The budget impact of Belimumab SC compared to the standard of care in adult patients with antibody-positive systematic lupus erythematosus in the Dutch setting

MSc Health Sciences thesis research report

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Abstract

Objective

This study evaluates the budget impact and the direct and indirect costs of using Belimumab subcutaneous (SC) for systemic lupus erythematosus (SLE) patients in the Dutch setting.

Methods

The budget impact model of Belimumab SC was developed from a Dutch societal perspective with a time horizon of three years (2023 – 2025). The budget impact of Belimumab SC was calculated as the cost difference between the two scenarios: the future scenario (with Belimumab SC) and the current scenario (without Belimumab SC). The eligible prevalence population could be defined as adult, antibody-positive SLE patients with moderate to severe active disease activity in the Netherlands (n = 937). The included direct costs were the pharmacological costs, administration costs, adverse events costs, and management of flares costs. Besides, the included indirect costs were the costs of organ damage, dialysis or transplantations due to End Stage Kidney Disease (ESKD), and productivity loss or absenteeism. The data from the BLISS-SC trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of Belimumab SC in adult subjects with active SLE, formed the basis for the budget impact model of Belimumab SC. In addition, the model was informed by published peer-reviewed literature, market research data, and official publications. Sensitivity and scenario analyses were performed.

Results

For the pharmacological cost factor, the budget impact of Belimumab SC over three years was approximately €9.6 million. In addition, the budget impact of Belimumab SC for managing flares was about -€1.9 million over three years. Furthermore, the budget impact for adverse events was approximately -€800,000 over three years. The budget impact for productivity loss or absenteeism was about -€2.6 million over three years. The second last factor, dialysis or transplantation due to ESKD, gave a budget impact of approximately -€450,000 over three years. Finally, the irreversible organ damage factor gave a budget impact of around -€110,000 over three years. Based on these cost factors used in the budget impact model, the total budget impact of Belimumab SC resulted in an expenditure of approximately €3.7 million over three years in the Dutch setting.

Conclusion

The budget impact model developed in this study indicated that Belimumab SC in addition to the standard of care (BSoC), resulted in increased expenditure compared to the patients treated with the standard of care (SoC) in the Dutch setting over three years. The budget impact analysis provides decision-makers on a national level with an overview of the direct and indirect costs, allowing better management of the hospital budgets regarding expensive intramural drugs. For this study, we used assumptions and values that were, to the best of our knowledge, the most suitable in the Dutch setting to assess the future impact of Belimumab SC. This data emphasizes the importance of controlling and monitoring flares, loss of productivity, and pharmacological costs, which are the leading causes of rising societal costs. Future improvements can be made using a retrospective cohort study in the Dutch setting to demonstrate the impact of BSoC on SLE patients.

Keywords

Systemic lupus erythematosus, Belimumab, Budget Impact Model, Dutch setting, Flares

Index

Abbreviations and Dutch terms

Abbreviation or Dutch term	*Spelled out in full or English translation*
BSoC	Belimumab SC + Standard of Care
SoC	Standard of Care
SC	Subcutaneous
IV	Intravenous
ANA-test	Antinuclear Antibodies Test
CNS	Central Nervous System
EULAR/ACR	European Alliance of Associations for Rheumatology
Integraal Zorgakkoord	Integral Care Agreement
Middelbaarberoepsonderwijs-4 (MBO-4)/ Hogerberoepsonderwijs (HBO)	Secondary vocational education/ Higher vocational education
SLICC/ACR	Systemic Lupus International Collaborating Clinics/ American College of Rheumatology
SDI	SLICC Damage Index
Zorginstituut Nederland (ZiN)	National Healthcare Institute
Nederlandse Zorgautoriteit (NZa)	Dutch Healthcare Authority
Diagnose Behandeling Combinatie (DBC)	Diagnosis Treatment Combination (DTC)
Nederlandse Vereniging voor Ziekenhuizen (NVZ)	Dutch Association of Hospitals
Nederlandse Federatie van Universitair Medische Centra (NFU)	Dutch Federation of University Medical Centers

Introduction

Systemic lupus erythematosus (SLE) is a chronic auto-immune disease that can cause inflammation in multiple organs. The organs and systems most likely involved include the kidneys, skin, and joints [1]. As a result of the inflammation in connective tissues, patients may experience flares and exacerbations when their condition deteriorates. This can negatively affect the patient's quality of life or, at worst, be life-threatening [2,3]. To suppress flares and exacerbations, the treatment mainly consists of drugs such as antimalarials, corticosteroids, and immunosuppressive drugs [4]. However, the treatment used for SLE patients depends on the severity of the disease manifestations, which can be categorized as mild, moderate, or severe disease activity [5]. In addition, patients with this progressive chronic disease may eventually develop lupus nephritis (LN), the most common manifestation of SLE. In about 40.0% of patients, there is evidence of developing LN from SLE annually [2]. As a result of the flares or inflammations of progressive disease and possible LN manifestation, the risk of developing organ complications, irreversible organ damage, and mortality is high [5]. Therefore, it is essential to reduce the number of flares or inflammations with adequate drug treatment.

Despite the availability of several drugs to treat SLE, the treatment goal, decrease in disease activity, less frequent flares, and lower dose of corticosteroids is frequently not (yet) achieved [6]. One of the drugs that can be used to treat moderate to severe SLE is Belimumab in either a subcutaneous (SC) or intravenous (IV) formulation. Belimumab is a human IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble BLyS protein [7]. Belimumab thereby inhibits BLyS-mediated survival and maturation of B-cells and the generation of autoreactive antibodies [8]. Belimumab SC was initially investigated in the BLISS-SC trial, a phase 3, multicenter, randomized, double-blind, placebo-controlled, 52-week study, to evaluate the efficacy and safety of Belimumab SC in adult subjects with active SLE. The study demonstrated a significant reduction in disease activity and flare-ups in moderate to severe SLE [9]. These are successful endpoints for an SLE treatment that is sufficient to meet patients' needs for safe and more effective treatment [3,6].

Minimizing healthcare costs of flares and inflammations is of interest. The costs of frequently occurring flares are a relatively large share of the economic burden of SLE by increasing the annual costs of SLE management by 97.4% in Europe [10,11]. In addition, healthcare budgets are under more and more pressure [12]. Based on the Integral Care Agreement, in which agreements were made between the Ministry of Health, Welfare and Sport and many healthcare parties, only 1.0% budget growth is allowed for specialized medical care in 2023. Drugs are only a tiny part of this, but the budget impact for these ‘expensive’ drugs becomes increasingly important [13]. However, despite a large number of studies on the efficacy of Belimumab, there is limited evidence available on the health economic impact of Belimumab in SLE in Europe [11]. Only two studies in Europe evaluated the budget impact of Belimumab. Both studies were conducted from a country-specific perspective (Italian and Spanish) of the NHS. As a result, incidence, prevalence, mortality rates, and demographic characteristics are also country-specific. Besides that, both studies used country-specific costs such as pharmacological costs, administration costs, and management of flare costs [14,15]. In addition, the Spanish research used a different comparison, looking at standard therapy and intravenous Belimumab compared to patients who switched from Belimumab IV to Belimumab SC until 17.0% of the total market share was reached [14]. As a result, these studies are not applicable or relevant to the Dutch setting.

No studies have yet taken place on the budget impact of Belimumab SC in addition to the standard of care (SoC) consisting of a corticosteroid, an immunosuppressant, and an antimalarial for patients with SLE in the Dutch setting [4]. The decision-makers on a national level do not yet know how to manage the budgets regarding Belimumab SC as an expensive intramural drug. This is because the budget impact of Belimumab SC is not yet available to prescribe the decision-makers with information. This study aims to evaluate the budget impact of Belimumab SC + SoC (BSoC) compared to SoC in adult patients with antibody-positive SLE from a Dutch societal perspective. Therefore, a budget impact model of Belimumab SC will be developed.

Background

Population eligible for Belimumab

Belimumab can be used as an adjunctive treatment for patients aged five years and older in auto-antibody-positive SLE patients with moderate to severe disease activity [3,7]. SLE is a chronic auto-immune disease that can cause multiple organ inflammation [1]. As a result of the inflammation in connective tissues, patients may experience flares and exacerbations when their condition deteriorates. This can negatively affect the patient's quality of life or, at worst, be life-threatening [2,3].

The effect of Belimumab

Belimumab is an addition to the SoC, meaning adding the additional drug may enhance the therapeutic effect [16]. Indeed, studies have shown that using Belimumab as an addition to the SoC significantly reduces disease activity and flare-ups [2,3,16]. Belimumab is a human IgG1λ monoclonal antibody that binds and antagonizes the biological activity of soluble BLyS protein [7]. Belimumab thereby inhibits BLyS-mediated survival and maturation of B-cells and the generation of autoreactive antibodies [8].

Administration of Belimumab

The administration route of Belimumab can be either IV or SC; the therapeutic value of both ways of administration is the same [17]. Based on the medicine overview of the European Medicines Agency (EMA), the patient should receive doses of 10.0 mg/kg of Belimumab IV on days 0, 14, and 28 and at a 4-week interval base after that. Therefore, 15 IV administrations are given in the first year because patients receive three doses in the first month and 12 doses after. In subsequent years, patients also receive the doses at 4-week intervals, so a quantity of 12 administrations. Besides Belimumab IV, Belimumab SC's dosing and dosing schedule should also be considered [7]. The recommended dosage for Belimumab SC, according to the medicine overview of the EMA, is 200 mg once a week for SLE patients [7]. In addition, the BLISS-SC trial also maintained a quantity of 52 administrations of Belimumab SC per year [18]. Therefore, the estimation is 52 administrations per year.

Belimumab in the basic insurance package

Residents of the Netherlands are required to have basic health insurance to receive medically necessary care. The central government compiled this medically necessary care, called the basic insurance package [19]. Most prescription drugs are also reimbursed from this basic health insurance. This also includes the biological treatment Belimumab, which has been added to the basic package by the National Healthcare Institute since 2018 due to the added value this treatment provides for patients with SLE [6].

Effect of Belimumab on flares

One significant effect of Belimumab SC is the prevention of flares in SLE patients. Indeed, flares in a progressive disease like SLE and the possible manifestation of LN increase the risk of hospitalization, the development of organ complications, and irreversible organ damage. This ultimately results in increased mortality among these patients [20].

Irreversible organ damage

By using Belimumab SC, the disease activity is reduced. As a result, flares occur less frequently, and the patient needs to use corticosteroids to a lesser extent [21]. SLE patients treated with Belimumab SC are more likely to use lower doses of corticosteroids than those treated with SoC alone. This is advantageous for the SLE patient treated with BSoC, because prolonged use of corticosteroids in the presence of persistence of disease or during flares can contribute to organ damage [22]. The Systemic Lupus International Collaborating Clinics/American College Rheumatology (SLICC/ACR) Damage Index (SDI) is accepted to be the instrument to measure irreversible organ damage across multiple organs in SLE patients from SLE disease activity and treatment. The scoring of irreversible organ damage starts when a patient is diagnosed with SLE. In this regard, it does not matter whether the

damage is ascribed to lupus or not [23]. At SLE diagnosis, the SDI score is, in definition, zero. However, the mean SDI tends to increase over the years. Therefore, the mean change in SDI is the change in SDI score from the baseline. This instrument was also used in the BLISS-SC trial and is the only validated measure to assess irreversible organ damage across multiple organs in SLE patients [24].

Progression to End Stage Kidney Disease from SLE

As mentioned earlier, LN is SLE's most common and severe manifestation. Up to 40.0% of the SLE patients develop LN annually [25]. LN results in inflammation of the glomeruli present in the kidneys. The glomeruli are small blood vessels that filter waste substances in the body. Like SLE, LN is also an autoimmune disease, with autoantibodies causing kidney inflammation [26]. At every inflammation in the kidneys, irreversible damage occurs, making filtration impossible and significantly reducing the lifespan of the kidneys per flare. This results in the patient progressing to end-stage kidney disease (ESKD). About 10.0-25.0% develop ESKD annually from onset LN due to kidney damage [27]. Because of the incidence rates, there is minimal risk of progressing to LN due to renal flares in SLE and eventually progressing to ESKD. To treat ESKD, dialysis or kidney transplantation should be used. These two forms of treatment significantly impact these patients' mortality and greatly affect their quality of life [28].

Materials and methods

The pharmacy and medical costs budget impact model of Belimumab SC was developed to compare the SoC from a Dutch societal perspective with a time horizon of three years (2023 – 2025). Discounting was not applied in the budget impact model because the results should be presented annually. The included direct costs within healthcare were the pharmacological costs, administration costs, adverse events costs, and management of flare costs. Besides, the included indirect costs within health care were the costs of organ damage, dialysis, and transplantations. Also, the indirect costs outside healthcare consisted of productivity and absenteeism loss. The direct costs outside healthcare were excluded.

The BLISS-SC trial data formed the basis for the budget impact model of Belimumab SC, which was described in the identification of the base cohort. In addition, the model was supplemented by published peer-reviewed literature, market research data, and official publications. The budget impact model was built using Microsoft Excel (Version 2208 Build 16.0.15601.20526) on a national submission level under the supervision of GlaxoSmithKline. Finally, some data consisted of assumptions. A superscript in the text indicated the assumptions, see Appendix 5: Overview of the assumptions in the study. Since the pharmacological costs contained the most recent prices from 2023, we considered these current prices. However, we used the 2021 CPI for the other cost factors. This is because the complete data for productivity loss also dates from 2021.

Identification of the base cohort

Demographic and baseline disease activity data were needed to evaluate the budget impact model of Belimumab SC that could match the population characteristics of the Dutch setting and treatment groups. Through collaboration with GlaxoSmithKline, we identified the BLISS-SC study as the preferred source of BSoC and SoC data for this study. The BLISS-SC trial is a phase 3, multicenter, randomized, double-blind, placebo-controlled, 52-week study to evaluate the efficacy and safety of Belimumab SC in adult subjects with active systematic lupus erythematosus. This multicenter study was conducted in 30 countries in North America, Central America, South America, Western Europe, Eastern Europe, and Asia. The demographics were generally comparable between the treatment groups. Most subjects were women (94.4%), and the mean age was 38,6 years. The intention-to-treat population in the BLISS-SC trial was predominantly white (60.0%) [9]. See Appendix 2: Demographics summary of the BLISS-SC trial. Besides assuming the demographic characteristics of the BLISS-SC trial as the basis for the budget impact model[1], the baseline disease activity was also considered the basis[2]. The efficacy assessments measured in the BLISS-SC trial included the clinical disease activity scales (SELENA SLEDAI, British Isles Lupus Assessment Group [BILAG], modified SLE Flare Index, disease activity index, Physician's Global Assessment [PGA], SLICC/ ACR Damage Index, the Prednisone dose (percentage change from baseline), renal flares and proteinuria (percentage change from baseline >0.5 g/24h) [9]. See Appendix 3: Baseline disease activity of the BLISS-SC trial. The primary endpoint was the SLE Responder Index (SRI4) at week 52. Secondary endpoints were reduced corticosteroid dosage and time to severe flare [9]. GlaxoSmithKline was involved from the study's design to the interpretation of the data. The study sponsor, Human Genome Sciences Inc., organized and paid for the clinical BLISS-SC trial.

Study design

A retrospective design was used for this study, looking back in particular at previously obtained data from the BLISS-SC trial. Quantitative research supplemented the data from the BLISS-SC trial.
In addition, this study focused on the SC administration form of Belimumab. Studies indicated that the therapeutic effects of both the IV and SC administration forms are similar [17,29]. However, Belimumab SC is more convenient, time-saving, easier to use, and easier to incorporate into patients' daily routines [29]. Looking to the future, where more efficient care through convenient routes of administration will be increasingly demanded, Belimumab SC may be a real advantage over IV [30]. Hence, in this study, we assumed that 100.0% of SLE patients used Belimumab SC[3].

Market share

The market share for the future scenario was estimated at 27.0% in 2023, 2024, and 2025 for eligible Dutch SLE patients. This market share estimation came from GlaxoSmithKline data, where approximately 27.0% of the potential SLE patients were treated with Belimumab SC or Belimumab IV in combination with SoC compared to the SoC in 2023. We also used this market share in this study, where we assumed that 27.0% of the eligible SLE population with moderate to severe disease activity and antibody positivity used BSoC in the year 2023, 2024, and 2025 compared to 73.0% of the eligible SLE population treated with SoC. However, our current situation in the budget impact model started with no use of Belimumab SC, 0.0% market share for BSoC[4].

Treatment compliance

The BLISS-SC trial indicated that the mean overall treatment compliance was equal to 96.4% in both the BSoC and SoC treatment groups. This percentage was calculated by multiplying 100.0 by the number of injections prescribed minus the number of injections missed, divided by the number of injections prescribed. So, using the overall treatment compliance, we saw that some injections were also missed compared to the prescribed amount. However, this high treatment compliance rate indicated that this population could self-administer Belimumab SC outside a clinical setting. As there was only a small number of patients (3.6%) who did not remain treatment in the BLISS-SC for both BSoC and SoC, we did not consider this relevant to include potential costs of this in terms of waste in the budget impact model of Belimumab SC. We, therefore, assumed treatment compliance of 100.0%[5].

Patient population

The eligible population to receive Belimumab SC as an addition to the SoC was calculated from the Netherlands' general adult (≥ 18.0 years) population. Using epidemiological data from the National Healthcare Institute of 2019, the prevalence of SLE is 28.0–40.0 per 100,000 inhabitants (0.028% - 0.04%) in the Netherlands [31]. This indicated that 7,137 inhabitants were diagnosed with SLE in the Netherlands. However, in Italy, the prevalence of SLE patients was 39.2-81.0 per 100,000 inhabitants (0.08%) in 2022 [32]. Based on the 2019 European Alliance of Associations for Rheumatology (EULAR/ ACR) criteria, inhabitants diagnosed with SLE due to a negative antinuclear antibodies test (ANA-test) were excluded. These criteria have a sensitivity of 96.0%, where the ANA-test looks at anti-dsDNA antibodies, anti-Sm-antibodies, and antiphospholipid antibodies [4]. Therefore, the diagnosed SLE patients with a positive ANA-tested SLE were included. In addition, positive-tested SLE patients suffering from severe active Central Nervous System (CNS) lupus were excluded [33]. Again, based on the 2019 EULAR/ACR criteria, a sensitivity of 96.0% is maintained for SLE patients not suffering from CNS lupus. For the treatment of Belimumab SC, non-renal SLE patients were considered. LN involves renal treatment in approximately 25.0% to 40.0% of the cases [5,25]. Therefore, a range between 60.0% and 75.0% of the SLE population with a non-renal treatment was used. Belimumab SC can be used in active SLE with moderate to severe disease activity. According to the 2019 EULAR/ACR criteria, moderate to severe disease activity can be classified with the SLE disease activity index (SLEDAI) with a score of >6 [4]. Based on a study by Speyer B et al. (2020), about 28.0% experience moderate to severe disease activity according to the SLE Disease Activity Index-2000 (SLEDAI-2K), with a score of ≥6 [34]. The number of patients suffering from moderate to severe disease activity may thus reach about 28.0%. In addition, based on an expert in the area and studies, an average annual incidence of 19.0% was also a good representation of patients experiencing high disease activity levels [35,36]. Therefore, a range between 19.0% and 28.0% of the SLE population with moderate to severe disease activity was assumed. As shown in Table 1, the target population can be defined as adult, antibody-positive SLE patients with moderate to severe active disease activity (SLEDAI >6) without CNS.

In the budget impact model, the annual incidence and mortality were considered. Several studies in other European countries showed incidence rates between 1.2 – 8.6 per 100,000 person-years. The studies explained that the trigger for the development of SLE depends on genetic background, environmental factors, and endogenous conditions (especially hormonal factors). SLE is more common in women; 90.0% of SLE patients are women. Besides, SLE is more common in individuals

of African American, Afro-Caribbean, and Asian descent. In addition, exposure to sunlight (UV) is a factor that can trigger SLE [37–39]. Since these factors are present to a lesser extent in the Netherlands, we assumed an incidence rate of 1.4 per 100,000 person-years. This overlapped with a study by Brinks R et al. which estimated the incidence rate of SLE for German males and females[6] [38]. Also, there is little recent data available about mortality rates, and no figures were found for the Dutch setting. However, several European studies did show consistent mortality rates ranging between 13.8 and 16.0 deaths per 1,000 person-years [40–42]. Due to the lack of meta-analyses on mortality in the literature, a mortality rate of 14.9 per 100,000 person-years was assumed.

