by 1 or more British Isles Lupus Assessment Group (BILAG-2004) A or 2 or more BILAG-2004 B items
   - No worsening from baseline in participants lupus disease activity. Worsening was defined as an increase of ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)
   - No discontinuation of investigational product and no use of restricted medications beyond the pre-specified analysis threshold

*SRI(5), SRI(6), SRI(7), and SRI(8) responses are defined similarly to SRI(4) response with the exception that the point reduction in SLEDAI-2K score is ≥5, ≥6, ≥7, or ≥8 for SRI(5), (6), (7), and (8), respectively.

2. Numbers of swollen and tender joints at week 52
3. ≥50% reduction at week 52 in both swollen and tender joint counts in patients with ≥8 swollen and ≥8 tender joints at baseline
4. Change in Systemic Lupus International Collaborating Clinics/American College of Rheumatology Damage Index (SDI) global score at week 52
5. Resolution of involvement in SLEDAI-2K organ systems at week 52 in those with involvement at baseline (%)
6. Major clinical response (BILAG-2004 C scores or better at week 24, no new A or B scores weeks 24 to 52)
7. Partial clinical response (BILAG-2004 max. 1 B score or better at week 24, no new A score, and max. 1 new B score from weeks 24 to 52)
8. ≥50% reduction in Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) activity score from baseline to week 52 in patients with CLASI score ≥10 at baseline
9. Active (swollen plus tender) joint count, change from baseline to week 52
10. Physician's Global Assessment (PGA) score change from baseline to week 52
11. Short Form 36 Health Survey (SF-36-v2) Physical Component Summary (PCS) score responders at week 52
12. SF-36-v2 Mental Component Summary (MCS) score responders at week 52
13. Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT–F) responders at week 52
14. ≥20% reduction in both swollen and tender joints at week 52 among patients with ≥8 swollen and ≥8 tender joints at baseline
15. Change from baseline in pain numeric rating scale score at week 52
16. Change from baseline in Patient Global Assessment score at week 52
17. Change from baseline in European Quality of Life 5 dimensions (EQ-5D-5L) visual analog scale (VAS) score at week 52
18. Change from baseline in EQ-5D-5L utility index at week 52



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| **Trial name:** Efficacy and Safety of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-2) | **NCT number:** NCT02446899 |
|---|---|

| | |
|---|---|
| | Safety Assessments:<br>1. Adverse events<br>2. Serious adverse events<br>3. Adverse events of special interest<br>o non-opportunistic serious infections<br>o opportunistic infections<br>o anaphylaxis<br>o malignancy<br>o herpes zoster<br>o tuberculosis [including latent tuberculosis]<br>o influenza<br>o non–SLE-related vasculitis<br>o adjudicated major adverse cardiac events<br>4. Clinical laboratory assessments<br>5. Vital signs<br>6. Electrocardiograms<br>7. Physical examination<br><br>**Endpoints included in this application:**<br><br>The primary endpoint was BICLA response at week 52. Secondary endpoints were BICLA response at week 52 in the IFN Test-High Sub-group, reduction in OCS dose to ≤7.5 mg/Day from Weeks 40 to 52, ≥50% Reduction in CLASI at Week 12, ≥50% Reduction in Joint Counts at Week 52, annualized flare rate at Week 52, and Safety.<br><br>**Other endpoints:**<br><br>Number of Participants Who Achieved a SRI[4]), SRI[5], SRI[6], SRI[7], and SRI[8] at Week 52 are not included in this application. |
| **Method of analysis** | Efficacy analyses included all the patients who underwent randomization and who received at least one dose of anifrolumab or placebo (modified intention-to-treat population).<br><br>The primary end point compared the percentage of patients having a BICLA response at week 52 in the anifrolumab group and in the placebo group with the use of a stratified Cochran‑Mantel‑Haenszel test, with strata corresponding to the stratification factors used for randomization (SLEDAI-2K score, baseline glucocorticoid dose, and type I interferon gene signature). Key secondary end points were analyzed similarly, except the flare rate, which was analyzed with the use of a negative binomial regression model. |
| **Subgroup analyses** | Prespecified subgroup analysis of BICLA response was conducted for the following subgroups:<br>• SLEDAI-2K score at screening (<10 and ≥10)<br>• Glucocorticoid dosage at baseline (<10 mg/day and ≥10 mg/day)<br>• Result of Type 1 IFN test (high and low)<br>• Sex<br>• Age<br>• BMI<br>• Race<br>• Ethnicity<br>• Baseline anti-dsDNA, C3 and C4 |

| **Trial name:** Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-1) | **NCT number:** NCT02446912 |
|---|---|
| **Objective** | The purpose of this study is to evaluate the efficacy and safety of an intravenous treatment regimen of two doses of anifrolumab versus placebo in adult subjects with moderately to severely active, autoantibody-positive systemic lupus erythematosus (SLE). |
| **Publication** | Furie RA, Morand EF, Bruce IN, et al. Type I interferon inhibitor anifrolumab in active systemic lupus erythematosus (TULIP-1): a randomised, controlled, phase 3 trial. Lancet Rheumatol. 2019;1(4): e208-e219. |
| **Study type and design** | Phase 3, multicentre, multinational, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of an intravenous treatment regimen of two doses of anifrolumab versus placebo in subjects with moderately to severely active, autoantibody-positive systemic lupus erythematosus (SLE) while receiving standard of care (SoC) treatment.<br><br>Enrolled patients were randomly assigned 2:1:2 to receive intravenous infusions of anifrolumab 300 mg, anifrolumab 150 mg or placebo, in addition to SoC treatment, every 4 weeks for 48 weeks. Final assessment occurred at 52 weeks. |
| **Sample size (n)** | 457 patients underwent randomization (180 to anifrolumab 300 mg, 93 to anifrolumab 150 mg, and 184 to placebo).<br><br>All 457 patients received at least one dose of anifrolumab or placebo and were included in the full analysis set. |

**Main inclusion and exclusion criteria**

Inclusion Criteria:

1. Aged 18 through 70 years at the time of screening
2. Diagnosis of paediatric or adult SLE with a diagnosis of SLE according to the ACR 1982 revised criteria ≥24 weeks prior to signing the Informed Consent form (ICF)
3. Currently receiving at least 1 of the following:
    - Where prednisone is the single standard of care medication (ie, the subject is not concurrently receiving any medication listed in inclusion criterion 3(c)), a dose of oral prednisone ≥7.5 mg/day but ≤40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to Day 1. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation
    - Where prednisone is not the single standard of care medication (ie, the subject is concurrently receiving at least one medication listed in inclusion criterion 3(c), a dose of oral prednisone (≤40 mg/day) (or prednisone equivalent) for a minimum of 2 weeks prior to signing of the ICF. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation
    - Any of the following medications administered for a minimum of 12 weeks prior to signing the informed consent, and at a stable dose for a minimum of 8 weeks prior to signing the informed consent and through Day 1:
        - (i) Azathioprine ≤200 mg/day (ii) Antimalarial (eg, chloroquine, hydroxychloroquine, quinacrine) (iii) Mycophenolate mofetil ≤2 g/day or mycophenolic acid ≤1.44 g/day (iv) Oral, subcutaneous (SC), or intramuscular methotrexate ≤25 mg/week (v) Mizoribine ≤150 mg/day
4. Fulfils at least 4 of the 11 ACR modified 1982 classification criteria for SLE, at least 1 of which must be:
    - Positive antinuclear antibody (ANA) test at screening by immunofluorescent assay (IFA) at the central laboratory with titre ≥1:80; OR
    - Anti-dsDNA antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; OR
    - Anti-Smith (anti-Sm) antibody at screening elevated to above normal as per the central laboratory
5. At Screening, Disease Activity Adjudication Group confirmation of:
    - SLEDAI-2K Criteria: SLEDAI-2K score ≥6 points and "Clinical" SLEDAI-2K score ≥4 points. The "Clinical" SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures.
6. Must not have active or latent TB on either chest radiograph or by quantiferon gold test
7. Day 1 "Clinical" SLEDAI-2K score ≥4 points
8. OCS dose stable for at least 2 weeks prior to randomisation
9. Stable SLE SOC treatment at the time of randomisation
10. Women of child-bearing potential must have a negative serum β-hCG test at and negative urine pregnancy test at randomisation prior to administration of investigational product

Exclusion Criteria:

1. Receipt of any investigational product (small molecule or biologic agent) within 4 weeks or 5 half-lives prior to signing of the ICF, whichever is greater
2. Receipt of any of the following: Intra-articular, intramuscular or IV glucocorticosteroids within 6 weeks prior to Day 1
3. History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome.
4. Active severe or unstable neuropsychiatric SLE
5. Active severe SLE-driven renal disease
6. Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE or SSc
7. History of, or current, inflammatory joint or skin disease other than SLE
8. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than 2 weeks within the last 24 weeks prior to signing the ICF

| **Trial name:** Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-1) | **NCT number:** NCT02446912 |
|---|---|
| | 9. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the subject to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at screening. Subjects refusing HIV testing during the screening period will not be eligible for study participation<br>10. Confirmed positive test for hepatitis B or hepatitis C<br>11. Any severe herpes infection at any time prior to Week 0 (Day 1)<br>12. Opportunistic infection requiring hospitalisation or intravenous antimicrobial treatment within 3 years prior to randomization<br>13. History of cancer, apart from:<br>14. Squamous or basal cell carcinoma of the skin that has been successfully treated<br>15. Cervical cancer in situ that has been successfully treated |
| **Intervention** | Anifrolumab 300 mg or 150 mg every 4 weeks for 48 weeks. There were 180 patients randomly assigned to receive anifrolumab 300 mg and 93 patients randomly assigned to receive anifrolumab 150 mg. All patients received at least one dose of anifrolumab. |
| **Comparator(s)** | Placebo intravenous injections every 4 weeks for 48 weeks. There were 184 patients randomly assigned to receive placebo, and all patients received at least one dose of placebo. |
| **Follow-up time** | 52 weeks |
| **Is the study used in the health economic model?** | Yes |



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**Primary, secondary and exploratory endpoints**

Primary Endpoint:

Proportion of patients who achieved a Systemic Lupus Erythematosus (SLE) Responder Index ≥4 (SRI[4]) at Week 52.

*SRI(4) response was defined as meeting all of the following criteria:*

- Reduction from baseline of ≥4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)
- No new organ systems affected, defined by 1 or more British Isles Lupus Assessment Group (BILAG-2004) A or 2 or more BILAG-2004 B items
- No worsening from baseline in participants lupus disease activity. Worsening was defined as an increase of ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)
- No discontinuation of investigational product and no use of restricted medications beyond the pre-specified analysis threshold.

Key Secondary Endpoints (adjusted for multiplicity):

1. Proportion of patients with high interferon gene signature at baseline who achieved SRI(4) response at week 52
2. Proportion of patients on ≥10 mg/day OCS at baseline who achieved a sustained dose reduction to ≤7.5 mg/day from week 40 to 52
3. Proportion of patients with a Cutaneous lupus disease area and severity index (CLASI), activity of ≥10 at baseline who achieved a ≥50% reduction in CLASI score by week 12
4. Proportion of patients who achieved SRI(4) response at week 24
5. Annualised flare rate through week 52 (flare was defined as ≥1 new BILAG-2004 A or ≥2 new BILAG-2004 B organ domains scores vs the previous visit)

Prespecified Secondary Endpoints (not adjusted for multiplicity):

1. Proportion of patients who achieved the British Isles Lupus Assessment Group Based Composite Lupus Assessment (BICLA) Response at Week 52.
2. Proportion of patients who achieved a Systemic Lupus Erythematosus (SLE) Responder Index ≥5-8 (SRI[5-8]) at Week 52.
3. Mean change from baseline in PGA score
4. Mean change from baseline in SLEDAI-2K total score and the proportion of patients with improvement from baseline
5. Mean BILAG global score and proportion of patients with BILAG-2004 (A and B) by organ system
6. Mean change from baseline in active, swollen, and tender joint count and the proportion of responders (20% and 50% reduction from baseline)
7. Proportion of patients who achieved at least a 50% reduction from baseline in CLASI

Other Secondary Endpoints:

1. SLEDAI-2K and BILAG-2004 organ system scores
2. Major and partial clinical responses
3. SDI global score at week 52
4. SF-36 (v2) outcomes
5. FACIT-F
6. Pain numeric rating scale
7. Patient global assessment
8. LUPUS quality-of-life scale
9. European quality of life five dimensions assessment

Safety Assessments:

1. Adverse events
2. Serious adverse events
3. Adverse events of special interest
    - non-opportunistic serious infections
    - opportunistic infections
    - anaphylaxis

| **Trial name:** Efficacy and Safety of Two Doses of Anifrolumab Compared to Placebo in Adult Subjects With Active Systemic Lupus Erythematosus (TULIP-1) | **NCT number:** NCT02446912 |
|---|---|

- malignancy
- herpes zoster
- tuberculosis [including latent tuberculosis]
- influenza
- non–SLE-related vasculitis
- adjudicated major adverse cardiac events

4. Clinical laboratory assessments
5. Vital signs
6. Electrocardiograms
7. Physical examination

**Endpoints included in this application:**

The primary endpoint was the proportion of patients who achieved SRI[4] response at week 52. Secondary endpoints were BICLA response at week 52, reduction in OCS dose to ≤7.5 mg/Day from weeks 40 to 52, ≥50% Reduction in CLASI at Week 12, ≥50% reduction in joint counts at weel 52, annualized flare rate at week 52, and Safety.

**Other endpoints:**

| | |
|---|---|
| **Method of analysis** | Efficacy analyses included all the patients who underwent randomization and who received at least one dose of anifrolumab or placebo (modified intention-to-treat population).<br><br>The primary endpoint was assessed using a stratified Cochran-Mantel-Haenszel test with the same stratification factors used at randomisation. To adjust for stratification factors, the Cochran-Mantel-Haenszel method uses a weighted average across strata of the stratum-specific difference in proportions, where the strata are defined on the basis of the eight possible combinations of the three factors. Key secondary endpoints were analysed similarly, except flare rate, which was analysed using a negative binomial regression model. A weighted Holm procedure with pre-established weights was used to control the familywise type I error rate at 0.05 across the primary and key secondary endpoints. This procedure splits the $\alpha$ of 0.05 according to predefined weights and, after initial null hypothesis rejections, recycles the corresponding $\alpha$ in proportion to these weights. |
| **Subgroup analyses** | Prespecified subgroup analysis of BICLA response was conducted for the following subgroups:<br>• SLEDAI-2K score at screening (<10 and ≥10)<br>• Glucocorticoid dosage at baseline (<10 mg/day and ≥10 mg/day)<br>• Result of Type 1 IFN test (high and low)<br>• Sex<br>• Age<br>• BMI<br>• Race<br>• Ethnicity<br>• Baseline anti-dsDNA, C3 and C4 |

| **Trial name:** A study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus (MUSE) | **NCT number:** NCT01438489 |
|---|---|
| **Objective** | The purpose of this study was to evaluate the efficacy and safety of MEDI-546 (anifrolumab) compared to placebo in subjects with chronic, moderately-to-severely active systemic lupus erythematosus (SLE) with an inadequate response to standard of care treatment for SLE. |
| **Publication** | Furie R, Khamashta M, Merrill JT, Werth VP, Kalunian K, Brohawn P, Illei GG, Drappa J, Wang L, Yoo S; CD1013 Study Investigators. Anifrolumab, an Anti-Interferon-α Receptor Monoclonal Antibody, in Moderate-to-Severe Systemic Lupus Erythematosus. Arthritis Rheumatol. 2017 Feb;69(2):376-386. |
| **Study type and design** | Phase 2b, multinational, multicenter, randomized, double-blind, placebo controlled, parallel-group study to evaluate the efficacy and safety of 2 intravenous (IV) treatment regimens in adult participants with chronic, moderately-to-severely active SLE with an inadequate response to standard of care (SoC) SLE. The investigational product (anifrolumab or placebo) will be administered as a fixed dose every 4 weeks (28 days) for a total of 13 doses.<br><br>Enrolled patients were randomized 1:1:1 to receive intravenous infusions of placebo, anifrolumab 300 mg, or anifrolumab 1,000 mg. Treatment was administered every 4 weeks with the final dose administered at week 48. |
| **Sample size (n)** | 307 patients underwent randomization. All but 2 patients received at least one dose of anifrolumab or placebo.<br><br>The modified intent-to-treat population consisted of 305 patients (99 received anifrolumab 300 mg, 104 received anifrolumab 1000 mg, and 102 received placebo). |

**Main inclusion and exclusion criteria**

Inclusion Criteria:

1. Aged 18 through 70 years at the time of screening
2. Diagnosis of paediatric or adult SLE with a diagnosis of SLE according to the ACR 1982 revised criteria ≥24 weeks prior to signing the Informed Consent form (ICF)
3. Currently receiving at least 1 of the following:
    a. Where prednisone is the single standard of care medication (ie, the subject is not concurrently receiving any medication listed in inclusion criterion 3(c)), a dose of oral prednisone ≥7.5 mg/day but ≤40 mg/day (or prednisone equivalent) for a minimum of 8 weeks prior to Day 1. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation
    b. Where prednisone is not the single standard of care medication (ie, the subject is concurrently receiving at least one medication listed in inclusion criterion 3(c), a dose of oral prednisone (≤40 mg/day) (or prednisone equivalent) for a minimum of 2 weeks prior to signing of the ICF. In addition, the dose of oral prednisone or prednisone equivalent the subject is taking must be stable for a minimum of 2 weeks prior to randomisation.
    c. Any of the following medications administered for a minimum of 12 weeks prior to signing the informed consent, and at a stable dose for a minimum of 8 weeks prior to signing the informed consent and through Day 1:
        (i) Azathioprine ≤200 mg/day (ii) Antimalarial (eg, chloroquine, hydroxychloroquine, quinacrine) (iii) Mycophenolate mofetil ≤2 g/day or mycophenolic acid ≤1.44 g/day (iv) Oral, subcutaneous (SC), or intramuscular methotrexate ≤25 mg/week (v) Mizoribine ≤150 mg/day
4. Fulfils at least 4 of the 11 ACR modified 1982 classification criteria for SLE, at least 1 of which must be:
    a. Positive antinuclear antibody (ANA) test at screening by immunofluorescent assay (IFA) at the central laboratory with titre ≥1:80; OR
    b. Anti-dsDNA antibodies at screening elevated to above normal (including indeterminate), as per the central laboratory; OR
    c. Anti-Smith (anti-Sm) antibody at screening elevated to above normal as per the central laboratory
5. At Screening, Disease Activity Adjudication Group confirmation of:
    a. SLEDAI-2K Criteria: SLEDAI-2K score ≥6 points and "Clinical" SLEDAI-2K score ≥4 points. The "Clinical" SLEDAI-2K is the SLEDAI-2K assessment score without the inclusion of points attributable to any urine or laboratory results including immunologic measures.
6. Must not have active or latent TB on either chest radiograph or by quantiferon gold test
7. Day 1 "Clinical" SLEDAI-2K score ≥4 points
8. OCS dose stable for at least 2 weeks prior to randomisation
9. Stable SLE SOC treatment at the time of randomisation
10. Women of child-bearing potential must have a negative serum β-hCG test at and negative urine pregnancy test at randomisation prior to administration of investigational product

Exclusion Criteria:

1. Receipt of any investigational product (small molecule or biologic agent) within 4 weeks or 5 half-lives prior to signing of the ICF, whichever is greater
2. Receipt of any of the following:
    (a) Intra-articular, intramuscular or IV glucocorticosteroids within 6 weeks prior to Day 1
3. History of, or current diagnosis of, a clinically significant non SLE-related vasculitis syndrome.
4. Active severe or unstable neuropsychiatric SLE
5. Active severe SLE-driven renal disease
6. Diagnosis (within 1 year of signing the ICF) of mixed connective tissue disease or any history of overlap syndromes of SLE or SSc.

| **Trial name:** A study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus (MUSE) | **NCT number:** NCT01438489 |
|---|---|
| | 7. History of, or current, inflammatory joint or skin disease other than SLE<br>8. History of any non-SLE disease that has required treatment with oral or parenteral corticosteroids for more than 2 weeks within the last 24 weeks prior to signing the ICF<br>9. Known history of a primary immunodeficiency, splenectomy, or any underlying condition that predisposes the subject to infection, or a positive result for human immunodeficiency virus (HIV) infection confirmed by central laboratory at screening. Subjects refusing HIV testing during the screening period will not be eligible for study participation<br>10. Confirmed positive test for hepatitis B or hepatitis C<br>11. Any severe herpes infection at any time prior to Week 0 (Day 1)<br>12. Opportunistic infection requiring hospitalisation or intravenous antimicrobial treatment within 3 years prior to randomization<br>13. History of cancer, apart from:<br>(a) Squamous or basal cell carcinoma of the skin that has been successfully treated<br>(b) Cervical cancer in situ that has been successfully treated |
| **Intervention** | Anifrolumab 300 mg or 1000 mg every 4 weeks for 48 weeks. There were 99 patients who received anifrolumab 300 mg and 104 patients who received anifrolumab 1000 mg. |
| **Comparator(s)** | Placebo intravenous injections every 4 weeks for 48 weeks. There were 102 patients who received placebo. |
| **Follow-up time** | 52 weeks |
| **Is the study used in the health economic model?** | Yes |

| **Trial name:** A study of the Efficacy and Safety of MEDI-546 in Systemic Lupus Erythematosus (MUSE) | **NCT number:** NCT01438489 |
|---|---|
| **Primary, secondary and exploratory endpoints** | Primary Endpoint:<br>Proportion of patients who achieved SRI(4) response at week 24, with sustained OCS reduction (<10 mg/day and less than or equal to the dose at week 1 from week 12 through 24)<br>*SRI(4) response was defined as meeting all of the following criteria:*<br>• Reduction from baseline of ≥4 points in the Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)<br>• No new organ systems affected, defined by 1 or more British Isles Lupus Assessment Group (BILAG-2004) A or 2 or more BILAG-2004 B items<br>• No worsening from baseline in participants lupus disease activity. Worsening was defined as an increase of ≥0.30 points on a 3-point Physician's Global Assessment (PGA) visual analogue scale (VAS)<br>• No discontinuation of investigational product and no use of restricted medications beyond the pre-specified analysis threshold.<br>Key Secondary Endpoints:<br>1. Proportion of patients with high interferon gene signature at baseline who achieved SRI(4) response at week 52 with a sustained OCS reduction from week 40 through 52<br>2. Proportion of patients on ≥10 mg/day OCS at baseline who achieved a sustained dose reduction to ≤7.5 mg/day at week 52<br>Other Efficacy Endpoints:<br>1. Proportion of patients with a CLASI activity of ≥10 at baseline who achieved a ≥50% reduction in CLASI score by week 12<br>2. Proportion of patients with ≥50% improvement in swollen and tender joint count (28 joints assessed) for patients with ≥8 swollen and ≥8 tender joints at baseline<br>3. Response in BILAG-based Composite Lupus Assessment (BICLA)<br>4. Modified SRI response requiring SLEDAI-2K reductions of 5-8 points<br>5. Physician's global assessment<br>6. Proportion of patients with a SLEDAI-2K score of ≤2<br>7. Proportion of patients with a SLEDAI-2K score of 0<br>8. Major clinical response defined as BILAG 2004 score of C or better in all organ domains at week 24 with maintenance of this response through week 52;<br>9. Proportion of patients with a >3-point improvement in FACIT-F<br>10. SF-36 health survey<br>11. Anti-dsDNA, C3 and C4 complement concentrations |
| **Method of analysis** | Efficacy analyses included all the patients who underwent randomization and who received at least one dose of anifrolumab or placebo (modified intention-to-treat population).<br>Analysis of the primary end point compared response rates at week 24 between each anifrolumab group and placebo using a logistic regression model adjusted for randomization stratification factors. The secondary end points and other binary end points were analyzed using the same approach as for the primary end point. Continuous end points were analyzed using an analysis of covariance model adjusted for randomization stratification factors, with the relevant baseline value as the covariate. |
| **Subgroup analyses** | Prespecified subgroup analysis of SRI(4) response (including and excluding OCS taper) at weeks 24 and 52 for the following subgroup:<br>• Result of Type 1 IFN test (high and low) |

| **Trial name:** A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS-76) | **NCT number:** NCT00410384 |
|---|---|
| **Objective** | The purpose of this study is to evaluate the efficacy, safety, tolerability, and impact on quality of life of two different doses of belimumab administered in addition to standard therapy in subjects with active, autoantibody-positive systemic lupus erythematosus (SLE) disease. |
| **Publication** | Furie R, Petri M, Zamani O, Cervera R, Wallace DJ, Tegzová D, Sanchez-Guerrero J, Schwarting A, Merrill JT, Chatham WW, Stohl W, Ginzler EM, Hough DR, Zhong ZJ, Freimuth W, van Vollenhoven RF; BLISS-76 Study Group. A phase III, randomized, placebo-controlled study of belimumab, a monoclonal antibody that inhibits B lymphocyte stimulator, in patients with systemic lupus erythematosus. Arthritis Rheum. 2011 Dec;63(12):3918-30. |
| **Study type and design** | Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial. Enrolled patients were randomly assigned 1:1:1 to receive intravenous infusions of placebo, belimumab 1 mg/kg, or belimumab 10 mg/kg on days 0, 14, 28, and every 28 days thereafter through 72 weeks. Randomization was stratified according to the SELENA-SLEDAI score at screening (6–9 vs. ≥10), proteinuria (<2 gm/24 hours vs. ≥2 gm/24 hours), and race (African or indigenous American descent vs. other). |
| **Sample size (n)** | Analyses were performed in a modified intent-to-treat population, defined as all patients who underwent randomization and received at least one dose of study agent. 826 patients underwent randomization and 819 received at least one dose of study therapy (275 with placebo, 271 with belimumab 1 mg/kg, and 273 with belimumab 10 mg/kg). |
| **Main inclusion and exclusion criteria** | Inclusion Criteria:<br>1. Aged 18 years or older<br>2. Clinical diagnosis of SLE by ACR criteria<br>3. Active SLE disease (SELENA-SLEDAI score ≥6 at screening)<br>4. Autoantibody-positive defined by 2 positive ANA (titre ≥1:80) or anti-dsDNA (≥30 IU/ml) test results, of which ≥1 test result had to be obtained during screening<br>5. On stable SLE treatment regimen for ≥30 days before the first study dose, including prednisone (or equivalent) alone (7.5–40 mg/day) or combined (0–40 mg/day) with antimalarial drugs, non-steroidal anti-inflammatory drugs, and/or immunosuppressive therapies<br><br>Exclusion Criteria:<br>1. Pregnant or nursing<br>2. Have received treatment with any B cell targeted therapy<br>3. Have received treatment with a biologic investigational agent in the past year<br>4. Have received treatment with non-biologic investigational agent in the past 60 days<br>5. Have received IV cyclophosphamide within 180 days of Day 0<br>6. TNF inhibitor, IVIg, prednisone >100 mg/day, or plasmapheresis within 3 months of screening<br>7. Have severe lupus kidney disease<br>8. Have active central nervous system (CNS) lupus<br>9. Have requirement management of acute or chronic infections within the past 60 days<br>10. Have current drug or alcohol abuse or dependence<br>11. Have a historically positive test or test positive at screening for HIV, hepatitis B, or hepatitis C |
| **Intervention** | Belimumab 1 mg/kg IV plus standard therapy; belimumab 1 mg/kg administered on Days 0, 14, 28, and every 28 days thereafter through 72 weeks<br><br>Belimumab 10 mg/kg IV plus standard therapy; belimumab 10 mg/kg administered on Days 0, 14, 28, and every 28 days thereafter through 72 weeks |

| **Trial name:** A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (BLISS-76) | **NCT number:** NCT00410384 |
|---|---|
| **Comparator(s)** | Placebo IV plus standard therapy; placebo administered on Days 0, 14, 28, and every 28 days thereafter through 72 weeks |
| **Follow-up time** | 76 weeks |
| **Is the study used in the health economic model?** | Yes |
| **Primary, secondary and exploratory endpoints** | Primary Endpoint:<br>SLE Responder Index (SRI) Response Rate at Week 52 [Time Frame: Baseline, 52 Weeks]<br>*Composite endpoint SRI was defined by meeting all of the following criteria:*<br>○ ≥ 4 point reduction from baseline in SELENA SLEDAI score compared with baseline<br>○ No worsening (increase of < 0.30 points from baseline) in PGA compared with baseline<br>○ No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline<br>Patients who withdrew from the study or had changes in concomitant medications that were restricted by the protocol were considered treatment failures.<br>Secondary Endpoints:<br>1. SRI Response Rate at Week 76 [Time Frame: Baseline, 76 Weeks]<br>2. Percent of Subjects With a ≥ 4 Point Reduction From Baseline in SELENA SLEDAI Score at Week 52. [Time Frame: Baseline, 52 Weeks]<br>3. Mean Change in Physician's Global Assessment (PGA) at Week 24. [Time Frame: Baseline, 24 Weeks]<br>4. Mean Change From Baseline in Medical Outcomes 36-Item Short Form Health Survey (SF-36) Physical Component Summary Score (PCS) at Week 24. [Time Frame: Baseline, 24 Weeks]<br>5. Percent of Subjects Whose Average Prednisone Dose Has Been Reduced by ≥ 25% From Baseline to ≤ 7.5 mg/Day During Weeks 40 Through 52 [Time Frame: Baseline, Weeks 40-52] |
| **Method of analysis** | Analyses were performed in a modified intent-to-treat population, defined as all patients who underwent randomization and received at least one dose of study agent.<br>The primary efficacy end point compared SRI response rates at week 52 between each belimumab treatment group and the placebo group using a logistic regression model adjusted for baseline randomization stratification factors. Patients who withdrew from the study or had changes in concomitant medications that were restricted by the protocol were considered treatment failures.<br>For secondary end points, analyses of categorical variables were performed using a logistic regression model. Analysis of covariance was used for continuous variables, such as physician's global assessment score changes from baseline to week 24. The analyses were adjusted for baseline stratification factors. |
| **Subgroup analyses** | No subgroup analysis on the BLISS-76 study are included in this application |