Table 1 Estimated adult Dutch population with moderate to severe disease activity and positive ANA-test

	N	***References***
Dutch adult population 2023	17,842,995	CBS population counter [43]
Prevalence SLE (diagnosed)	7,137 (**0.04%** - 0.081%)	Horizonscangeneesmiddelen [31] Margherita Zen, Laura Salmoso et al. Systemic lupus erythematosus incidence and prevalence in a large population-based study in northeastern Italy [32]
ANA-test	6,852 (96.0%)	2019 EULAR/ACR [4]
Severe active CNS lupus excluded	6,578 (96.0%)	2019 EULAR/ACR [4]
SLE population non renal	4,933 (60.0% - **75.0%**)	Bultink I, Tsang-A-Sjoe M. Systemische lupus erythematosus. Amsterdam: 2022 [5]
SLE population with moderate to severe disease activity	937 (**19.0%** - 28.0%)	Expert opinion Speyer CB, Li D, Guan H, Kazuki Yoshida ·, Stevens E, Jorge AM, et al. Comparison of an administrative algorithm for SLE disease severity to clinical SLE Disease Activity Index scores [34]

* *The numbers in bold are the numbers used for the calculations in the budget impact model*

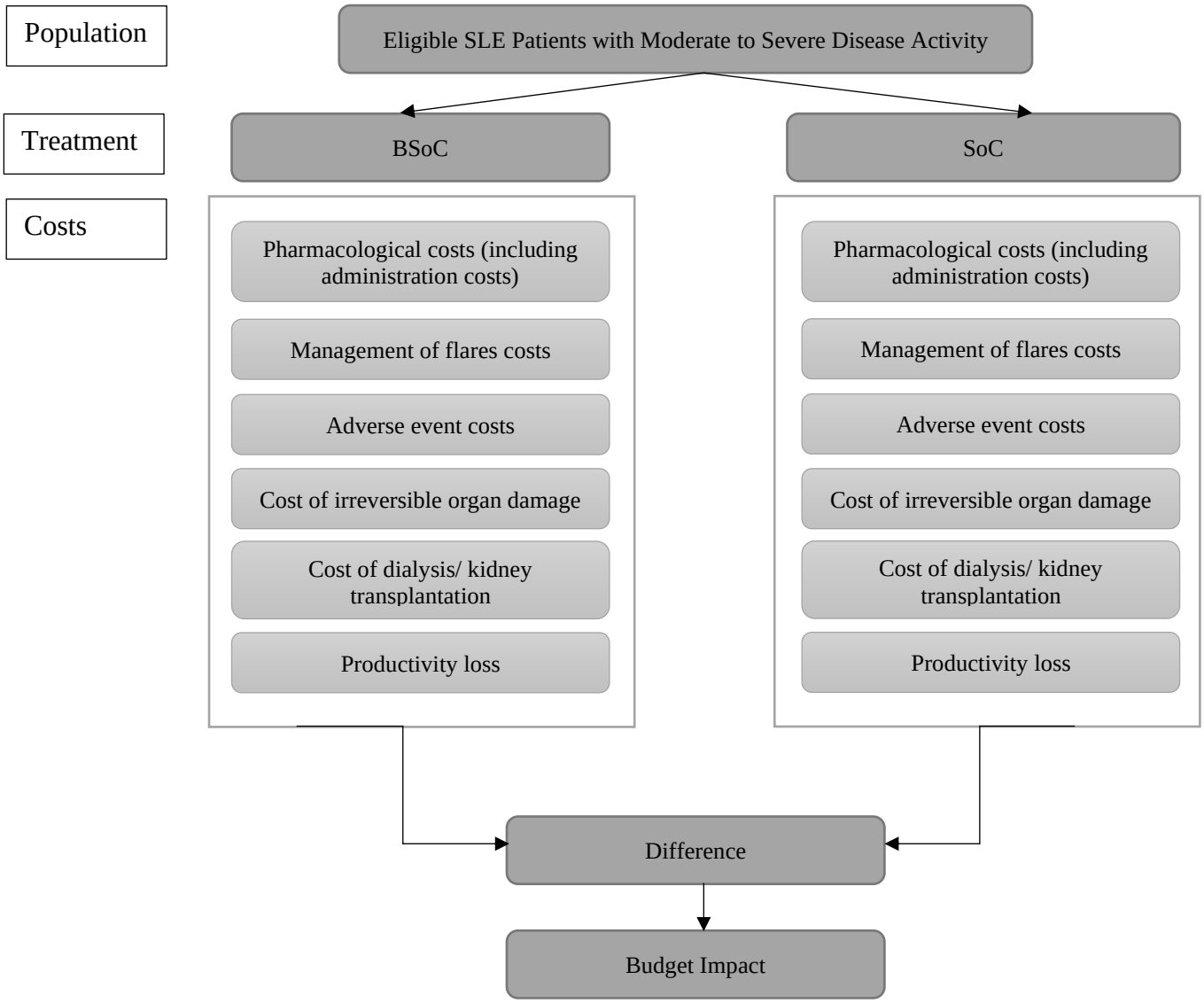
Despite retaining the demographic characteristics of the BLISS-SC trial as the basis of this study, the weight and height were adjusted to the Dutch population. According to the statistics of the CBS, the average weight of women is 72.0 kg, and the average weight of men is 85.0 kg in the Netherlands [44]. Based on this data, a gender-adjusted weighted average of 72.7 kg that applies to the Dutch setting was assumed[8]. In addition, for height, we used the average height of the Dutch population, with women having a height of 170.36 cm and men having a height of 183.78 cm [45]. A gender-adjusted average height of 171.11 cm was assumed[9].

Finally, we incorporated so-called responders and non-responders. According to the BLISS-SC trial, the response was defined as a decrease of at least four points in the SLEDAI score during the first year. Based on expert opinion and the Dutch Autoimmune Registry (DAiRE-register) 2018, the percentages of responders and non-responders to BSoC and SoC were determined. The data collected in the DAiRE made a start with a national SLE register. The registry will be continued to contribute more knowledge, but it is still being determined when this will be restarted. However, based on the DAiRE 2018, a percentage of 30.0% of non-responders to BSoC and SoC present in the target population was assumed [46]. The responders are the SLE patients who completed their first year of using BSoC or SoC. In contrast, non-responders discontinue BSoC or SoC during the first year due to treatment failure. We assumed that in the first year, 100.0% of the patients continued with their BSoC or SoC treatment, but in the second year, only 70.0% (responders) continued with BSoC or SoC[10].

Factors influencing the budget impact model

The budget impact model included both direct and indirect costs. Below, the methods used for the different cost factors included in the Belimumab SC budget impact model were explained. In addition, Figure 1 provides the budget impact model structure, including the various cost factors.

Figure 1 Budget Impact model structure



** The market share in the current scenario is 0.0% and in the future scenario 27.0% for BSoC*

Exchange Rate and Consumer Price Index

In case costs from another country or costs from the past had to be used, the exchange rate (ER) and the consumer price index (CPI) had to be applied. These costs had to be converted to euros in 2021 using the ER and the CPI.

Exchange rate and the corresponding date

The used average exchange rates over a year were used from different years. The prices in euros were calculated by multiplying the foreign currency with the exchange rate to euros in the same year as the foreign currency [47]. The corresponding date (CD), therefore, indicated the year of the foreign currency.

$$Exchange\ rate = \frac{\text{Starting amount (base currency)}}{\text{Ending amount (foreign currency)}}$$

Consumer Price Index
The reference price dates from different years were used in this formula. The prices were indexed to 2021 using the Dutch-derived CPI values [47]. In the formula below, we used a price out of 2018 as an example to indicate the use of the price out of 2018 and the CPI out of 2018 in the formula. In combination with the CPI out of 2021, it was possible to calculate the value of 2021.

$$Value_{2021} = Value_{2018} \times \frac{CPI_{2021}}{CPI_{2018}}$$

Direct costs within healthcare
Pharmacological
For direct costs within healthcare, the budget impact model of Belimumab SC included the pharmacological costs. The pharmacological costs considered are the costs of BSoC and SoC, and the administration costs of BSoC and SoC. The dosage and dosing schedule were used to estimate the annual treatment cost of BSoC and SoC. The dosing schedule for Belimumab SC requires the patient to receive two doses of 200 mg/kg (two pre-filled pens) for the first four weeks. This is followed by weekly doses of one pre-filled 200 mg/kg Belimumab SC pen. Therefore, 56 administrations for the first year when using Belimumab SC and 52 administrations in the years after the first year were assumed[11] [9]. As a result, four additional doses were allocated in the first year in patients treated with BSoC. Based on the Z-index of February 2023, the cost for one Belimumab SC 200 mg dose was €235.79. This resulted in a price per mg of €1.18 for Belimumab SC.

In addition, the drug usage of SoC needed to be considered. The EULAR/ACR 2019 criteria guidelines considered the SoC drugs used in the BLISS-SC trial. In this study, the costs of the corticosteroid Prednisone, the antimalarial Hydroxychloroquine, and the immune-suppressants Methotrexate, Mycophenolate Mofetil, and Azathioprine were considered. Based on the DAiRE 2018 report, 85.0% of patients are believed to use Hydroxychloroquine, 85.0% Prednisone, 43.0% Mycophenolate Mofetil, 48.0% Azathioprine, 35.0% Methotrexate. Non-steroidal anti-inflammatory drugs (NSAIDs) are not considered in the DAiRE 2018 report [48]. The NSAIDs usage was not considered, except for the baseline use of the NSAIDs, in the BLISS-SC trial. Based on the EULAR/ACR 2019, we could explain this given that these guidelines do not use NSAIDs as standard care for SLE patients [4]. Therefore, NSAIDs were not included. The CADTH Pharmacoeconomic Review Report of Belimumab (Benlysta) was used for strength, dosage form, and the recommended dose to identify the dosage schedule of the SoC [49]. The average doses were derived from the recommended doses. In addition, based on the pharmacotherapeutic compass of Zorginstituut Nederland (ZiN), the prices per mg were estimated according to the prices per piece in May 2023 [50–54]. The dosing schedule and prices for the SoC are shown in Table 2.

Table 2 Standard of care treatment dosage schedule and prices

Drug/ Comparator	***Strength***	***Dosage form***	***Recommended dose***	***Average dose***	***Price per piece (€)***	***Price per mg (€)***
Corticosteroids						
Prednisone (generic)	5 mg	Oral tablet	≤ 7.5 mg/day	10.90 mg/day	0.05	0.01
Antimalarials						
Hydroxychloroquine (Plaquenil, generic)	200 mg	Oral tablet	200 to 400 mg/day	300 mg/day	0.13	0.00065
Immunosuppressants						
Methotrexate (generic)	10 mg	Oral tablet	7.5 to 10 mg/week	8.75 mg/week	0.20	0.02
Mycophenolate Mofetil (generic)	500 mg	Oral tablet	1000 to 1500 mg/day	1250 mg/day	1.98	0.00396
*Azathioprine (generic)**	50 mg	Oral tablet	50 to 100 mg/day	75 mg/day	0.46	0.0092
Reference	[49]	[49]	[49]		[50–54]	

** Azathioprine was used as a base immunosuppressant as it is the most used among SLE patients (48,0%)*

The treatment usage needed to be considered to estimate the pharmacological costs for the SoC. The immunosuppressant Azathioprine was used as the base because it is the most used immunosuppressant in SLE patients, according to the 2018 DAiRE report [48]. In addition to using Azathioprine, the pharmacological costs included Hydroxychloroquine as an antimalarial drug and Prednisone as a corticosteroid. Since the BLISS-SC demonstrated a mean Prednisone dose of 10.9 mg/day at baseline, we assumed this treatment dose for the eligible SLE patients[12] [9]. For the other drugs, we used the average dose. The average drug cost per mg by the dose per month (mg) was estimated by multiplying it with the total average monthly drug costs for SoC. Besides, the total average annual drug costs were calculated by multiplying the dose per year (mg) by the average drug cost per mg. For the SoC, the total average annual or monthly drug costs of the corticosteroid, antimalarial and immunosuppressant Azathioprine were added together to arrive at the total average annual or monthly drug costs. These total average annual or monthly drug costs were added to the total average annual or monthly drug costs of BSoC, which were also estimated by multiplying the average drug cost per mg by the dose per month (mg) or dose per year (mg), respectively. See Appendix 6: Treatment dosage and costs for an overview of the treatment dosage and costs.

The SLE patient can inject Belimumab SC through a pen. However, the SLE patient needs to learn how to use this subcutaneous administration of Belimumab. The SLE patient should therefore have two administration appointments of half an hour each in the first year with a higher-educated nurse (MBO-4/ HBO-V) to explain the administration method [3]. The administration costs were estimated using the cost guide for economic evaluations (2016) to obtain the reference price. Based on the cost guide, an hourly rate of €32.39 was assumed for the higher-educated nurse [55]. However, based on the CBS's Customer Price Index (CPI) values, we took an hourly rate of €35.64 for 2021[13]. For the SoC, there were no administration costs as the drug was administered orally. The administration costs due to treatment with BSoC were allocated as additional costs along with the four additional doses to the first year of treatment.

Finally, since the BLISS-SC trial demonstrated a corticosteroid dosage reduction by ≥ 25.0% (to ≤ 7.5 mg/day) during weeks 40-52 in 18.2% of the patients in the BSoC treatment group and 11.9% in SoC treatment group (OR 1.65 [95% CI 0.95–2.84]; P = 0.0732) [9], we assumed a mean corticosteroid usage for the BSoC of 8.6 mg and a mean corticosteroid usage of 10.7 mg for the SoC at 52 weeks[14] [56]. To estimate the reduced use of the corticosteroids in the cost, the cost of the difference in dosage from week 52, for BSoC 2.2 mg/day and SoC 0.2 mg/day, compared to the mean use at baseline in the overall population (10.9 mg/day) was subtracted from the total mean annual cost in years two and

three after starting treatment with BSoC or SoC. This reduction was only applied to 18.2% of the BSoC treatment group population and 11.9% of the SoC treatment group population.

Management of flares

The Lupus Foundation of America (LFA) defined a flare as a measurable increase in disease activity in one or more organ systems involving new or worse clinical signs and symptoms and laboratory measurements. The assessor must consider it clinically significant, and usually, there would be at least consideration of change or an increase in treatment [57]. The number of flares from the BLISS-SC trial were estimated using the SLEDAI score. The mild, moderate, and severe disease activity was divided into SLEDAI scores ≤ 6, 7-12, and >12, respectively. According to existing validated indices, flares in SLE can be defined as an increase by >3 for mild/moderate flares and an increase by >10 for severe flares in the SLEDAI scores or can require hospital admission [58]. According to the BLISS-SC trial, the proportion of patients experiencing a severe flare over 52 weeks was 10.6% in the BSoC treatment group and 18.2% in the SoC treatment group. In addition, the percentage of patients that experienced mild/moderate flares was 60.4% in the BSoC treatment group and 67.5% in the SoC treatment group [59]. On behalf of these percentages, the annual proportion of patients out of eligible SLE patients, who may have experienced a severe or mild/moderate flare, was estimated. As demonstrated in the BLISS-SC trial, the BSoC had an annual mean amount of 1.23 mild/moderate flares and 0.04 severe flares. In addition, the SoC had an annual mean amount of 1.69 mild/moderate flares and 0.22 severe flares [9]. We did not distinguish between the mild and moderate flares based on the BLISS-SC trial[15].

A within-trial economic analysis of flare data from the BLISS-SC trial (2021) analyzed the claims to compute the unit costs of flares by severity. The mean unit cost obtained per severe flare was $9,273 [60]. Based on the average ER and corresponding date CD, the assumed mean unit cost per severe flare was considered €7,843 (ER:0.8458, CD:2021) [47]. In addition, the average cost for mild/moderate flares was estimated. The average unit cost was $2,303 per mild/moderate flare [60]. Converted to euros, we assumed that the mean unit cost per mild/moderate flare was €1,948 (ER:0.8458, CD:2021)[16] [47]. The costs for the severe and mild/moderate flares included the costs of staff, hospitalizations and biopsy, laboratory tests, and imaging techniques [60]. The flare costs were estimated by multiplying the costs of the severe or mild/moderate flares with the associated annual mean number of severe or mild/moderate flares and the annual proportion of patients who may have experienced a severe or mild/moderate flare.

Adverse events

The costs of the adverse events (AEs) of both BSoC and SoC were evaluated in the budget impact model of Belimumab SC. The adverse events are defined in the protocol of the BLISS-SC as 'any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. The AEs were graded according to the Adverse Event Severity Frading Tables and grouped using the Medical Dictionary for Regulatory Activities (MedDRA) by System Organ Class (SOC) [9]. As demonstrated in the clinical study report of the BLISS-SC trial, the AEs that occurred in ≥ 20.0% of the patients in the BSoC or SoC treatment group were included [61]. The incidence of the AEs by SOC that occurred in ≥ 20.0% of the patients during the 52-week BLISS-SC trial is shown in Table 3.

Adverse event	***BSoC (n = 556)***	***SoC (n = 280)***
Infections and infestations, n (%)	308.0 (55.4%)	159.0 (56.8%)
Gastrointestinal disorders, n (%)	125.0 (22.5%)	68.0 (24.3%)
Musculosketal and connective tissue disorders, n (%)	124.0 (22.3%)	66.0 (23.6%)
Nervous system disorders, n (%)	111.0 (20.0%)	53.0 (18.9%)
Skin and subcutaneous disorders, n (%)	80.0 (14.4%)	60.0 (21.4%)
	[18]	[18]

Table 3 Incidences of the adverse events during the BLISS-SC trial

Despite plenty of literature on what type of AEs can occur in SLE patients, no literature was found on the direct cost of these AEs per SLE patient. However, a study by Petri M et al. considered the cost of treating specific corticosteroid-associated AEs in SLE patients [62]. These adverse events largely overlapped with the AEs by SOC that occurred in ≥ 20.0% of the patients during the BLISS-SC trial. However, the study by Petri M et al. did not include information on adverse events in the area of skin and subcutaneous disorders. Therefore, the Ogunsanya M et al. (2018) study was used [63]. Based on the literature, we examined which manifestations of the AEs by BSoC and SoC were common in SLE patients. We considered the extent to which these manifestations corresponded to the AEs mentioned in Petri M et al. (2014) and Ogunsanya M et al. (2018) to use the total mean costs assigned to them for this study. The adverse events costs were estimated by multiplying the incidences of AEs by their associated costs.

The total mean costs of the AEs in the study by Petri M et al. were derived from literature or claims analysis, including the costs of productivity loss or absenteeism, specialist visits (including laboratory tests, radiology services, and other types of testing), primary care physician visit, emergency room visit, hospitalization and out-of-pocket [64]. For the AE infections and infestations in this study, the costs of the 'serious infection requiring hospitalization' named in the study of Petri M et al. were assumed. The cost was $11,660, equivalent to €8,793 (ER = 0.7541, CD = 2014) [62]. Based on the values of the CPI by the CBS, we assumed that the mean cost for the AE infections and infestations was €9,765 for the year 2021 [65]. In addition, for the AE gastrointestinal disorder in this study, we considered which gastrointestinal manifestations were common in SLE. Based on the literature, ulcers, dysphagia, anorexia, nausea, vomiting, hemorrhage, and abdominal pain were common manifestations [66]. On this basis, the costs of the 'gastrointestinal ulcer/hemorrhage' mentioned in the study of Petri M et al. were used for the AE gastrointestinal disorders. The costs were $7,750, converted to €5,844 (ER = 0.7541, CD = 2014). Based on the values of the CPI by the CBS, we assumed that the mean cost for the AE gastrointestinal disorders was €6,490 for the year 2021 [65].

Furthermore, for the AE musculoskeletal and connective tissue disorders, we considered which musculoskeletal manifestations are common in SLE. Arthralgia, arthritis, osteonecrosis (avascular necrosis of bone), and myopathy are the principal manifestations of SLE [67]. In the study of Petri M et al., costs were defined for avascular necrosis. Based on the literature that this manifestation is common in SLE, according to Petri M et al., the cost was $14,460, equivalent to €10,904 (ER = 0.7541, CD = 2014) for AE muscle and connective tissue disorders [62]. Based on the values of the CPI by the CBS, we assumed that the mean cost for this AE was €12,110 for the year 2021 [65]. Finally, based on the study of Petri M et al., we could also consider the cost of AE nervous system disorders. For this, we again first looked in the literature for common nervous system disorders. In particular, mood disorders and headaches are common in patients with SLE [68]. The costs were $2,710, equivalent to €2,044 (ER = 0.7541, CD = 2014), for the AE 'mood disorders' defined in the study by Petri M et al. [62]. Based on the values of the CPI by the CBS, we assumed that the mean cost for the AE nervous system disorders was €2,270 for the year 2021 [65]. In the study by Petri M et al., no cost was found on the AE skin and subcutaneous disorders. We used the Ogunsanya M et al. (2018) study to estimate the cost for AE skin and subcutaneous disorders. This study evaluated the economic burden of cutaneous lupus erythematosus (CLE) and showed that it was estimated that the average annual incremental cost be $10,119, also converted to €8,576 (ER = 0.8475, CD = 2018) [63]. According to the literature, CLE is a distinction of SLE that can be associated with SLE symptoms. CLE can be a skin disease alone or may occur in the SLE setting. For both CLE and SLE, a butterfly-shaped rash occurs across different body parts, also called malar rash [69]. Due to the similarity in the severity of the adverse events of CLE and SLE, we consider it plausible to use Ogunsanya M et al. costs in this study. Based on the values of the CPI by the CBS, we assumed that the mean cost for this AE was €9,152 for the year 2021 [65]. These include inpatient, outpatient, emergency room visits, other medical expenses, and drug costs [63][17].

Direct costs outside of healthcare

Furthermore, we considered costs such as transport, household helpers, and adaptations to the patient's home for direct costs outside of healthcare. However, transport costs are almost non-existent because

the SoC drugs are taken orally, and when BSoC is used, Belimumab is administered subcutaneously by the patient himself. So, the patient does not have to travel to the hospital to receive the treatment. Only follow-up visits or a visit in response to complaints to a medical specialist may be charged for. However, annual follow-up visits occur every three months in equal proportions for BSoC and SoC [70,71]. In addition, visits to the medical specialist are not frequent due to complaints [70,71]. As the extent to which these potential costs could contribute to answering the research question is low, we excluded transport costs.

Furthermore, the potential costs included household helpers and adaptations to the patient's home. The BLISS-SS clinical study report demonstrated that no research was performed on the quality of life or activities of daily living. However, a cross-sectional study by Dashiell-Aje E et al. examined through a questionnaire in SLE patients (n = 43) who completed a phase IIb open-label, multi-dose usability, tolerability, and safety study of Belimumab SC, improvements in HRQoL. These SLE patients had a mean age of 46.2 and mainly consisted of women (88.4%). In addition, the vast majority of the SLE patients were white in race (74.4%). The study demonstrated that improvements in HRQoL were apparent due to treatment with Belimumab SC. Daily activities (ADL) such as grooming, bathing, and running errands were improved in 69.0% of the patients using Belimumab SC [72]. Despite this improvement in the ADL-based study, making household helpers unnecessary in some cases, the relevance of this information was limited. The extent to which this information could contribute to the budget impact of Belimumab SC was likely to be small. Hence, we also excluded the household helpers' cost from the study. The same applied to adaptations made to the patient's home, such as using a work chair on castors in the kitchen, a (sturdy) plastic stool in the shower, and a portable phone [73]. Despite improvement in ADL, costs to perform adaptations in a home setting were low and limited to a small group of SLE patients. As a result, the information did not add value to the budget impact of Belimumab SC. Therefore, the household helpers' costs and adaptations to the patient's home costs were excluded from the Belimumab SC budget impact model.

Indirect cost within healthcare

Irreversible organ damage

The irreversible organ damage of the SLE patients from the BLISS-SC was estimated using the Systemic Lupus International Collaborating Clinics-criteria (SLICC)/ACR Damage Index (SDI). The SLICC classification criteria for SLE requires that a minimum of four criteria be present, including at least one clinical and one immunological criterion. The SDI consists of 42 items in 12 domains. Damage, defined as an organ's irreversible change, was considered if the SDI-score > 1 [74]. The clinical study report of the BLISS-SC trial demonstrated similar mean changes from baseline in SDI from week 52 between the SoC and the BSoC, see Appendix 3: Baseline disease activity of the BLISS-SC trial. However, no differences were observed for the mean change from baseline to week 52 in the SDI, with adjusted mean changes of 0.1 for the SoC treatment group. There were also no SDI changes observed in the subgroups, no damage (SDI = 0), and the damage (SDI ≥ 1) in both treatment groups [9]. Therefore, the SDI scores of the BLISS-SC couldn't be used. Based on expert opinion, a longer term than just 52 weeks should be considered to indicate the impact of Belimumab SC on organ damage. To gain insight into the progression of organ damage based on the mean change in SDI from baseline to five years, a real-world, post hoc, propensity score-matched analysis of the Toronto Lupus Cohort by Urowitz MB et al. (2018) was used. Based on the study of Urowitz MB et al., we assumed that the reduction in progression of organ damage based on the mean change in SDI from baseline to five years for the SoC treatment group was equal to 0.717 (n = 99) and for the BSoC treatment group, it was equal to 0.283 (n = 99) [23]. However, the budget impact model considered an annual change. Therefore, we assumed a proportional annual mean change by dividing the mean change over five years by five to get the annual mean change. So, the annual mean change was 0.143 for the SoC treatment group and 0.057 for the BSoC treatment group[18]. Thereby, we assumed the annual probability of progression based on the increase in SDI score of the BLISS-SC trial per year for the SoC treatment group was equal to 8.7% (n = 179), and for the BSoC treatment group, it was equivalent to 3.5% (n = 179)[19] [9]. We then multiplied these rates by the eligible population to estimate the SLE patients with irreversible organ damage.