| **Trial name:** A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (SLE) (BLISS-52) | **NCT number:** NCT00424476 |
|---|---|
| **Objective** | The purpose of this study is to evaluate the efficacy, safety, tolerability, and impact on quality of life of two different doses of belimumab administered in addition to standard therapy in subjects with active, autoantibody-positive systemic lupus erythematosus (SLE) disease. |
| **Publication** | Navarra SV, Guzmán RM, Gallacher AE, Hall S, Levy RA, Jimenez RE, Li EK, Thomas M, Kim HY, León MG, Tanasescu C, Nasonov E, Lan JL, Pineda L, Zhong ZJ, Freimuth W, Petri MA; BLISS-52 Study Group. Efficacy and safety of belimumab in patients with active systemic lupus erythematosus: a randomised, placebo-controlled, phase 3 trial. Lancet. 2011 Feb 26;377(9767):721-31. |
| **Study type and design** | Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial. Enrolled patients were randomly assigned 1:1:1 to receive intravenous infusions of placebo, belimumab 1 mg/kg, or belimumab 10 mg/kg on days 0, 14, 28, and every 28 days thereafter through Week 48. Randomization was stratified according to the SELENA-SLEDAI score at screening (6–9 vs. ≥10), proteinuria (<2 gm/24 hours vs. ≥2 gm/24 hours), and ethnic origin (African descent or indigenous American vs. other). |
| **Sample size (n)** | 867 patients underwent randomization (288 with placebo, 289 with belimumab 1 mg/kg, and 290 with belimumab 10 mg/kg). |
| **Main inclusion and exclusion criteria** | Inclusion Criteria:<br>1. Aged 18 years or older<br>2. Clinical diagnosis of SLE by ACR criteria<br>3. Active SLE disease (score ≥6 at screening on SELENA-SLEDAI)<br>4. Autoantibody-positive (ANA title ≥1:80 or anti-dsDNA antibody ≥30 IU/mL)<br>5. On stable SLE treatment regimen with fixed doses of prednisone (0–40 mg/day), or non-steroidal anti-inflammatory, antimalarial, or immunosuppressive drugs for at least 30 days before first study dose<br><br>Exclusion Criteria:<br>1. Pregnant or nursing<br>2. Have received treatment with any B cell targeted therapy<br>3. Have received treatment with a biological investigation agent in the past year<br>4. Have received IV cyclophosphamide within 180 days of Day 0<br>5. Have received IV Ig or prednisone (>100 mg/day) within 3 months<br>6. Have severe lupus kidney disease<br>7. Have active central nervous system (CNS) lupus<br>8. Have required management of acute or chronic infections within the past 60 days<br>9. Have current drug or alcohol abuse or dependence<br>10. Have a historically positive test or test positive at screening for HIV, hepatitis B, or hepatitis C |
| **Intervention** | Belimumab 1 mg/kg IV plus standard therapy; belimumab 1 mg/kg administered on Days 0, 14, 28, and every 28 days thereafter through Week 48<br><br>Belimumab 10 mg/kg IV plus standard therapy; belimumab 10 mg/kg administered on Days 0, 14, 28, and every 28 days thereafter through Week 48 |
| **Comparator(s)** | Placebo IV plus standard therapy; placebo administered on Days 0, 14, 28, and every 28 days thereafter through Week 48 |
| **Follow-up time** | 56 weeks |

| **Trial name:** A Study of Belimumab in Subjects With Systemic Lupus Erythematosus (SLE) (BLISS-52) | **NCT number:** NCT00424476 |
|---|---|
| **Is the study used in the health economic model?** | Yes |
| **Primary, secondary and exploratory endpoints** | Primary Endpoint:<br>SLE Responder Index (SRI) Response Rate at Week 52 [Time Frame: Baseline, 52 Weeks]<br>*Composite endpoint SRI was defined by meeting all of the following criteria:*<br>○ ≥ 4 point reduction from baseline in SELENA SLEDAI score compared with baseline<br>○ No worsening (increase of < 0.30 points from baseline) in PGA compared with baseline<br>○ No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline<br>Patients who withdrew from the study or had changes in concomitant medications that were restricted by the protocol were considered treatment failures.<br>Secondary Endpoints:<br>1. Percent of Subjects With a ≥ 4 Point Reduction From Baseline in SELENA SLEDAI Score at Week 52. [Time Frame: Baseline, 52 Weeks]<br>2. Mean Change in Physician's Global Assessment (PGA) at Week 24. [Time Frame: Baseline, 24 Weeks]<br>3. Mean Change From Baseline in Medical Outcomes 36-Item Short Form Health Survey (SF-36) Physical Component Summary Score (PCS) at Week 24. [Time Frame: Baseline, 24 Weeks]<br>4. Percent of Subjects Whose Average Prednisone Dose Has Been Reduced by ≥ 25% From Baseline to ≤ 7.5 mg/Day During Weeks 40 Through 52 [Time Frame: Baseline, Weeks 40-52]<br>Other Endpoints:<br>Adverse events (AE) overview [Time Frame: Up to 56 Weeks] |
| **Method of analysis** | Analysis was done in a modified intent-to-treat population, defined as all randomly assigned patients who received a dose of the study drug.<br>The response rate at week 52 (primary endpoint) was assessed with SRI in each belimumab group and was compared with the placebo group by use of a logistic regression model adjusted for baseline randomization stratification factors. Patients who withdrew or required changes in background drugs for systemic lupus erythematosus that were other than those permitted by protocol were judged to be treatment failures.<br>Binary efficacy variables were assessed with a logistic regression model, continuous variables were analysed with an analysis of covariance model, and time-to-flare variables were analysed by use of a Cox proportional hazards model. All analyses were adjusted for baseline randomisation factors. |
| **Subgroup analyses** | No subgroup analysis on the BLISS-52 study are included in this application |

| **Trial name:** A Study of Belimumab Administered Subcutaneously in Subjects With Systemic Lupus Erythematosus (SLE) (BLISS-SC) | **NCT number:** NCT01484496 |
|---|---|
| **Objective** | The purpose of this study is to evaluate the efficacy, safety and tolerability of belimumab administered subcutaneously (SC) to adult subjects with Systemic Lupus Erythematosus (SLE). |
| **Publication** | Stohl W, Schwarting A, Okada M, Scheinberg M, Doria A, Hammer AE, Kleoudis C, Groark J, Bass D, Fox NL, Roth D, Gordon D. Efficacy and Safety of Subcutaneous Belimumab in Systemic Lupus Erythematosus: A Fifty-Two-Week Randomized, Double-Blind, Placebo-Controlled Study. Arthritis Rheumatol. 2017 May;69(5):1016-1027. |
| **Study type and design** | Phase 3, randomized, double-blind, placebo-controlled, parallel-group trial. Enrolled patients were randomly assigned 2:1 to receive subcutaneous injections of belimumab 200 mg or placebo administered on Days 0 and then weekly through Week 51. Randomization was stratified according to the SELENA-SLEDAI score at screening (≤9 vs. ≥10), complement level (low C3 and/or low C4 vs. other), and race (black vs. non-black). |
| **Sample size (n)** | The intent-to-treat population was defined as all patients who were randomized and received at least 1 dose of study mediciation. 839 patients were randomized and 836 received at least one dose of study therapy (280 with placebo and 556 with belimumab 200 mg). |
| **Main inclusion and exclusion criteria** | Inclusion Criteria:<br>1. At least 18 years of age<br>2. Clinical diagnosis of SLE by ACR criteria<br>3. Active SLE disease (score ≥8 at screening on SELENA-SLEDAI)<br>4. Autoantibody-positive (ANA or anti-dsDNA antibodies)<br>5. On stable SLE treatment regimen which may include corticosteroids (for example, prednisone), antimalarial (for example, hydroxychloroquine), and/or immunosuppressants (for example, azathioprine, methotrexate, mycophenolate, etc.)<br><br>Exclusion Criteria:<br>1. Pregnant or nursing<br>2. Have received treatment with any B cell targeted therapy<br>3. Have received treatment with a biological investigation agent in the past year<br>4. Have received IV cyclophosphamide within 90 days of Day 0<br>5. Have severe active lupus kidney disease<br>6. Have severe active central nervous system (CNS) lupus<br>7. Have required management of acute or chronic infections within the past 60 days<br>8. Have current drug or alcohol abuse or dependence<br>9. Have a positive test for HIV, hepatitis B, or hepatitis C<br>10. Have a history of hypersensitivity reactions to contrast agents or biological medicines |
| **Intervention** | Belimumab 200 mg SC plus standard therapy; belimumab administered on Day 0 and then weekly (ie, every 7 days) through Week 51 |
| **Comparator(s)** | Placebo SC plus standard therapy; placebo administered on Day 0 and then weekly (ie, every 7 days) through Week 51 |
| **Follow-up time** | 52 weeks |
| **Is the study used in the health economic model?** | Yes |

| **Trial name:** A Study of Belimumab Administered Subcutaneously in Subjects With Systemic Lupus Erythematosus (SLE) (BLISS-SC) | **NCT number:** NCT01484496 |
|---|---|
| **Primary, secondary and exploratory endpoints** | Primary Endpoint:<br>Percentage of patients achieving a SLE Responder Index (SRI) Response Rate at Week 52 [Time Frame: Baseline, 52 Weeks]<br>*Composite endpoint SRI was defined by meeting all of the following criteria:*<br>○ ≥ 4 point reduction from baseline in SELENA SLEDAI score compared with baseline<br>○ No worsening (increase of < 0.30 points from baseline) in PGA compared with baseline<br>○ No new BILAG A organ domain score or 2 new BILAG B organ domain scores compared with baseline<br>Patients who withdrew from the study or had changes in concomitant medications that were restricted by the protocol were considered treatment failures.<br>Secondary Endpoints:<br>1. Time to first severe flare (as measured by the modified SLE Flare Index) [Time Frame: Baseline (Day 0, prior to dosing) to Week 52]<br>2. Percentage of patients whose average prednisone dose had been reduced by ≥25% from baseline to ≤7.5 mg/day during Weeks 40 through 52 in patients receiving >7.5 mg/day at baseline [Time Frame: Baseline (Day 0, prior to dosing), Weeks 40 through Week 52] |
| **Method of analysis** | The proportion of patients with an SRI4 response at week 52 was compared between treatment groups using a logistic regression model. Analyses of other efficacy end points (all 2-sided with a significance level of 0.05) were not subjected to a multiple comparison procedure. Patients who withdrew or were deemed to have failed treatment were analyzed as non-responders in the primary analysis. |
| **Subgroup analyses** | No subgroup analysis on the BLISS-SC study are included in this application |

# Appendix C. Baseline characteristics of patients in studies used for the comparative analysis of efficacy and safety

**Table C1. Baseline characteristics of patients in the studies of anifrolumab included for the comparative analysis of efficacy and safety**

| | TULIP-2 | | TULIP-1 | | MUSE | |
|---|---|---|---|---|---|---|
| | Anifrolumab 300 mg (*N* = 180) | Placebo (*N* = 182) | Anifrolumab 300 mg (*N* = 180) | Placebo (*N* = 184) | Anifrolumab 300 mg (*N* = 99) | Placebo (*N* = 102) |
| *Age (years), mean (SD)* | 43.1 (12.0) | 41.1 (11.5) | 42.0 (12.0) | 41.0 (12.3) | 39.1 (11.9) | 39.3 (12.9) |
| *Female, n (%)* | 168 (93.3%) | 170 (93.4%) | 165 (91.7) | 171 (92.9) | 93 (93.9) | 93 (91.2) |
| *Race, n (%)* | | | | | | |
| • *White* | 110 (61.1%) | 107 (58.8) | 125 (69.4) | 137 (74.5) | 35 (35.4) | 41 (40.2) |
| • *Black/African American* | 17 (9.4%) | 25 (13.7%) | 29 (16.1) | 23 (12.5) | 19 (19.2) | 12 (11.8) |
| • *Asian* | 30 (16.7%) | 30 (16.5%) | 11 (6.1) | 5 (2.7) | 3 (3.0) | 13 (12.7) |
| • *Other* | 23 (12.8%) | 20 (11.0%) | 15 (8.3) | 18 (9.8) | 42 (42.4) | 36 (35.3) |
| *Disease duration (years), mean (SD)* | 10.9 (9.1) | 9.0 (8.3) | 9.7 (8.1) | 8.6 (7.5) | 8.0 (6.4) | 7.5 (7.2) |
| *SLEDAI-2K score* | | | | | | |
| • *Mean (SD)* | 11.4 (3.6) | 11.5 (3.9) | 11.3 (4.0) | 11.6 (3.5) | 10.7 (3.7) | 11.1 (4.4) |
| • *≥10, n (%)* | 129 (71.7) | 131 (72.0) | 125 (69.4) | 135 (73.4) | 59 (59.6) | 61 (59.8) |
| *BILAG 1A or 2B score, n (%)* | 172 (95.6) | 173 (95.1) | 172 (95.6) | 168 (91.3) | 93 (93.9) | 97 (95.1) |
| *PGA score, mean (SD)* | 1.7 (0.4) | 1.8 (0.4) | 1.9 (0.4) | 1.8 (0.4) | 1.9 (0.4) | 1.8 (0.4) |
| *CLASI activity score* | | | | | | |
| • *Mean (SD)* | 8.9 (7.9) | 7.6 (7.8) | 8.5 (7.3) | 8.1 (6.7) | 7.5 (6.3) | 6.7 (5.1) |
| • *≥10, n (%)* | 49 (27.2) | 40 (22.0) | 58 (32.2) | 54 (29.3) | 27 (28.3) | 26 (25.5) |
| *Type 1 IFN gene signature high, n (%)* | 150 (83.3) | 151 (83.0) | 148 (82.2) | 151 (82.1) | 75 (75.8) | 76 (74.5) |
| *Receiving prednisone, n (%)* | 141 (78.3) | 151 (83.0) | 150 (83.3) | 153 (83.2) | 79 (79.8) | 88 (86.3) |
| • *Dose (mg/day), mean (SD)* | 8.3 (7.2) | 8.9 (8.0) | 10.7 (11.9) | 9.9 (8.3) | 11.3 (6.4) | 12.8 (8.1) |
| • *>7.5 mg/day, n (%)* | 88 (48.9) | 85 (46.7) | 103 (57.2) | 103 (56.0) | 59 (59.6) | 68 (66.7) |
| • *≥10 mg/day, n (%)* | 87 (48.3) | 83 (45.6) | 103 (57.2) | 102 (55.4) | 59 (59.6) | 64 (62.7) |
| *Receiving immunosuppressant, n (%)* | 88 (48.9) | 86 (47.3) | 85 (47.2) | 91 (49.5) | 51 (51.5) | 46 (45.1) |
| • *Mycophenolate* | 23 (12.8) | 23 (12.6) | 31 (17.2) | 22 (12.0) | 11 (11.1) | 11 (10.8) |
| • *Azathioprine* | 30 (16.7) | 27 (14.8) | 32 (17.8) | 34 (18.5) | 23 (23.2) | 19 (18.6) |
| • *Methotrexate* | 34 (18.9) | 35 (19.2) | 22 (12.2) | 38 (20.7) | 19 (19.2) | 16 (15.7) |
| *Receiving antimalarial, n (%)* | 119 (66.1) | 133 (73.1) | 124 (68.9) | 134 (72.8) | 76 (76.8) | 75 (73.5) |
| *Biomarkers, n (%)* | | | | | | |

| | TULIP-2 | | TULIP-1 | | MUSE | |
|---|---|---|---|---|---|---|
| • *ANA positive* | 160 (88.9) | 165 (90.7) | 164 (91.1) | 165 (89.7) | 98 (99.0) | 99 (97.1) |
| • *Anti-dsDNA positive* | 86 (47.8) | 73 (40.1) | 81 (45.0) | 82 (44.6) | 56 (55.6) | 66 (64.7) |
| • *Low C3 concentration* | 72 (40.0) | 72 (39.6) | 58 (32.2) | 65 (35.3) | 28 (28.3) | 43 (42.2) |
| • *Low C4 concentration* | 49 (27.2) | 46 (25.3) | 35 (19.4) | 39 (21.2) | 21 (21.2) | 25 (24.5) |

All three anifrolumab studies were similar in baseline characteristics, though the MUSE study randomized slightly fewer patients of white race and disease activity as measured by the SLEDAI-2K was marginally lower in the study though levels of moderate to severe activity on the BILAG and scores on the PGA and CLASI were similar between all studies. Patients in TULIP-2 were on slightly lower doses of prednisone at baseline, though similar number of patients had steroids as part of their standard of care between all studies. Use of immunosuppressants and antimalarials were similar between studies. More patients in the MUSE study were ANA and/or anti-dsDNA positive at baseline, and fewer patients in TULIP-1 had low complement at baseline compared to the other studies.