As demonstrated by the CADTH pharmacoeconomic review report Belimumab (Benlysta), the predicted annual direct medical cost per unit SDI was about $1,424, converted to €1,272 (ER = 0.8931, CD = 2019) [49]. Based on the values of the CPI by the CBS, we assumed that the mean cost for this AE was about €1,323 for the year 2021[18] [65]. However, this needed to include the cost of losing productivity, as irreversible organ damage leaves you unable to work. That is why the total average annual costs due to productivity loss were summed up to the cost per unit SDI and multiplied by the annual mean change in SDI.

In addition, according to the study of Urowitz MB et al., irreversible organ damage can also result from using corticosteroids, even though we did include this reduction in costs due to the reduced use of corticosteroids in the pharmacological costs [23]. The budget impact model did not include the reduction in costs by lowering organ damage due to reduced corticosteroid usage. We considered this cost reduction irrelevant as only 18.2% of the BSoC treatment group and 11.9% of the SoC treatment group had a decrease in corticosteroids. Of these, only 3.5% of BSoC and 8.7% of SoC progressed to irreversible organ damage annually, as demonstrated in the BLISS-SC trial [9]. Therefore, the cost reduction was assumed to be nil.

Use of dialysis or transplantation in End Stage Kidney Disease
The BLISS-SC trial demonstrated SLE patients with a renal flare over 52 weeks due to proteinuria >0.5g/24 h. The cut-off of proteinuria of >0.5/24h is in SLE defined as a 24H-P higher than 0.5g/day to be clinically significant [61]. This cut-off of proteinuria has been accepted as one of the features for the case definition in the American College of Rheumatology (ACR) guidelines [75], the European League Against Rheumatism and European Renal Association-European Dialysis and the Transplant Association recommendations for screening, treatment, and diagnosis of LN [76]. According to the BLISS-SC trial, 27.1% of the SoC treatment group experienced a renal flare, and 11.1% of the BSoC treatment group experienced a renal flare over 52 weeks [61]. Research indicated that kidney-related events or death could be significantly reduced by using Belimumab SC in treatment (HR 0.51 95% CI, 0.34 to 0.77; P=0.001). An event was defined as a possible progression to ESKD that could be prevented using Belimumab SC [77,78]. Flares cause substantial damage to the kidneys and progress to LN, but when the kidneys are too damaged, patients become dialysis dependent or in need of a transplant when progressing to ESKD. Therefore, we assumed that the SLE population with progression to ESKD could be calculated by multiplying the percentage of SLE patients who experienced renal flares among the BSoC and SoC users with the annual progression probabilities of 40.0% of going from SLE to LN [25] and the annual progression probability of 10.0% of going from LN to ESKD[21] [27]. It was impossible to base this assumption on the BLISS-SC data as it was missing.

According to a study of Dutch health insurance claim data (2019), it is possible to receive Continuous Hemodialysis (CHD) or Continuous Ambulatory Peritoneal Dialysis (CAPD) to treat ESKD. Based on the Dutch health insurance claim data, we assumed these treatments cost €77,566 for CAPD and €92,616 for CHD [79]. However, CPI needed to be considered. Based on the values of the CPI by the CBS, the assumed costs were about €80,657 for a CAPD treatment and €96,306 for a CHD treatment in 2021[22] [65]. Besides, according to a Dutch health insurance claim data study, patients with ESKD can receive a living or deceased donor transplant. The mean annual cost of a living donor kidney transplant was about €73,000, and the cost of a deceased donor kidney transplant was about €99,000 in the year of transplantation [79]. Based on the CPI values of the CBS, we assumed that the mean annual costs for a living donor kidney transplant were about €75,909 and for a deceased donor kidney transplant €102,945 in 2021[23] [65].

Based on a report by Nefrovisie (2022) on renal function replacement therapy trends in the Netherlands, we assumed the annual distributions of renal replacement therapies for 2020. Here 10.0% received a living donor kidney transplantation, 2.0% a deceased donor kidney transplantation, 69.0% Continuous Haemodialysis (CHD), and 19.0% Continuous Ambulatory Peritoneal Dialysis (CAPD)[24]. An overview of the costs per renal replacement therapy and the corresponding distribution is shown in Table 4.

Renal replacement therapy	*Cost (€)*	*Renal replacement therapy distribution (2020)*
Living donor kidney transplantation	75,908.72	10.0%
Deceased donor kidney transplantation	102,944.71	2.0%
Continuous Hemodialysis (CHD)	96,306.33	69.0%
Continuous Ambulatory Peritoneal Dialysis (CAPD)	80,656.66	19.0%
	[79]	[80]

Table 4 Renal replacement therapy costs and distributions

Indirect cost outside of healthcare

Productivity loss/ absenteeism

Besides the high drug and hospitalization costs, lost productivity because of sick leave and work disability related to SLE were considered. According to the economic evaluation guideline, productivity loss can be defined as the costs arising from productivity losses and replacement costs due to illness, absenteeism, disability, and death of productive persons, both paid and unpaid work [81]. The friction-cost method was used to calculate the productivity loss. By using this method, the employer's perspective was considered. Only those hours not worked until another employee takes over the patient's work count when this method was used [82]. To calculate productivity losses under the friction cost method, the absenteeism frequency, duration, and costs per friction period needed to be known [81]. Since this was hard to determine, we used the data from 2021 on job vacancies in the Netherlands.

Based on Central Bureau for Statistics data (2021), 1,334,800 vacancies were open, and 1,243,800 vacancies were filled in the Netherlands [83]. In addition, we adjusted the number of people employed (n = 6,069,269) and the number of work hours per week ($\mu = 29.8$) based on the gender distribution of the BLISS-SC trial and the gender-distributed employment rates. The Central Bureau for Statistics showed a net employment rate of 68.2% among women and 76.5% among men in 2021 [84]. These employment rates of women and men were used to determine the working population based on the gender distribution in the study. According to the study of Aalabaf-Sabaghi et al., we assumed an SLE-specific employment rate of 46.0%[25] [85]. The cost of the friction period was multiplied by the 46.0% SLE-specific employment rate. In addition, the cost guide for economic evaluations (2016) used a reference price of €31.60 for women and €37.90 for men for the average salary costs per hour. Based on the CPI values of the CBS, we assumed an average salary cost per hour for women of €34.77 and men of €41.40. Again, we corrected the average salary costs per hour based on the gender distribution of the BLISS-SC trial, resulting in €35.16 that was assumed for the salary cost per hour[26].

The friction period was estimated by dividing the total filled vacancies by the average number of open vacancies in a quartile year. Then 365 days were divided by the number calculated for this purpose, and four weeks were added. Without this addition of four weeks, we arrived at the number of days a vacancy was open. This resulted in a friction period of about 18 weeks. We then used the average salary cost per hour of €35.16 for the friction cost method throughout the total friction period. In contrast, the average salary of the working population during the entire friction period was multiplied by the SLE-specific employment rate.

To distinguish between BSoC and SoC, we used the average number of flares per year. Besides the number of flares, we needed to determine how many hospitalization days were required because of the flares. Based on a study by Lee J et al., a mean length of stay of 11.8 days due to an SLE severe flare was assumed [86]. Based on the opinion of a rheumatologist working in a hospital in the Netherlands, we know that no hospitalization is required for a mild/moderate flare because they are treated on an outpatient basis. Adding or changing drugs is often sufficient. Therefore, we assumed one working day for a mild/moderate flare. For the days surrounding this outpatient treatment, we counted an average of two days a patient cannot work. We assumed the patient could not work for an average of eight days due to a severe flare surrounding the hospitalization days. Exact data on days could not be obtained from literature, nor could the rheumatologist give an exact answer[27].

For the absenteeism due to follow-up hospital visits, the annual follow-up visits for which the SLE patient cannot work were considered. As mentioned, SLE patients visit the hospital for a consult with a specialist every three months [70,71]. Therefore, we assumed that the patients could not work for two working days because the amount of time needed for these visits was not found in the literature. However, we assumed that a consultation with a specialist and some accompanying physical examinations, laboratory tests, and imaging techniques would take at least half a working day[28].

In a study by Abu Bakar F et al., productivity was defined using various factors such as hematology manifestation, mucocutaneous manifestation, SLEDAI-2K score, SLE flare frequency, and LN [87]. Since we used SLE flare frequency as the decreased productivity, we did not include it for productivity loss. In addition, we also did not include LN because the cost of productivity loss was already included in the price per SDI for irreversible organ damage costs. As demonstrated in the BLISS-SC trial, 35.9% of BSoC users and 45.6% of SoC users had experienced no improvement in mucocutaneous manifestation over 52 weeks. In addition, 55.1% of BSoC users and 64.0% of SoC users had experienced no improvement in hematology manifestation within 52 weeks. Similarly, regarding the SLEDAI-2K, 38.3% of BSoC and 53.4% of SoC had no response. See Table 5 for an overview of the productivity loss factors. Based on this, we assumed that 43.1% of BSoC users and 54.3% of SoC experienced no annual improvement or response that impacted productivity loss[29]. This annual average was multiplied by the average salary costs per friction period.

Productivity loss factors	***BSoC***	***SoC***
Mucocutaneous manifestation, n	487	248
No. (%) of subjects no improved	175 (35.9)	113 (45.6)
Hematology manifestation, n	49	25
No. (%) of subjects no improved	27 (55.1)	16 (64.0)
SLEDAI-2K, n	554	279
No. (%) no response	212 (38.3)	149 (53.4)
Total, annual average (%) of no improvement/ response	**43.1**	**54.3**

Table 5 Productivity loss factors

Sensitivity analyses

Besides having exact data, we also used assumptions in the budget impact model. Because of the budget impact model assumptions, we expected some uncertainty in the results. The impact of this uncertainty on the results needed to be clarified, and for this purpose, we used probabilistic sensitivity analyses (PSA) and deterministic sensitivity analyses (DSA). Based on the report for economic evaluations, the effects of variation of the factors influencing the budget impact were presented. Therefore, as the economic evaluation report recommends, we used a Tornado diagram for the DSA [81]. The PSA and DSA were performed in Microsoft Excel. Uncertainty intervals were estimated using data from the literature, and in the absence of data, we used a range of variation of +/- 20.0% from the base case. This range of variation was also used in the studies investigating the budget impact of Belimumab in the Italian and Spanish settings [14,15]. The ranges of variation can be found in Appendix 9: Summary parameter table.

To examine the relationship between the variable data, we used triangular distributions. We chose this type of continuous probability distribution as there was relatively little data available to perform a full statistical analysis [88]. For the PSA, 10.000 iterations were performed using different random values with two decimals, calculating the outcomes for year one, year two, year three, and the total. Some parameter values were minimal, so hardly any difference was visible without using two decimal places. The various assumptions used can be found in Appendix 5: Overview of the assumptions in the study.

Scenario analyses

In addition to the sensitivity analyses, univariate and multivariate scenario analyses were performed. Some values were used to estimate certain risks and financial consequences of the choices. We,

therefore, performed various scenarios with minimum and maximum values in the budget impact model. The investigated univariate scenarios were the market share of 2025, the Belimumab SC costs, the adverse events costs, the annual mean severe flares in BSoC and SoC, the annual mean mild/moderate flares in BsoC and SoC, the hospitalizations days due to a severe flare, the outpatient treatment days due to a mild/moderate flare, the working days surrounding hospitalization not able to work due to a severe flare, the working days surrounding outpatient treatment not able to work due to a mild/moderate flare, and the annual direct medical costs per unit SDI. Besides, the multivariate scenarios were the drug pricing, annual mean amount of flares, hospitalization or outpatient treatment and the working days surrounding, and the annual mean change in SDI. An overview and reasoning of the univariate and multivariate scenarios can be found in Table 6 and Table 7, respectively.

Scenario	***Base case value***	***Scenario value(s)***	***Explanation***
Scenario 1: Market Share of 2025, %	27.0%	15.2% 49.3%	For market share, we maintained a market share of 27.0% over the three years. However, there is increasing competition in the market for Belimumab SC, such as Anifrolumab. As a result, the market share was expected to decrease in the coming years. We, therefore, chose a range of variation based on a study by Pierotti et al. This study showed that the market share for Belimumab varied between 15.2% and 49.3% [89]. This scenario would provide a more realistic estimation of the budget impact when competition is coming to the market of Belimumab SC.
Scenario 2: Belimumab SC costs, €	1.18	1.06 1.30	The Wet Geneesmiddelprijzen (WGP), translated as the Medicines Pricing Act by the Minister of Health, Welfare, and Sport, sets the maximum prices for medicines. Following the WGP, the minister examines twice a year whether there is a reason to recalibrate the maximum prices [90]. GSK NL must reduce the list price of Belimumab SC if there is a reference price decrease, and if there is a reference price increase, GSK NL may decide whether the list price of Belimumab SC should go up. Therefore, the price of Belimumab SC could be lower or higher. We assumed a range of variation of +/- 10.0% of the base case because we do not expect a more extensive or lower change in price in consultation with an expert.
Scenario 3: Adverse events skin and subcutaneous disorders costs, €	9,152.05	2,745.62 15,558.49	A scenario analysis analyzed the adverse events costs of the skin and subcutaneous disorders. This cost derived from the Ogunsanya M et al. (2018) study might overestimate the cost when used in the Dutch setting. This cost included inpatient, outpatient, emergency room visits, other medical expenses, and drug costs. Besides, the difference in the incidence of these adverse events was the largest between the BSoC and SoC, according to the BLISS-SC trial [63]. Some of these included costs are also separately considered in the budget impact model, possibly leading to double counting. To correct this, in the scenario analysis, we assumed that of the adverse event cost described in the Ogunsanya M et al. study, about 30.0% consisted of annual direct medical costs. Therefore, the applied range of variation was +/- 70.0% compared to the base case.
Scenario 4: Annual mean severe flares in BSoC, n	0.04	0.03 0.54	Based on the BLISS-SC trial, this study retained an annual mean number of severe flares of 0.04 in the BSoC treatment group. However, a study by Cevey M et al. showed that annual mean amount of severe flares could also be higher for the BSoC treatment group. The study found that the BSoC treatment group experienced an average of 0.54 severe flares annually [91]. We, therefore, assumed in this scenario that the SLE patients experienced at most the number of severe flares as described in the study by Petri M et al. and at least

			20.0% fewer severe flares than the amount from the BLISS-SC trial. This 20.0% was estimated as there was no data about a lower amount of mean annual severe flares in the BSoC treatment group.
Scenario 5: Annual mean severe flares in SoC, n	0.22	0.18 1.01	Based on the BLISS-SC trial, this study retained an annual mean number of severe flares of 0.22 in the SoC treatment group. However, a study by Cevey M et al. showed that the amount of annual mean severe flares could also be higher for the SoC treatment group. The study found that the SoC treatment group experienced an average of 1.01 severe flares annually [91]. We, therefore, assumed in this scenario that the SLE patients experienced at most the number of severe flares as described in the study by Petri M et al. and at least 20.0% fewer severe flares than the amount from the BLISS-SC trial. This 20.0% was estimated as there was no data about a lower amount of mean annual severe flares in the SoC treatment group.
Scenario 6: Annual mean mild/moderate flares in BSoC, n	1.23	0.98 2.15	For the mild/moderate flares in BSoC, we retained the average annual number of mild/moderate flares in the BSoC treatment group from the BLISS-SC trial. However, the study by Cevey M et al. showed that the mean annual number of mild/moderate flares could also be higher, with a mean amount of 2.15 in the BSoC group [91]. No data was available for the minimum number of mild/moderate flares when using BSoC. Therefore, in this study, we assumed 20.0% fewer mild/moderate flares compared to the values of the BLISS-SC as the minimum number of mild/moderate flares. This scenario reflected the impact of mild/moderate flares in the BSoC treatment group on the budget.
Scenario 7: Annual mean mild/moderate flares in SoC, n	1.69	1.35 2.50	Also, for the mild/moderate flares in SoC, the average annual number of mild/moderate flares in the SoC treatment group was retained from the BLISS-SC trial. However, the study by Cevey M et al. showed that the mean annual number of mild/moderate flares could also be higher, with a mean amount of 2.50 mild/moderate flares per year in the SoC [91]. No data was available for the minimum number of mild/moderate flares when using SoC. Therefore, in this study, we assumed 20.0% fewer mild/moderate flares compared to the values of the BLISS-SC as the minimum number of mild/moderate flares. This scenario reflected the impact of mild/moderate flares in the SoC treatment group on the budget.
Scenario 8: Hospitalizations days severe flare, n	11.8	9.44 14.16	Due to a severe flare, hospitalization is quite plausible. A study by Lee J et al., assumed an average hospitalization duration for a severe flare of 11.8 days [86]. However, this hospitalization time depends on several factors, such as age and the severity of the severe flare. Therefore, an SLE patient with a severe flare may be hospitalized for a longer or shorter period. Despite the lack of this data in the literature, we assumed a range of +/- 20.0% variation concerning the 11.8 hospitalization days. As a result, this scenario provided insight into the influence of hospitalization due to a severe flare on the budget impact of Belimumab SC.
Scenario 9: Outpatient treatment days mild/moderate flare, n	1.0	0.80 1.20	No hospitalization occurred for a mild/moderate flare, but they treated the patient on an outpatient basis. Based on an opinion by a rheumatologist, this outpatient treatment takes about one working day on average. However, outpatient treatment may take shorter or longer. Due to the lack of data, we assumed a range of variation of +/- 20.0% relative to one working day. Since the mild/moderate flares occur in higher amounts in the treatment groups than the severe flares, we considered the possibility that this scenario provided insight into the impact of these outpatient admissions on productivity loss.

Scenario 10: Working days surrounding hospitalization not able to work due to a severe flare, n	8.0	0.0 16.0	Beyond hospitalization due to a severe flare, the patient may also be unable to perform their work before and after hospitalization. However, we did not have data confirming this assumption. Based on a rheumatologist's opinion, we assumed that surrounding hospitalization, the patient cannot perform work for an average of eight working days due to a severe flare. The number of working days may vary by SLE patient, so we examined it in a scenario analysis with a range of variation of +/- 8.0 days from the base case.
Scenario 11: Working days surrounding outpatient treatment not able to work due to a mild/moderate flare, n	2.0	0.0 4.0	Similarly, for mild/moderate flares, the patient may be unable to resume work outside of outpatient treatment immediately. Since we used one day for outpatient treatment, we assumed that the working days an SLE patient could not work surrounding outpatient treatment equals an average of two working days. In the scenario analysis, we used a +/- 2.0 days range of variation to determine the impact of an increase or a decrease in the average number of working days surrounding hospitalization an SLE patient cannot work due to mild/moderate flare.
Scenario 12: Annual direct medical costs per unit SDI, €	1,322.64	661.32 1,983.96	According to an expert from GSK NL, the annual direct medical cost per SDI unit was relatively low despite being reported by the CADTH pharmacoeconomic review report Belimumab (Benlysta) in 2019 [49]. Despite the lack of data that higher or lower costs could attribute to the annual direct medical costs per unit SDI, we determined the influence of this variation in costs on the budget impact of Belimumab SC through a scenario analysis. The range of variation used was +/- 50.0% from the base case.

Table 6 Explanation of the univariate scenarios

Scenario	***Explanation***
Scenario 1: Drug pricing	In this multivariate scenario, we looked at drug prices. For this, we have set the average drug costs per mg of Belimumab SC, corticosteroids, antimalarial drugs and the immunosuppressant Azathioprine to the minimum and maximum values. Since the maximum prices of medicines are set for the purpose of the Medicines Pricing Act (WGP), translated as the Medicines Pricing Act of the Minister of Health, Welfare and Sport. Following the WGP, the minister reviews twice a year whether there is reason to recalibrate the maximum prices [90]. As a result, the average drug cost per mg price may be lower or higher. We used a +/- 20.0% from the base case as a range of variation.
Scenario 2: Annual mean amount of flares	In this multivariate scenario analysis, we investigated the influence of mild/moderate and severe flares by minimising and maximising them in both the BSoC and the SoC. For this purpose, flares were first set to minimum in both treatment groups and then all flares were set to maximum. We used a +/- 20.0% from the base case as a range of variation.
Scenario 3: Hospitalization/ outpatient treatment days and working days surrounding	To identify, for productivity, the influence of hospitalisation days, outpatient treatment days and working days around these 'admissions' on the budget impact, we had also performed a multivariate scenario analysis on these. As these parameters consisted largely of assumptions, this gave some uncertainty about the values used. For the working days surrounding hospitalization due to a severe flare, we used a +/- of 8.0 days from the base case as the range of variation. Besides, for the working days surrounding outpatient treatment we used a range of +/- 2.0 days from the base case as a range of variation. Finally, for the hospitalization days/ outpatient treatment we used a +/- 20.0% from the base case as a range of variation.
Scenario 4: Annual mean change in SDI	In a multivariate scenario analysis, the annual average change in SDI for both the BSoC and the SoC was set to minimum and maximum to determine its impact on the budget impact. Since we netted a five-year SDI to an annual SDI, some values needed to be clarified. For this scenario, we used a +/- 50.0% from the base case as a range of variation.

Table 7 Explanation of the multivariate scenarios

Results

The budget impact of Belimumab SC was calculated as the cost difference between the future scenario (with Belimumab SC) and the current scenario (without Belimumab SC). The budget impact was calculated for the eligible prevalence SLE population who were auto-antibody positive and had moderate to severe disease activity (n = 937). Based on the cost factors used in the budget impact model of Belimumab SC, the total budget impact indicated an expenditure in the Dutch setting of approximately €3.7 million over three years.

Factors influencing the budget impact model

Direct costs within healthcare

Pharmacological costs

The annual costs for only using Belimumab SC in the first year with 56 administrations were approximately €13,562. For the years after that, with 52 administrations, the costs were approximately €12,261. However, the first year also needed to include administration costs, which gave us an annual cost of about €13,598 for Belimumab SC in the first year. For the SoC treatment, the annual costs per drug are shown in Table 8. Based on the use of the immunosuppressant Azathioprine, antimalarial Hydroxychloroquine, and corticosteroid Prednisone, the average annual cost for the SoC was approximately €358. They gave an average annual cost for the treatment with BSoC of about €13,598 for the first year and €12,619 for the following years. However, from the second year of treatment with BSoC and SoC, corticosteroid use was reduced by €8.42 for BSoC and €0.72 for SoC. As a result, costs were slightly lower on average from the second year of treatment. All in all, the cost increased by an average of approximately €12,261 per patient per year due to the use of Belimumab SC.