Compared to Danish clinical practice, patients were somewhat young than the average age at diagnosis reported.[53] In the absence of other specific characteristics of moderate to severe SLE patients in Denmark, comparisons have been drawn to the characteristics reported for the regional cohort in Sweden reported in Table 2. Disease activity was generally lower in Swedish clinical practice compared to the trials. In terms of sex, time since diagnosis, complement levels, and the number of patients receiving steroids or antimalarials as part of their standard of care, the trial populations are similar to Swedish patients. However, more patients in the Nordics are expected to be of white race, and the number of patients who are ANA and/or anti-dsDNA positive were similar to the higher levels observed in MUSE. The average prednisone-equivalent dose was also higher in Sweden, but the proportion of patients with doses ≥10 mg/day were lower, suggesting there are a select few particularly high dose patients in Swedish clinical practice and therefore the average dose without these outliers may be more in line with what was observed in the anifrolumab trials. It should be noted that the Swedish population is an approximation of patients considered to meet the marketing authorization criteria for anifrolumab, but not necessarily those who will be considered candidates for biologic therapy in clinical practice.

As for the trials of belimumab reported below, studies were largely homogenous, though BLISS-52 recruited more Asian patients and those with a shorter duration of disease. Fewer patients in this study were also observed to have a BILAG 1A or 2B score at baseline, but far more were treated with glucocorticoids and at higher doses. Patients in the BLISS-SC study were generally less likely to have low complement at baseline compared with the other belimumab studies.

Compared to the anifrolumab trials, patients in the BLISS studies were younger, less likely to be of white race, had a shorter disease duration, had lower disease activity at baseline (as assessed by the SLEDAI and PGA), and were also less likely to have moderate to severe disease as defined by the BILAG. However, the BILAG was not an inclusion criteria in the BLISS studies whereas it was for the TULIP and MUSE studies. Steroid use was also higher in the BLISS trials. More patients in all three BLISS studies were anti-dsDNA positive, and in BLISS-52 and BLISS-76 many more patients had low complement. Both of these factors are known treatment effect modifiers for belimumab. Given that many of these differentiating factors are either known prognostic factors or treatment-effect modifiers it was determined that an adjusted indirect comparison would aid in the interpretation of the relative efficacy of anifrolumab and belimumab.

**Table C2. Baseline characteristics of patients in the studies of belimumab included for the comparative analysis of efficacy and safety**

| | BLISS-52 | | BLISS-76 | | BLISS-SC | |
|---|---|---|---|---|---|---|
| | Belimumab 10mg/kg (*N* = 290) | Placebo (*N* = 287) | Belimumab 10 mg/kg (*N* = 273) | Placebo (*N* = 275) | Belimumab 200 mg (*N* = 556) | Placebo (*N* = 280) |
| *Age (years), mean (SD)* | 35.4 (10.8) | 36.2 (11.8) | 40.5 (11.1) | 40.0 (11.9) | 38.1 (12.1) | 39.6 (12.6) |
| *Female, n (%)* | 280 (96.6) | 270 (94.1) | 259 (94.9) | 252 (91.6) | 521 (93.7) | 268 (95.7) |
| *Race, n (%)* | | | | | | |
| • *White* | 71 (24.5) | 82 (28.6) | 189 (69.2) | 188 (68.4) | 326 (58.6) | 160 (57.1) |
| • *Black/African American* | 11 (3.8) | 11 (3.8) | 39 (14.3) | 39 (14.2) | 56 (10.1) | 30 (10.7) |
| • *Asian* | 116 (40.0) | 105 (36.6) | 11 (4.0) | 11 (4.0) | 119 (21.4) | 63 (22.5) |
| • *Other* | 92 (31.7) | 89 (31.0) | 34 (12.5) | 36 (13.1) | 55 (9.9) | 27 (9.6) |
| *Disease duration (years), mean (SD)* | 5.0 (5.1) | 5.9 (6.2) | 7.2 (7.5) | 7.4 (6.7) | 6.4 (6.6) | 6.8 (6.8) |
| *SLEDAI-2K score* | | | | | | |
| • *Mean (SD)* | 10.0 (3.9) | 9.7 (3.6) | 9.5 (3.6) | 9.8 (4.0) | 10.5 (3.2) | 10.3 (3.0) |
| • *≥10, n (%)* | 160 (55.2) | 158 (55.1) | 136 (49.8) | 140 (50.9) | 352 (63.3) | 168 (60.0) |
| *BILAG 1A or 2B score, n (%)* | 172 (59.3) | 166 (57.8) | 160 (58.6) | 187 (68.0) | 388 (69.8) | 210 (75.0) |
| *PGA score, mean (SD)* | 1.4 (0.5) | 1.4 (0.5) | 1.4 (0.5) | 1.5 (0.5) | 1.6 (0.4) | 1.5 (0.5) |
| *Type 1 IFN gene signature high, n (%)* | NR (80.3)* | NR (84.2)* | NR (80.3)* | NR (84.2)* | NR | NR |
| *Receiving prednisone, n (%)* | 278 (95.9) | 276 (96.2) | 200 (73.3) | 212 (77.1) | 481 (86.5) | 241 (86.1) |
| • *Dose (mg/day), mean (SD)* | 13.2 (9.5) | 11.9 (7.9) | 8.4 (7.9) | 9.4 (8.9) | 10.8 (8.2) | 11.2 (9.1) |
| • *>7.5 mg/day, n (%)* | 204 (70.3) | 192 (66.9) | 120 (44.0) | 126 (45.8) | 335 (60.3) | 168 (60.0) |
| *Receiving immunosuppressant, n (%)* | 123 (42.4) | 122 (42.5) | 148 (54.2) | 154 (56.0) | 244 (43.9) | 137 (48.9) |
| • *Mycophenolate* | 17 (5.9) | 19 (6.6) | 50 (18.3) | 42 (15.3) | 70 (12.6) | 34 (12.1) |
| • *Azathioprine* | 84 (29.0) | 68 (23.7) | 58 (21.2) | 57 (20.7) | 107 (19.2) | 58 (20.7) |
| • *Methotrexate* | 20 (6.9) | 35 (12.2) | 39 (14.3) | 60 (21.8) | 52 (9.4) | 39 (13.9) |
| *Receiving antimalarial, n (%)* | 185 (63.8) | 201 (70.0) | 168 (61.5) | 180 (65.5) | 391 (70.3) | 189 (67.5) |
| *Biomarkers, n (%)* | | | | | | |
| • *ANA positive* | 276 (95.2) | 264 (92.0) | 245 (89.7) | 253 (92.0) | 492 (88.5) | 254 (90.7) |
| • *Anti-dsDNA positive* | 218 (75.2) | 205 (71.4) | 179 (65.6) | 174 (63.3) | 404 (72.7) | 193 (68.9) |
| • *Low C3 concentration* | 147 (50.7) | 132 (46.0) | 115 (42.1) | 116 (42.2) | 245 (44.1) | 111 (39.6) |
| • *Low C4 concentration* | 180 (62.1) | 160 (55.7) | 147 (53.8) | 143 (52.0) | 146 (26.3) | 71 (25.4) |

* In a post hoc analysis of the pooled BLISS-52 and BLISS-76 trials, 281 patients who had received belimumab and 273 patients who had received placebo had an mRNA sample which passed quality control to determine IFN levels. The values reported are for the pooled data across studies.[128]

# Appendix D. Efficacy and safety results per study

**Table D1. Definition, validity and clinical relevance of included outcome measures**

| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| **BICLA** (British Isles Lupus Assessment Group‑based Composite Lupus Assessment) **response at week 52** | - Reduction of all severe (BILAG-2004 A) or moderately severe (BILAG-2004 B) disease activity at baseline to lower levels (BILAG-2004 B, C, or D and C or D, respectively) and no worsening in other organ systems (with worsening defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items);<br>- No worsening in disease activity, as determined by the SLEDAI-2K score (no increase from baseline) and by the PGA score (no increase of ≥0.3 points from baseline);<br>- No discontinuation of the trial intervention; and no use of restricted medications beyond protocol-allowed thresholds. | BILAG-2004 demonstrated construct and criterion validity in a multicenter study of 369 SLE patients. Increased BILAG-2004 scores were associated with increased erythrocyte sedimentation rates, decreasing C3 and C4 levels, elevated anti-dsDNA, and increased SLEDAI-2K scores.[A]<br>An expert panel was consulted to review characteristics of disease activity indices (DAIs) commonly used in SLE trials, including BILAG-2004. Following this review, BICLA was developed as a composite of multiple DAIs based on early epratuzumab clinical trial data. The BICLA requires patients to meet response criteria across three assessment tools.[B] | The use of BILAG as the primary component of the BICLA requires simultaneous improvement across all body systems with severe or moderate disease activity at baseline. BILAG gives balanced weight to all affected body systems and distinguishes between inactive disease, partial or complete improvement, and deterioration of disease activity; and can reflect incremental improvements within a body system.[B,C]<br>The BICLA was first used to evaluate response in the EMBLEMTM phase II study (SL0007), a 12-week, randomized, double-blind, placebo-controlled study in moderate to severe SLE patients. BICLA was sensitive to epratuzumab treatment response with a limited placebo response rate.[B]<br>In the TULIP-1 and TULIP-2 phase III studies of anifrolumab, BICLA responders had greater improvements in global and organ-specific disease activity (Physician's Global Assessment, SLE Disease Activity Index 2000, Cutaneous Lupus Erythematosus Disease Area and Severity Index Activity, and joint counts; all nominal $P < 0.001$). BICLA responders achieved significantly improved outcomes compared with non-responders, including lower flare rates, higher rates of attainment of sustained oral glucocorticoid taper to ≤7.5 mg/day, greater improvements in PROs (Functional Assessment of Chronic Illness Therapy‑Fatigue, Short Form 36 Health Survey), and fewer SLE-related hospitalizations/emergency department visits (all nominal $P < 0.001$). Compared with non-responders, BICLA responders had fewer lupus-related serious adverse events than non-responders.[C] |
| **SRI(4)** (Systemic Lupus Erythematosus Responder Index) | - At least a 4-point reduction in SLEDAI-2K;<br>- Less than one new BILAG-2004 A or less than two new BILAG-2004 B organ domain scores; | Data from a phase II, randomized, double-blind, placebo-controlled study in 449 patients of 3 doses of belimumab (1, 4,10 mg/kg) or placebo plus standard of care therapy (SOC) over a 56-week period were analyzed.[D] | A reduction from baseline SLEDAI score by 4 points has been defined as clinically meaningful. In a study conducted to determine whether SLEDAI scores correlate with the clinician's impression of level of disease activity, median SLEDAI scores ranged from 2 (inactive disease) to 8 (persistently active or flare). When the clinician assessed the patient to be improved, the median SLEDAI score decreased by 2. When the clinician assessed that the patient was experiencing a flare, the SLEDAI score increased by a median of 4. As a |

| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| **response at week 52** | - Less than 0.3-point increase in PGA from baseline;<br>- No use of restricted medications beyond protocol-allowed thresholds, and no discontinuation of investigational product. | The SRI was calculated any time the SLEDAI scores were measured in individual patients.[D]<br>Evaluation of the evidence from the phase II study showed that the SRI(4) responder index detected improvements (at least 4 points) in disease activity without worsening of the overall condition or the development of significant disease activity in other organ systems.[D] | result, the following outcomes were proposed for patients with SLE: flare, an increase in SLEDAI > 3; improvement is a reduction in SLEDAI of > 3; persistently active disease is change in SLEDAI +/- 3; and remission a SLEDAI of 0.[E] |
| **Sustained reduction in OCS** (oral corticosteroid) **dose** | OCS dose reduction to 7.5mg or less per day, sustained from week 40 to week 52 among patients with a baseline dose of 10mg or more per day | Studies have demonstrated that OCS dose over 7.5 mg can substantially increase the risk of organ damage.[I,J,K] | EULAR treatment guidelines state that the OCS dose should be minimized to a daily dose of 7.5 mg or less per day, or to discontinue them. Long-term OCS use can have detrimental effects, including organ damage. These risks are increased at doses over 7.5 mg/day.[H] |
| **≥50% reduction in CLASI** (Cutaneous Lupus Erythematosus Disease Area and Severity Index) **activity at week 12** | A reduction of 50% or more in the CLASI; a measure of skin-disease severity with scores ranging from 0 [least severe] to 70 [most severe] at week 12 among patients with moderate-to-severe cutaneous activity (CLASI ≥10) at baseline. | The final instrument was evaluated by five dermatologists and six residents who scored nine patients to estimate inter- and intra-rater reliability in two sessions. CLASI was assessed for content validity, inter-rater validity, intra-rater validity, and practical applicability. Consultation with experts established validity.[F] | CLASI is based on the degree of erythema, scale, mucous membrane lesions, and non-scarring alopecia. CLASI scores are not based solely on the area of involved skin; rather, parts of the body that are most visible are weighted more heavily. Patients who improved clinically had a mean 3-point decrease in their CLASI activity scores. Decrease in the CLASI activity score has correlated well with improvements in the physician's global skin assessment, the patient's global skin assessment, and the pain score.[G] |

| Outcome measure | Definition | Validity | Clinical relevance |
|---|---|---|---|
| **≥50% reduction in swollen and tender joints** | **TULIP-2:** A reduction of 50% or more from baseline in counts of both swollen joints and tender joints at week 52 among patients with 6 or more swollen and 6 or more tender joints at baseline (28 joints were assessed)<br><br>**TULIP-1/MUSE:** A reduction of 50% or more from baseline in counts of both swollen joints and tender joints at week 52 among patients with 8 or more swollen and 8 or more tender joints at baseline (28 joints were assessed) | There are no rigorously validated or widely accepted endpoints to assess musculoskeletal treatment response for patients with SLE, and there is no composite musculoskeletal outcome measure. Tender, swollen and symptomatic joint counts have shown similar responsiveness to the SLEDAI.[L]<br><br>Improvement in swollen and tender joint counts was evaluated in patients with at least moderately severe arthritis at baseline, defined as either at least six or at least eight swollen joints or at least six or at least eight tender joints, similar to cutoffs used for enrolment in many trials of inflammatory joint disease.[M] | There is a lack of consensus on thresholds of treatment response in joint counts in SLE confounds data interpretation and comparisons between studies.<br><br>In the TULIP trials, among patients with at least six or at least eight tender or swollen joints at baseline, or a baseline CLASI-A of 10 or more, anifrolumab was associated with greater mean reduction in glucocorticoid dose versus placebo across multiple timepoints; this difference was significant at week 52 only in relation to patients with at least six or at least eight tender joints at baseline. [M]<br><br>A higher proportion of patients treated with anifrolumab achieved a 50% or more reduction in baseline swollen and tender joint counts compared with those receiving placebo. The treatment effect was significant for swollen joints but not tender joints. Joint swelling among patients with SLE may result from inflammation and therefore might potentially be more responsive to immune-targeting treatments. Joint tenderness may not be attributed as much to active SLE-mediated inflammation and could be confounded by comorbidities, such as osteoarthritis or fibromyalgia.[M] |
| **Annualised flare rate** | The annualised rate of flare through week 52, with a flare defined as ≥1 new BILAG-2004 A item or ≥2 new BILAG-2004 B items as compared with the previous visit | Although there is no universally accepted definition of a flare, most experts agree that a flare is a measurable increase in disease activity usually leading to change of treatment [H] | EULAR treatment guidelines state that treatment in SLE should aim to prevent flares in all organ systems. Flares are common in the disease course and contribute significantly to organ damage accrual and worse outcomes. [H] |

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[G]Klein R, Moghadam-Kia S, LoMonico J, Okawa J, Coley C, Taylor L, Troxel AB, Werth VP. Development of the CLASI as a tool to measure disease severity and responsiveness to therapy in cutaneous lupus erythematosus. Arch Dermatol. 2011 Feb;147(2):203-8.