Table 8 Standard of care average annual drug costs per SLE patient

Drug/ Comparator	***Average annual SoC drug cost per patient (€)***
Corticosteroids	
Prednisone (Plaquenil, generic)	39.24
Antimalarials	
Hydroxychloroquine (generic)	70.20
Immunosuppressants	
Methotrexate (generic)	8.40
Mycophenolate Mofetil (generic)	1,782.00
Azathioprine (generic)	248.40
Total SoC average annual drug cost[1], €	**357.84**

[1] *The total average annual drug cost was based on using Azathioprine as the immunosuppressant.*

Flare costs

Based on the annual mean of mild/moderate flares per patient, the annual mean of severe flares per patient, and the associated costs, the total annual mean flare cost for BSoC was about €2,743, and for SoC, the cost was €5.063. See Table 9 for a summary of the annual mean flare costs. The costs of mild/moderate flares were higher on average because they were more common in the SoC treatment group than in the BSoC treatment group. The use of Belimumab SC reduced the costs surrounding the management of flares by an annual average of approximately €2,320 per patient per year.

Flare costs	***BSoC***	***SoC***
Severe flare costs (annual mean per patient), €	313.72	1,725.48
Mild/moderate flare costs (annual mean per patient), €	2,429.10	3,337.55
Total flare costs, €	**2,742.83**	**5,063.03**

Table 9 Annual mean flare costs per SLE patient

Adverse events costs
The average annual costs for BSoC users amounted to approximately €11,342 per patient. In addition, the average annual costs for the SoC users were around €12,369 per year per patient. Using Belimumab SC resulted in an average reduction of about €1,027 per patient per year in terms of AEs. The AE 'Skin and subcutaneous disorders' showed the most considerable average reduction of approximately €641 per patient per year by using Belimumab SC.

Indirect costs within healthcare
Cost of irreversible organ damage
For the BSoC treatment group, the annual average cost was approximately €510 per patient per year due to irreversible organ damage. In addition, the annual average cost for the SoC treatment group was about €1,888 per patient per year due to irreversible organ damage. A total annual cost reduction of about €1,378 per patient per year due to using Belimumab SC.

Cost of dialysis and kidney transplantation
In this cost category, the average costs per patient were the same for both kidney transplantation and dialysis in the BSoC and the SoC treatment group. In the BSoC treatment group, an average of only one patient per year had dialysis or kidney transplantation. On the other hand, the average number of patients per year in the SoC treatment group undergoing dialysis or kidney transplantation was eight. Besides, the renal flares were more frequent among SoC users in 16.0% of cases, resulting in an average higher cost of approximately €955,455 for the SoC treatment group. In comparison, the use of BSoC resulted in higher costs of about €803,146 over the 3-year time horizon.

Indirect costs outside of healthcare
Cost of productivity loss/ absenteeism
As a result of the friction cost method, the total average annual productivity cost (loss + absenteeism) was approximately €11,400 per patient for the BSoC treatment group and a total average annual productivity cost (loss + absenteeism) of about €15,500 per patient for the SoC treatment group. A total average annual productivity cost reduction of approximately €4,000 by using BSoC. See Table 10 for a complete summary of costs in terms of productivity.

Productivity loss/ absenteeism costs	***BSoC***	***SoC***
Total average annual costs due to absence per patient (€)	2,036.54	3,720.28
Total average annual costs due to loss of productivity per patient (€)	9,393.69	11,843.26
Total average annual productivity costs (€)	**11,431.23**	**15,563.54**

Table 10 Productivity loss/absenteeism costs

Budget Impact analysis
The number of eligible patients for BSoC in year one was 937; this number decreased in year two to 896 and increased in year three to 1059. The drop in year two results from the non-responders (*n* = 291) who left the cohort in the current scenario in the second year. Besides, in the future scenario, 253 patients were treated with BSoC in the first year, 242 in the second year, and 286 in the third year. The same explanation applies here for the drop, in this situation, 79 non-responders left the BSoC cohort. See Table 11 for the population flow over the years. The total of the different cost factors resulted in expenditures in the total direct and indirect costs of approximately €3.7 million over three years when using Belimumab SC in the Dutch setting. Besides, the average annual budget impact per patient treated with BSoC was approximately €4,750. See Table 11 for the budget impact summary of Belimumab SC.

Category	*Year 2023*	*Year 2024*	*Year 2025*	*Average over 3 years*	*Total over 3 years*
Total number of patients eligible for BSoC	937	896	1059	964	2892
Total patients on BSoC treatment	253	242	286	260	781
Total costs in current scenario without Belimumab SC	€ 28,136,905	€ 26,901,028	€ 31,782,810	€ 28,940,248	€ 86,820,744
Total costs in future scenario with Belimumab SC	€ 29,341,921	€ 28,051,929	€ 33,142,550	€ 30,178,800	€ 90,536,400
Annual budget impact	**€ 1,205,016**	**€ 1,150,901**	**€ 1,359,740**	**€ 1,238,552**	**€ 3,715,657**
Budget Impact (%)	4.28%	4.28%	4.28%	4.28%	4.28%
Annual budget impact per patient treated with BSoC	€ 4,761.50	€ 4,756.59	€ 4,756.53	€ 4,758.16	€14,274,62
Annual budget impact per patient treated with BSoC per month	€ 396.79	€ 396.38	€ 396.38	€ 396.51	€ 396.51

Table 11 Budget impact summary of Belimumab SC over three years

The budget impact of the different cost factors used could explain the total budget impact of Belimumab SC. The pharmacological budget impact indicated that BSoC could generate expenditures of approximately €9.6 million over the three years in the Dutch setting. This expenditure came from the higher annual treatment costs of BSoC compared to SoC. However, potential savings could be realized over three years in the remaining cost categories. The AE budget impact could generate approximately -€800,000 of savings over three years when treated with BSoC within the Dutch setting. This could be explained by the infections and infestations, gastrointestinal disorders, musculoskeletal and connective tissue disorders, and skin and subcutaneous disorders which had a lower incidence rate in the BSoC treatment group than in the SoC treatment group. In addition, the budget impact of flares was calculated by using the flare cost. BSoC treatment could generate approximately -€1.9 million in savings over three years in the Dutch setting. As mentioned earlier, severe and mild/moderate flares were more common in the SoC treatment group compared to the BSoC treatment group. This difference indicated the higher annual costs for SoC compared to BSoC.

Furthermore, the budget impact of the productivity was calculated, giving a potential saving of approximately -€2.6 million in the Dutch setting over three years. This saving came from the higher average annual productivity costs based on the mild/moderate and severe flares. Also, the budget impact of using dialysis or transplantation due to ESKD was calculated, resulting in potential savings of about -€460,000 over three years. These higher costs resulted from the incidence of renal flares being higher in the SoC treatment group than in the BSoC treatment group. Finally, the budget impact of irreversible organ damage, with a potential cost saving of approximately -€114,000 in the Dutch setting using BSoC compared to the SoC over three years. This cost-saving resulted from the annual progression probability and the annual mean change in the SDI being higher in the SoC treatment group. See Figure 2 for the total costs with and without using BSoC divided over the different cost categories. The exact numbers for the different cost categories are in Appendix 7: Budget impact of the direct and indirect costs using Belimumab SC.

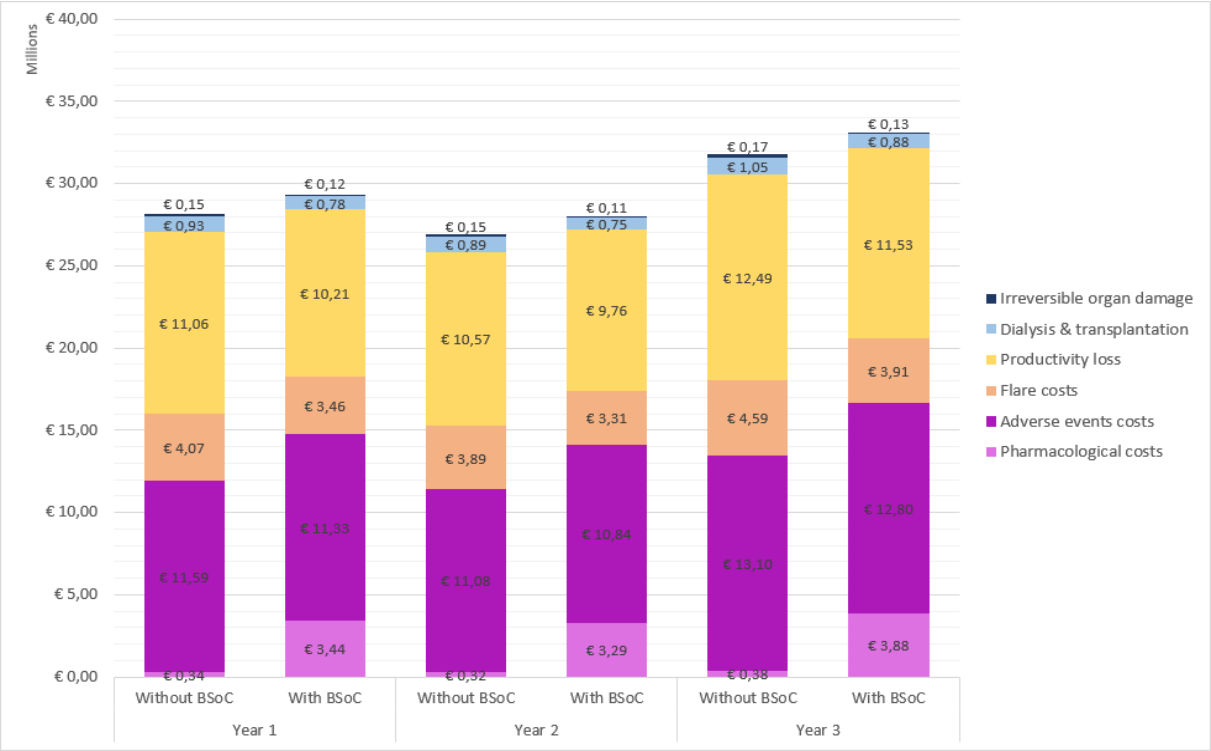


Figure 2 Total costs with and without the use of BSoC per year

Sensitivity analysis

The DSA, presented in Figure 3, changed one value of different parameter values at a time. The various budget impacts were compared to the base case budget impact. Figure 3 shows the range of variation of the budget impact for each parameter that had been changed. The eighteen factors with substantial differences in budget impact between the minimum and maximum were included in the figure. The ranges used for the factors influencing the budget impact are in Appendix 9: Summary parameter table.

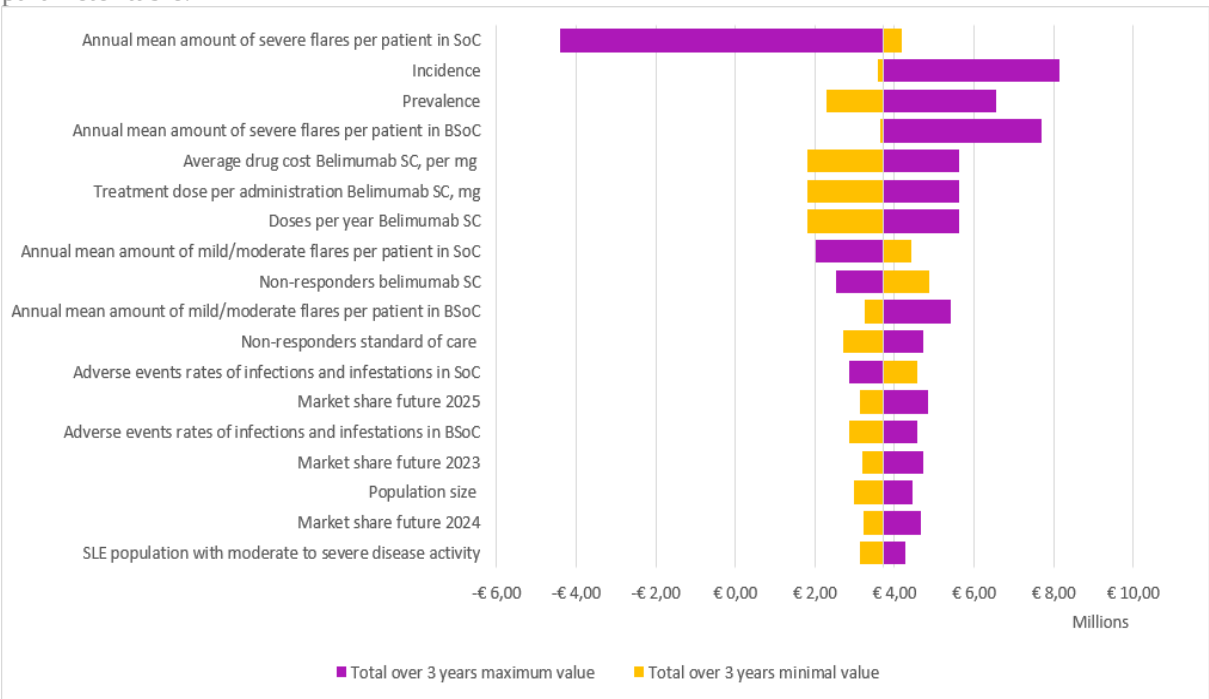


Figure 3 Tornado diagram of the deterministic sensitivity analysis

According to the Tornado diagram in Figure 3, the annual mean number of severe flares per patient in SoC was the factor that mainly affected the budget impact of Belimumab SC. In comparison with the base case value of 0.22 severe flares in the SoC, the minimum value of 0.18 for the annual mean severe flares per patient in SoC gave a budget impact of approximately €4.1 million, while the maximum value of 1.01 gave a budget impact of about -€4.4 million. In addition, incidence, prevalence, and the annual mean number of severe flares per patient in BSoC also substantially affected the budget impact of Belimumab SC.

According to the PSA, the total budget impact over three years of Belimumab SC ranged from approximately -€9.0 to €17.6 million excluding outliers. This indicated that there is some variability but also consistency in the results from the base case. Besides, the average budget impact over three years after performing the PSA was approximately €4.3 million. This corresponds with the deterministic base case budget impact of about €3.7 million. Also, the median from the PSA was about €4.1 million with an Interquartile Range (IQR) of approximately €6.6 million, indicating some uncertainty in the results. See Figure 4 for an overview of the spread for the different years and the total. These boxplots are independent of each other.

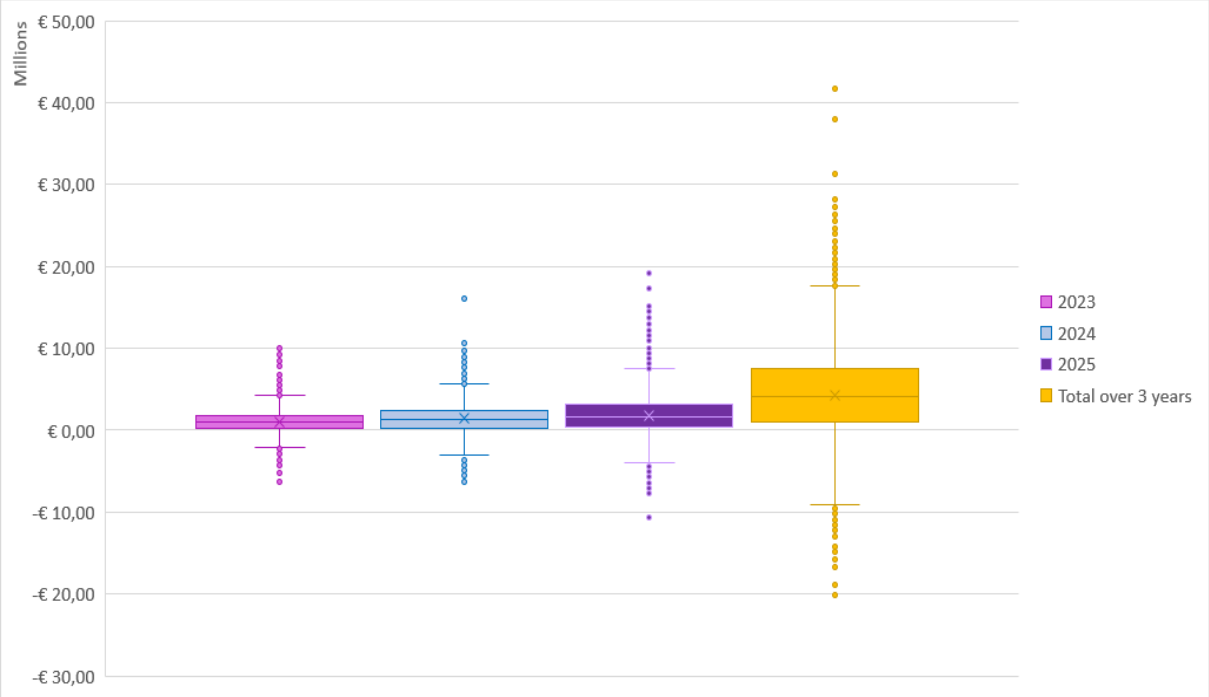


Figure 4 Boxplot of the probabilistic sensitivity analysis per year and the total over three years

Scenario analysis

Analyses were carried out on different univariate and multivariate scenarios. The four most influential scenarios on the budget impact of Belimumab SC are listed below. Other scenario analyses performed and associated results can be found in Table 12 and Table 13.

For univariate scenario 5, we considered the annual mean severe flares in the SoC treatment group. Using this scenario, the budget impact was approximately -€4.4 million of Belimumab SC at a maximum annual mean amount of severe flares (1.01) in the SoC. In addition, at the minimum value (0.18), the budget impact was about €4.1 million. This scenario showed that with an increase in the average annual amount of severe flares in the SoC treatment group, the impact on the budget is smaller and can therefore lead to cost savings in the Dutch setting. With a decrease in the average annual amount of severe flares in the SoC treatment group, the budget impact of Belimumab SC would generate more expenditures compared to the base case.

In univariate scenario 4, we considered the annual mean severe flares in the BSoC treatment group. Using the maximum value (0.54), the budget impact was approximately €7.7 million. Besides using the minimum value (0.03), the budget impact was about €3.6 million. Based on this, we saw that with an increasing average amount of severe flares per year in the BSoC treatment group, the budget impact of Belimumab SC resulted in an increase in expenditure. With a decrease in the average amount of severe flares, the budget impact of Belimumab SC led to a slight reduction in expenditure.

Univariate scenario 2 considered that due to the WGP the list price of Belimumab SC may change. A plausible change was mentioned in the budget impact of Belimumab SC from the base case. For the maximum value (€1.30), the budget impact was approximately €4.7 million, and for the minimum value (€1.06), the budget impact was about €2.7 million. The increase and decrease in the budget impact of Belimumab SC were evident because the same number of patients in the budget impact model used a cheaper or more expensive Belimumab SC treatment. However, the budget impact for the minimum and maximum values indicated that a slight increase or decrease in the Belimumab SC cost of only +/- €0.12 cents had a severe impact.

Multivariate scenario 2 considered the annual mean amount of flares. Using the maximum values for the mild/moderate flares and the severe flares in both the BSoC and SoC treatment groups resulted in a budget impact of about -€418,000. So, even if the maximum amount of flares were used in the BSoC treatment group, the budget impact would generate relevant savings.

Table 12 Performed univariate scenario analyses

Scenarios	***Rational***	***BSoC***	***SoC***	***Δ BSoC - SoC***
Base case budget impact	-	€90,536,400	€86,820,744	€3,715,656.64
Scenario 1: Market share BSoC future 2025	The market share of BSoC may be lower in 2025.	€89,942,144	€89,942,144	€3,121,400.00
	The market share of BSoC may be higher in 2025.	€91,659,445	€86,820,744	€4,838,700.95
Scenario 2: Belimumab SC costs per mg, using immunosuppressant Azathioprine	As a result of the Wet Geneesmiddelprijzen (WGP), price of Belimumab SC could be lower.	€89,578,836	€86,820,744	€2,679,908.22
	As a result of the Wet Geneesmiddelprijzen (WGP), price of Belimumab SC could be higher.	€91,493,965	€86,820,744	€4,673,221.38
Scenario 3: Adverse event skin and subcutaneous disorders costs	The adverse events costs for skin and subcutaneous disorders may be lower.	€86,921,415	€82,855,562	€4,065,852.59
	The adverse events costs for skin and subcutaneous disorders may be higher.	€94,151,386	€90,785,925	€3,365,460.69
Scenario 4: Annual mean severe flares per patient in BSoC	Annual mean severe flares per patient in BSoC may be lower.	€90,472,892	€86,820,744	€3,652,148.36
	Annual mean severe flares per patient in BSoC may be higher.	€94,505,668	€86,820,744	€7,684,924.22
Scenario 5: Annual mean severe flares per patient in SoC	Annual mean severe flares per patient in SoC may be lower.	€89,313,080	€85,144,962	€4,168,117.70
	Annual mean severe flares per patient in SoC may be higher.	€112,500,566	€116,908,642	-€4,408,076.02
Sceanrio 6: Annual mean mild/ moderate flares per patient in BSoC	Annual mean mild/ moderate flares per patient in BSoC may be lower.	€90,079,398	€86,820,744	€3,258,654.36
	Annual mean mild/ moderate flares per patient in BSoC may be higher.	€92,245,515	€86,820,744	€5,424,770.84
Scenario 7: Annual mean mild/	Annual mean mild/ moderate flares per patient in SoC may be lower.	€88,631,536	€84,211,341	€4,420,195.49

moderate flares per patient in SoC	Annual mean mild/ moderate flares per patient in SoC may be higher.	€95,101,312	€93,074,047	€2,027,264.70
Scenario 8: Hospitalization days per severe flare	Hospitalization days per severe flare may me lower.	€90,150,760	€86,331,812	€3,818,948.28
	Hospitalization days per severe flare may be higher.	€90,922,041	€87,309,676	€3,612,364.99
Scenario 9: Outpatient treatment days per mild/moderate flare	Outpatient treatment days per mild/moderate flare may be lower.	€90,241,497	€86,502,448	€3,739,048.53
	Outpatient treatment days per mild/moderate flare may be higher.	€90,831,304	€87,139,039	€3,692,264.74
Scenario 10: Working days surrounding hospitalization not able to work due to a severe flare	The average amount of working days surrounding the hospitalization the patient is not able to work due to a severe flare may be lower.	€89,302,911	€85,163,347	€4,139,564.31
	The average amount of working days surrounding the hospitalization the patient is not able to work due to a severe flare may be higher.	€91,769,890	€88,478,141	€3,291,748.96
Scenario 11: Working days surrounding outpatient treatment not able to work due to a mild/moderate flare	The average amount of working days surrounding the outpatient treatment the patient is not able to work due to a mild/moderate flare may be lower.	€87,587,364	€83,637,788	€3,949,575.61
	The average amount of working days surrounding the outpatient treatment the patient is not able to work due to a mild/moderate flare may be lower.	€93,485,437	€90,003,699	€3,481,737.66
Scenario 12: Annual direct medical costs per unit SDI	The annual direct medical costs per unit SDI may be lower.	€90,518,120	€86,796,881	€3,721,239.11
	The annual direct medical costs per unit SDI may be higher.	€90,554,680	€86,844,606	€3,710,074.16

* The red blocks indicate that the budget impact of the scenario is higher than the base case budget impact of Belimumab SC. The green blocks indicate that the budget impact of the scenario is lower than the budget impact of the base case.

Table 13 Performed multivariate scenario analyses

Scenarios	***Rational***	***BSoC***	***SoC***	***Δ BSoC - SoC***
Base case budget impact	-	€90,536,400	€86,820,744	€3,715,656.64
Scenario 1: Drug pricing	The costs of the different drugs used may be lower.	€89,371,983	€86,613,778	€2,758,205.65
	The costs of the different drugs used may be higher.	€91,700,818	€87,027,710	€4,673,107.62
Scenario 2: Annual mean amount of flares	The annual mean amount of mild/moderate or severe flares may be lower.	€85,063,357	€80,392,966	€4,670,390.67
	The annual mean amount of mild/moderate or severe flares may be higher.	€122,743,860	€123,161,946	-€418,086.16
Scenario 3: Hospitalization/ outpatient treatment days and working days surrounding	The hospitalization/ outpatient treatment days and working days surrounding can be lower.	€85,340,135	€80,769,550	€4,570,585.45
	The hospitalization/ outpatient treatment days and working days surrounding can be higher.	€95,746,819	€92,871,938	€2,874,881.52
Scenario 4: Annual mean change in SDI	The annual mean change in SDI can be lower.	€90,356,031	€86,583,212	€3,772,818,74
	The annual mean change in SDI can be higher.	€90,716,770	€87,058,276	€3,658,494.54

* The red blocks indicate that the budget impact of the scenario is higher than the base case budget impact of Belimumab SC. The green blocks indicate that the budget impact of the scenario is lower than the budget impact of the base case.

Discussion

The budget impact model developed in this study indicated that Belimumab SC, in addition to the SoC, showed a relevant total expenditure of €3.7 million in the Dutch setting over three years. However, looking at the cost factors affecting the budget impact model, most cost factors resulted in cost savings when using Belimumab SC, except for the pharmacological costs. The pharmacological budget impact generated an expenditure of €9.6 million because Belimumab SC is an additional therapy to the SoC. No evidence was available for its use in substituting or displacing the SoC. Therefore, the pharmacological budget impact had a prominent effect on the total budget impact. The budget impact analysis provides decision-makers on a national level with an overview of the direct and indirect costs of using Belimumab SC in combination with SoC in SLE patients in the Dutch setting. This will support them in managing and reorganizing healthcare budgets.

Findings in relation to other studies

This is the first study that explicitly investigated the budget impact of Belimumab SC in combination with the SoC in antibody-positive SLE patients with moderate to severe disease activity compared with using SoC from a Dutch societal perspective. However, Pierotti et al. (2016) investigated the budget impact of the introduction of Belimumab in treating SLE patients in the Italian setting with a time horizon of 4 years. Their budget impact ranged from €4.1 million in the first year to €20.3 million in the third year. The differences in the costs for treatment resulted in a higher expenditure due to BSoC in comparison with SoC over the years (€5,107,173, €16,886,435, €23,680,003, respectively). In contrast, the cost for flares resulted in cost savings due to BSoC over the years (-€670,681, -€2,275,094, -€3,292,775, respectively) [15]. These findings align with our findings since the increase in pharmacological costs due to using BSoC did not offset the reduction in costs of treating flares. Cevey M et al. (2019) conducted a budget impact analysis on the direct costs of introducing Belimumab SC into the Spanish NHS in patients with SLE. They revealed that the introduction of Belimumab SC could generate savings (-€164,316.75, -€321,725.98, -€377,150.47, respectively) compared to the use of SoC or SoC with Belimumab IV. Also, in this study, only the direct costs of pharmacological treatment and the flares were used. Cost savings were found because Belimumab SC resulted in lower annual treatment costs, due to the reduction in administration and acquisition costs, compared to Belimumab IV [14]. These findings are consistent with our assumption that Belimumab SC is more cost-effective and patient-friendly by reducing hospital visits than Belimumab IV. The other cost factors of this study, such as the adverse events, productivity loss/absenteeism, irreversible organ damage, and dialysis or transplantation due to ESKD, are not comparable to previous studies as they have not been examined in a budget impact analysis of Belimumab SC. Moreover, the DSA of this study showed that the budget impact of Belimumab SC was reduced by approximately -€4.4 million when the mean annual amount of severe flares increased from 0.22 at baseline to 1.01 in the SoC treatment group. Also, in both the studies mentioned before, a higher mean annual amount of severe flares in the SoC treatment group was used. This stresses that the total budget impact becomes cost-saving only with a minor increase in the mean annual amount of severe flares in the SoC treatment group.

Strengths

One of the strengths of this study is that most of the data used came from the phase 3, multicentre, international, randomized, double-blind, placebo-controlled, 52-week BLISS-SC trial. The BLISS-SC trial contains a large population with similar patient characteristics to the Dutch setting. This improves the representativeness and generalizability of many results. In addition, the budget impact model of Belimumab SC can be adapted to possible changes in the future from a Dutch societal perspective. For instance, population size, prevalence, mortality, incidence, market share, and changes in cost factors. This improves the use of the budget impact model of Belimumab SC in the future. Moreover, Belimumab SC is more convenient, time-saving, easier to use, and easier to incorporate into patients' daily routines due to administration costs and transport costs than Belimumab IV [29]. Looking to the future, where more efficient care through convenient routes of administration will be increasingly demanded, Belimumab SC is more socially responsible than IV [30]. On this basis, this further improves the use of the budget impact model in the future, which is beneficial for subsequent analyses.

Additionally, we used a sample size of eligible SLE patients (n = 937) large enough to increase the internal validity of this study. Another strength of this study concerns the discouragement of the Dutch National Healthcare Institute from using DBC products in economic evaluations according to the cost guide for economic evaluations. For the use of DBC, patients were divided into more or less homogeneous groups in terms of diagnosing medical conditions and treatments [55]. Therefore, the spread of average costs between DBC products can be considerable, making the calculated costs in specialist care less accurate. Therefore, we did not use DBC products in this study.

Based on the PSA, the budget impact over three years resulted in an average of approximately €4.3 million. This corresponds with the deterministic base case budget impact of about €3.7 million, which is beneficial for the reliability of this study. To our knowledge, the analyses in this study were carried out correctly with the best-fit input values in the base case. That's why we considered the base case total budget impact as the true value of this study. Besides, the DSA demonstrated that there are only a few factors, particularly the annual mean amount of mild/moderate or severe flares, with a relatively more extensive range and thus more uncertainty. However, only a few factors are involved, indicating that the output is not very sensitive to changes in the factors affecting the budget impact model. Finally, the scenario analyses were carried out to examine events that may happen in the future and predict possible outcomes to help decision-makers to make better decisions and manage the budgets regarding Belimumab SC as an expensive intramural drug.

Limitations

However, this study also contains several limitations that need to be considered. One of the limitations is that we estimated the number of SLE patients with moderate to severe disease activity who are eligible to be treated with Belimumab SC. However, this is speculative because it depends on the prevalence rate, the detection of positive autoantibodies with an ANA test, the exclusion of patients with severe active CNS lupus, the non-renal rate, and the moderate to severe disease activity rate. Nevertheless, we checked the eligible SLE population by experts from GlaxoSmithKline. They indicated that it might reflect the Dutch-eligible SLE population well based on the values used in the base case. Another limitation is that we used a market share of 27.0% over the three years. However, there is increasing market competition, such as the drug Anifrolumab, which could adversely affect Belimumab's market share. For this reason, the market share may be overestimated for the years 2024 and 2025. A further limitation of this study is the annual mean change in SDI. The budget impact model of Belimumab SC considered an annual change, but we used a mean change over five years and divided it by five to create a proportional annual mean change. This did not take into account any possible trend. Therefore, the annual mean change in SDI may be overestimated or underestimated.

Another study limitation concerns the costs used for the different cost categories. This study attempted to obtain the best estimate for the factors influencing the budget impact model. Therefore, we were sometimes forced to use costs from the past or another country. These costs were converted to euros in 2021 using the ER and CPI. As a result, we have tried as best we could, both in terms of inflation and exchange rates, to keep Dutch euro values that meet today's values. However, costs from other countries with a different healthcare system than the Netherlands may not be entirely comparable to healthcare costs in the Dutch setting. The same applies to costs from the past that, despite correcting for inflation, do not quite match today's healthcare costs. Furthermore, a limitation of this study is that we estimated the number of SLE patients with annual progression to ESKD based on different annual probabilities from the literature. We expected some bias here as we needed to know whether the annual probabilities used reflected the correct percentage of the annual probability of going from SLE to ESKD. However, the sensitivity analysis indicated that the impact on the budget was insignificant when we used the range of variation of 20.0% from the base case. Due to the need for more data, we are still determining whether it is possible, for example, to have a progression from SLE directly to ESKD or whether you can have a progression from SLE to LN to ESKD over one year. Based on this, we may have overestimated or underestimated the annual probability of going from SLE to ESKD. Furthermore, we made some assumptions regarding the number of work days needed for outpatient treatment due to a mild/moderate flare, the workdays surrounding hospitalization, and the workdays surrounding outpatient treatment. No data was available on absenteeism and presenteeism of the SLE

patient in the Netherlands (or Europe). In addition, comparable data were also unavailable from other rheumatic diseases with arthritis, such as LN. To validate our assumptions, these were sent to a rheumatologist working in a Dutch hospital. The medical specialist confirmed that no data was available on the absenteeism and presenteeism of the SLE patient in the Netherlands. Based on experience, the medical specialist couldn't suggest other values than the values we assumed. Besides, we approached only one rheumatologist for this validation, which does not improve the reliability of the values.

Another limitation is that we assumed that 100.0% continued their first year of treatment with BSoC and SoC, and only 70.0% (responders) continued the treatment for the years after that. No data was available on the average treatment duration of the non-responders in the first year. However, this assumption overestimated the number of patients treated with BsoC or SoC, resulting in possibly higher costs in this first year. Besides, we stressed that a minor change in the mean annual amount of severe flares in the SoC treatment group resulted in a negative total budget impact. This study used the mean annual amount of severe flares from the BLISS-SC trial. However, other studies indicated a higher mean annual amount of severe flares [14,15]. Furthermore, we used a constant value over the years because no data about a trend in the mean annual amount of flares was available. This indicated some uncertainty about the base case value used for the mean annual amount of severe flares in SoC. To evaluate the uncertainty surrounding the parameters in the model, distributions for all parameters were used in the PSA. One of the limitations was that the distributions were unknown for the vast majority of parameters, and therefore triangular distributions were used to draw the parameter values in the PSA. Future research should focus on collecting these distributions to better reflect the true uncertainty in the budget impact of belimumab.

Implications for practice

Since 2018, the ZiN has decided that using Belimumab SC in adult autoantibody-positive SLE patients with moderate to severe disease activity will be reimbursed from the basic package. As Belimumab SC is a relatively expensive drug compared to the SoC, this may lead to cost homogeneity [6]. Therefore, Belimumab SC is designated as an add-on therapy, allowing it to be declared additionally to a Diagnose Behandeling Combinatie (DBC) care product to health insurers, also known as Diagnosis Treatment Combination (DTC) [92]. The Nederlandse Zorgautoriteit (NZa) sets the WGP maximum price as the maximum rate for Belimumab SC [93]. Since Belimumab SC is already reimbursed, it is already covered as a separate component (add-on) of the DBC. Health insurers and hospitals make joint agreements on possible changes in the average price per DBC. This is because the price of a DBC is based on an average of the care provided and the corresponding average cost of care. The budget impact analysis of Belimumab SC showed an average annual budget impact per patient treated with BSoC of approximately €4,750. To our knowledge, this study has been the first to examine the budget impact for Belimumab SC in the Dutch setting so that the budget impact can serve as input for possible changes in the average price per DBC.

Furthermore, this study was performed from a societal perspective. However, costs and cost savings within the healthcare sector may only be relevant for some of the Dutch society since these costs are paid by the DBC. On the other hand, cost and cost savings outside of healthcare may not be relevant for Dutch hospitals. However, the budget impact can be used by national decision-makers to remove savings from the DBC by 'cleaning up' the DBC. Subsequently, Dutch hospital boards can determine how this will affect hospital budgets and implement changes in their policies regarding the prescription of Belimumab SC.

According to Strategies in Regulated Markets (SiRM) research, healthcare costs are rising faster and faster. One of the rising shares of hospital budgets is represented by expensive intramural drugs, with a 7.0% year-on-year increase. However, according to the Integraal Zorgakkoord (IZA), only 1.0% annual budget growth is allowed for specialized medical care, with 'expensive drugs' being only a tiny part of this [13]. As a result, hospital budgets are under increasing pressure, leaving little budget for the growth of other hospital care and essential care [12]. A study by NZa (2022) on contracting and

purchasing medicines in specialist medical care showed that managing the rising cost of intramural drugs concerning the hospitals' total budget and the associated limited possibilities for growth in the administrative outline agreement is a problem. As a result, decision-makers may experience uncertainty when deciding on contracts that impact the available budget for expensive intramural medicines in the Dutch setting [94]. To reduce this uncertainty, we recommend that decision-makers on a national level use the budget impact of Belimumab SC to manage the overall hospital budget better when procuring expensive intramural drugs. Belimumab SC is an additional therapy to the SoC, making substituting or displacing SoC impossible. Therefore, using Belimumab SC generates additional expenditure. However, the budget impact of Belimumab SC addresses successful endpoints for the SLE treatment that is sufficient to meet patients' needs for safe and more effective treatment [3,6].

Implications for future research

The adverse events costs for BSoC and SoC influence the model. Nevertheless, the cost difference between BSoC and SoC is mainly affected by the high skin and subcutaneous disorder costs. The exact data about the adverse events cost in SLE patients treated with BSoC in the Netherlands (Europe) wasn’t available in the literature. Future research would therefore be of added value, as it limits any overestimation of this cost and, in addition, could be better applied to the Dutch setting. Real-world evidence derived from Dutch health insurance claims data could be used for this purpose. Besides, the SLE patient's productivity loss and absenteeism greatly impacted the model by generating the highest savings. However, assumptions were made regarding absenteeism and presenteeism of the SLE patient in the Netherlands due to the missing data. Therefore, future research is of added value because the costs regarding absenteeism and presenteeism are high. Besides, future research may indicate a clear distinction between BSoC and SoC when a more extended period is used. Follow-up studies on absenteeism and presenteeism through an SLE cohort would be a possibility. The number of patients progressing from SLE to ESKD substantially influences the model. However, reasonable estimations were not available in the literature. Since the costs of treating ESKD with transplantation or dialysis are high but equal per patient (depending on the choice of therapy), it is valuable to collect information on the progression of SLE to ESKD between SLE patients treated with BSoC and SoC to determine the effect of Belimumab SC. Another implication for future research is the annual mean change in SDI. We assumed that the mean annual change might be overestimated or underestimated, with implications for the budget impact of Belimumab SC. In the future, a better calculation should be used for the annual mean change in SDI if it can be derived from a mean change in SDI over a longer period. In addition, an annual measurement of mean change in SDI may be possible in SLE patients. Furthermore, implications for future research are possible as the model did not consider the degree of organ damage and in which organ damage occurred. This may impact annual direct medical costs more than those currently held per SDI unit. Besides, the budget impact model didn't consider slowing the progression of SLE. We recommend using organ scans, especially after a mild/moderate or severe flare, to determine the degree of organ damage and in which organ damage occurred after having mild/moderate or severe flares.

The long-term safety and efficacy of Belimumab were investigated in open-label extension studies of the phase 2 study, BLISS-52, BLISS-76, BLISS-SC, and BLISS-NEA. Based on these studies, the long-term use of Belimumab is supported and associated with improvements in monitoring and controlling SLE symptoms. Besides, the health-related quality of life (HRQoL) and patient-reported outcomes further improved due to the long-term use of Belimumab. Finally, during a follow-up period of eight years during the BLISS-52 and BLISS-76 (n = 738 from both studies combined), no new safety signals and minimal organ damage progression were observed. Future research will need to demonstrate the impact of the long-term use of Belimumab SC on the budget. However, based on the open-label studies described above, we expect further savings to be favorable to the impact of Belimumab SC on the budget as Belimumab continues to improve efficacy and safety over the long term.

Finally, even though the triangular distribution reduced the uncertainty in the PSA, other distributions could have been used to better reflect the true uncertainty in the budget impact of Belimumab SC.

Therefore, the triangular distributions can be optimized using more standard distributions like beta, gamma, and uniform distributions. We recommend performing beta distributions for prevalence, non-renal population, and moderate to severe disease activity [95]. In addition, a gamma distribution should be performed for costs and a uniform distribution for market shares. A normal distribution with a 95.0% interval should be used for the uncertainty intervals [96].

Conclusion

The budget impact model developed in this study indicated that Belimumab SC, in addition to the SoC, increased expenditures of approximately €3.7 million compared to the patients treated with SoC in the Dutch setting over a 3-year time horizon. The budget impact analysis provides decision-makers on a national level with an overview of the direct and indirect costs, allowing better management of the hospital budgets regarding expensive intramural drugs. For this study, we used assumptions and values that were, to the best of our knowledge, the most suitable in the Dutch setting to assess the future impact of Belimumab SC. This data emphasizes the importance of controlling and monitoring flares, loss of productivity, and pharmacological costs, which are the leading causes of rising healthcare costs. Future improvements can be made using a retrospective cohort study in the Dutch setting to demonstrate the impact of BSoC in SLE patients.

References

[1] Kiriakidou M, Editors S, Cotton D, Taichman D, Williams S. Systemic lupus erythematosus. Ann Intern Med 2013;159. https://doi.org/10.7326/0003-4819-159-7-201310010-01004.

[2] Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. New England Journal of Medicine 2020;383:1117–28. https://doi.org/10.1056/nejmoa2001180.

[3] 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;63:3918–30. https://doi.org/10.1002/art.30613.

[4] Fanouriakis A, Kostopoulou M, Alunno A, Aringer M, Bajema I, Boletis JN, et al. 2019 update of the EULAR recommendations for the management of systemic lupus erythematosus. Ann Rheum Dis 2019;78:736–45. https://doi.org/10.1136/annrheumdis-2019-215089.

[5] Bultink I, Tsang-A-Sjoe M. Systemische lupus erythematosus. Amsterdam: 2022.

[6] Zorginstituut Nederland. Standpunt belimumab subcutaan (Benlysta) en voorwaardelijke toelating belimumab intraveneus. ’s Gravenhage: 2018.

[7] Committee for Medicinal Products for Human Use (CHMP). Assessment report Benlysta EPAR. 2021.

[8] Zorginstituut Nederland. Standpunt belimumab subcutaan (Benlysta) en voorwaardelijke toelating belimumab intraveneus. ’s Gravenhage: 2018.

[9] 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;69:1016–27. https://doi.org/10.1002/art.40049.

[10] Garris C, Jhingran P, Bass D, Engel-Nitz NM, Riedel A, Dennis G. Healthcare utilization and cost of systemic lupus erythematosus in a US managed care health plan. J Med Econ 2013;16:667–77. https://doi.org/10.3111/13696998.2013.778270.

[11] Doria A, Amoura Z, Cervera R, Khamastha MA, Schneider M, Richter J, et al. Annual direct medical cost of active systemic lupus erythematosus in five European countries. Ann Rheum Dis 2014;73:154–60. https://doi.org/10.1136/annrheumdis-2012-202443.

[12] Meisters R, Westra D, Putrik P, Bosma H, Ruwaard D, Jansen M. Regional differences in healthcare costs further explained: The contribution of health, lifestyle, loneliness and mastery. TSG 2022;100:189–96. https://doi.org/10.1007/s12508-022-00369-4.

[13] Kienhuis R. Integraal Zorgakkoord en Impact Ziekenhuisfinanciering & Contractering 2023.

[14] Cevey M, Calvo-Alén J, Crespo C, Robles-Marhuenda A, Smolen L, Cortés-Hernández J. Budget Impact Analysis Of Subcutaneous Belimumab In Patients With Systemic Lupus Erythematosus In Spain. ClinicoEconomics and Outcomes Research 2019;Volume 11:757–65. https://doi.org/10.2147/CEOR.S218464.

[15] Pierotti F, Palla I, Pippo L, Lorenzoni V, Turchetti G. BUDGET IMPACT ANALYSIS OF BELIMUMAB IN TREATING SYSTEMIC LUPUS ERYTHEMATOSUS. Int J Technol Assess Health Care 2016;32:348–54. https://doi.org/10.1017/S026646231600057X.

[16] van Vollenhoven RF, Petri MA, Cervera R, Roth DA, Ji BN, Kleoudis CS, et al. Belimumab in the treatment of systemic lupus erythematosus: high disease activity predictors of response. Ann Rheum Dis 2012;71:1343–9. https://doi.org/10.1136/annrheumdis-2011-200937.

[17] Ramachandran S, Parks D, Kurtinecz M, Roth DA, Alfonso-Cristancho R. An indirect comparison of intravenous and subcutaneous belimumab efficacy in patients with SLE and high disease activity. J Comp Eff Res 2018;7:581–93. https://doi.org/10.2217/cer-2017-0085.
[18] 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;69:1016–27. https://doi.org/10.1002/art.40049.
[19] Ministerie van Volksgezondheid W en S. Het Nederlandse zorgstelsel 2016.
[20] McElhone K, Abbott J, Hurley M, Burnell J, Lanyon P, Rahman A, et al. Flares in patients with systemic lupus erythematosus. Rheumatology 2021;60:3262–7. https://doi.org/10.1093/rheumatology/keaa777.
[21] Doria A, Stohl W, Schwarting A, Okada M, Scheinberg M, van Vollenhoven R, et al. Efficacy and Safety of Subcutaneous Belimumab in Anti-Double-Stranded DNA-Positive, Hypocomplementemic Patients With Systemic Lupus Erythematosus. Arthritis & Rheumatology 2018;70:1256–64. https://doi.org/10.1002/art.40511.
[22] Al Sawah S, Zhang X, Zhu B, Magder LS, Foster SA, Iikuni N, et al. Effect of corticosteroid use by dose on the risk of developing organ damage over time in systemic lupus erythematosus--the Hopkins Lupus Cohort. Lupus Sci Med 2015;2:e000066–e000066. https://doi.org/10.1136/lupus-2014-000066.
[23] Urowitz MB, Ohsfeldt RL, Wielage RC, Kelton KA, Asukai Y, Ramachandran S. Organ damage in patients treated with belimumab versus standard of care: a propensity score-matched comparative analysis. Ann Rheum Dis 2019;78:372. https://doi.org/10.1136/ANNRHEUMDIS-2018-214043.
[24] Bruce IN, O'Keeffe AG, Farewell V, Hanly JG, Manzi S, Su L, et al. Extended report: Factors associated with damage accrual in patients with systemic lupus erythematosus: results from the Systemic Lupus International Collaborating Clinics (SLICC) Inception Cohort. Ann Rheum Dis 2015;74:1706. https://doi.org/10.1136/ANNRHEUMDIS-2013-205171.
[25] Pryor KP, Barbhaiya M, Costenbader KH, Feldman CH. Disparities in Lupus and Lupus Nephritis Care and Outcomes among U.S. Medicaid Beneficiaries. Rheum Dis Clin North Am 2021;47:41. https://doi.org/10.1016/J.RDC.2020.09.004.
[26] NIDDK. Lupus and Kidney Disease (Lupus Nephritis) n.d. https://www.niddk.nih.gov/health-information/kidney-disease/lupus-nephritis (accessed March 31, 2023).
[27] Braga FNHF, das Chagas Medeiros MM, Junior ABV, de Sousa Lima ME, Barros LCM, Pontes MX, et al. Proteinuria and serum creatinine after 12 months of treatment for lupus nephritis as predictors of long-term renal outcome: a case–control study. Advances in Rheumatology 2022;62:2. https://doi.org/10.1186/s42358-021-00232-1.
[28] Anders H-J, Saxena R, Zhao M, Parodis I, Salmon JE, Mohan C. Lupus nephritis. Nat Rev Dis Primers 2020;6:7. https://doi.org/10.1038/s41572-019-0141-9.
[29] Ahmed HMA, Abohamad S, Elfishawi M, Tharwat Hegazy M, Vijaykumar K. Subcutaneous formulation of belimumab in treatment of systemic lupus erythematosus: a critical review with focus on safety and satisfaction. Patient Prefer Adherence 2018;Volume 12:2475–9. https://doi.org/10.2147/PPA.S147163.
[30] Pascoe K, Lobosco S, Bell D, Hoskin B, Chang DJ, Pobiner B, et al. Patient- and Physician-reported Satisfaction With Systemic Lupus Erythematosus Treatment in US Clinical Practice. Clin Ther 2017;39:1811–26. https://doi.org/10.1016/j.clinthera.2017.07.039.