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[K]Thamer MAE, Hernan MA, Zhang YI, et al. Prednisone, lupus activity, and permanent organ damage. J Rheumatol 2009;36:560–4.

[L]Mahmoud K, Zayat AS, Yusof Y, et al. Responsiveness of clinical and ultrasound outcome measures in musculoskeletal systemic lupus erythematosus. Rheumatology 2019; 58: 1353–60.

[M]Morand EF, Furie RA, Bruce IA, et al. Efficacy of anifrolumab across organ domains in patients with moderate-to-severe systemic lupus erythematosus: a post-hoc analysis of pooled data from the TULIP-1 and TULIP-2 trials. Lancet Rheumatology 2022;4(4):e282-e292.

## Results per study

All efficacy analyses included all patients who underwent randomisation and received at least one dose of anifrolumab 300 mg or placebo (modified intent-to-treat [mITT] population). All binary outcomes in TULIP-1 and TULIP-2, including the response assessments on the BICLA, SRI(4), OCS dose reduction, CLASI, joint count reduction, were assessed using a stratified Cochran-Mantel-Haenszel test, with the strata corresponding to the factors used for randomisation (i.e., SLEDAI-2K score, baseline steroid dose, and type I interferon gene signature). In MUSE, these outcomes were analysed using a logistic regression model adjusted for the randomisation stratification factors (same as for the TULIP studies). Patients who discontinued the investigational product were considered non-responders. Intermittent missing data (e.g., because of a missed visit) were imputed with the use of the last observation carried forward (LOCF) for one visit and were imputed as non-response if there was more than one consecutive missed visit. The annualised flare rate was analysed with the use of a negative binomial regression model, incorporating follow-up time as the offset variable to adjust for patients having different exposure times. For the MUSE study, no statistical test on flare rate was conducted. The measure of relative effect on flare rate presented here is an unadjusted incidence rate ratio.

For TULIP-1 and TULIP-2, a weighted Holm procedure with predetermined weights was used to control the familywise type I error rate at 0.05 across primary and key secondary end points. This procedure splits the alpha of 0.05 according to predefined weights and, after initial rejections of the null hypothesis, recycles the corresponding alpha in proportion to these weights. Due to the failure of TULIP-1 on the primary endpoint, only nominal *p* values are reported for some secondary endpoints. As in the protocol and statistical analysis plans for TULIP-1 and TULIP-2, measures of effect were a priori planned to be absolute (i.e., difference in proportions), *p* values have not been calculated for measures of relative effect except for flare rate where the planned analysis method was the incidence rate ratio (IRR). In MUSE, the type I error rate was controlled at 0.10 (2-sided) for the primary endpoint by performing a Cochran-Armitage trend test of all treatment groups prior to performing pairwise comparisons between each anifrolumab group and placebo. No multiplicity adjustment for the 2 study populations or other end points was applied and *p* values reported are nominal.

Rules specifying restricted medications were prospectively defined, however the original rules used in TULIP-1 to classify responders by non-steroidal anti-inflammatory drug (NSAID) use were inconsistent with the intention of the protocol and inappropriately classified patients who used new NSAIDs or had an increase in NSAID dose as non-responders for all binary response endpoints, even if NSAID use was transient or early in the trial. These rules did not have any effect on study procedures (e.g., medical decisions, treatment of patients, or data collection), but affected analysis of the data. After unmasking, a group of SLE experts assessed the clinical appropriateness of all restricted medication rules and revised them accordingly. Key analyses in TULIP-1 were repeated using the amended restricted medication rules, and results are also presented here.

**Table D2. Results of TULIP-2 (NCT02446899)**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value‡ | | |
| ***BICLA response at week 52*** | Anifrolumab | 180 | 47.8% | 16.3% | 6.3%, 26.3% | 0.0013 | OR: 1.99 | 1.30, 3.06 | N/A | Stratified Cochran–Mantel–Haenszel test | Morand et al. 2020 |
| | Placebo | 182 | 31.5% | | | | | | | | |
| ***SRI(4) response at week 52*** | Anifrolumab | 180 | 55.5% | 18.2% | 8.1%, 28.3% | 0.0004 | OR: 2.10 | 1.38, 3.19 | N/A | Stratified Cochran–Mantel–Haenszel test | Morand et al. 2020, suppl. |
| | Placebo | 182 | 37.3% | | | | | | | | |
| ***≥4-point reduction in SLEDAI score*** | Anifrolumab | 180 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | OR: [redacted] | [redacted], [redacted] | N/A | Naïve estimation of absolute difference | Data on file |
| | Placebo | 182 | [redacted]% | | | | | | | | |
| ***Sustained reduction in OCS dose*** | Anifrolumab | 87 | 51.5% | 21.2% | 6.8%, 35.7% | 0.0135 | OR: 2.45 | 1.31, 4.61 | N/A | Stratified Cochran–Mantel–Haenszel test | Morand et al. 2020 |
| | Placebo | 83 | 30.2% | | | | | | | | |
| | Anifrolumab | 49 | 49.0% | 24.0% | 4.3%, 43.6% | 0.0392 | OR: 2.88 | 1.16, 7.15 | N/A | | |

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***≥50% reduction in CLASI activity at week 12*** | Placebo | 40 | 25.0% | | | | | | | Stratified Cochran–Mantel–Haenszel test | Morand et al. 2020 |
| ***≥50% reduction in swollen and tender joints*** | Anifrolumab | 71 | 42.2% | 4.7% | -10.6%, 20.0% | 0.5469 | OR: 1.22 | 0.64, 2.30 | N/A | Stratified Cochran–Mantel–Haenszel test | Morand et al. 2020 |
| | Placebo | 90 | 37.5% | | | | | | | | |
| ***Annualised flare rate*** | Anifrolumab | 180 | 0.43 | N/A | N/A | N/A | IRR: 0.67 | 0.48, 0.94 | 0.0809 | Negative binomial regression model | Morand et al. 2020 |
| | Placebo | 182 | 0.64 | | | | | | | | |
| ***New BILAG 1A or 2B flare*** | Anifrolumab | 180 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | OR: [redacted] | [redacted], [redacted] | N/A | Naïve estimation of absolute difference | Data on file |
| | Placebo | 182 | [redacted]% | | | | | | | | |

**Table D3. Results of TULIP-1 (NCT02446912): Pre-specified analysis**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value‡ | | |
| ***BICLA response at week 52*** | Anifrolumab | 180 | 37.1% | 10.1% | 0.6%, 19.7% | N/A | OR: 1.59 | 1.02, 2.49 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 184 | 27.0% | | | | | | | | |
| ***SRI(4) response at week 52*** | Anifrolumab | 180 | 36.2% | -4.2% | -14.2%, 5.8% | 0.412 | OR: 0.84 | 0.55, 1.28 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 184 | 40.4% | | | | | | | | |

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Sustained reduction in OCS dose*** | Anifrolumab | 103 | 41.0% | 8.9% | -4.1%, 21.9% | 0.180 | OR: 1.47 | 0.83, 2.60 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 102 | 32.1% | | | | | | | | |
| ***≥50% reduction in CLASI activity at week 12*** | Anifrolumab | 58 | 41.9% | 17.0% | -0.3%, 34.3% | 0.054 | OR: 2.18 | 0.98, 4.85 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 54 | 24.9% | | | | | | | | |
| ***≥50% reduction in swollen and tender joints*** | Anifrolumab | 70 | 47.0% | 14.7% | -1.4%, 30.8% | N/A | OR: 1.86 | 0.93, 3.71 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 68 | 32.3% | | | | | | | | |
| ***Annualised flare rate*** | Anifrolumab | 180 | 0.60 | N/A | N/A | N/A | IRR: 0.83 | 0.60, 1.14 | 0.258 | Negative binomial regression model | Furie et al. 2019 |
| | Placebo | 184 | 0.72 | | | | | | | | |
| ***New BILAG 1A or 2B flare*** | Anifrolumab | 180 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | OR: [redacted] | [redacted], [redacted] | N/A | Naïve estimation of absolute difference | Data on file |
| | Placebo | 184 | [redacted]% | | | | | | | | |

**Table D4. Results of TULIP-2 (NCT02446912): Amended medication rules**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value‡ | | |
| ***BICLA response at week 52*** | Anifrolumab | 180 | 46.1% | 16.4% | 6.7%, 26.2% | N/A | OR: 2.03 | 1.32, 3.13 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 184 | 29.6% | | | | | | | | |

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***SRI(4) response at week 52*** | Anifrolumab | 180 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | OR: [redacted] | [redacted], [redacted] | N/A | Stratified Cochran–Mantel–Haenszel test | Data on file |
| | Placebo | 184 | [redacted]% | | | | | | | | |
| ***≥4-point reduction in SLEDAI score*** | Anifrolumab | 180 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | OR: [redacted] | [redacted], [redacted] | N/A | Naïve estimation of relative difference | Data on file |
| | Placebo | 184 | [redacted]% | | | | | | | | |
| ***Sustained reduction in OCS dose*** | Anifrolumab | 103 | 48.8% | 16.7% | 3.5%, 29.8% | 0.013 | OR: 2.02 | 1.14, 3.55 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 102 | 32.1% | | | | | | | | |
| ***≥50% reduction in CLASI activity at week 12*** | Anifrolumab | 58 | 43.6% | 18.7% | 1.4%, 36.0% | 0.034 | OR: 2.33 | 1.05, 5.19 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 54 | 24.9% | | | | | | | | |
| ***≥50% reduction in swollen and tender joints*** | Anifrolumab | 70 | 53.0% | 20.7% | 4.7%, 36.7% | N/A | OR: 2.36 | 1.18, 4.72 | N/A | Stratified Cochran–Mantel–Haenszel test | Furie et al. 2019 |
| | Placebo | 68 | 32.3% | | | | | | | | |

**Table D5. Results of MUSE (NCT01438489)**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value‡ | | |
| ***BICLA response at week 52*** | Anifrolumab | 99 | 53.5% | 27.8% | 14.8%, 40.8% | N/A | OR: 3.42 | 1.87, 6.26 | <0.001 | Logistic regression adjusted for randomization stratification factors | Furie et al. 2017 |
| | Placebo | 101 | 25.7% | | | | | | | | |

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect† | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***SRI(4) response at week 52*** | Anifrolumab | 99 | 62.6% | 22.4% | 8.9%, 35.9% | N/A | OR: 2.66 | 1.50, 4.73 | <0.001 | Logistic regression adjusted for randomization stratification factors | Furie et al. 2017 |
| | Placebo | 102 | 40.2% | | | | | | | | |
| ***≥4-point reduction in SLEDAI score*** | Anifrolumab | 99 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | OR: [redacted] | [redacted], [redacted] | [redacted] | Naïve estimate of odds ratio | Data on file |
| | Placebo | 102 | [redacted]% | | | | | | | | |
| ***Sustained reduction in OCS dose*** | Anifrolumab | 55 | 56.4% | 29.8% | 12.8%, 46.8% | N/A | OR: 3.59 | 1.65, 7.81 | 0.001 | Logistic regression adjusted for randomization stratification factors | Furie et al. 2017 |
| | Placebo | 64 | 26.6% | | | | | | | | |
| ***≥50% reduction in CLASI activity at week 12*** | Anifrolumab | 27 | 63.0% | 32.2% | 6.8%, 57.6% | N/A | OR: 4.49 | 1.38, 14.65 | 0.013 | Logistic regression adjusted for randomization stratification factors | Furie et al. 2017 |
| | Placebo | 26 | 30.8% | | | | | | | | |
| ***≥50% reduction in swollen and tender joints*** | Anifrolumab | 46 | 69.6% | 21.0% | 0.1%, 41.9% | N/A | OR: 2.67 | 1.06, 6.75 | 0.038 | Logistic regression adjusted for randomization stratification factors | Furie et al. 2017 |
| | Placebo | 37 | 48.6% | | | | | | | | |
| ***Annualised flare rate*** | Anifrolumab | 99 | [redacted]% | [redacted]% | [redacted]%, [redacted]% | [redacted] | IRR: [redacted] | [redacted], [redacted] | N/A | Naive estimation of incidence rate ratio | Data on file (MUSE CSR) |
| | Placebo | 102 | [redacted]% | | | | | | | | |
| ***New BILAG 1A or 2B flare*** | Anifrolumab | 99 | 12.1% | -4.5% | -14.2%, 5.1% | N/A | OR: 0.71 | 0.36, 1.42 | 0.328 | Logistic regression adjusted for randomization stratification factors | Furie et al. 2017 |
| | Placebo | 102 | 16.7% | | | | | | | | |

† Relative difference in effect is a naïve estimate based on the reported percentages in each arm and is not adjusted for using the randomization stratification criteria as specified in the study protocol or used in the estimates of absolute difference in effect. ‡ Where *P* values have not been estimated for relative differences in effect, this is where the relative effect was not protocol-specified (only absolute difference).

**Table D6. Relevant results of BLISS-76 (NCT00410384)**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| ***SRI(4) response at week 52*** | Belimumab | 273 | 43.2% | 9.8% | 1.7%, 17.9% | 0.0181 | OR: 1.51 | 1.07, 2.14 | 0.0189 | Naïve estimate of odds ratio | Furie et al. 2011 |
| | Placebo | 275 | 33.5% | | | | | | | | |
| ***≥4-point reduction in SLEDAI score*** | Belimumab | 273 | 46.5% | 11.2% | 3.1%, 19.4% | 0.0070 | OR: 1.60 | 1.13, 2.25 | 0.0076 | Naïve estimate of odds ratio | Furie et al. 2011 |
| | Placebo | 275 | 35.3% | | | | | | | | |
| ***Sustained reduction in OCS dose*** | Belimumab | 120 | 17.5% | 4.8% | -4.1%, 13.7% | 0.2928 | OR: 1.46 | 0.72, 2.95 | 0.2941 | Naïve estimate of odds ratio | Furie et al. 2011 |
| | Placebo | 126 | 12.7% | | | | | | | | |
| ***New BILAG 1A or 2B flare*** | Belimumab | 273 | 31.5% | -2.7% | -10.5%, 5.2% | 0.5040 | OR: 0.89 | 0.62, 1.27 | 0.5043 | Naïve estimation of odds ratio | Petri et al. 2010 |
| | Placebo | 275 | 34.2% | | | | | | | | |

**Table D6. Relevant results of BLISS-52 (NCT00424476)**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| ***SRI(4) response at week 52*** | Belimumab | 290 | 57.6% | 14.0% | 6.0%, 22.1% | 0.0007 | OR: 1.83 | 1.30, 2.59 | 0.0006 | Logistic regression model adjusted for randomization stratification factors | Navarra et al. 2011 |
| | Placebo | 287 | 43.6% | | | | | | | | |

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***≥4-point reduction in SLEDAI score*** | Belimumab | 290 | 58.3% | 12.3% | 4.2%, 20.4% | 0.0029 | OR: 1.71 | 1.21, 2.41 | 0.0024 | Logistic regression model adjusted for randomization stratification factors | Navarra et al. 2011 |
| | Placebo | 287 | 46.0% | | | | | | | | |
| ***Sustained reduction in OCS dose*** | Belimumab | 204 | 18.6% | 6.6% | -0.4%, 13.7% | 0.0644 | OR: 1.75 | 0.99, 3.08 | 0.0526 | Logistic regression model adjusted for randomization stratification factors | Navarra et al. 2011 |
| | Placebo | 192 | 12.0% | | | | | | | | |
| ***New BILAG 1A or 2B flare*** | Belimumab | 290 | 18.6% | -11.3% | -18.3%, -4.4% | 0.0014 | OR: 0.58 | 0.41, 0.81 | 0.0016 | Logistic regression model adjusted for randomization stratification factors | Navarra et al. 2011 |
| | Placebo | 287 | 30.0% | | | | | | | | |

**Table D6. Relevant results of BLISS-SC (NCT01484496)**

| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | Difference | 95% CI | *P* value | Difference | 95% CI | *P* value | | |
| ***SRI(4) response at week 52*** | Belimumab | 554 | 61.4% | 13.0% | 5.9%, 20.1% | 0.0004 | OR: 1.68 | 1.25, 2.25 | 0.0006 | Logistic regression model adjusted for randomization stratification factors | Stohl et al. 2017 |
| | Placebo | 279 | 48.4% | | | | | | | | |
| ***≥4-point reduction in SLEDAI score*** | Belimumab | 554 | 62.3% | 13.2% | 6.0%, 20.3% | 0.0003 | OR: 1.71 | 1.28, 2.29 | 0.0003 | Naïve estimation of odds ratio | Stohl et al. 2017 |
| | Placebo | 279 | 49.1% | | | | | | | | |
| | Belimumab | 335 | 18.2% | 6.3% | -0.1%, 12.7% | 0.0538 | OR: 1.65 | 0.95, 2.84 | 0.0732 | | |

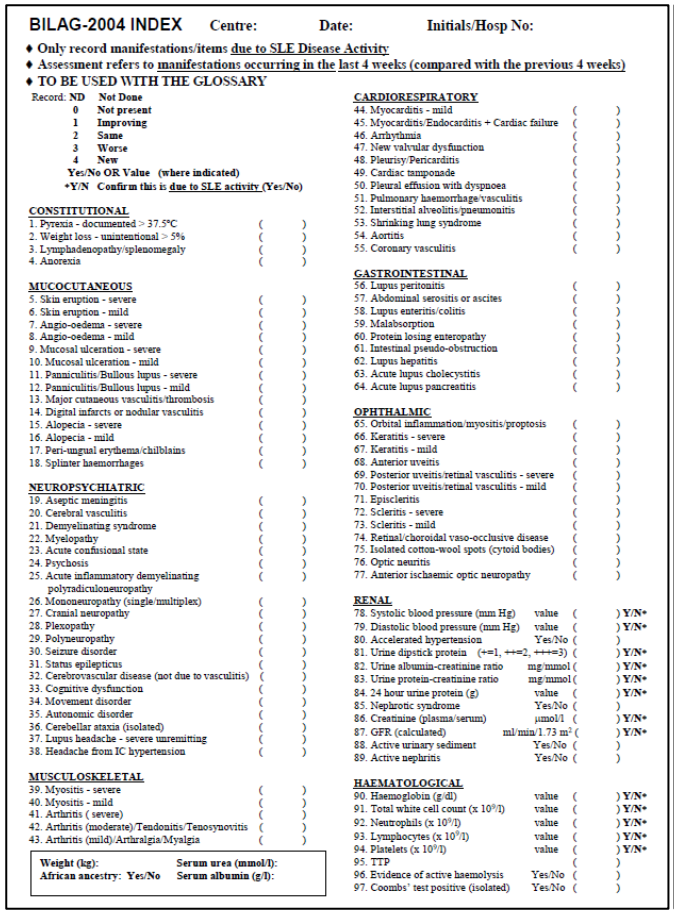
| Outcome | Study arm | N | Result | Estimated absolute difference in effect | | | Estimated relative difference in effect | | | Method used for estimation | References |
|---|---|---|---|---|---|---|---|---|---|---|---|
| ***Sustained reduction in OCS dose*** | Placebo | 168 | 11.9% | | | | | | | Logistic regression model adjusted for randomization stratification factors | Stohl et al. 2017 |
| ***New BILAG 1A or 2B flare*** | Belimumab | 554 | 19.3% | -6.5% | -12.6%, -0.4% | 0.0369 | OR: 0.69 | 0.49, 0.97 | 0.0318 | Naïve estimation of odds ratio | Stohl et al. 2017 |
| | Placebo | 279 | 25.8% | | | | | | | | |



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

## British Isles Lupus Assessment Group's (BILAG-2004) disease activity index

(Reference: Isenberg DA, Rahman A, Allen E, Farewell V, Akil M, Bruce IN, D'Cruz D, Griffiths B, Khamashta M, Maddison P, McHugh N, Snaith M, Teh LS, Yee CS, Zoma A, Gordon C. BILAG 2004. Development and initial validation of an updated version of the British Isles Lupus Assessment Group's disease activity index for patients with systemic lupus erythematosus. Rheumatology (Oxford). 2005 Jul;44(7):902-6).



**BILAG-2004 INDEX** Centre: Date: Initials/Hosp No:

- Only record manifestations/items due to SLE Disease Activity
- Assessment refers to manifestations occurring in the last 4 weeks (compared with the previous 4 weeks)
- TO BE USED WITH THE GLOSSARY

Record: ND Not Done
0 Not present
1 Improving
2 Same
3 Worse
4 New
Yes/No OR Value (where indicated)
*Y/N Confirm this is due to SLE activity (Yes/No)

**CONSTITUTIONAL**
1. Pyrexia - documented > 37.5°C ( )
2. Weight loss - unintentional > 5% ( )
3. Lymphadenopathy/splenomegaly ( )
4. Anorexia ( )

**MUCOCUTANEOUS**
5. Skin eruption - severe ( )
6. Skin eruption - mild ( )
7. Angio-oedema - severe ( )
8. Angio-oedema - mild ( )
9. Mucosal ulceration - severe ( )
10. Mucosal ulceration - mild ( )
11. Panniculitis/Bullous lupus - severe ( )
12. Panniculitis/Bullous lupus - mild ( )
13. Major cutaneous vasculitis/thrombosis ( )
14. Digital infarcts or nodular vasculitis ( )
15. Alopecia - severe ( )
16. Alopecia - mild ( )
17. Peri-ungual erythema/chilblains ( )
18. Splinter haemorrhages ( )

**NEUROPSYCHIATRIC**
19. Aseptic meningitis ( )
20. Cerebral vasculitis ( )
21. Demyelinating syndrome ( )
22. Myelopathy ( )
23. Acute confusional state ( )
24. Psychosis ( )
25. Acute inflammatory demyelinating polyradiculoneuropathy ( )
26. Mononeuropathy (single/multiplex) ( )
27. Cranial neuropathy ( )
28. Plexopathy ( )
29. Polyneuropathy ( )
30. Seizure disorder ( )
31. Status epilepticus ( )
32. Cerebrovascular disease (not due to vasculitis) ( )
33. Cognitive dysfunction ( )
34. Movement disorder ( )
35. Autonomic disorder ( )
36. Cerebellar ataxia (isolated) ( )
37. Lupus headache - severe unremitting ( )
38. Headache from IC hypertension ( )

**MUSCULOSKELETAL**
39. Myositis - severe ( )
40. Myositis - mild ( )
41. Arthritis ( severe) ( )
42. Arthritis (moderate)/Tendonitis/Tenosynovitis ( )
43. Arthritis (mild)/Arthralgia/Myalgia ( )

Weight (kg): Serum urea (mmol/l):
African ancestry: Yes/No Serum albumin (g/l):

**CARDIORESPIRATORY**
44. Myocarditis - mild ( )
45. Myocarditis/Endocarditis + Cardiac failure ( )
46. Arrhythmia ( )
47. New valvular dysfunction ( )
48. Pleurisy/Pericarditis ( )
49. Cardiac tamponade ( )
50. Pleural effusion with dyspnoea ( )
51. Pulmonary haemorrhage/vasculitis ( )
52. Interstitial alveolitis/pneumonitis ( )
53. Shrinking lung syndrome ( )
54. Aortitis ( )
55. Coronary vasculitis ( )

**GASTROINTESTINAL**
56. Lupus peritonitis ( )
57. Abdominal serositis or ascites ( )
58. Lupus enteritis/colitis ( )
59. Malabsorption ( )
60. Protein losing enteropathy ( )
61. Intestinal pseudo-obstruction ( )
62. Lupus hepatitis ( )
63. Acute lupus cholecystitis ( )
64. Acute lupus pancreatitis ( )

**OPHTHALMIC**
65. Orbital inflammation/myositis/proptosis ( )
66. Keratitis - severe ( )
67. Keratitis - mild ( )
68. Anterior uveitis ( )
69. Posterior uveitis/retinal vasculitis - severe ( )
70. Posterior uveitis/retinal vasculitis - mild ( )
71. Episcleritis ( )
72. Scleritis - severe ( )
73. Scleritis - mild ( )
74. Retinal/choroidal vaso-occlusive disease ( )
75. Isolated cotton-wool spots (cytoid bodies) ( )
76. Optic neuritis ( )
77. Anterior ischaemic optic neuropathy ( )

**RENAL**
78. Systolic blood pressure (mm Hg) value ( ) Y/N*
79. Diastolic blood pressure (mm Hg) value ( ) Y/N*
80. Accelerated hypertension Yes/No ( )
81. Urine dipstick protein (+=1, ++=2, +++=3) ( ) Y/N*
82. Urine albumin-creatinine ratio mg/mmol ( ) Y/N*
83. Urine protein-creatinine ratio mg/mmol ( ) Y/N*
84. 24 hour urine protein (g) value ( ) Y/N*
85. Nephrotic syndrome Yes/No ( )
86. Creatinine (plasma/serum) µmol/l ( ) Y/N*
87. GFR (calculated) ml/min/1.73 m² ( ) Y/N*
88. Active urinary sediment Yes/No ( )
89. Active nephritis Yes/No ( )

**HAEMATOLOGICAL**
90. Haemoglobin (g/dl) value ( ) Y/N*
91. Total white cell count (x $10^9$/l) value ( ) Y/N*
92. Neutrophils (x $10^9$/l) value ( ) Y/N*
93. Lymphocytes (x $10^9$/l) value ( ) Y/N*
94. Platelets (x $10^9$/l) value ( ) Y/N*
95. TTP ( )
96. Evidence of active haemolysis Yes/No ( )
97. Coombs' test positive (isolated) Yes/No ( )

## BILAG-2004 INDEX SCORING

- scoring based on the principle of physician's intention to treat

| Category | Definition |
|---|---|
| A | **Severe disease activity requiring any of the following treatment:**<br>**1. systemic high dose oral glucocorticoids (equivalent to prednisolone > 20 mg/day)**<br>**2. intravenous pulse glucocorticoids (equivalent to pulse methylprednisolone ≥ 500 mg)**<br>**3. systemic immunomodulators (include biologicals, immunoglobulins and plasmapheresis)**<br>**4. therapeutic high dose anticoagulation in the presence of high dose steroids or immunomodulators**<br>**eg: warfarin with target INR 3 - 4** |
| B | **Moderate disease activity requiring any of the following treatment:**<br>**1. systemic low dose oral glucocorticoids (equivalent to prednisolone ≤ 20 mg/day)**<br>**2. intramuscular or intra-articular or soft tissue glucocorticoids injection (equivalent to methylprednisolone < 500mg)**<br>**3. topical glucocorticoids**<br>**4. topical immunomodulators**<br>**5. antimalarials or thalidomide or prasterone or acitretin**<br>**6. symptomatic therapy**<br>**eg: NSAIDs for inflammatory arthritis** |
| C | **Mild disease** |
| D | **Inactive disease but previously affected** |
| E | **System never involved** |

## Systemic Lupus Erythematosus Disease Activity Index 2000 (SLEDAI-2K)

(Reference: Gladman DD, Ibañez D, Urowitz MB. Systemic lupus erythematosus disease activity index 2000. J Rheumatol. 2002 Feb;29(2):288-91).

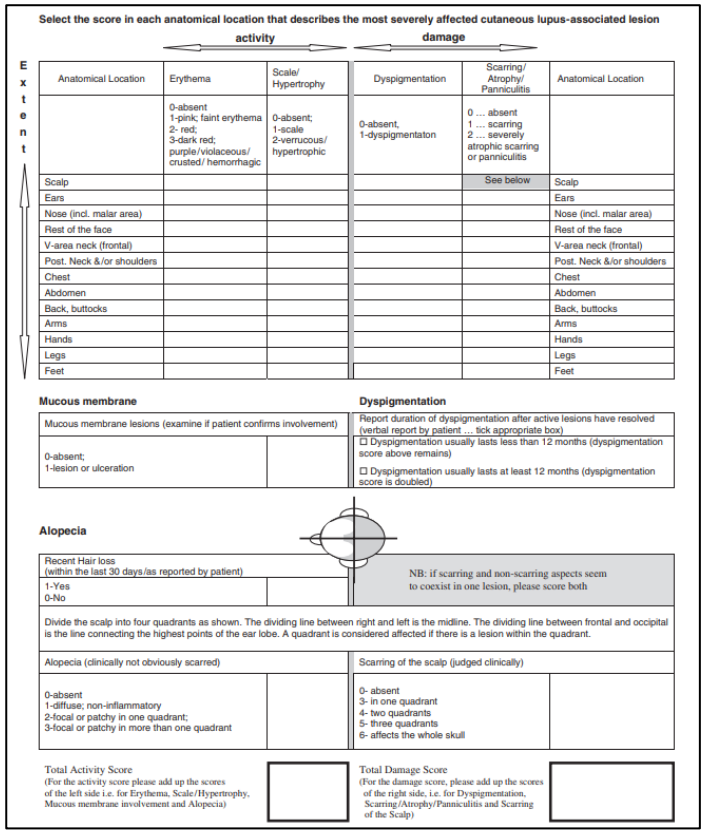
Study No.: _____ Patient Name: _____ _____ Visit Date: ___

(Enter weight in SLEDAI Score column if descriptor is present at the time of the visit or in the preceding 10 days.)