[31] Zorginstituut Nederland. Belimumab | Horizonscan geneesmiddelen 2019. https://www.horizonscangeneesmiddelen.nl/geneesmiddelen/belimumab-chronische-immuunziekten-chronische-immuunziekten-overig/versie2 (accessed May 4, 2023).
[32] Zen M, Salmaso L, Barbiellini Amidei C, Fedeli U, Bellio S, Iaccarino L, et al. Systemic lupus erythematosus incidence and prevalence in a large population-based study in northeastern Italy. Rheumatology 2022. https://doi.org/10.1093/RHEUMATOLOGY/KEAC685.
[33] Rúa-Figueroa Í, Richi P, López-Longo FJ, Galindo M, Calvo-Alén J, Olivé-Marqués A, et al. Comprehensive Description of Clinical Characteristics of a Large Systemic Lupus Erythematosus Cohort from the Spanish Rheumatology Society Lupus Registry (RELESSER) With Emphasis on Complete Versus Incomplete Lupus Differences. Medicine 2015;94:e267. https://doi.org/10.1097/MD.0000000000000267.
[34] Speyer CB, Li D, Guan H, Kazuki Yoshida ·, Stevens E, Jorge AM, et al. Comparison of an administrative algorithm for SLE disease severity to clinical SLE Disease Activity Index scores. Rheumatol Int 2020;40:257–61. https://doi.org/10.1007/s00296-019-04477-4.
[35] Mok CC, Ho LY, Ying SKY, Leung MC, To CH, Ng WL. Long-term outcome of a randomised controlled trial comparing tacrolimus with mycophenolate mofetil as induction therapy for active lupus nephritis. Ann Rheum Dis 2020;79:1070–6. https://doi.org/10.1136/annrheumdis-2020-217178.
[36] Houssiau FA, D'Cruz D, Sangle S, Remy P, Vasconcelos C, Petrovic R, et al. Azathioprine versus mycophenolate mofetil for long-term immunosuppression in lupus nephritis: results from the MAINTAIN Nephritis Trial. Ann Rheum Dis 2010;69:2083–9. https://doi.org/10.1136/ard.2010.131995.
[37] Hermansen M-LF, Lindhardsen J, Torp-Pedersen C, Faurschou M, Jacobsen S. Incidence of Systemic Lupus Erythematosus and Lupus Nephritis in Denmark: A Nationwide Cohort Study. J Rheumatol 2016;43:1335–9. https://doi.org/10.3899/jrheum.151221.
[38] Brinks R, Hoyer A, Weber S, Fischer-Betz R, Sander O, Richter JG, et al. Age-specific and sex-specific incidence of systemic lupus erythematosus: an estimate from cross-sectional claims data of 2.3 million people in the German statutory health insurance 2002. Lupus Sci Med 2016;3:e000181. https://doi.org/10.1136/lupus-2016-000181.
[39] Arnaud L, Fagot J-P, Mathian A, Paita M, Fagot-Campagna A, Amoura Z. Prevalence and incidence of systemic lupus erythematosus in France: A 2010 nation-wide population-based study. Autoimmun Rev 2014;13:1082–9. https://doi.org/10.1016/j.autrev.2014.08.034.
[40] Kedves M, Kósa F, Kunovszki P, Takács P, Szabó MZ, Karyekar C, et al. Large-scale mortality gap between SLE and control population is associated with increased infection-related mortality in lupus. Rheumatology 2020;59:3443–51. https://doi.org/10.1093/rheumatology/keaa188.
[41] Bultink IEM, de Vries F, van Vollenhoven RF, Lalmohamed A. Mortality, causes of death and influence of medication use in patients with systemic lupus erythematosus *vs* matched controls. Rheumatology 2021;60:207–16. https://doi.org/10.1093/rheumatology/keaa267.
[42] Jorge AM, Lu N, Zhang Y, Rai SK, Choi HK. Unchanging premature mortality trends in systemic lupus erythematosus: a general population-based study (1999–2014). Rheumatology 2018;57:337–44. https://doi.org/10.1093/rheumatology/kex412.
[43] Centraal Bureau voor Statistiek. Bevolkingsteller n.d. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/visualisaties/dashboard-bevolking/bevolkingsteller (accessed April 5, 2023).

[44] Centraal Bureau voor Statistiek. Lichaamsgroei 1981–2018: recent vooral gewichtstoename 2019. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/nieuws/2019/48/lichaamsgroei-1981-2018-recent-vooral-gewichtstoename (accessed March 3, 2023).
[45] NCD-RisC. Average Height by Country 2023 n.d. https://worldpopulationreview.com/country-rankings/average-height-by-country (accessed April 24, 2023).
[46] van Son J, Moens HB, Voskuyl A. Report conditional reimbursement trajectory belimumab. 2018.
[47] Turner HC, Lauer JA, Tran BX, Teerawattananon Y, Jit M. Adjusting for Inflation and Currency Changes Within Health Economic Studies. Value in Health 2019;22:1026–32. https://doi.org/10.1016/j.jval.2019.03.021.
[48] van Son J, Moens HB, Voskuyl A. Report conditional reimbursement trajectory belimumab. 2018.
[49] Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Review Report Belimumab (Benlysta) (GlaxoSmithKline Inc.). Ottawa (ON): 2020.
[50] Zorginstituut Nederland. Prednison n.d. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/p/prednison#kosten (accessed April 20, 2023).
[51] Zorginstituut Nederland. Hydroxychloroquine n.d. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/h/hydroxychloroquine#doseringen (accessed April 20, 2023).
[52] Zorginstituut Nederland. Methotrexaat (bij inflammatoire aandoening) n.d. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/m/methotrexaat__bij_inflammatoire_aandoening_#kosten (accessed April 20, 2023).
[53] Zorginstituut Nederland. Mycofenolaatmofetil n.d. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/m/mycofenolaatmofetil (accessed April 20, 2023).
[54] Zorginstituut Nederland. Azathioprine n.d. https://www.farmacotherapeutischkompas.nl/bladeren/preparaatteksten/a/azathioprine (accessed April 20, 2023).
[55] Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Diemen: 2016.
[56] Canadian Agency for Drugs and Technologies in Health. Pharmacoeconomic Review Report Belimumab (Benlysta) (GlaxoSmithKline Inc.). Ottawa (ON): 2020.
[57] Ruperto N, Hanrahan L, Alarcón G, Belmont H, Brey R, Brunetta P, et al. International consensus for a definition of disease flare in lupus. Lupus 2011;20:453–62. https://doi.org/10.1177/0961203310388445.
[58] Adamichou C, Bertsias G. Flares in systemic lupus erythematosus: diagnosis, risk factors and preventive strategies. Mediterr J Rheumatol 2017;28:4–12. https://doi.org/10.31138/mjr.28.1.4.
[59] Rovin BH, Furie R, Teng YKO, Contreras G, Malvar A, Yu X, et al. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney Int 2022;101:403–13. https://doi.org/10.1016/j.kint.2021.08.027.
[60] Lokhandwala T, Yue B, Coutinho AD, Bell CF. Within-trial economic analysis of flare data from the BLISS-SC trial of subcutaneous belimumab in systemic lupus

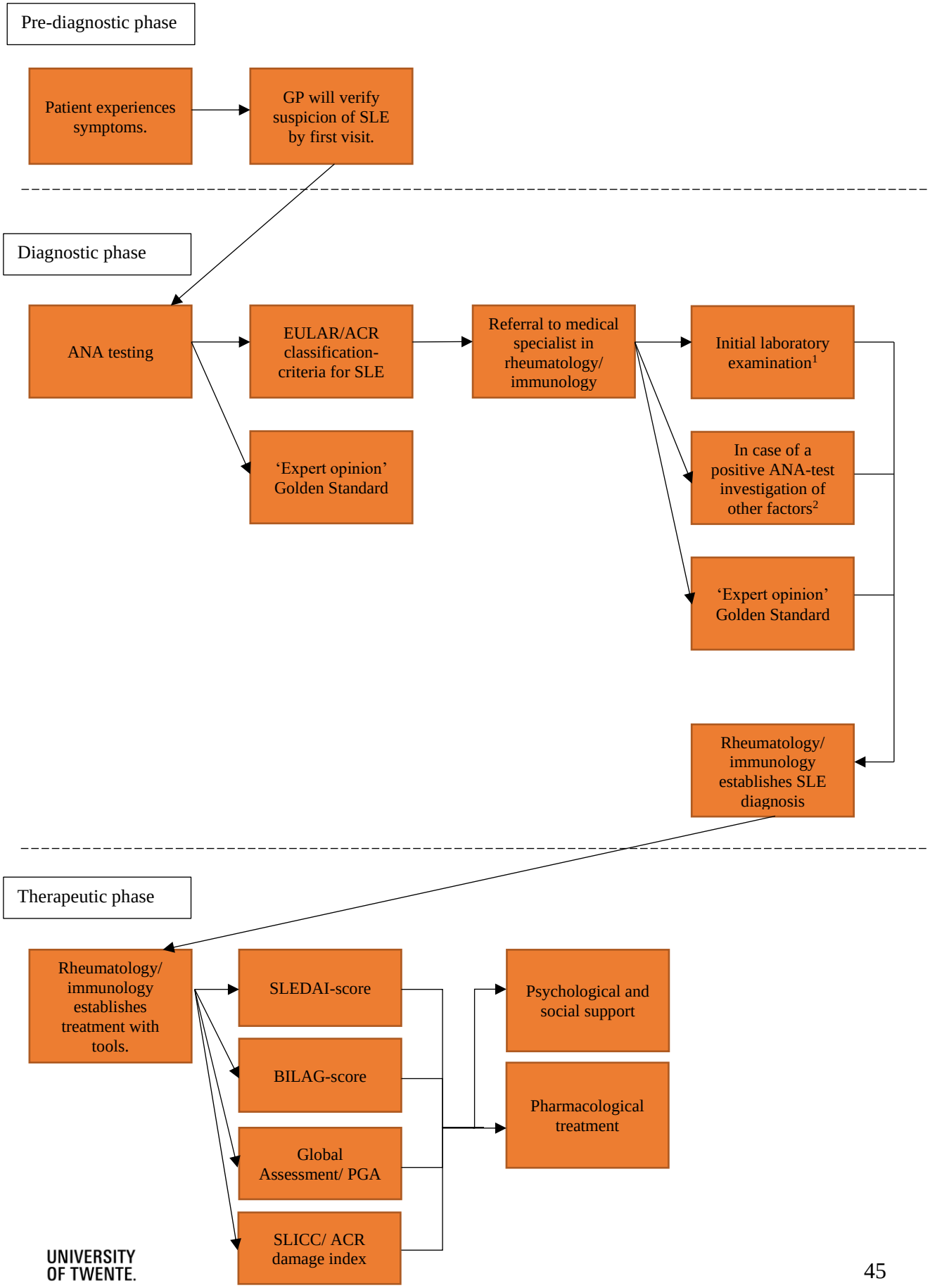
erythematosus. Lupus Sci Med 2021;8:e000438. https://doi.org/10.1136/lupus-2020-000438.
[61] GlaxoSmithKline. Clinical Study Report: A Phase 3, Multi-Center, Randomized, Double-Blind, Placebo-Controlled, 52-Week Study to Evaluate the Efficacy and Safety of Belimumab (HGS1006) Administrated Subcutaneously (SC) to Subjects with Systemic Lupus Erythematosus (SLE) - Double Blind Endpoint Analysis . 2016.
[62] Petri M, Bechtel B, Dennis G, Shah M, McLaughlin T, Kan H, et al. Burden of corticosteroid use in patients with systemic lupus erythematosus: results from a Delphi panel. Lupus 2014;23:1006–13. https://doi.org/10.1177/0961203314532699.
[63] Ogunsanya ME, Nduaguba SO, Brown CM. Incremental health care services and expenditures associated with depression among individuals with cutaneous lupus erythematosus (CLE). Lupus 2018;27:1107–15. https://doi.org/10.1177/0961203318762604.
[64] Petri M, Bechtel B, Dennis G, Shah M, McLaughlin T, Kan H, et al. Burden of corticosteroid use in patients with systemic lupus erythematosus: results from a Delphi panel. Lupus 2014;23:1006–13. https://doi.org/10.1177/0961203314532699.
[65] Centraal Bureau voor Statistiek. Inflatie 10 procent in 2022. 2023 n.d. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/nieuws/2023/02/inflatie-10-procent-in-2022 (accessed May 12, 2023).
[66] Mohapatra S, Goldstein D, Kumar A, Saha T, Penigalapati D. Acute Acalculous Cholecystitis as a Presenting Manifestation in Systemic Lupus Erythematosus. Eur J Case Rep Intern Med 2016;3. https://doi.org/10.12890/2016_000408.
[67] Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD. Manifestations of systemic lupus erythematosus. Maedica (Bucur) 2011;6:330–6.
[68] Hanly JG, Su L, Urowitz MB, Romero-Diaz J, Gordon C, Bae S-C, et al. Mood Disorders in Systemic Lupus Erythematosus: Results From an International Inception Cohort Study. Arthritis & Rheumatology 2015;67:1837–47. https://doi.org/10.1002/art.39111.
[69] Hersh AO, Arkin LM, Prahalad S. Immunogenetics of cutaneous lupus erythematosus. Curr Opin Pediatr 2016;28:470–5. https://doi.org/10.1097/MOP.0000000000000383.
[70] Nossent J, Kiss E, Rozman B, Pokorny G, Vlachoyiannopoulos P, Olesinska M, et al. Disease activity and damage accrual during the early disease course in a multinational inception cohort of patients with systemic lupus erythematosus. Lupus 2010;19:949–56. https://doi.org/10.1177/0961203310366572.
[71] Ibanez D, Gladman DD, Touma Z, Nikpour M, Urowitz MB. Optimal Frequency of Visits for Patients with Systemic Lupus Erythematosus to Measure Disease Activity Over Time. J Rheumatol 2011;38:60–3. https://doi.org/10.3899/jrheum.100575.
[72] Dashiell-Aje E, Harding G, Pascoe K, DeVries J, Berry P, Ramachandran S. Patient Evaluation of Satisfaction and Outcomes with an Autoinjector for Self-Administration of Subcutaneous Belimumab in Patients with Systemic Lupus Erythematosus. The Patient - Patient-Centered Outcomes Research 1090;11:119–29. https://doi.org/10.1007/s40271-017-0276-2.
[73] NVLE. Wat kan je doen? n.d. https://www.nvle.org/leven-met/zelf-doen/omgaan-met-vermoeidheid/wat-kunt-u-doen/ (accessed April 23, 2023).
[74] Ghazali WSW, Daud SMM, Mohammad N, Wong KK. SLICC damage index score in systemic lupus erythematosus patients and its associated factors. Medicine 2018;97:e12787. https://doi.org/10.1097/MD.0000000000012787.
[75] Fanouriakis A, Kostopoulou M, Cheema K, Anders HJ, Aringer M, Bajema I, et al. 2019 Update of the Joint European League Against Rheumatism and European Renal Association-European Dialysis and Transplant Association (EULAR/ERA-EDTA)

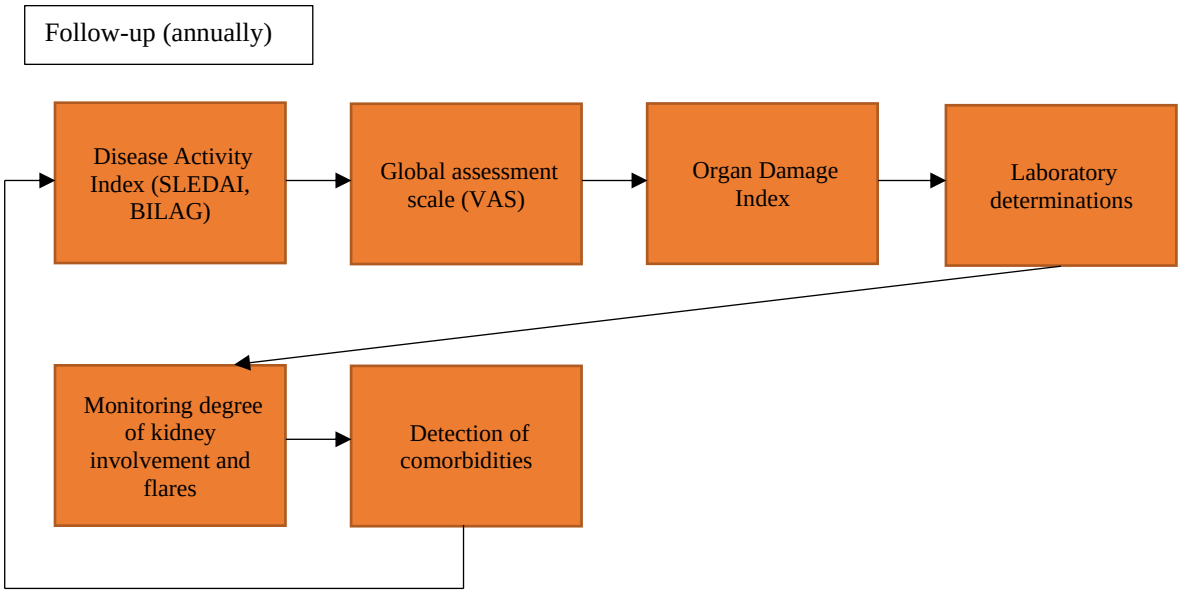
recommendations for the management of lupus nephritis. Ann Rheum Dis 2020;79:S713–23. https://doi.org/10.1136/ANNRHEUMDIS-2020-216924.
[76] Hahn BH, McMahon MA, Wilkinson A, Wallace WD, Daikh DI, Fitzgerald JD, et al. American College of Rheumatology guidelines for screening, treatment, and management of lupus nephritis. Arthritis Care Res (Hoboken) 2012;64:797–808. https://doi.org/10.1002/ACR.21664.
[77] Furie R, Rovin BH, Houssiau F, Malvar A, Teng YKO, Contreras G, et al. Two-Year, Randomized, Controlled Trial of Belimumab in Lupus Nephritis. New England Journal of Medicine 2020;383:1117–28. https://doi.org/10.1056/nejmoa2001180.
[78] Rovin BH, Furie R, Teng YKO, Contreras G, Malvar A, Yu X, et al. A secondary analysis of the Belimumab International Study in Lupus Nephritis trial examined effects of belimumab on kidney outcomes and preservation of kidney function in patients with lupus nephritis. Kidney Int 2022;101:403–13. https://doi.org/10.1016/j.kint.2021.08.027.
[79] Mohnen SM, van Oosten MJM, Los J, Leegte MJH, Jager KJ, Hemmelder MH, et al. Healthcare costs of patients on different renal replacement modalities – Analysis of Dutch health insurance claims data. PLoS One 2019;14:e0220800. https://doi.org/10.1371/journal.pone.0220800.
[80] Nefrovisie. Trends in nierfunctievervanging in Nederland Ouderen COVID-19 Transplantatie in samenwerking met 2022:8–9.
[81] Hakkaart-van Roijen L, van der Linden N, Bouwmans C, Kanters T, Swan Tan S. Kostenhandleiding: Methodologie van kostenonderzoek en referentieprijzen voor economische evaluaties in de gezondheidszorg. Diemen: 2016.
[82] van den Hout WB. The value of productivity: human-capital versus friction-cost method. Ann Rheum Dis 2010;69:i89–91. https://doi.org/10.1136/ard.2009.117150.
[83] Centraal Bureau voor Statistiek. Vacatures; stroomcijfers, seizoengecorrigeerd 2023. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/cijfers/detail/84545NED#shortTableDescription (accessed April 26, 2023).
[84] Centraal Bureau voor Statistiek. Arbeidsparticipatie naar leeftijd en geslacht 2021. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/visualisaties/dashboard-arbeidsmarkt/werkenden/arbeidsparticipatie-naar-leeftijd-en-geslacht (accessed April 26, 2023).
[85] Aalabaf-Sabaghi M. Decision modelling for health economic evaluation. Journal of Epidemiology & Community Health 2007;61:839–839. https://doi.org/10.1136/jech.2007.059576.
[86] Lee J, Dhillon N, Pope J. All-cause hospitalizations in systemic lupus erythematosus from a large Canadian referral centre. Rheumatology 2013;52:905–9. https://doi.org/10.1093/rheumatology/kes391.
[87] Abu Bakar F, Sazliyana Shaharir S, Mohd R, Mohamed Said MS, Rajalingha S, Wei Yen K. Burden of Systemic Lupus Erythematosus on Work Productivity and Daily Living Activity: A Cross-Sectional Study Among Malaysian Multi-Ethnic Cohort. Arch Rheumatol 2020;35:205–13. https://doi.org/10.46497/ArchRheumatol.2020.7405.
[88] Kissell R, Poserina J. Advanced Math and Statistics. Optimal Sports Math, Statistics, and Fantasy, Elsevier; 2017, p. 103–35. https://doi.org/10.1016/B978-0-12-805163-4.00004-9.
[89] Pierotti F, Palla I, Treur M, Pippo L, Turchetti G. Assessment of the Economic Impact of Belimumab for the Treatment of Systemic Lupus Erythematosus in the Italian Setting: A Cost-Effectiveness Analysis. PLoS One 2015;10:e0140843. https://doi.org/10.1371/journal.pone.0140843.

[90] Ministerie van Volksgezondheid W en S. Wet geneesmiddelenprijzen | Prijsvorming | Farmatec 2023. https://www.farmatec.nl/prijsvorming/wet-geneesmiddelenprijzen (accessed May 17, 2023).
[91] Cevey M, Calvo-Alén J, Crespo C, Robles-Marhuenda A, Cortés J. Direct cost offsets related to belimumab subcutaneous administration in patients with systemic lupus erythematosus in Spain 2019. https://tools.ispor.org/ScientificPresentationsDatabase/Presentation/85326?pdfid=56520 (accessed May 9, 2023).
[92] Nederlandse Zorgautoriteit. Registreren en declareren van geneesmiddelen in de msz | Medisch-specialistische zorg | Nederlandse Zorgautoriteit n.d. https://www.nza.nl/zorgsectoren/medisch-specialistische-zorg/registreren-en-declareren-van-geneesmiddelen (accessed March 24, 2023).
[93] Nederlandse Zorgautoriteit. Prestatie- en tariefbeschikking add-ongeneesmiddelen, december 2022 (ambtshalve vastgesteld) - TB/REG-22674-01 - 2022. https://puc.overheid.nl/nza/doc/PUC_726934_22/1/ (accessed May 26, 2023).
[94] Nederlandse Zorgautoriteit. Monitor Contractering en inkoop geneesmiddelen in de medisch-specialistische zorg. 2016.
[95] Sinharay S. Continuous Probability Distributions. International Encyclopedia of Education, Elsevier; 2010, p. 98–102. https://doi.org/10.1016/B978-0-08-044894-7.01720-6.
[96] Mantopoulos T, Mitchell PM, Welton NJ, McManus R, Andronis L. Choice of statistical model for cost-effectiveness analysis and covariate adjustment: empirical application of prominent models and assessment of their results. The European Journal of Health Economics 2016;17:927–38. https://doi.org/10.1007/s10198-015-0731-8.
[97] Brinks R, Hoyer A, Weber S, Fischer-Betz R, Sander O, Richter JG, et al. Age-specific and sex-specific incidence of systemic lupus erythematosus: an estimate from cross-sectional claims data of 2.3 million people in the German statutory health insurance 2002. Lupus Sci Med 2016;3. https://doi.org/10.1136/LUPUS-2016-000181.
[98] Arnaud L, Fagot J-P, Mathian A, Paita M, Fagot-Campagna A, Amoura Z. Prevalence and incidence of systemic lupus erythematosus in France: A 2010 nation-wide population-based study. Autoimmun Rev 2014;13:1082–9. https://doi.org/10.1016/j.autrev.2014.08.034.
[99] Lokhandwala T, Yue B, Coutinho AD, Bell CF. Within-trial economic analysis of flare data from the BLISS-SC trial of subcutaneous belimumab in systemic lupus erythematosus. Lupus Sci Med 2021;8:e000438. https://doi.org/10.1136/lupus-2020-000438.
[100] Centraal Bureau voor Statistiek. Mannen en vrouwen 2022. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/visualisaties/dashboard-bevolking/mannen-en-vrouwen#:~:text=Op%201%20januari%202022%20telde,meerderheid%2C%20op%20hogere%20leeftijden%20vrouwen. (accessed May 1, 2023).
[101] Centraal Bureau voor Statistiek. Hoeveel werken mannen meer dan vrouwen? 2021. https://www-cbs-nl.ezproxy2.utwente.nl/nl-nl/faq/emancipatie/hoeveel-werken-mannen-meer-dan-vrouwen- (accessed May 1, 2023).

Appendix 1: Framework of a clinical SLE patient pathway

Figure 5 Framework of a clinical SLE patient pathway





[1] *Complete hematological profile, serum creatine, urine sediment, qualitative examination for proteinuria*
[2] *Anti-dsDNA antibodies, anti-Sm antibodies, antiphospholipid antibodies*

Appendix 2: Demographics summary of the BLISS-SC trial

Demographic characteristics	***Total (n = 836)***	***Belimumab SC (n = 556)***	***Standard of care (n = 280)***
Gender, n (%)			
Woman	789 (94.4)	521 (93.7)	268 (95.7)
Man	47 (5.6)	35 (6.3)	12 (4.3)
Race, n (%)			
White	502 (60.0)	336 (60.4)	166 (59.3)
Asian	182 (21.8)	119 (21.4)	63 (22.5)
African American/ African	86 (10.3)	56 (10.1)	30 (10.7)
Heritage	64 (7.7)	43 (7.7)	21 (7.5)
American Indian or Alaska Native	2 (0.2)	2 (0.4)	0
Native Hawaiian or Other Pacific Islander	9 (1.1)	6 (1.1)	3 (1.1)
Multiracial			
Ethnicity, n (%)			
Hispanic or Latino	240 (28.7)	160 (28.8)	80 (28.6)
Not Hispanic or Latino	596 (71.3)	396 (71.2)	200 (71.4)
Age (years), n	836	556	280
Mean (SD)	38.6 (12.3)	38.1 (12.1)	39.6 (12.6)
Min, Max	18, 77	18, 77	18, 74
Age groups (years), n (%)			
<= 45	596 (71.3)	403 (72.5)	193 (68.9)
> 45 - < 65	221 (26.4)	141 (25.4)	80 (28.6)
>= 65	19 (2.3)	12 (2.2)	7 (2.5)
BMI (kg/m^2), n	835	555	280
Mean (SD)	26.1 (6.6)	26.0 (6.3)	26.5 (7.2)

Table 14 Demographics summary of the BLISS-SC trial

Appendix 3: Baseline disease activity of the BLISS-SC trial

Table 15 Baseline disease activity of the BLISS-SC trial

Disease activity	***Total (n = 836)***	***Belimumab SC (n = 556)***	***Standard of care (n = 280)***
SLE Disease duration (years), n	836	556	280
Mean (SD)	6.5 (6.7)	6.4 (6.6)	6.8 (6.8)
BILAG organ domain involvement, n (%)[a]	598 (71.5)	388 (69.8)	210 (75.0)
At least 1A or 2B	138 (16.5)	87 (15.6)	51 (18.2)
At least 1A	757 (90.6)	499 (89.7)	258 (91.1)
At least 1B	42 (5.0)	29 (5.2)	13 (4.6)
No A or B			
SELENA SLEDAI category, n (%)			
0-3	4 (0.5)	4 (0.7)	0
<=9	312 (37.3)	200 (36.0)	112 (40.0)
10-11	235 (28.1)	161 (29.0)	74 (26.4)
>=12	285 (34.1)	191 (34.4)	94 (33.6)
SELENA SLEDAI score, n	836	556	280
Mean (SD)	10,4 (3.14)	10,5 (3.19)	10.3 (3.04)
SLE Flare Index, n (%)	836	556	280
At least 1 flare	149 (17.8)	92 (16.5)	57 (20.4)
At least 1 severe flare	12 (1.4)	8 (1.4)	4 (1.4)
PGA Category, n (%)			
0-1	59 (7.1)	40 (7.2)	19 (6.8)
>1-2,5	762 (91.1)	507 (91.2)	255 (91.1)
>2,5	12 (1.4)	7 (1.3)	5 (1.8)
Missing	3 (0.4)	2 (0.4)	1 (0.4)
PGA, n	833	554	279
Mean (SD)	1.6 (0.43)	1.6 (0.43)	1.5 (0.45)
SLICC/ ACR Damage Index score, n	836	556	280
Mean (SD)	0.6 (1.05)	0.6 (0.99)	0.7 (1.17)
Proteinuria category (g/24 h), n(%)			
>= 2	39 (4.7)	19 (3.4)	20 (7.1)
Proteinuria level (g/24 h). n	836	556	280
Mean (SD)	0.4 (0.75)	0.4 (0.71)	0.4 (0.84)

[a] *Subject may be included in more than one category*

Appendix 4: Allowable SLE drug usage at baseline in the BLISS-SC trial

Table 16 Allowable SLE drug usage at baseline in the BLISS-SC trial

Drug usage	***Total (n = 836)***	***Belimumab SC (n = 556)***	***Standard of care (n = 280)***
Average Daily Prednison[a] Dose, n (%)			
0 mg/day	114 (13.6)	75 (13.5)	39 (13.9)
>0 – <= 7,5 mg/day	219 (26.2)	146 (26.3)	73 (26.1)
> 7,5 mg/day	503 (60.2)	335 (60.3)	168 (60.0)
Average Daily Prednisone Dose (mg/day), n	836	556	280
Mean (SD)	10.9 (8.51)	10.8 (8.21)	11.2 (9.09)
Number (%) of subjects taking			
Steroids	722 (86.4)	481 (86.5)	241 (86.1)
Antimalarials	580 (69.4)	391 (70.3)	189 (67.5)
Immunosuppressants	381 (45.6)	244 (43.9)	137 (48.9)
Aspirin	139 (16.6)	94 (16.9)	45 (16.1)
NSAIDs	196 (23.4)	124 (22.3)	72 (25.7)

[a] *Steroids were converted to Prednisone equivalent*

Appendix 5: Overview of the assumptions in the study

Table 17 Overview of the assumptions in the study

Number	*Assumption*
1	The demographic characteristics of the BLISS-SC trials are assumed as a basis for the budget impact model of Belimumab SC.
2	The baseline disease activity of the BLISS-SC trial is assumed as a basis for the budget impact model of Belimumab SC.
3	Currently, the ratio of Belimumab SC to Belimumab IV use is 80:20. However, we assumed the ratio to be 100:0 for this study with a view to the future. This means that 100,0% of SLE patients use Belimumab SC.
4	The market share was estimated for the future market scenario at 27.0% in 2023, 2024, and 2025 for eligible Dutch SLE patients. This market share estimation came from GlaxoSmithKline data, where approximately 27.0% of the potential SLE patients are treated with Belimumab SC or Belimumab IV in combination with SoC compared to the SoC in 2023. We also used this market share in this study where we assumed that 27.0% of the eligible SLE population with moderate to severe disease activity and antibody positivity was used BSoC in the year 2023, 2024, and 2025 compared to 73.0% of the eligible SLE population using the SoC. However, our current situation in the budget impact model started with no use of Belimumab SC, 0.0% market share for BSoC.
5	The BLISS-SC trial found that mean overall treatment compliance was equal to 96.4% in both the BSoC and SoC treatment groups. This indicates that this population can self-administer Belimumab SC outside a clinical setting. As there is only a small number of patients (3.6%) who did not remain treatment compliance in the BLISS-SC for both BSoC and SoC, we did not consider this relevant to include potential costs of this in terms of waste in the budget impact model of Belimumab SC. We, therefore, assumed treatment compliance of 100.0%.
6	SLE is more common in individuals of African American, Afro-Caribbean, and Asian descent. In addition, exposure to sunlight (UV) is a factor that can trigger SLE. Since these factors are present to a lesser extent in the Netherlands, we assumed an incidence rate of 1.9 per 100,000 person-years based on a study by Brinks R et al., who estimated the incidence rate of SLE for German men and women [97].
7	European studies did show consistent mortality rates ranging between 13.8 and 16.0 deaths per 1000 person-years [40–42]. Due to the lack of meta-analyses on mortality in the literature, we assumed a mortality rate between these values. We therefore used a mortality rate of 14.9 per 100,000 person-years.
8	According to the statistics of the CBS, the average weight of women is 72.0 kg, and the average weight of men is 85.0 kg in the Netherlands. Based on this data, we assumed a gender-adjusted weighted average of 72.7 kg applicable to the Dutch setting.
9	For height, we retained the lengths of the Dutch population, with women having a height of 170.36 cm and men having a height of 183.78 cm. We assumed a gender adjusted average weight for our study population of 171.11 cm.
10	Based on expert opinion and on the Dutch Autoimmune Registry (DAiRE-register) 2018, a percentage of 30.0% of non-responders to BsoC and SoC present in the target population was used [48]. The responders are the SLE patients who complete their first year of using BsoC or SoC. In contrast, non-responders discontinue BsoC or SoC during the first year due to treatment failure. We assumed that in the first year, 100.0% of the patients continue with their BSoC or SoC treatment, but in the second year, only 70.0% (responders) continue with BSoC or SoC.
11	The dosing schedule for Belimumab SC requires the patient to receive two doses of 200 mg/kg (two pre-filled pens) for the first four weeks. This is followed by weekly doses of one pre-filled pen of 200 mg/kg Belimumab SC. Therefore, the estimation will be 56 administrations for the first year when using Belimumab SC and 52 administrations in the years after the first year.

12	Based on the BLISS-SC, a mean Prednisone dose of 10.9 mg/day at baseline is assumed as the treatment dose for eligible SLE patients. For the other drugs, we used the average dose.
13	We used the cost guide for economic evaluations (2016) to obtain the reference price for the administration costs. Based on the cost guide, an hourly rate of €32.39 was used for the HBO-V nurse [55]. However, based on CBS's Customer Price Index (CPI) values, we assumed an hourly rate of €35.64 for 2021.
14	Since the BLISS-SC trial demonstrated a corticosteroid dosage reduction by ≥ 25.0% (to ≤ 7.5 mg/day) during weeks 40-52 in 18.2% of the patients in the BSoC treatment group and 11.9% in SoC treatment group (OR 1.65 [95% CI 0.95–2.84]; P = 0.0732) [9], we assumed a mean corticosteroid usage for the BSoC of 8,56 mg and a mean corticosteroid usage of 10.70 mg for the SoC at 52 weeks [56].
15	As demonstrated in the BLISS-SC trial, the BSoC had an annual mean number of 1.23 mild/ moderate flares and 0.04 severe flares. In addition, the SoC had an annual mean number of 1.69 mild/moderate and 0.22 severe [9]. We did not distinguish between mild and moderate flares based on the BLISS-SC trial.
16	A within-trial economic analysis of flare data from the BLISS-SC trial (2021) analyzed the claims to compute the unit costs of flares by severity. The mean unit cost obtained per severe flare was $9,273 [60]. Based on the average ER and corresponding date CD, the assumed mean unit cost per severe flare was considered €7,843 (ER:0.8458, CD:2021) [47]. In addition, the average cost for mild/moderate flares was estimated. The average unit cost was $2,303 per mild/moderate flare [60]. Converted to euros, we assumed that the mean unit cost per mild/moderate flare was €1,948 (ER:0.8458, CD:2021)[60][60]
17	For the AE infections and infestations in this study, the costs of the 'serious infection requiring hospitalization' named in the study of Petri M et al. were assumed. The cost was $11,660, equivalent to €8,793 (ER = 0.7541, CD = 2014) [62]. Based on the values of the CPI by the CBS, we assumed that the mean cost for the AE infections and infestations was €9,765 for the year 2021 [65]. In addition, for the AE gastrointestinal disorder in this study, we considered which gastrointestinal manifestations were common in SLE. Based on the literature, ulcers, dysphagia, anorexia, nausea, vomiting, hemorrhage, and abdominal pain were common manifestations [66]. On this basis, the costs of the 'gastrointestinal ulcer/hemorrhage' mentioned in the study of Petri M et al. were used for the AE gastrointestinal disorders. The costs were $7,750, converted to €5,844 (ER = 0.7541, CD = 2014). Based on the values of the CPI by the CBS, we assumed that the mean cost for the AE gastrointestinal disorders was €6,490 for the year 2021 [65]. Furthermore, for the AE musculoskeletal and connective tissue disorders, we considered which musculoskeletal manifestations are common in SLE. Arthralgia, arthritis, osteonecrosis (avascular necrosis of bone), and myopathy are the principal manifestations of SLE [67]. In the study of Petri M et al., costs were defined for avascular necrosis. Based on the literature that this manifestation is common in SLE, according to Petri M et al., the cost was $14,460, equivalent to €10,904 (ER = 0.7541, CD = 2014) for AE muscle and connective tissue disorders.[62]. Based on the values of the CPI by the CBS, we assumed that the mean cost for this AE was €12,110 for the year 2021 [65]. Finally, based on the study of Petri M et al., we could also consider the cost of AE nervous system disorders. For this, we again first looked in the literature for common nervous system disorders. In particular, mood disorders and headaches are common in patients with SLE [68]. The costs were $2,710, equivalent to €2,044 (ER = 0.7541, CD = 2014), for the AE 'mood disorders' defined in the study by Petri M et al. [62]. Based on the values of the CPI by the CBS, we assumed that the mean cost for the AE nervous system disorders was €2,270 for the year 2021 [65]. In the study by Petri M et al., no cost was found on the AE skin and subcutaneous disorders. We used the Ogunsanya M et al. (2018) study to estimate the cost for AE skin and subcutaneous disorders. This study evaluated the economic burden of cutaneous lupus erythematosus (CLE) and showed that it was estimated that the average annual incremental cost be $10,119, also converted to €8,576 (ER = 0.8475, CD = 2018) [63]. According to the literature, CLE is a distinction of SLE that can be associated with SLE symptoms. CLE can be a skin disease alone or may occur in the SLE setting. For both

	CLE and SLE, a butterfly-shaped rash occurs across different body parts, also called malar rash [69]. Due to the similarity in the severity of the adverse events of CLE and SLE, we consider it plausible to use Ogunsanya M et al. costs in this study. Based on the values of the CPI by the CBS, we assumed that the mean cost for this AE was €9,152 for the year 2021 [65]. These include inpatient, outpatient, emergency room visits, other medical expenses, and drug costs.
18	Based on the study of Urowitz MB et al., we assumed that the reduction in progression of organ damage based on the mean change in SDI from baseline to five years for the SoC treatment group was equal to 0.717 (n = 99) and for the BSoC treatment group, it was equal to 0.283 (n = 99). However, in the budget impact model of Belimumab SC, we are looking at an annual change. We, therefore, assumed a proportional annual mean change by dividing the mean change over five years by five to get the annual mean change. So, the annual mean change is 0.143 for the SoC treatment group and 0.057 for the BSoC treatment group.
19	We assumed the annual probability of progression based on the increase in SDI score per year for the SoC treatment group was equal to 8.7% (n = 179), and for the BSoC treatment group, it was equal to 3.5% (n = 179).
20	The CADTH pharmacoeconomic review report Belimumab (Benlysta) calculated the costs per unit SDI. Based on a sponsor's pharmacoeconomic submission in 2019, the predicted annual direct medical costs per unit SDI were $1424.21, converted to €1.271,96 (ER = 0.8931, CD = 2019) [49]. Based on the values of the CPI by the CBS, we assumed that the mean costs for this AE were €1.322,64 for the year 2021 [65].
21	We assumed that the SLE population with progression to ESKD could be by multiplying the percentage of SLE patients who experienced renal flares among the BSoC and SoC users within the annual progression probabilities going from SLE to LN (40.0%) and the annual progression probability of going from LN to ESKD (10.0%).
22	According to a study of Dutch health insurance claim data in 2019, the costs of dialysis are estimated between €77,000 and €105,000 per patient per year. The range of these costs depends on the form of dialysis used for renal replacement therapy. It is possible to receive Continuous Hemodialysis (CHD) for ESKD, but it is also possible to receive Continuous Ambulatory Peritoneal Dialysis (CAPD). Based on the Dutch health insurance claim data, we assumed that these treatments cost €77,566 for CAPD to €92,616 for CHD [79]. However, we considered the CPI values. Based on the values of the CPI by the CBS, the assumed costs are €80,656.66 for a CAPD treatment and €96,306.33 for a CHD treatment in 2021 [65].
23	According to a study of Dutch health insurance claim data in 2019, the mean cost of kidney transplantation was estimated at €85,000 in the year of the transplantation [79]. Transplant costs differ regarding receiving a donor kidney from a living or deceased donor. According to the study, the mean annual costs of a living donor kidney transplant were about €73,000, and the costs of a deceased donor kidney transplant were about €99,000 in the year of transplantation [79]. Based on the CPI values of the CBS, we assumed that the mean annual costs for a living donor kidney transplant were about €75,908.72 and for a deceased donor kidney transplant €102,944.71 in 2021 [65].
24	Based on a report by Nefrovisie (2022) on renal function replacement therapy trends in the Netherlands, we assumed annual distributions of renal replacement therapies according to the year 2020. Here 10.0% received a living donor kidney transplantation, 2.0% a deceased donor kidney transplantation, 69.0% Continuous Haemodialysis (CHD), and 19.0% Continuous Ambulatory Peritoneal Dialysis (CAPD).
25	According to the study of Aalabaf-Sabaghi et al., we assume an SLE-specific employment rate of 46.0% [85]. We multiplied the cost of the friction period with the 46.0% SLE-specific employment rate.
26	The cost guide for economic evaluations (2016) uses a reference price of €31.60 for women and €37.90 for men for the average salary costs per hour. Based on the CPI values of the CBS, we assumed an average salary cost per hour for women of €34.77 and men of €41.40. Again, we corrected the average salary costs per hour based on the gender

	distribution of the BLISS-SC trial, resulting in €35.16 we assumed for the salary cost per hour.
27	Based on a study by Lee J et al., a mean length of stay of 11.8 days due to an SLE flare was found [86]. However, there was no literature about the differences in hospitalization length of stay depending on the severity of flares. We, therefore, assumed 11.8 hospitalization days for the severe flares. Based on the opinion of a rheumatologist working in a hospital in the Netherlands, SLE patients do not need hospitalization for mild/moderate flare. However, hospitals use outpatient treatment. Adding or changing drugs is often sufficient. Therefore, we assume one working day for a mild/moderate flare. For the days surrounding this outpatient treatment, we count an average of two days a patient cannot work. For a severe flare, we assumed that, in addition to the hospitalization days, the patient could not work for an average of 8 days because of the flare. We do not have exact data about these assumptions, nor can the rheumatologist give an exact answer.
28	For the reduction in productivity due to follow-up hospital visits, we considered the annual follow-up visits for which the SLE patient cannot go to work. As mentioned before, based on the literature, SLE patients visit the hospital for a consult with a specialist every three months [70,71]. Therefore, we assumed that the patients could not work for two working days because there is no data about the time needed for these visits in the literature. However, we assume that a consultation with a specialist and some accompanying physical examinations, laboratory tests, and imaging techniques will take at least half a working day.
29	Using the BLISS-SC, we noticed that 35.9% of BSoC users and 45.6% of SoC users had experienced no improvement in mucocutaneous manifestation over 52 weeks. In addition, 55.1% of BSoC users and 64.0% of SoC users had experienced no improvement in hematology manifestation within 52 weeks. Similarly, regarding the SLEDAI-2K, 38.3% of BSoC and 53.4% of SOC had no response. Based on this, we assumed that 43.1% of BSoC users and 54.3% of SoC experienced no annual improvement or response that impacted productivity loss.

** Assumptions are referred to by a superscript at the end of the assumption*

Appendix 6: Treatment dosage and costs

Table 18 Treatment dosage

Treatment dosage	***Belimumab SC***	***SoC***	***Cortico-steroids[1]***	***Anti-malarials[2]***	***Immuno-suppressant[3]***	***Aza-thioprine[4]***	***Mycopheno-late mofetil[5]***	***Metho-trexate[6]***
Treatment dose per administration (mg)	200.0	255.0	5.0	200.0	50.0	50.00	500.00	10.00
Doses per month	4.0	155.4	65.4	45.0	45.0	45.00	75.00	3.50
Dose per month (mg)	800.0	11577.0	327.0	9000.0	2250.0	2250.00	37500.00	35.00
Doses per year	52.0	1864.8	784.8	540.0	540.0	540.00	900.00	42.00
Dose per year (mg)	10400.0	138924.0	3924.0	108000.0	27000.0	27000.00	450000.00	420.00
Additional doses in the first year	4.0	0.0	0.0	0.0	0.0	0.00	0.00	0.00

[1] The corticosteroid treatment dosage was based on a Prednsione (generic) oral tablet of 5 mg

[2] The antimalarial treatment dosage was based on a Hydroxychloroquine (generic) oral tablet of 200 mg

[3] According to the EULAR/ACR 2019 and the BLISS-SC trial the SoC consisted out of an antimalarial, a corticosteroid and an immunosuppressant. Therefore, in the column immunosuppressant the values of one type of immunosuppressant were used for the SoC.