| Weight | SLEDAI SCORE | Descriptor | Definition |
|---|---|---|---|
| 8 | _____ | Seizure | Recent onset, exclude metabolic, infectious or drug causes. |
| 8 | _____ | Psychosis | Altered ability to function in normal activity due to severe disturbance in the perception of reality. Include hallucinations, incoherence, marked loose associations, impoverished thought content, marked illogical thinking, bizarre, disorganized, or catatonic behavior. Exclude uremia and drug causes. |
| 8 | _____ | Organic brain syndrome | Altered mental function with impaired orientation, memory, or other intellectual function, with rapid onset and fluctuating clinical features, inability to sustain attention to environment, plus at least 2 of the following: perceptual disturbance, incoherent speech, insomnia or daytime drowsiness, or increased or decreased psychomotor activity. Exclude metabolic, infectious, or drug causes. |
| 8 | _____ | Visual disturbance | Retinal changes of SLE. Include cytoid bodies, retinal hemorrhages, serous exudate or hemorrhages in the choroid, or optic neuritis. Exclude hypertension, infection, or drug causes. |
| 8 | _____ | Cranial nerve disorder | New onset of sensory or motor neuropathy involving cranial nerves. |
| 8 | _____ | Lupus headache | Severe, persistent headache; may be migrainous, but must be nonresponsive to narcotic analgesia. |
| 8 | _____ | CVA | New onset of cerebrovascular accident(s). Exclude arteriosclerosis. |
| 8 | _____ | Vasculitis | Ulceration, gangrene, tender finger nodules, periungual infarction, splinter hemorrhages, or biopsy or angiogram proof of vasculitis. |
| 4 | _____ | Arthritis | ≥ 2 joints with pain and signs of inflammation (i.e., tenderness, swelling or effusion). |
| 4 | _____ | Myositis | Proximal muscle aching/weakness, associated with elevated creatine phosphokinase/aldolase or electromyogram changes or a biopsy showing myositis. |
| 4 | _____ | Urinary casts | Heme-granular or red blood cell casts. |
| 4 | _____ | Hematuria | >5 red blood cells/high power field. Exclude stone, infection or other cause. |
| 4 | _____ | Proteinuria | >0.5 gram/24 hours |
| 4 | _____ | Pyuria | >5 white blood cells/high power field. Exclude infection. |
| 2 | _____ | Rash | Inflammatory type rash. |
| 2 | _____ | Alopecia | Abnormal, patchy or diffuse loss of hair. |
| 2 | _____ | Mucosal ulcers | Oral or nasal ulcerations. |
| 2 | _____ | Pleurisy | Pleuritic chest pain with pleural rub or effusion, or pleural thickening. |
| 2 | _____ | Pericarditis | Pericardial pain with at least 1 of the following: rub, effusion, or electrocardiogram or echocardiogram confirmation. |
| 2 | _____ | Low complement | Decrease in CH50, C3, or C4 below the lower limit of normal for testing laboratory |
| 2 | _____ | Increased DNA binding | Increased DNA binding by Farr assay above normal range for testing laboratory. |
| 1 | _____ | Fever | >38° C. Exclude infectious cause. |
| 1 | _____ | Thrombocytopenia | <100,000 platelets / x10⁹/L, exclude drug causes. |
| 1 | _____ | Leukopenia | < 3,000 white blood cells / x10⁹/L, exclude drug causes. |
| **TOTAL SLEDAI SCORE** | _____ | | |

## Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI)

(Reference: Albrecht J, Taylor L, Berlin JA, Dulay S, Ang G, Fakharzadeh S, Kantor J, Kim E, Militello G, McGinnis K, Richardson S, Treat J, Vittorio C, Van Voorhees A, Werth VP. The CLASI (Cutaneous Lupus Erythematosus Disease Area and Severity Index): an outcome instrument for cutaneous lupus erythematosus. J Invest Dermatol. 2005 Nov;125(5):889-94).



**Select the score in each anatomical location that describes the most severely affected cutaneous lupus-associated lesion**

| | activity | | damage | | |
|---|---|---|---|---|---|
| Extent | Anatomical Location | Erythema | Scale/ Hypertrophy | Dyspigmentation | Scarring/ Atrophy/ Panniculitis | Anatomical Location |
| | | 0-absent<br>1-pink; faint erythema<br>2- red;<br>3-dark red;<br>purple/violaceous/ crusted/ hemorrhagic | 0-absent;<br>1-scale<br>2-verrucous/ hypertrophic | 0-absent,<br>1-dyspigmentaton | 0 … absent<br>1 … scarring<br>2 … severely atrophic scarring or panniculitis | |
| | Scalp | | | | See below | Scalp |
| | Ears | | | | | Ears |
| | Nose (incl. malar area) | | | | | Nose (incl. malar area) |
| | Rest of the face | | | | | Rest of the face |
| | V-area neck (frontal) | | | | | V-area neck (frontal) |
| | Post. Neck &/or shoulders | | | | | Post. Neck &/or shoulders |
| | Chest | | | | | Chest |
| | Abdomen | | | | | Abdomen |
| | Back, buttocks | | | | | Back, buttocks |
| | Arms | | | | | Arms |
| | Hands | | | | | Hands |
| | Legs | | | | | Legs |
| | Feet | | | | | Feet |

**Mucous membrane**

| Mucous membrane lesions (examine if patient confirms involvement) | |
|---|---|
| 0-absent;<br>1-lesion or ulceration | |

**Dyspigmentation**

Report duration of dyspigmentation after active lesions have resolved (verbal report by patient … tick appropriate box)

☐ Dyspigmentation usually lasts less than 12 months (dyspigmentation score above remains)

☐ Dyspigmentation usually lasts at least 12 months (dyspigmentation score is doubled)

**Alopecia**

| Recent Hair loss (within the last 30 days/as reported by patient)<br>1-Yes<br>0-No | | NB: if scarring and non-scarring aspects seem to coexist in one lesion, please score both |
|---|---|---|

Divide the scalp into four quadrants as shown. The dividing line between right and left is the midline. The dividing line between frontal and occipital is the line connecting the highest points of the ear lobe. A quadrant is considered affected if there is a lesion within the quadrant.

| Alopecia (clinically not obviously scarred) | | Scarring of the scalp (judged clinically) | |
|---|---|---|---|
| 0-absent<br>1-diffuse; non-inflammatory<br>2-focal or patchy in one quadrant;<br>3-focal or patchy in more than one quadrant | | 0- absent<br>3- in one quadrant<br>4- two quadrants<br>5- three quadrants<br>6- affects the whole skull | |

| Total Activity Score<br>(For the activity score please add up the scores of the left side i.e. for Erythema, Scale/Hypertrophy, Mucous membrane involvement and Alopecia) | | Total Damage Score<br>(For the damage score, please add up the scores of the right side, i.e. for Dyspigmentation, Scarring/Atrophy/Panniculitis and Scarring of the Scalp) | |
|---|---|---|---|

# Appendix E. Safety data for intervention and comparator(s)

Anifrolumab 300 mg was generally well tolerated in patients with SLE. Across clinical trials, the most commonly reported adverse events were mild to moderate in severity and included nasopharyngitis, upper respiratory tract infection, urinary tract infection, bronchitis and infusion related reactions.[73,74,92] Adverse events that were more common in the anifrolumab group than in the placebo group (i.e., ≥5% difference or ≥5% incidence in the anifrolumab group and at least twice the rate of the placebo group) were nasopharyngitis, upper respiratory tract infection, bronchitis, and herpes zoster.[129] Adverse events leading to discontinuation were infrequent and balanced between the groups.

A total of 54/459 patients (11.8%) receiving anifrolumab 300 mg and 78/466 (16.7%) receiving placebo experienced ≥1 serious adverse event during treatment. Serious adverse events included infections (anifrolumab: 22 (4.8%) and placebo: 26 (5.6%), of which pneumonia accounted for eight (1.7%) and nine (1.9%), respectively), as well as worsening of SLE that met criteria for an SAE (7 (1.5%) and 14 (3.0%), respectively).[129]

Non-opportunistic serious infection rates were similar and occurred in 4.8% and 5.6% of patients receiving anifrolumab and placebo, respectively.[129] Hypersensitivity reactions were reported by 2.8% (13/459) and 0.6% (3/466) of patients receiving anifrolumab 300 mg and placebo, respectively. These events were predominantly mild or moderate in intensity and occurred during the first 12 weeks of treatment.[129] Infusion-related reactions occurred in 43/459 patients (9.4%) receiving anifrolumab 300 mg and 33/466 (7.1%) receiving placebo. All were mild to moderate in intensity, occurred in the first 24 weeks, and the most common symptoms were headache, nausea, vomiting and fatigue.[129]

Herpes zoster infections were predominantly of cutaneous presentation, mild or moderate in severity and resolved without discontinuation of anifrolumab.[74] Across all three studies, 34 patients from both the anifrolumab 300 mg and placebo groups experienced Herpes zoster; 32 patients had a mild or moderate case and 2 patients had a severe case. One patient receiving anifrolumab 300 mg discontinued therapy due to transverse myelitis with a positive PCR test for Herpes zoster in cerebrospinal fluid.[129] This patient was treated and fully recovered without sequela. This adverse event was assessed by the investigator to be unrelated to treatment. Overall, 32 of 34 patients with herpes zoster adverse events continued in the study. Subgroup analyses of pooled data has not suggested any clear trend by demographics, baseline disease characteristics, or SLE-related medication use.[129]

**Table E1. Adverse events with a frequency of ≥2% of patients across MUSE, TULIP-1 and TULIP-2**

| Adverse Event,* n (%) | Anifrolumab 300 mg (*N* = 459) | Placebo (*N* = 466) |
|---|---|---|
| **Nasopharyngitis**[a] | 75 (16.3) | 44 (9.4) |
| **Upper respiratory tract infection**[a] | 71 (15.5) | 45 (9.7) |
| **Urinary tract infection** | 55 (12.0) | 63 (13.5) |
| **Bronchitis**[a] | 45 (9.8) | 20 (4.3) |
| **Infusion-related reaction** | 43 (9.4) | 33 (7.1) |
| **Headache** | 37 (8.1) | 45 (9.7) |
| **Herpes zoster**[a] | 28 (6.1) | 6 (1.3) |
| **Back pain** | 24 (5.2) | 20 (4.3) |
| **Sinusitis** | 24 (5.2) | 24 (5.2) |
| **Cough** | 23 (5.0) | 15 (3.2) |
| **Arthralgia** | 22 (4.8) | 9 (1.9) |
| **Pharyngitis** | 21 (4.6) | 17 (3.6) |

| Adverse Event,* n (%) | Anifrolumab 300 mg (*N* = 459) | Placebo (*N* = 466) |
|---|---|---|
| **Vomiting** | 18 (3.9) | 12 (2.6) |
| **Nausea** | 17 (3.7) | 25 (5.4) |
| **Oral herpes** | 17 (3.7) | 12 (2.6) |
| **Pneumonia** | 15 (3.3) | 13 (2.8) |
| **Diarrhoea** | 14 (3.1) | 25 (5.4) |
| **Respiratory tract infection** | 14 (3.1) | 2 (0.4) |
| **Depression** | 13 (2.8) | 8 (1.7) |
| **Gastroenteritis** | 13 (2.8) | 14 (3.0) |
| **Hypersensitivity** | 13 (2.8) | 3 (0.6) |
| **Influenza** | 12 (2.6) | 9 (1.9) |
| **Gastroenteritis (viral)** | 11 (2.4) | 7 (1.5) |
| **Gastro-oesophageal reflux disease** | 11 (2.4) | 12 (2.6) |
| **Pain in extremity** | 11 (2.4) | 3 (0.6) |
| **Anxiety** | 10 (2.2) | 8 (1.7) |
| **Dizziness** | 10 (2.2) | 12 (2.6) |
| **Fatigue** | 10 (2.2) | 9 (1.9) |
| **Peripheral oedema** | 10 (2.2) | 4 (0.9) |
| **SLE** | 10 (2.2) | 14 (3.0) |
| **Insomnia** | 9 (2.0) | 19 (4.1) |

Source: Tummala et al (2021)[129]

*AEs are coded using MedDRA version 22.1. An AE during treatment was defined as an AE with a date of onset on or after the day of the first dose of anifrolumab and on or before the date of the last dose of anifrolumab plus 28 days;

[a]AEs more common in the anifrolumab 300 mg group than in the placebo group. (ie, ≥5% difference, or ≥5% incidence in the anifrolumab group and at least twice the reported rate of the placebo group).

AE, adverse event; MeDRA, Medical Dictionary for Regulatory Activities

# Appendix F. Comparative analysis of efficacy and safety

A systematic literature review (SLR) was conducted to identify randomized controlled trials (RCT) assessing active treatments among patients with moderate to severe, active SLE. Due to considerations for payer's reimbursement and the perspectives of health technology assessment (HTA) bodies, for the indirect treatment comparison only comparator studies that investigated approved treatments were considered for inclusion (i.e., belimumab 10 mg/kg or 200 mg). Anchored simulated treatment comparisons (STC) were conducted following the methodology outlined in the NICE DSU TSD 18. This involves a regression model incorporating treatment effect modifiers (TEMs) as predictor variables are fitted to the pooled individual patient data (IPD) from TULIP-1, TULIP-2, and MUSE. Predicted outcomes for belimumab were estimated based on the fitted models while covariate values were set equal to the published means. Model performance was assessed through model convergence and model fit statistics (i.e., Akaike Information Criteria [AIC]). The relative importance of TEMs was ranked according to the quantitative differences between models with each treatment effect modifier and the unadjusted model. Four different outcomes (i.e., reduction in glucocorticoid [OCS] dose, proportion of patients that had British Isles Lupus Assessment Group [BILAG] flares, at least 4-point reduction in Systematic Lupus Erythematosus Disease Activity Index [SLEDAI] score, SLE responder index-4 [SRI(4)] response) were finally assessed at week 52 for examining comparative effectiveness of anifrolumab versus belimumab. Sensitivity analyses were also performed to test the robustness of primary results.

Anifrolumab 300 mg was compared to belimumab 10 mg/kg for the four outcomes reported in the comparator trials (i.e., BLISS-52 and BLISS-76): OCS reduction, BILAG flares, SLEDAI reduction, and SRI(4) response. There were statistically significant results in favor of anifrolumab 300 mg compared to belimumab 10 mg/kg for the outcomes of SRI(4) response (OR = 2.68, 95% CI: 1.24, 5.80) and SLEDAI score reduction (OR = 2.57, 95% CI: 1.19, 5.54). There were no significant differences between treatments for OCS reduction (OR = 0.99, 95% CI: 0.44, 2.23) or BILAG flares (OR = 0.75, 95% CI: 0.35, 1.61), although the point estimates numerically favored belimumab and anifrolumab, respectively.

Results of unadjusted indirect comparisons demonstrated no significant difference between anifrolumab and belimumab; in contrast, the STC results demonstrated that anifrolumab 300 mg was statistically superior to belimumab 10 mg/kg for SLEDAI reduction and SRI(4) response after accounting for key TEMs.

Because STCs account for between-study differences that may cause bias in unadjusted estimate, results from both the adjusted and unadjusted analyses should be considered when assessing comparative efficacy between anifrolumab and belimumab. While STC are able to adjust for important baseline and study characteristics, there have been some remaining differences in patients and study characteristics between the TULIP studies and the pooled BLISS study that cannot be accounted for due to the lack of reporting.

The full report of the indirect comparison can be found in Appendix K.