[4] The Azathioprine treatment dosage was based on an Azathioprine (generic) oral tablet of 50 mg

[5] The Mycophenolate Mofetil treatment dosage was based on Mycophenolate Mofetil (generic) oral tablet 500 mg.

[6] The Methotrexate treatment dosage was based on a Methotrexate (generic) oral tablet 10 mg

Table 19 Treatment costs

Treatment costs	***BSoC[1,2]***	***SoC***	***Cortico-steroid***	***Anti-malarial***	***Immuno-suppressant[3]***	***Azathioprine***	***Mycophenolate Mofetil***	***Metho-trexate***	***Weighted usage immuno-suppressants***
Average drug cost per mg	€ 1.18	€ 0.02	€ 0.01	€ 0.00	€ 0.01	€ 0.01	€ 0,00	€ 0.02	€0.01
Total average monthly drug costs	€ 972.98	€ 29.82	€ 3.27	€ 5.85	€ 20.70	€ 20.70	€ 148.50	€ 0.70	€58.76
Total average annual drug costs	**€ 12,618.92**	**€ 357.84**	**€ 39.24**	**€ 70.20**	€ 248.40	**€ 248.40**	**€ 1,782.00**	**€ 8.40**	**€705.10**
Additional costs first year (additional dose + administrations)	€ 978.80	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€ 0.00	€0.00

[1] The average drug cost per mg for the BSoC was based on the cost of Belimumab SC 200 mg from the Z index February 2023; 235,79 euro

[2] The total average annual drug costs for BSoC were a combination of the costs of SoC and Belimumab SC

[3] According to the EULAR/ACR 2019 and the BLISS-SC trial the SoC consisted out of an antimalarial, a corticosteroid and an immunosuppressant. Therefore, in the column immunosuppressant the values of one type of immunosuppressant was used for the SoC.

Appendix 7: Budget impact of the direct and indirect costs using Belimumab SC

Table 20 Budget Impact of the direct and indirect costs of using Belimumab SC

	Year 2023	***Year 2024***	***Year 2025***	***Total over 3 years***
Total number of patient eligible for Belimumab SC	937	896	1059	2892
Total patients on Belimumab SC treatment	253	242	286	781
Current Scenario without Belimumab SC				
Pharmacological costs	€ 335,408.42	€ 320,621.33	€ 378,801.27	€ 1,034,831.01
Adverse events costs	€ 11,593,734.72	€ 11,084,518.00	€ 13,096,048.66	€ 35,774,301.38
Flare costs	€ 4,067,020.20	€ 3,888,389.70	€ 4,594,023.90	€ 12,549,433.80
Productivity loss	€ 11,057,851.56	€ 10,572,171.75	€ 12,490,725.86	€ 34,120,749.17
Dialysis & transplantation	€ 928,931.32	€ 888,131.06	€ 1,049,302.06	€ 2,866,364.44
Irreversible organ damage	€ 153,958.71	€ 147,196.58	€ 173,908.65	€ 475,063.93
Total costs	**€ 28,136,904.93**	**€ 26,901,028.42**	**€ 31,782,810.39**	**€ 86,820,743.73**
Future scenario with Belimumab SC				
Pharmacological costs	€ 3,439,357.14	€ 3,287,050.88	€ 3,883,537.28	€ 10,609,945.30
Adverse events costs	€ 11,333,916.85	€ 10,836,111.78	€ 12,802,563.63	€ 34,972,592.25
Flare costs	€ 3,461,764.25	€ 3,309,717.62	€ 3,910,339.00	€ 10,681,820.87
Productivity loss	€ 10,209,123.24	€ 9,760,721.04	€ 11,532,019.49	€ 31,501,863.77
Dialysis & transplantation	€ 780,850.75	€ 746,554.45	€ 882,033.25	€ 2,409,438.45
Irreversible organ damage	€ 116,908.52	€ 111,773.70	€ 132,057.51	€ 360,739.74
Total costs	**€ 29,341,920.76**	**€ 28,051,929.47**	**€ 33,142,550.15**	**€ 90,536,400.37**
Annual budget impact	€ 1,205,015.83	€ 1,150,901.05	€ 1,359,739.75	€ 3,715,656.64
Annual budget impact per patient treated with BSoC	€ 4,757.21	€4,752.30	€4,752.24	€4,753.87

Appendix 8: Budget impact of Belimumab SC over the three years

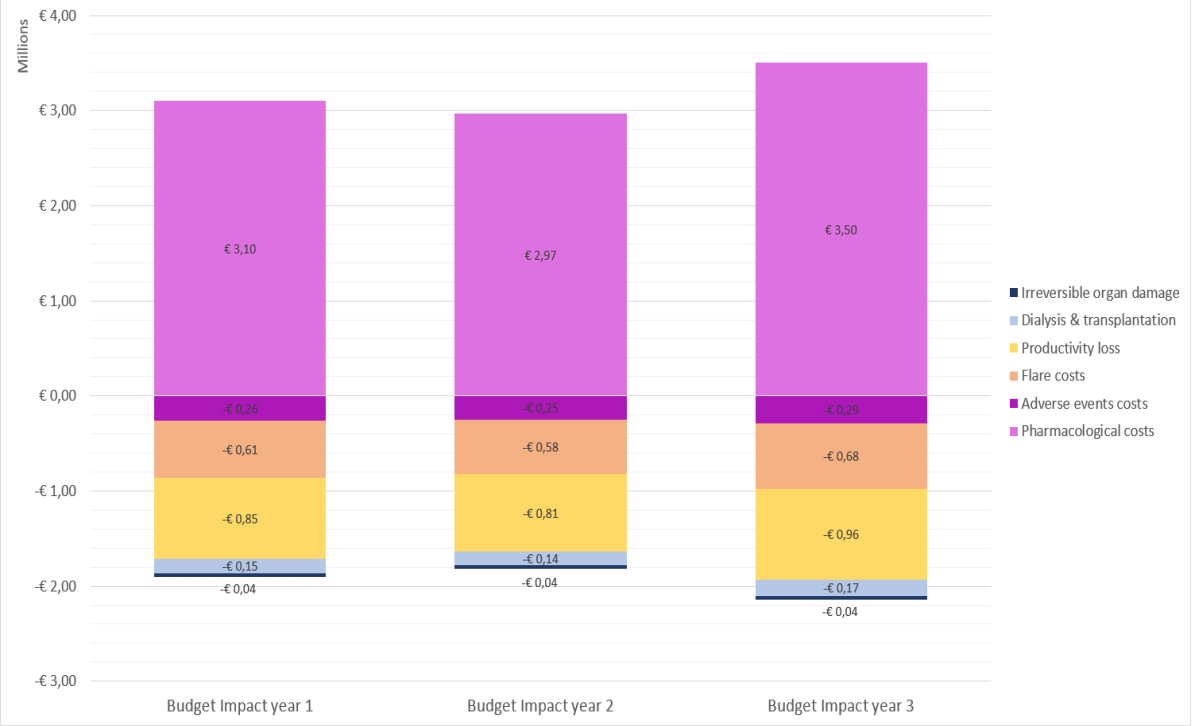


Figure 6 Budget Impact of Belimumab SC over three years

Appendix 9: Summary parameter table

Table 21 Summary parameter table

Parameters	***Base case value***	***Minimum value***	***Maximum value***	***Source related range of variation or reference (minimum value. maximum value)***
Population size	17842995	14274396	21411594	"+/- 20.0% base case"
Prevalence	0.04%	0.02%	0.08%	[31], [32]
SLE population non renal	75.00%	60.00%	90.00%	[5], "+ 20.0% base-case"
SLE population with moderate to severe disease activity	19.00%	15.20%	22.80%	[20],"+ 20.0% base case".
Non-responders belimumab SC	30.00%	24.00%	36.00%	"+/- 20.0% base case"
Non-responders standard of care	30.00%	24.00%	36.00%	"+/- 20.0% base case"
Female population	94.40%	75.52%	100.00%	"+/- 20.0% base case"
Mean age males	38.60	30.88	46.32	"+/- 20.0% base case"
Mean age females	38.60	30.88	46.32	"+/- 20.0% base case"
% aged > 35 years	55.90%	44.72%	67.08%	"+/- 20.0% base case"
Mean body weight (gender adjusted weighted average)	72.70	58.16	87.24	"+/- 20.0% base case"
Mean patient height (gender adjusted weighted average)	171.11	136.89	205.33	"+/- 20.0% base case"
Mortality rates per year, per 1000 person-years	14.90	13.80	16.00	[37,38,98], [37,38,98]
Incidence rates per year, per 100.000 person-years	1.40	1.20	8.60	[38,40,98], [38,40,98]
Market share current 2023	0.00%	0.00%	0.00%	"+ 20.0% base case"
Market share current 2024	0.00%	0.00%	0.00%	"+ 20.0% base case"
Market share current 2025	0.00%	0.00%	0.00%	"+ 20.0% base case"
Market share future 2023	27.00%	15.20%	49.30%	[15], [15]
Market share future 2024	27.00%	15.20%	49.30%	[15], [15]
Market share future 2025	27.00%	15.20%	49.30%	[15], [15]
Treatment dose per administration Belimumab SC. mg	200.00	160.00	240.00	"+/- 20.0% base case"
Treatment dose per administration Corticosteroids. mg	5.00	4.00	6.00	"+/- 20.0% base case"
Treatment dose per administration Antimalarials. mg	200.00	160.00	240.00	"+/- 20.0% base case"
Treatment dose per administration Azathioprine. mg	50.00	40.00	60.00	"+/- 20.0% base case"
Treatment dose per administration Mycophenolate mofetil. mg	500.00	400.00	600.00	"+/- 20.0% base case"
Treatment dose per administration Methotrexate. mg	10.00	8.00	12.00	"+/- 20.0% base case"
Doses per month Belimumab SC. n	4.00	3.20	4.80	"+/- 20.0% base case"
Doses per year Belimumab SC. n	52.00	41.60	62.40	"+/- 20.0% base case"
Additional doses in the first year Belimumab SC. n	4.00	3.20	4.80	"+/- 20.0% base case"
Additional doses in the first year Corticosteroids. n	0.00	0.00	0.00	"+/- 20.0% base case"

Additional doses in the first year Antimalarials. n	0.00	0.00	0.00	"+/- 20.0% base case"
Additional doses in the first year Azathioprine. n	0.00	0.00	0.00	"+/- 20.0% base case"
Additional doses in the first year Mycophenolate mofetil. n	0.00	0.00	0.00	"+/- 20.0% base case"
Additional doses in the first year Methotrexate. n	0.00	0.00	0.00	"+/- 20.0% base case"
Recommended doses Antimalarials. mg/day	300.00	200.00	400.00	[49], [49]
Recommended doses Azathioprine. mg/day	75.00	50.00	100.00	[49], [49]
Recommended doses Mycophonolate mofetil. mg/day	1250.00	1000.00	1500.00	[49], [49]
Recommended doses Methotrexate. mg/day	8.75	7.50	10.00	[49], [49]
Mean treatment dose usage prednisone at baseline population. mg/day	10.90	2.39	19.41	[56], [56]
Mean treatment dose usage prednisone in BSoC after 52 weeks	8.56	6.85	10.27	"+/- 20.0% base case"
Mean treatment dose usage prednisone in SoC after 52 weeks	10.70	8.56	12.84	"+/- 20.0% base case"
Average amount of days in a month	30.00	28.00	31.00	-
Average amount of weeks in a month	4.00	3.2	4.8	"+/- 20.0% base case"
Months per year	12.00	12	12	-
Number of supervised visits in year 1 for BSoC	4.00	3.20	4.80	"+/- 20.0% base case"
Cost per supervised visits per half an hour in BSoC	€ 17.82	€ 14.26	€ 21.38	"+/- 20.0% base case"
Number of supervides visits in year 1 for SoC	€ 0.00	0.00	0.00	-
Cost per supervised visits per half an hour in SoC	€ 0.00	0.00	0.00	-
Cost per 200 mg Belimumab SC	€ 235.79	€ 188.63	€ 282.95	"+/- 20.0% base case"
Average drug cost Belimumab SC. per mg	€ 1.18	€ 0.94	€ 1.41	"+/- 20.0% base case"
Average drug cost Corticosteroids. per mg	€ 0.01	€ 0.01	€ 0.01	"+/- 20.0% base case"
Average drug cost Antimalarials. per mg	€ 0.00	€ 0.00	€ 0.00	"+/- 20.0% base case"
Average drug cost Azathioprine. per mg	€ 0.01	€ 0.01	€ 0.01	"+/- 20.0% base case"
Average drug cost Micophenolate mofetil. per mg	€ 0.00	€ 0.00	€ 0.00	"+/- 20.0% base case"
Average drug cost Methotrexate. per mg	€ 0.02	€ 0.02	€ 0.02	"+/- 20.0% base case"
Proportion of patients with corticosteroid reduction in BSoC	18.20%	14.56%	21.84%	"+/- 20.0% base case"
Proportion of patients with corticosteroid reduction in SoC	11.90%	9.52%	14.28%	"+/- 20.0% base case"
Treatment usage according to the DAiRE 2018 report for azathioprine	48.00%	38.40%	57.60%	"+/- 20.0% base case"

Treatment usage according to the DAiRE 2018 report for mycophenolate mofetil	43.00%	34.40%	51.60%	"+/- 20.0% base case"
Treatment usage according to the DAiRE 2018 report for methotrexate	35.00%	28.00%	42.00%	"+/- 20.0% base case"
Adverse events rates of infections and infestations in BSoC	55.40%	44.32%	66.48%	"+/- 20.0% base case"
Adverse events rates of gastrointestinal disorders in BSoC	22.50%	18.00%	27.00%	"+/- 20.0% base case"
Adverse events rates of muculosketal and connective tissue disorders in BSoC	22.30%	17.84%	26.76%	"+/- 20.0% base case"
Adverse events rates of nervous system disorders in BSoC	20.00%	16.00%	24.00%	"+/- 20.0% base case"
Adverse events rates of skin and subcutaneous disorders in BSoC	14.40%	11.52%	17.28%	"+/- 20.0% base case"
Adverse events rates of infections and infestations in SoC	56.80%	45.44%	68.16%	"+/- 20.0% base case"
Adverse events rates of gastrointestinal disorders in SoC	24.30%	19.44%	29.16%	"+/- 20.0% base case"
Adverse events rates of muculosketal and connective tissue disorders in SoC	23.60%	18.88%	28.32%	"+/- 20.0% base case"
Adverse events rates of nervous system disorders in SoC	18.90%	15.12%	22.68%	"+/- 20.0% base case"
Adverse events rates of skin and subcutaneous disorders in SoC	21.40%	17.12%	25.68%	"+/- 20.0% base case"
Adverse events costs of Infections and infestations	€ 9.764.97	€ 7.811.98	€ 11.717.97	"+/- 20.0% base case"
Adverse events costs of Gastrointestinal disorders	€ 6.490.44	€ 5.192.35	€ 7.788.53	"+/- 20.0% base case"
Adverse events costs of Muculosketal and connective tissue disorders	€ 12.109.91	€ 9.687.92	€ 14.531.89	"+/- 20.0% base case"
Adverse events costs of Nervous system disorders	€ 2.269.56	€ 1.815.65	€ 2.723.47	"+/- 20.0% base case"
Adverse events costs of Skin and subcutaneous disorders	€ 9.152.05	€ 7.321.64	€ 10.982.46	"+/- 20.0% base case"
Proportion of patients experiencing a severe flare over 52 weeks in BSoC	10.60%	8.48%	12.72%	"+/- 20.0% base case"
Proportion of patients experiencing a mild/moderate flare over 52 weeks in BSoC	60.40%	48.32%	72.48%	"+/- 20.0% base case"
Proportion of patients experiencing a severe flare over 52 weeks in SoC	18.20%	14.56%	21.84%	"+/- 20.0% base case"
Proportion of patients experiencing a mild/moderate flare over 52 weeks in SOC	67.50%	54.00%	81.00%	"+/- 20.0% base case"
Annual mean amount of mild/moderate flares per patient in BSoC	1.23	0.98	2.15	"- 20.0% base-case", [91]
Annual mean amount of severe flares per patient in BSoC	0.04	0.03	0.54	"- 20.0% base-case", [91]
Annual mean amount of mild/moderate flares per patient in SoC	1.69	1.35	2.5	"- 20.0% base-case", [91]

Annual mean amount of severe flares per patient in SoC	0.22	0.18	1.01	"- 20.0% base-case", [91]
Annual mean costs per severe flare	€ 7.843.10	€ 6.274.48	€ 9.411.72	"+/- 20.0% base case"
Annual mean costs per mild/moderate flare	€ 1.974.88	€ 1.579.90	€ 2.369.86	"+/- 20.0% base case"
Renal flare over 52 week with a proteinuria >0.5g/24h in BSoC	11.10%	8.88%	13.32%	"+/- 20.0% base case"
Renal flare over 52 week with a proteinuria >0.5g/24h in SoC	27.10%	21.68%	32.52%	"+/- 20.0% base case"
Annual progression probability from SLE to LN	40.00%	32.00%	48.00%	"+/- 20.0% base case"
Annual progression probability from LN to ESKD	10.00%	8.00%	12.00%	"- 20.0% base case", [27]
Annual renal replacement therapy distribution for a living donor kidney transplantation	10.00%	8.00%	12.00%	"+/- 20.0% base case"
Annual renal replacement therapy distribution for a deceased donor kidney transplantation	2.00%	1.60%	2.40%	"+/- 20.0% base case"
Annual renal replacement therapy distribution for a Continuous Hemodialysis	69.00%	55.20%	82.80%	"+/- 20.0% base case"
Annual renal replacement therapy distribution for a Continuous Ambulantory Peritoneal Dialysis	19.00%	15.20%	22.80%	"+/- 20.0% base case"
Renal replacement therapy costs of living donor kidney transplantation	€ 75.908.72	€ 60.726.98	€ 91.090.47	"+/- 20.0% base case"
Renal replacement therapy costs of deceased donor kidney transplantation	€ 102.944.71	€ 82.355.76	€ 123.533.65	"+/- 20.0% base case"
Renal replacement therapy costs of Continuous Hemodialysis	€ 96.306.33	€ 77.045.07	€ 115.567.60	"+/- 20.0% base case"
Renal replacement therapy costs of Continuous Ambulantory Peritoneal Dialysis	€ 80.656.66	€ 64.525.33	€ 96.787.99	"+/- 20.0% base case"
Number of open vacancies in Q1 of 2021 (x 1000)	248.70	198.96	298.44	"+/- 20.0% base case"
Number of open vacancies in Q2 of 2021 (x 1000)	324.30	259.44	389.16	"+/- 20.0% base case"
Number of open vacancies in Q3 of 2021 (x 1000)	370.00	296.00	444.00	"+/- 20.0% base case"
Number of open vacancies in Q4 of 2021 (x 1000)	391.80	313.44	470.16	"+/- 20.0% base case"
Total number of vacancies fulfilled in Q1 of 2021	262.40	209.92	314.88	"+/- 20.0% base case"
Total number of vacancies fulfilled in Q2 of 2021	296.60	237.28	355.92	"+/- 20.0% base case"
Total number of vacancies fulfilled in Q3 of 2021	331.50	265.20	397.80	"+/- 20.0% base case"
Total number of vacancies fulfilled in Q4 of 2021	353.30	282.64	423.96	"+/- 20.0% base case"
Number of women in 2020	8845204.00	7076163.20	10614244.80	"+/- 20.0% base case"
Number of men in 2020	8745468.00	6996374.40	10494561.60	"+/- 20.0% base case"
Employment rate of females (2021)	68.20%	54.56%	81.84%	"+/- 20.0% base case"

Employment rate of males (2021)	76.50%	61.20%	91.80%	"+/- 20.0% base case"
SLE specific employement rate	46.00%	36.80%	55.20%	"+/- 20.0% base case"
Number of working hours per week per female	29.20	23.36	35.04	"+/- 20.0% base case"
Numer of working hours per week per male	39.40	31.52	47.28	"+/- 20.0% base case"
Average salary costs per hour per female	€ 40.25	€ 32.20	€ 48.30	"+/- 20.0% base case"
Average salary costs per hour per male	€ 48.28	€ 38.62	€ 57.94	"+/- 20.0% base case"
Weeks in a year	52.00	41.60	62.40	"+/- 20.0% base case"
Holidays in a year	20.00	16.00	24.00	"+/- 20.0% base case"
Amount of quartiles in a year	4.00	4.00	4.00	-
Days in a week	7.00	7.00	7.00	-
Amount of working hours in a day	8.00	6.40	9.60	"+/- 20.0% base case"
Hospitalization day per severe flare	11.80	9.44	14.16	"+/- 20.0% base case"
Outpatient treatment days per mild/moderate flare	1.00	0.80	1.20	"+/- 20.0% base case"
Workdays needed for the annual 4 hospitals visits	2.00	1.60	2.40	"+/- 20.0% base case"
Working days surrounding outpatient treatment not able to work due to a severe flare	8.00	6.40	9.60	"+/- 20.0% base case"
Working days surrounding hospitalization not able to work due to a mild/moderate flare	2.00	1.60	2.40	"+/- 20.0% base case"
Productivity loss factor mucocutaneous manifestation in BSoC. No (%) of subjects no improvement	35.90%	28.72%	43.08%	"+/- 20.0% base case"
Productivity loss factor hematology manifestation in BSoC. No (%) of subjects no improvement	55.10%	44.08%	66.12%	"+/- 20.0% base case"
Productivity loss factor SLEDAI-2K in BSoC. No (%) no response	38.30%	30.64%	45.96%	"+/- 20.0% base case"
Productivity loss factor mucocutaneous manifestation in SoC. No (%) of subjects no improvement	45.60%	36.48%	54.72%	"+/- 20.0% base case"
Productivity loss factor hematology manifestation in SoC. No (%) of subjects no improvement	64.00%	51.20%	76.80%	"+/- 20.0% base case"
Productivity loss factor SLEDAI-2K in SoC. No (%) no response	53.40%	42.72%	64.08%	"+/- 20.0% base case"
Annual mean change in SDI in BSoC	0.05	0.04	0.06	"+/- 20.0% base case"
Annual mean change in SDI in SoC	0.14	0.11	0.17	"+/- 20.0% base case"
Annual probability of progression in BSoC	3.50%	2.80%	4.20%	"+/- 20.0% base case"
Annual probability of progression in SoC	8.70%	6.96%	10.44%	"+/- 20.0% base case"
Annual direct medical costs per unit SDI	€ 1.322.64	€ 1.058.11	€ 1.587.17	"+/- 20.0% base case"