# Appendix G. Extrapolation

Only one parametric curves was fitted in the base case of the submitted economic model: the time to discontinuation of anifrolumab in the MUSE Open Label Extension (OLE) (NCT01753193). The data from this analysis were obtained from the final data cut of the MUSE OLE where patients were followed for a maximum of approximately 156 weeks, and therefore the majority of patients were censored for treatment discontinuation. As discontinuation data for patients treated with anifrolumab is required for up to five years within the time horizon of the economic model, of which discontinuation during the first year is assumed to come from alternative sources, the MUSE OLE data was required to provide up to four years of discontinuation data. As the follow-up in the study was only three years, outcomes must be extrapolated.

In the MUSE OLE, 79 of the 218 patients included discontinued treatment with anifrolumab. However, eight of these patients discontinued due to lack of access to anifrolumab, which is assumed not to occur if it is recommended and funded in clinical practice. Seven of these patients discontinued treatment due to the study sponsor closing the site and one patient relocated to an area without a study site in which to continue treatment. Therefore, for the purposes of estimating the discontinuation rate, these patients were assumed to be censored for discontinuation at the recorded discontinuation date, rather than considered a discontinuation event.

Prior to fitting the data a number of steps were considered to assess whether the data from the MUSE OLE were appropriate for extrapolating time on treatment with anifrolumab 300 mg for patients who are assumed to have received anifrolumab 300 mg for one year prior to the start point of using this data. Two factors were considered to potential bias this:

- **Patients are assumed to have received anifrolumab 300 mg for one year prior to applying long-term discontinuation rate:** patients enrolled in the MUSE OLE were included from all three arms of the randomized phase of MUSE. Of the 218 patients in the OLE, 65 (29.8%) had received placebo in the randomized phase and 73 (33.5%) had received anifrolumab 1000 mg, with only 80 (36.7%) receiving the licensed dose of 300 mg. Therefore, the assessment of whether prior anifrolumab exposure (including exposure at different doses) influence discontinuation rates needed to be assessed.
- **All patients initially received anifrolumab 1 000 mg in the OLE, but based on the benefit/risk profile from the RCT the 300 mg dose was selected for phase III studies and the dosage in the OLE was reduced to 300 mg:** As patients changed dose part way through the OLE, one must evaluate if the higher dose was associated with reduced tolerability and higher discontinuation rates, or conversely if some patients responded better on higher doses and the dose reduction led to a loss of efficacy.

To assess the validity of the data from the MUSE OLE as to whether the full population across the whole follow-up could be used, statistical tests were considered. Namely:

- Assessment of the relative hazard of discontinuation in the OLE between patients who had received anifrolumab 300 mg, anifrolumab 1000 mg, or placebo in the randomized phase of MUSE by visual inspection and Cox proportional hazards models
- Assessment of the time-dependent change in hazard of discontinuation by considering dose of anifrolumab (from 1000 mg to 300 mg) in the OLE as a time-varying covariate in a Cox model

Figure G1 shows the Kaplan-Meier plot of time to discontinuation for patients in the MUSE OLE, stratified by the therapy patients received in the randomized phase of MUSE. As can be seen, time on treatment was similar for all three groups. A Cox proportional hazards model fitted to the same data showed that time on treatment for patients receiving

anifrolumab 1000 mg (HR [redacted]; 95% CI [redacted], [redacted]) or placebo (HR [redacted]; 95% CI [redacted], [redacted]) in the randomized phase, was not significantly different to patients who received anifrolumab 300 mg. It is therefore assumed data from the full population, regardless of prior treatment, can be used as a reasonable approximation for the time on treatment for patients with anifrolumab with prior anifrolumab exposure.

**Figure G1. Kaplan-Meier plot of time on treatment in MUSE OLE, stratified by treatment received in randomised phase of MUSE**

As for the assessment in change in dose on discontinuation rate, the change in dose was not observed to change the hazard of discontinuation in the time-varying Cox model (HR [redacted]; 95% CI [redacted], [redacted]). This is supported by a naïve interpretation of the curves presented in Figure G2 below, where the observed time on treatment for patients following initiation of the 300 mg Q4W dose follows a similar trajectory for the time on treatment for the full population (from enrollment into the study, regardless of dose given). It was therefore assumed that the change in dose did not bias discontinuation rates of anifrolumab and the full trial follow-up could be used to reflect discontinuations rates, representative of a population of patients on anifrolumab 300 mg Q4W. Accordingly, parametric fitting to the data was done using the full population across the full follow-up of MUSE OLE.

**Figure G2. Kaplan-Meier plot of time on treatment in MUSE OLE for patients across the full trial follow-up, or just since initiating anifrolumab 300 mg Q4W**

The process for fitting and extrapolating parametric survival curves to the patient-level data was based on the methods guidance from the Decision Support Unit at the National Institute for Health and Care Excellence (NICE),[130] and guidelines from the Danish Medicines Council.[119] As the data from the MUSE OLE are single-arm (i.e., non-comparative), several steps of the guideline are not relevant to this case (e.g., statistical tests or graphical inspection of proportion hazards/accelerated failure time versus the comparator arm). Accordingly, only the following aspects were considered when fitting the data:

- Extrapolation of the curves on the range of standard parametric survival distributions (see Table G1 below)
- Visual inspection with regards to fit to the observed data (Kaplan-Meier curves) from the trial
- Goodness of fit statistics (Akaike Information Criteria [AIC] and Bayesian Information Criteria [BIC])
- External validation of curve extrapolation to support clinical plausibility

All survival modelling was conducted using the FlexSurv package in R and modelled using the flexsurvreg function. Six parametric models were considered for extrapolation of the full MUSE OLE population (see Table G1).

**Table G1. Parameteric functional forms fitted to the time to event data**

| Distribution | Survival Function | Characteristics |
|---|---|---|
| **Exponential** | $S(t) = \exp(-\lambda x)$ | Constant hazard function |
| **Weibull** | $S(t) = \exp\left(-\left(\frac{x}{b}\right)^{a}\right)$ | Hazard function can increase or decrease monotonically over time |
| **Gompertz** | $S(t) = \exp\left(-\frac{b}{a}(e^{ax} - 1)\right)$ | Hazard function can increase or decrease monotonically over time |

| Distribution | Survival Function | Characteristics |
|---|---|---|
| **Lognormal** | $S(t) = 1 - \Phi\left(\frac{\log(x) - \mu}{\sigma}\right)$ | Hazard function increases initially to a maximum, before decreasing over time |
| **Log-logistic** | $S(t) = 1 - \frac{1}{1 + \left(\frac{x}{a}\right)^{-b}}$ | Hazard function can be non-monotonic with respect to time, but often result in long tails in the survivor function |
| **Generalised Gamma** | $f(x\|\mu,\sigma,Q) = \frac{\|Q\|(Q^{-2})^{(Q^{-2})}}{\sigma x \Gamma(Q^{-2})}\exp\left(Q^{-2}(Qw - \exp(Qw))\right)$<br>$w = \frac{\log(Q^2\gamma)}{Q}$<br>$x = \exp(\mu + \sigma w)$ | Flexible three-parameter model that can be generalized to the Weibull, exponential, and lognormal distributions |

The parametric fits of the curves up to four years are shown compared to the three-year follow-up in the Kaplan-Meier data in Figure G3. As can be seen, within the trial period all six parametric fits provide a comparably good fit to the observed data. Even within the one year extrapolated period all six curves provide comparable results, ranging from [redacted]% at four years with the Weibull to [redacted]% for the generalized gamma (Δ[redacted]%). Given that these estimates only apply to patients continuing therapy beyond year one ([redacted]% in the base case), the extrapolated estimates of proportion of patients on treatment at the five year horizon in the model would only vary between [redacted]% and [redacted]% (Δ[redacted]%). Therefore, all explored model fits were considered to equally well fit the observed data and provide minimal variation in outcome. This is supported by the AIC and BIC criteria (reported in Table G2) that showed all model fits were comparable (ΔAIC <5).

**Figure G3. Fitted parametric curves compared to the Kaplan-Meier data from the MUSE OLE**

[redacted]

**Table G2. Goodness of fit statistics for the fitted time to discontinuation curves from the MUSE OLE**

| Functional Form | AIC | BIC |
|---|---|---|
| **Exponential** | [redacted] | [redacted] |
| **Weibull** | [redacted] | [redacted] |
| **Gompertz** | [redacted] | [redacted] |
| **Log-logistic** | [redacted] | [redacted] |
| **Lognormal** | [redacted] | [redacted] |
| **Generalised Gamma** | [redacted] | [redacted] |

Given that there is no evidence to suggest that any fit is superior to the other, and therefore a time-homogenous estimate was applied in the model to follow the Markov structure, as opposed to any semi-Markov approach. This is supported by the exponential distribution having the lowest BIC and providing a fit in line with all others explored.

This assumption was explored by comparing the estimated time on treatment to observed values for belimumab in the US (see Figure 31 in section 8.3.1). As can be seen, the modelled proportion of patients on treatment between months 12 and 20 (i.e., in the fitted period with RWE to compare on) is comparable to that as observed in the US data.

# Appendix H. Literature search for HRQoL data

As the submitted economic analysis was a cost minimization model, no health-related quality of data was included in the model and as such a literature search is not included in this submission.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

# Appendix I. Mapping of HRQoL data

As the submitted economic analysis was a cost minimization model, no health-related quality of data was included in the model and as such mapping was not required.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

# Appendix J. Probabilistic sensitivity analyses

No probabilistic sensitivity analysis is presented as the model is a cost-minimisation analysis, meaning a cost-effectiveness acceptability curve would be non-informative.



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

# Appendix K. Full report of the indirect treatment comparison on efficacy

*[Anifrolumab for adults with moderate to severe, active systemic lupus erythematosus (SLE): Simulated Treatment Comparison Technical Report]*

- Document appended to this submission



Medicinrådet Dampfærgevej 21-23, 3. sal DK-2100 København Ø +45 70 10 36 00 medicinraadet@medicinraadet.dk www.medicinraadet.dk

# Appendix L. Forecasting SLE prevalence for patient funnel

As anifrolumab is expected to be used in SLE patients without concurrent nephritis, contemporary estimates of the prevalence of SLE in Denmark were required. The latest published estimate of the prevalence of SLE and LN in Denmark is dated 31 December 2011.[53] As the prevalence of SLE in Denmark appears to be increasing, with each subsequent publication reporting a higher estimate,[53,60] it was determined that the prevalence estimates from 2011 would no longer be representative. Accordingly, these estimates were extrapolated.

The annual changes in the size of the prevalent SLE population is assumed to be a function of the prevalent SLE population in the previous year, the number of newly diagnosed SLE cases, and the number of deaths in SLE (given SLE is not curable and therefore patients will have their diagnosis for life). As a subset of this population, the prevalence of LN was also estimated based on the 2011 prevalence, the incidence, and the LN specific mortality rate.

The prevalence estimates for SLE (45.2 per 100 000) and LN (6.4 per 100 00) from 31 December 2011[53] were applied to the national population estimates for Denmark for adults (aged ≥18 years) on 1 January 2012 obtained from Danmarks Statistik.[131] As there were no clear temporal trends in the incidence of SLE between 1995 and 2011, the overall incidence is assumed to be constant at 2.35 per 100 000 per year in the extrapolation, and likewise for the incidence of LN at 0.45 per 100 000.

Mortality in SLE and LN was derived relative to general population lifetables, obtained from Danmarks Statistik.[113] In Danish SLE patients aged ≤50 years, the hazard ratio for mortality is 2.51-times greater than the general population, and it is 2.08-times greater in SLE patients aged >50 years.[33] Age- and sex-specific annualized mortality rates were derived by applying these estimates to the lifetables, and then an average probability of death in SLE was derived by creating a weighted average based on the average age and sex distributions of Danish SLE patients. According to the paper estimating the incidence and prevalence of SLE in Denmark, 86% of newly diagnosed cases are female where the median age of females at diagnosis is 46 years (IQR 34-57) and for males it is 54 years (IQR 42-65). The mean values and standard deviations were estimated using the formulae by Wan et al[115] in order to derive a distribution of ages for the weighted average. Based on this, the average annual probability of death in SLE patients overall in Denmark is approximately 3%.

To calculate the LN-specific mortality rate as a subset of that, the relative mortality rate was obtained from a Norwegian study where patients with LN had 3.8-times greater mortality than the general population. [132 132 125 124] Based on age and sex distributions of LN patients in Denmark,[53] the average annual probability of death in LN patients is estimated to be approximately 8%.

The table below shows the extrapolated estimates of the prevalence of SLE, LN, and non-nephritis SLE from 2012 up to 2022 as has informed the estimated number of patients and the patient funnel in the submission.



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| | 2012 | 2013 | 2014 | 2015 | 2016 | 2017 | 2018 | 2019 | 2020 | 2021 | 2022 |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **A) National population aged ≥18 years on 1 Jan** | 4 378 227 | 4 412 327 | 4 449 811 | 4 489 821 | 4 539 791 | 4 580 547 | 4 615 690 | 4 645 697 | 4 666 625 | 4 687 050 | 4 708 372 |
| **B) Adult SLE patients on 1 Jan** | 1 979 | 2 024 | 2 072 | 2 119 | 2 167 | 2 215 | 2 262 | 2 311 | 2 361 | 2 409 | 2 453 |
| C) Of which are patients with lupus nephritis | 280 | 278 | 276 | 275 | 275 | 274 | 274 | 274 | 275 | 276 | 276 |
| **D) Adults with newly diagnosed SLE during year** | 103 | 104 | 105 | 106 | 107 | 108 | 108 | 109 | 110 | 110 | 111 |
| **E) Adults developing LN during year** | 20 | 20 | 20 | 20 | 20 | 21 | 21 | 21 | 21 | 21 | 21 |
| **F) Deaths in adult SLE patients during year** | 58 | 55 | 58 | 58 | 59 | 60 | 60 | 59 | 61 | 66 | 67 |
| G) Of which are in patients with lupus nephritis | 22 | 21 | 21 | 21 | 21 | 21 | 20 | 20 | 20 | 21 | 21 |
| **H) Adult SLE patients without nephritis on 1 Jan** | 1 699 | 1 746 | 1 796 | 1 844 | 1 893 | 1 941 | 1 988 | 2 037 | 2 086 | 2 133 | 2 178 |
| **I) Patients with moderate to severe, active autoantibody-positive SLE despite standard therapy** | 614 | 631 | 649 | 666 | 684 | 701 | 718 | 736 | 753 | 771 | 787 |
| | | | | | | | | | | | |
| **Estimated prevalence of SLE per 100 000** | 45.2 | 45.9 | 46.6 | 47.2 | 47.7 | 48.4 | 49.0 | 49.7 | 50.6 | 51.4 | 52.1 |
| Estimated prevalence of non-nephritis SLE per 100 000 | 38.8 | 39.6 | 40.4 | 41.1 | 41.7 | 42.4 | 43.1 | 43.8 | 44.7 | 45.5 | 46.2 |

**Calculations:**

B[Y] = B[Y-1] + D[Y-1] - F[Y-1], derived from Hermansen (2016) in Y1
C[Y] = C[Y-1] + E[Y-1] - G[Y-1], derived from Hermansen (2016) in Y1
D[Y] = A[Y] * 2.35/100 000
E[Y] = A[Y] * 0.45/100 000
F[Y] = B[Y] * $q_{SLE}$[Y], where $q$ is age- and sex-weighted mortality rate
G[Y] = C[Y] * $q_{LN}$[Y], where $q$ is age- and sex-weighted mortality rate
H[Y] = B[Y] - C[Y]
I[Y] = H[Y] * 36.1% (see section 5.1.4)

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